INVESTIGATION INTO THE USE OF AN EPIDURAL MORPHINE SULFATE AND DETOMIDINE HYDROCHLORIDE COMBINATION IN HORSES

PART 1: EFFICACY IN ALLEVIATION OF HINDLIMB PAIN
PART 2: LONG-TERM SYSTEMIC AND LOCAL EFFECTS

by

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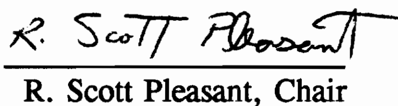
VETERINARY MEDICAL SCIENCES

Approved:



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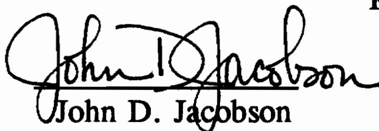

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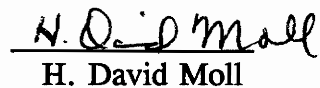

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In Part 1, amphotericin B-induced synovitis of the left tarsocrural joint was used to create hindlimb lameness in 11 horses. Caudal epidural catheters were placed and advanced to the lumbosacral region. Baseline heart and respiratory rates were recorded and horses were videotaped at a walk and trot. Treated horses received 0.2 mg/kg morphine sulfate and 30 ug/kg detomidine hydrochloride through the epidural catheter; control horses received an equivalent volume of physiologic saline solution through the catheter. At hourly intervals after epidural injection for a total of 6 hours, heart and respiratory rates were recorded and horses were videotaped walking and trotting. At the end of the observation period, video recordings were scrambled onto a master videotape. Lamenesses were scored by 3 investigators. Lameness grades, heart rates and respiratory rates were compared. There was a significant decrease in lameness grades after treatment with epidural morphine and detomidine. Initially, heart rates significantly increased in control horses and decreased in treated horses. A similar trend occurred for respiratory rates.

In Part 2, caudal epidural catheters were used to administer injections to 10 horses every 12 hours for 14 days. Treated horses received 0.2 mg/kg morphine sulfate and 30 ug/kg detomidine hydrochloride, and control horses received an equivalent volume of physiologic saline solution. Body weights were recorded on days 1 and 14. Rectal temperature, heart rate, respiratory rate and gastrointestinal motility were recorded twice daily, and daily hay and water consumption was measured. Horses were euthanatized on

day 15. Atlanto-occipital cerebrospinal fluid samples were submitted for bacteriologic culture and determination of white and red blood cell counts and protein and glucose concentrations. Post mortem examinations were performed and representative samples of the spinal cord and surrounding tissues were taken from cervicothoracic, thoracolumbar, lumbosacral, sacral and catheter entry point regions. Spinal tissue segments from these regions were graded for histologic degree of inflammation and fibrosis. Cerebrospinal fluid values and spinal tissue segment inflammation and fibrosis grades were compared between control and treated horses, and between all 10 catheterized study horses and 6 uncatheterized horses. No problems were encountered with epidural catheter maintenance or injection. No significant difference was identified in body weight change, daily variables or hay and water consumption between control and treated horses. All cerebrospinal fluid cultures were negative for growth. No significant difference in cerebrospinal fluid values or spinal tissue inflammation or fibrosis grades for any segment was demonstrated between control and treated horses. However, when compared to uncatheterized horses, cerebrospinal fluid red blood cell counts were marginally higher and protein concentrations were significantly higher in catheterized horses. As well, lumbosacral and sacral spinal tissue segment inflammation grades and sacral segment fibrosis grades were significantly higher in catheterized compared to uncatheterized horses.

Results of these studies indicate that an epidural combination of morphine and detomidine provides profound hindlimb analgesia in horses and is not associated with apparent adverse systemic effects. Localized epidural inflammation and fibrosis appear to be catheter-related.

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LIST OF ABBREVIATIONS

C	control group (epidural saline solution)
C+T	catheterized group (control plus treated horses)
cAMP	cyclic adenosine monophosphate
GABA	gamma-aminobutyric acid
G proteins	guanine nucleotide-binding proteins
IV	intravenously
T	treated group (epidural morphine + detomidine)
U	uncatheterized group

INTRODUCTION

> "The horse in a state of domesticity is of all the animal tribe the largest sharer with his master in his liability to the accidents and dangers which are among the incidents of civilized life. From his exposure to the missiles of war on the battlefield to his chance of picking up a nail from the city pavement there is no hour when he is not in danger of incurring injuries..." (Liautard, 1903).

Even in modern times, whether serving as athletes, work animals or pleasure companions, horses are susceptible to a wide variety of musculoskeletal injuries. Since the early part of the century, management of these types of injuries has changed considerably. One of the outstanding differences between treatment considerations for musculoskeletal injuries suggested some 90 years ago and those described today is the historical lack of mention of alleviation of pain from such injuries. It is shocking to realize that few pain-relieving medications were available to humans a century ago, let alone to horses.

We are indeed fortunate at this time to have a wide array of analgesic drugs available in our medical armamentarium. Today, nonsteroidal anti-inflammatory agents represent a significant contribution to mediation of equine musculoskeletal pain. Unfortunately, recovery periods from serious musculoskeletal injuries are often protracted, and prolonged use or employment of high dosages of nonsteroidal anti-inflammatory agents necessary to manage discomfort may result in serious side effects.

Recent discoveries in the field of human analgesia have led to the widespread use of opioids and alpha 2 adrenergic agonists, and their combinations, for alleviation of various types of pain. Furthermore, epidural and intrathecal routes of administration have broadened the use of such agents, and employment of indwelling catheters has extended their administration on a long-term basis. Today, terminally ill cancer patients and

patients with chronic pain unresponsive to other therapies are capable of leaving the hospital setting and ambulating in their home environment due to the profound and prolonged analgesia provided by administration of analgesics such as morphine and the alpha 2 adrenergic agonist, clonidine, through indwelling epidural catheters.

Historically, advances in veterinary analgesic therapy have often been made through adaptations of drugs, dosages and routes of administration from human medicine. It is through similar extrapolations that we elected to investigate an epidural combination of morphine and the commercially available alpha 2 adrenergic agonist, detomidine, for potential long-term treatment of musculoskeletal pain in horses.

LITERATURE REVIEW

Historical Perspective

Until a quarter of a century ago, the clinical significance of pain was unrecognized and few researchers devoted time either to the study of this field or to the field of analgesic pharmacology. Data published by the National Center for Health Statistics estimated that in 1988, 45 percent of the American population experienced acute pain requiring medical care (National Center for Health Statistics, 1989). Half of this group experienced pain that was moderate to severe or excruciating in intensity, and required major therapy in the form of opioids or other therapeutic modalities (National Center for Health Statistics, 1989). In that year, estimated total economic costs to the American population due to pain was in excess of 120 billion dollars for health care, lost workdays, compensation and other factors (National Center for Health Statistics, 1989). Since the socioeconomic ramifications of pain have become increasingly evident, scientists are beginning to intensively investigate anatomic, physiologic, biochemical, pathophysiologic and psychologic bases of pain in humans, as well as methods to relieve

acute and chronic pain.

Advances in pain identification and management in veterinary medicine only occurred long after the strides made in human patient care. This fact is surprising, since a great deal of the work that led to the discovery of analgesic agents and routes of administration in human medicine was first performed in animal species. Several factors may account for such slow development in the field of veterinary analgesia, including i) lack of awareness of the problem; ii) lack of objective criteria for pain assessment in patients unable to verbalize degree of discomfort; iii) variability among species with respect to pharmacokinetics and pharmacodynamics of analgesic agents; and iv) concern over development of serious undesirable side effects (Bonica, 1992). For both ethical and legal reasons, identification and pharmacologic control of animal pain is currently receiving world-wide attention, and funding from various sources is now being directed towards research into these subjects.

Equine Musculoskeletal Pain and Nonsteroidal Anti-Inflammatory Drugs

Musculoskeletal disorders in horses represent a significant proportion of cases that veterinarians are called upon to diagnose and manage. A study conducted of the British and Irish Thoroughbred racing industry between the years 1977 and 1980 indicated that 45 percent of horses in training did not start due to musculoskeletal conditions, and of the horses that did race, 53 percent experienced some period of lameness (Jeffcott et al, 1982).

Surgical treatment or medical management of serious musculoskeletal injuries in horses is often accompanied by prolonged convalescent periods. During these periods, mediation of pain associated with the injury is often brought about by administration of nonsteroidal anti-inflammatory agents. In fact, it has been suggested that nonsteroidal anti-inflammatory drugs are the most frequently used drugs in performance horses today (Kallings, 1993).

The analgesic properties of nonsteroidal anti-inflammatory drugs are, in part,

related to their ability to inhibit generation of prostenoids and leukotrienes, potent inflammatory mediators, via disruption of the arachidonic acid cascade. Agents such as phenylbutazone, flunixin meglumine, acetylsalicylic acid, acetaminophen and meclofenamic acid have been shown to bind to the enzyme cyclo-oxygenase and inhibit synthesis of prostenoids such as prostaglandins and thromboxanes (Kallings, 1993; Rubin, 1986), whereas the agent ketoprofen is believed to bind preferentially to the enzyme lipoxygenase and inhibit leukotriene synthesis (Kallings, 1993). Through inhibition of these mediators of inflammation, pain caused by the inflammatory response may be reduced (Kallings, 1993). Certain nonsteroidal anti-inflammatory drugs have also been shown to exert a direct spinal action by blocking glutamate and substance P receptor-activated hypersensitivity to pain (Malmberg and Yaksh, 1992). As well, some nonsteroidal anti-inflammatory drugs may inhibit enzyme systems which catalyze the formation of neurotransmitters involved in central pain pathways (Liles and Flecknell, 1992).

Nonsteroidal Anti-Inflammatory Drugs and Toxicity

Until the late 1970's, use of nonsteroidal anti-inflammatory drugs was considered to be safe in horses. This fact is somewhat surprising, since the toxic effects of the nonsteroidal anti-inflammatory agent, phenylbutazone, had been documented in humans as early as 1955 (Mauer, 1955). Currently, phenylbutazone is estimated to kill 22 human patients out of every million treated with the drug (Rang et al, 1995a). Side effects associated with nonsteroidal anti-inflammatory drug use in humans include dyspepsia, diarrhea, nausea, vomiting, oral and gastrointestinal ulceration and hemorrhage, skin rashes, urticaria, photosensitivity reactions, acute renal insufficiency, bone marrow disturbances including aplastic anemia, and liver disorders (Rang et al, 1995a; Rang et al, 1995b). As a result, use of nonsteroidal anti-inflammatory agents in human medicine has fallen under closer scrutiny, and use of certain agents such as phenylbutazone is currently restricted (Rang et al, 1995b; Insel, 1990).

Over the last decade, it has been shown that high dosages or prolonged use of maintenance dosages of nonsteroidal anti-inflammatory drugs may be associated with serious adverse effects in horses as well. Reported side effects in horses are similar to those observed in humans, and include oral, gastric, duodenal and colonic ulceration and necrosis (MacAllister et al, 1993; Meschter et al, 1990a; Meschter et al, 1990b; Traub-Dargatz et al, 1988), renal medullary crest necrosis (MacAllister et al, 1993; Gunson, 1983; Read, 1983), changes in cardiovascular, respiratory and neural function (Lees and Higgins, 1985), and blood dyscrasias and hepatotoxicity (Lees et al, 1986/1987). High-dose phenylbutazone administration has also been associated with degeneration of the walls of small veins, vascular thromboses at sites distant to administration and hematologic changes including neutropenia (Meschter et al, 1984; MacKay et al, 1983).

The toxic effects of nonsteroidal anti-inflammatory drugs have been attributed to disruption of prostaglandin synthesis. Prostaglandins E and I are normally produced in most body tissues including the gastric mucosa (Whittle and Vane, 1984), the vascular endothelium (Levin et al, 1984) and the kidney (Lands, 1979), as well as in inflammatory sites (Higgins and Lees, 1984). While these prostaglandins serve as vasoactive inflammatory mediators, they are also important in maintaining vascular perfusion to the gastrointestinal tract (Meschter et al, 1990a; Meschter et al, 1990b; Whittle and Vane, 1984) and to the renin/angiotensin-activated kidney (Rosenkrantz et al, 1981). Prostaglandins E and I also exert cytoprotective effects (Miller, 1983), decrease gastric acid production (Roth and Bennet, 1987), increase mucus production (Roth and Bennet, 1987) and increase migration of basal cells toward areas of mucosal injury (Tarnawski et al, 1985). Disruption of these normal physiologic functions has been suggested to cause many of the reported side effects through resultant vasoconstriction, hypoxia and necrosis (Lees and Higgins, 1985). More recently, studies conducted in horses have suggested that gastrointestinal lesions may result from direct toxic injury of nonsteroidal anti-inflammatory agents on microvasculature endothelium (Meschter et al, 1990a; Meschter et al, 1990b). In this event, lesions result from focal ischemia rather than from

reduction of prostaglandin-mediated functions (Meschter et al, 1990a; Meschter et al, 1990b).

Development of serious undesirable side effects following large dose or chronic use of nonsteroidal anti-inflammatory drugs cannot be overlooked. An alternative or supplemental form of analgesia producing few to no adverse effects could therefore improve long-term management of equine musculoskeletal pain.

Epidural Morphine

One of the greatest advances in human analgesic therapy occurred in 1979 with the first reported use of epidural morphine (Behar et al, 1979). Administered epidurally, morphine has been shown to produce greater and longer lasting analgesia than local anesthetics (Rawal et al, 1983) or than oral (Banning et al, 1986), intramuscular (Kilbride et al, 1992; Daley et al, 1990; Rawal et al, 1982), intra-articular (Ruwe et al, 1995) or intravenous (Bromage et al, 1980) morphine. Because of its ability to selectively block pain while leaving sensory, motor and sympathetic function intact (Cousins and Mather, 1984), morphine administered through indwelling epidural catheters has become a popular means of providing potent long-term analgesia in postoperative cases (Masuo et al, 1993; Kilbride et al, 1992; Rosen and Rosen, 1989; Behar et al, 1979), in terminally ill cancer patients (Ohlsson et al, 1992; Stamer and Maier, 1992, Gourlay et al, 1991; Plummer et al, 1991; Driessen et al, 1989; Behar et al, 1979) and in patients with chronic pain unresponsive to other therapies (Plummer et al, 1991; Arner et al, 1988; Behar et al, 1979).

With increasing attention being focused on identification and management of animal pain, epidural morphine has gradually made its appearance into veterinary medicine. In recent years, epidural morphine has been used successfully in dogs to provide analgesia following forelimb (Brock, 1995; Valverde et al, 1993; Valverde et al, 1989), hindlimb (Brock, 1995; Valverde et al, 1993; Dodman, 1992), thoracic (Brock, 1995; Pascoe and Dyson, 1993; Popilskis et al, 1991) and abdominal surgeries (Brock,

1995) and in goats after abdominal (Hendrickson et al, 1996) and orthopedic (Pablo, 1993) surgeries. Administration of caudal epidural morphine has been reported to provide cutaneous analgesia in the horse as far cranially as the ninth thoracic dermatome (Robinson et al, 1994) and deep analgesia to the hindlimb following digit amputation in one case (Valverde et al, 1990). However, results of an unpublished study in horses (Ewing, 1995) indicated that epidural morphine alone was not able to noticeably alleviate pain associated with septic arthritis of the hind fetlock, even when administered at up to 8 times the currently recommended dosage of 0.1 mg/kg (Valverde et al, 1993). Results of our pilot studies also indicated minimal analgesic efficacy of epidural morphine on hindlimb lameness in horses.

Epidural Morphine and Alpha 2 Adrenergic Agonists

Shortly after the introduction of epidural morphine analgesia into human medicine, the analgesic properties of epidurally-administered alpha 2 adrenergic agonists including clonidine (Eisenach et al, 1993; Smith et al, 1992; Bonnet et al, 1990), detomidine (Skarda and Muir, 1994a; Skarda and Muir, 1994b; Skarda and Muir, 1992), medetomidine (Duke et al, 1994a; Duke et al, 1994b; Branson et al, 1993), dexmedetomidine (Sabbe et al, 1994), guanfacine (Smith et al, 1992) and xylazine (Skarda and Muir, 1996; Skarda and Muir, 1994b; Grubb et al, 1992; Skarda and Muir, 1992; Fikes et al, 1989) were reported in various species. It was not long before research evaluating the efficacy of epidural combinations of morphine and alpha 2 adrenergic agonists began. Studies conducted in humans and dogs revealed that duration (Branson et al, 1993; Tamsen and Gordh, 1984) and intensity (Motsch et al, 1990; Petit et al, 1989) of epidural morphine analgesia could be enhanced by co-administration of an alpha 2 adrenergic agonist. Numerous investigations have suggested that opioid and alpha 2 adrenergic agonists act synergistically to modulate pain, and when combined, enhance the degree of modulation achieved over that when either agent is administered independently (Plummer et al, 1992; Omote et al, 1991; Ossipov et al, 1990; Ossipov

et al, 1989; Sherman et al, 1988; Wilcox et al, 1987; Nalda and Gonzalez, 1986; Yaksh and Reddy, 1981). In order to comment on the potential for synergy between epidural morphine and alpha 2 adrenergic agonists, a brief understanding of pain transmission and modulation is necessary.

Ascending Pain Pathways in the Peripheral Nervous System

Endings of sensory receptors that signal damage or the threat of damage are known as *nociceptors*. Nociceptors have been identified within skin and periosteum as well as within joint capsules, arterial walls, muscles, tendons, viscera and the tentorium of the cranial skull (Lasagna, 1986). Pain originating from muscles, bones and joints may be evoked by a variety of noxious stimuli, including mechanical, thermal or chemical insults (Sosnowski et al, 1992). When peripheral nociceptors are activated by a noxious stimulus, the membrane of the sensory ending of the receptor is depolarized. The noxious stimulus is then converted into a nerve impulse that is transmitted from the periphery to the central nervous system by way of an afferent nerve fiber.

Distinct subpopulations of afferent nerve fibers, grouped together by fiber diameter, have been described (Figure 1). The most important afferent fibers involved in pain transmission include myelinated *A-delta* fibers (2-5 um diameter) and small, unmyelinated *C* fibers (0.3-3 um diameter) (Fields, 1987b). A-delta fibers transmit impulses generated by either mechanical or thermal stimuli (Jessell and Kelly, 1991). In contrast, C fibers, the slowest conducting fibers, are responsive to mechanical, thermal or chemical stimuli, and are therefore known as *polymodal* fibers (Jessell and Kelly, 1991).

The pain perceived following injury is derived from a complex mixture of sensations involving transmission of peripheral impulses along fast A-delta fibers and slow C fibers (Sackman, 1991). The first perception of pain following noxious stimulation arises from A-delta fiber activation and is characterized as sharp or shooting (Ganong, 1993). The pain impulses which follow are carried by the slower C fibers and

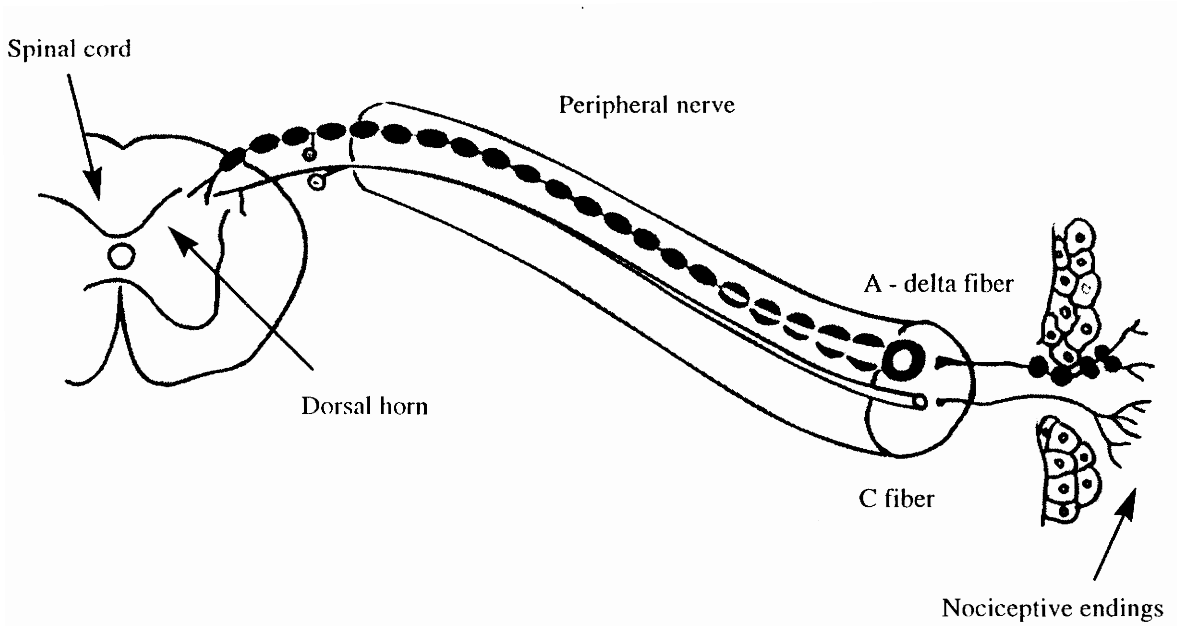

Figure 1. Components of a peripheral nociceptive nerve. When peripheral nociceptors are activated by a noxious stimulus, the membrane of the receptor ending is depolorized. The noxious stimulus is converted into a nerve impulse that is transmitted from the periphery to the central nervious system by way of either large myelinated A-delta fibers or small unmyelinated polymodal C fibers. (Adapted from Fields, 1987b)

tend to produce nonlocalized aching or burning sensations (Ganong, 1993). The farther from the brainstem that the painful stimulus arises, the greater the temporal separation between these 2 components of pain (Ganong, 1993).

Ascending Pain Pathways in the Central Nervous System

As the axons of A-delta and C fibers enter the spinal cord, they bifurcate and branches of the axons ascend and descend, for as many as three levels, in the dorsal grey horn of the spinal cord.

The dorsal grey horn is divided into numerous levels or *laminae*, based on characteristic cell content and morphology (Rexed, 1985). The laminae are numbered from the outside in, with lamina I being the most external. Present evidence indicates that afferent polymodal C fibers terminate predominantly in lamina II (substantia gelatinosa), whereas afferent A-delta fibers terminate in laminae I and V (Fields, 1987c).

Within the dorsal grey horn laminae, A-delta and polymodal C fiber axons synapse directly with three major categories of neurons: i) *projection neurons*, ii) *excitatory interneurons*, and iii) *inhibitory interneurons* (Fields, 1987c). Integrative activity between these neurons serves to regulate transmission of incoming nociceptive information (Figure 2). Cell bodies of *projection neurons* are located in laminae I and V (Fields, 1987c). Projection neurons are responsible for relaying sensory information from incoming afferent fibers to higher centers in the brain including the cerebral cortex (via the thalamus), the hypothalamus, the periaqueductal grey, the rostroventral medulla and the reticular activating system (Ganong, 1993). Axons of projection neurons transmit information to these higher brain centers through five ascending tracts that originate in different dorsal grey horn laminae. These tracts include: i) the spinothalamic tract, ii) the spinoreticular tract, iii) the spinomesencephalic tract, iv) the spinocervicothalamic tract, and v) the dorsal column (Jessell and Kelly, 1991). While all of these tracts are involved in nociceptive transmission to some degree, the spinothalamic tract (Figure 3) is considered to be the most prominent ascending nociceptive pathway in the spinal cord

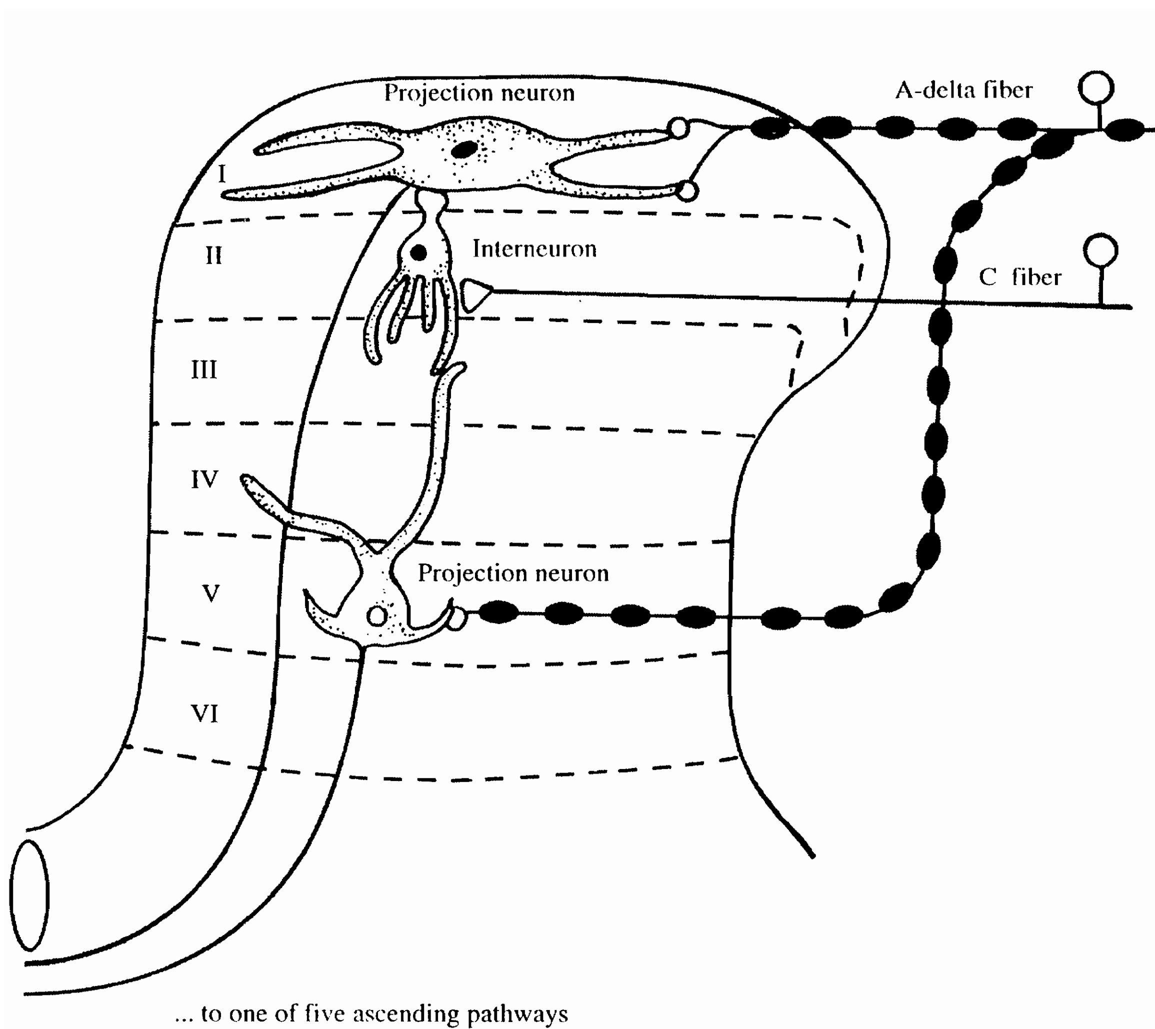

Figure 2. Synapses of afferent A-delta & C fiber axons in the dorsal horn of the spinal cord. The cell bodies of projection neurons are located in laminae I and V and are responsible for transmitting incoming impulses to higher centers in the brain. The cell bodies of interneurons are concentrated in lamina II, the substantia gelatinosa. Interneurons may be either excitatory or inhibitory and synapse with either projection neurons, other interneurons or motor neurons.(Adapted from Jessell and Kelly, 1991 and Fields, 1987c)

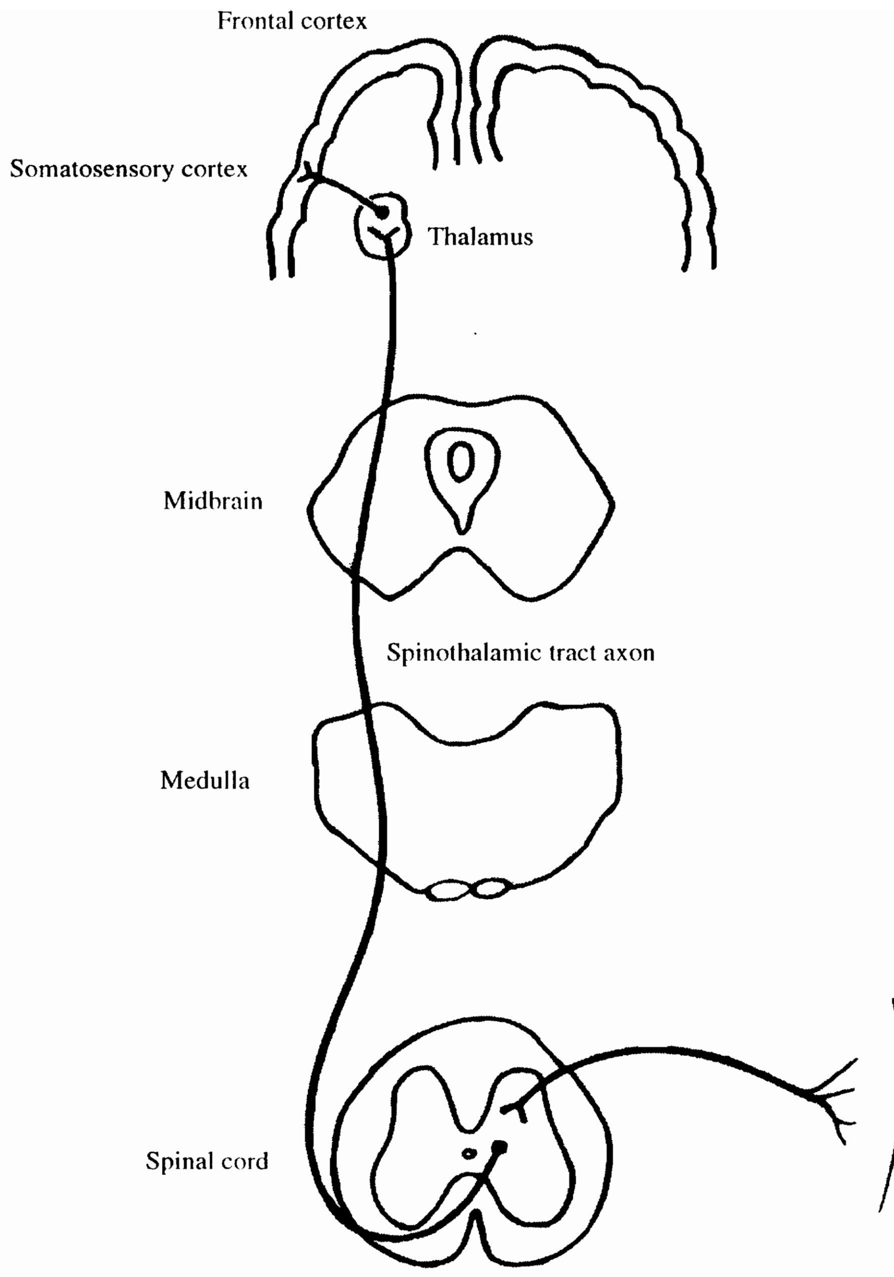

Figure 3. The ascending spinothalamic tract. Although the axons of projection neurons may ascend to the brain by any one of five pathways, the spinothalamic tract is considered to be the most prominent pathway involved in nociceptive transmission. (Adapted from Fields, 1987a)

and serves a principal role in pain transmission, as well as in discriminatory aspects of pain, including location, nature and intensity (Liss, 1987). At one time, anterolateral cordotomy was the standard surgical procedure used to treat intractable pain in humans, and the success of this operation was considered to be due to sectioning of the spinothalamic tract, the tract most clearly associated with pain (Sosnowski et al, 1992).

Cell bodies of interneurons are concentrated in lamina II. *Excitatory interneurons* relay nociceptive input from A-delta and C afferent fibers either to projection neurons, to other interneurons or to motor neurons that mediate spinal reflexes (Fields, 1987c). Neurotransmitters such as glutamate and substance P are stored within synaptic vesicles of A-delta and C afferent fiber terminals, and their release activates these excitatory interneurons (Willis et al, 1995; Jessell and Kelly, 1991).

Inhibitory interneurons share a similar location with excitatory interneurons. In contrast, these neurons are stimulated through release of inhibitory neurotransmitters including gamma-aminobutyric acid (GABA), glycine, enkephalin, dynorphin and somatostatin (Willis et al, 1995).

Transmission of painful impulses towards the brain is a balance between excitatory and inhibitory influences (Sosnowski et al, 1992). Pain results when an excess of nociceptive impulses is propagated without interruption to the brain (Sosnowski et al, 1992). Because processing of nociceptive impulses occurs within the dorsal grey horn of the spinal cord, this area is a target for mediation of pain through a variety of local mechanisms.

Pain Modulation in the Dorsal Horn of the Spinal Cord

Several receptor systems have been shown to modulate spinal processing of nociceptive input in the dorsal horn of the spinal cord, including opioid and alpha 2 adrenergic systems (Sosnowski et al, 1992). While these systems are capable of functioning independently, it is thought that they may also act together to disrupt transmission of pain between afferent nociceptive fibers and the brain (Sosnowski et al,

1992). High concentrations of opioid (mu) and alpha 2 adrenergic receptors have been identified in the dorsal grey horn of the spinal cord (Jessell and Kelly, 1991; Sullivan et al, 1987; Unnerstall et al, 1984). Presynaptic and post-synaptic locations have been suggested for both types of receptors (Simon and Hiller, 1994; Pertovaara, 1993; Daunt and Maze, 1992; Kamisaki et al, 1992; Calvillo and Guignone, 1986; Zieglgansberger, 1984; Carstens et al, 1979). Both opioid and alpha 2 adrenergic receptors are part of a superfamily of receptors that are coupled to guanine nucleotide-binding proteins, known as *G proteins*. G proteins couple these receptors to the generation of intracellular second messengers (Nestler and Duman, 1994). Multiple classes of G proteins exist in the nervous system. Each G protein is a heterotrimer composed of single alpha, beta and gamma subunits (Nestler and Duman, 1994). It is the alpha subunits (Figure 4) that are responsible for the specific functional activity of each type of G protein (Nestler and Duman, 1994).

Binding of agonists to either opioid or alpha 2 receptors causes the receptors to couple to a G protein. Coupling of the receptors with one specific type of G protein, known as the *G_o protein,* has been shown to alter gating of potassium ion channels (Nestler and Duman, 1994; Daunt and Maze, 1992; Simonds, 1988). Following receptor coupling, the alpha subunit is released from the G_o protein and opens potassium ion channels (Nestler and Duman, 1994). The resulting influx of potassium ions into neuronal cell bodies produces neuronal hyperpolarization (Miyake et al, 1989; Doze et al, 1988; Sullivan et al, 1987; North, 1986). The hyperpolarized state of the neurons subsequently inhibits their response to excitatory neurotransmitters, resulting in failure of propagation of nociceptive impulses beyond the afferent nerve fibers (William, 1986).

Coupling of alpha 2 receptors to the G_o protein has also been shown to have an inhibitory effect on voltage-gated calcium ion channels, prohibiting calcium ions from entering the neurons (Nestler and Duman, 1994). Decreased intraneuronal calcium concentrations cause reduced fusion of neurotransmitter-containing synaptic vesicles with synaptic cleft membranes, effectively decreasing the amount of neurotransmitters, such

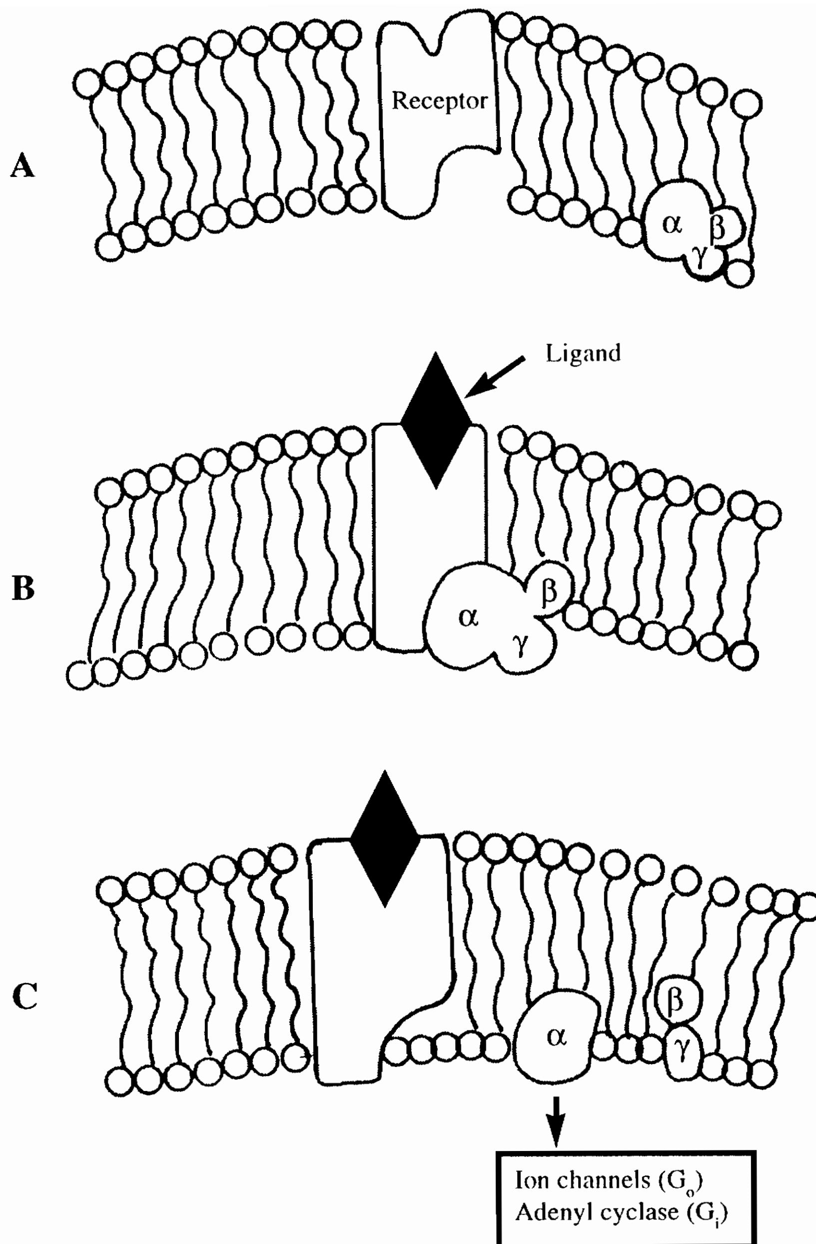

Figure 4. G protein function. **A**: Under basal conditions, G proteins exist in cell membranes asheterotrimers composed of single α, β and γ subunits and are not associated physically with receptors. **B**. Upon activation of the receptor by its ligand, the receptor physically associates with the α subunit. **C**. The α subunit then dissociates from its β and γ subunits as well as from the receptor. Free α subunits are functionally active and can directly regulate a number of activities, depending on the type of G protein and cell involved. (Adapted from Nestler and Duman, 1994)

as substance P, that are released (Daunt and Maze, 1992; Jessell and Kelly, 1991; Jessell and Dodd, 1989). This series of events functionally diminishes pain impulse propagation from A-delta and C afferent fibers to projection neurons and interneurons in the dorsal horn of the spinal cord (William, 1986). While a similar process is believed to occur at opioid receptors, it is uncertain whether closing of calcium ion channels occurs secondary to potassium-dependent intraneuronal hyperpolarization (Werz and MacDonald, 1985; Werz and MacDonald, 1983) or through mediation by the G_o protein (Hescheler et al, 1987).

Opioid and alpha 2 adrenergic receptors may also disrupt ascending pain transmission through coupling with an inhibitory G protein, known as G_i. Coupling of these receptors to G_i results in inhibition of adenyl cyclase activity (Nestler and Duman, 1994; Daunt and Maze, 1992; Simonds, 1988). Whether or not this effect is mediated by dissociation of the alpha subunit from the G_i protein is unknown (Nestler and Duman, 1994). The enzyme adenyl cyclase normally catalyzes the synthesis of cyclic adenosine monophosphate (cAMP), which is responsible for activating the enzyme, protein kinase. The resulting decrease in protein kinase concentrations subsequently disrupts phosphorylation of various target regulatory proteins and alters transmembrane voltages (Daunt and Maze, 1992). Again, the net effect is a disruption of nociceptive impulse transmission beyond the afferent nerve fibers.

In summary, ligand binding to either opioid or alpha 2 adrenergic receptors, followed by receptor coupling with various types of G proteins, has been shown to cause increased potassium ion conductance leading to neuronal hyperpolarization, decreased calcium ion conductance leading to decreased neurotransmitter release, and inhibition of adenyl cyclase activity causing disruption of protein phosphorylation and alteration of transmembrane voltage. The overall effect of any one of these processes is a disruption in transmission of nociceptive impulses at the level of the dorsal horn of the spinal cord.

Descending Pain Modulatory Pathways in the Central Nervous System

Pain modulation by opioid and alpha 2 adrenergic systems may occur not only in ascending transmission pathways but in descending modulatory pain pathways as well. The existence of these descending pathways, which extend from the brain to the spinal cord, were first discovered in rats, when it was shown that electrical stimulation of discrete areas of the brain could produce analgesia sufficient to perform abdominal surgery (Reynolds, 1969). Further studies in experimental animals confirmed that direct electrical stimulation to specific brain sites was capable of producing analgesia without behavioral depression (Fields, 1987d; Mayer and Liebeskind, 1974; Mayer et al, 1971). Electrical stimulation therapy soon extended into human medicine as a modality for treatment of pain (Baskin et al, 1986; Richardson and Akil, 1977). The fact that stimulation-produced analgesia could be elicited from homologous sites in rats, cats, primates and humans was considered indicative of the fact that some of the mechanisms underlying pain modulation were similar amongst species (Fields, 1987d).

The major areas within the central nervous system that make up the descending modulatory pain pathways include the *periaqueductal grey*, the *rostroventral medulla* and the *pons* (Figure 5). It is interesting that some of these areas serve as endpoints in ascending pain transmission, and that perception of pain by these higher centers is thought by some to activate the descending modulatory pathways (Beitz, 1992; Fields, 1987d).

The *periaqueductal grey* is located in the midbrain and receives its afferent supply from the frontal cortex (Hardy and Leichnetz, 1981), thalamus (Reichling et al, 1986), hypothalamus (Beitz, 1982a), pons (Fields, 1987d) and amygdala (Fields and Basbaum, 1989). Neurons from the periaqueductal grey project to the *rostroventral medulla,* where they make predominantly excitatory connections with the neurons there (Vanegas et al, 1984; Fields and Anderson, 1978). In addition to major input from the periaqueductal grey, the rostroventral medulla receives serotonergic input from certain areas of the midbrain (Beitz, 1982b) and noradrenergic input from the pons (Fields and Basbaum,

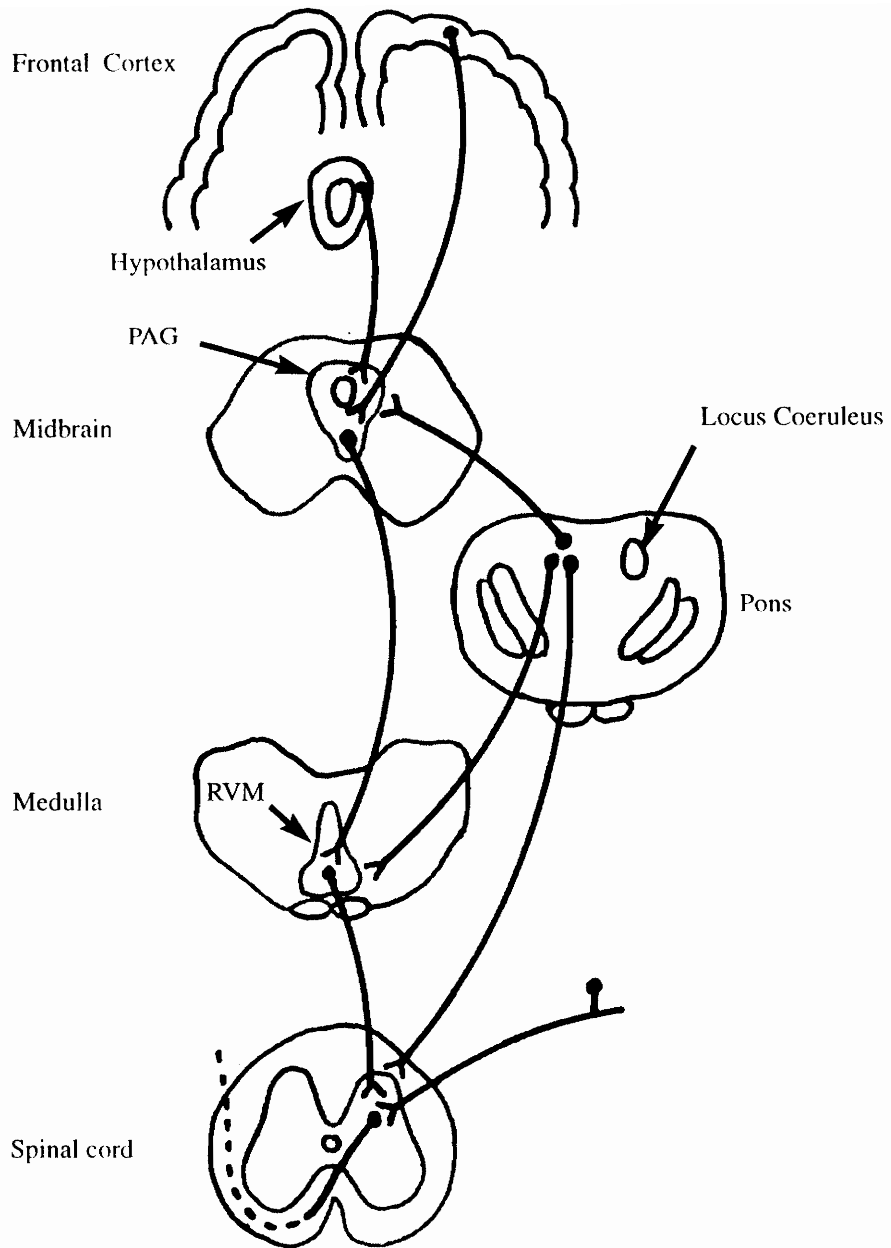

Figure 5. Descending modulatory pain pathways. Neurons from the periaqueductal grey (**PAG**) make excitatory connections with neurons in the rostroventral medulla (**RVM**). The RVM sends inhibitory projections to the dorsal horn of the spinal cord. The pons sends projections to the PAG and RVM as well as projections directly to the spinal cord. (Adapted from Fields, 1987a)

1989). The rostroventral medulla gives rise to major inhibitory neuronal projections to the spinal cord (Jessell and Kelly, 1991). Terminals of these rostroventral medullary projections are concentrated in laminae I, II and V of the dorsal horn, which contain terminals of afferent A-delta and C fibers, cell bodies of the spinothalamic tract neurons (projection neurons) and cell bodies of interneurons (Jessell and Kelly, 1991; Fields, 1987c).

The *locus coeruleus* region of the *pons* may also serve as a source of descending pain modulation (Beitz, 1992). This area of the pons, which contains many noradrenergic neurons, has not been as extensively studied as the periaqueductal grey or the rostroventral medulla. However, it is known that some of the neurons from this area project to the periaqueductal grey, some project to the rostroventral medulla and a large proportion project directly to the spinal cord (Fields, 1987d).

Neuronal projections from the rostroventral medulla and pons that reach the spinal cord are believed to inhibit nociceptive impulse transmission in the dorsal horn in one of three ways (Figure 6). The mechanisms thought to occur include: i) direct inhibition of projection neurons; ii) activation of inhibitory interneurons, which in turn inhibit projection neurons, and iii) presynaptic inhibition of afferent A-delta or C fibers (Fields, 1987d).

Modulation of Pain Through the Descending Pain Pathways

Various substances including opioids, adrenergic agonists, excitatory amino acid agonists, cholinergic agents, serotonergic agents and GABA antagonists are capable of activating descending pain modulatory pathways at some point along their length (Beitz, 1992). While all of these substances play an important role in the descending networks that modulate pain, the opioid links to the descending pathways have been the most extensively studied.

It has been shown that the periaqueductal grey region contains relatively dense concentrations of opioid (mu) receptors (Fields, 1987d), and that stimulation of these

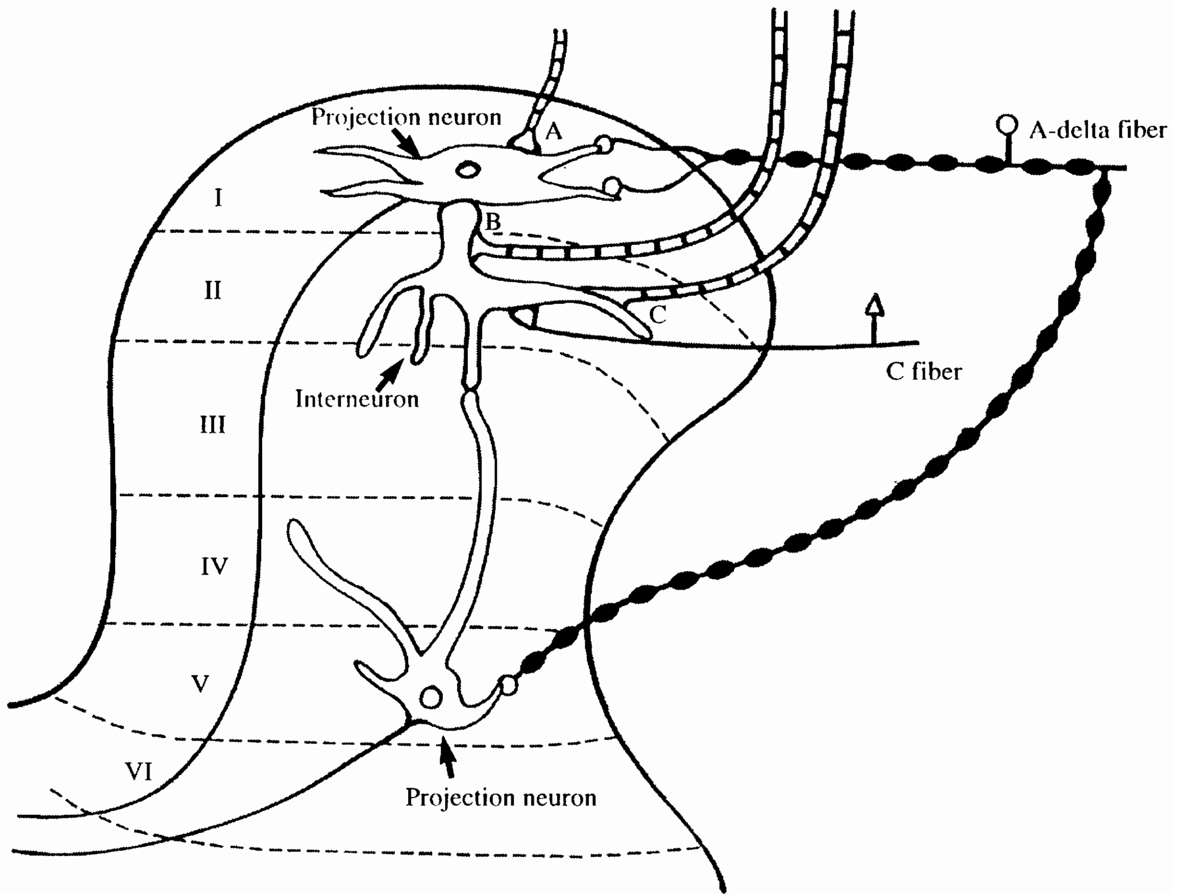

Figure 6. Spinal circuits underlying descending inhibition of pain transmission. Axons entering the spinal cord from the descending pain modulatory pathways may disrupt incoming pain transmission by **A**: directly inhibiting projection neurons, **B**: activating inhibitory interneurons which in turn inhibit projection neurons or **C**: activating inhibitory interneurons which presynaptically inhibit terminals of nociceptive primary afferents. The overall effect is disruption of pain impulse transmission beyond the level of the spinal cord.

receptors activates the descending pathways (Beitz, 1992). In the normal resting state, neuronal output from the periaqueductal grey to the rostroventral medulla is inhibited by means of a GABAergic (inhibitory) interneuron (Jessell and Kelly, 1991). Although the exact mechanism is not well understood, the binding of morphine to mu receptors in the periaqueductal grey is believed to *dis*inhibit the GABA interneuron, permitting excitation of neuronal projections between the periaqueductal grey and the rostroventral medulla (Jessell and Kelly, 1991; Fields and Basbaum; 1989). The rostroventral medulla is thereby stimulated to inhibit pain impulse transmission at the spinal cord level (Jessell and Kelly, 1991; Fields and Basbaum, 1989). While both the rostroventral medulla and pons are also sensitive to morphine administration (Jessell and Kelly, 1991; Yaksh and Aimone, 1989; Jones and Gebhart, 1988; Fields, 1987d), the mechanisms by which morphine binding may activate descending modulatory pathways at these levels is not as clear.

The significance of alpha 2 adrenergic agonist receptors in the descending modulatory pathways is even more ambiguous. Alpha 2 adrenergic receptors have been located in regions of the descending pathways including the periaqueductal grey, the ventral medulla and the locus coeruleus of the pons (Unnerstall et al, 1984). Although early studies suggested that administration of alpha 2 adrenergic agonists to these areas of the brain activated the descending inhibitory pathways (Lipman and Spencer, 1979; Schmitt et al, 1974), later work showed that direct stimulation of alpha 2 adrenergic receptors in the periaqueductal grey, the rostroventral medulla and the locus coeruleus failed to activate descending antinociceptive mechanisms (Hamalainen and Pertovaara, 1993; Pertovaara, 1993; Ossipov and Gebhart, 1983). It has been postulated that alpha 2 adrenergic receptor-mediated modulation of pain after alpha 2 agonist administration occurs by spread of the adrenergic agent to the spinal cord to directly activate alpha 2 adrenergic receptor-rich regions in the dorsal horn (Hamalainen and Pertovaara, 1993).

Opioid and Alpha 2 Adrenergic Agonist Synergism in Mediating Pain

When 2 drugs are administered together, their effects may be *additive* (ie. the simple sum of the effects produced by each agent alone), *antagonistic* (ie. less than the sum of the effects produced by each agent alone) or *synergistic* (ie. supra-additive or greater than the sum of the effects produced by each agent alone) (Solomon and Gebhart, 1994). Drugs which act synergistically rather than additively hold the most promise in development of potent new epidural analgesic regimes.

Numerous studies in a variety of species have documented synergistic interactions between the opioid agonist, morphine, and various alpha 2 adrenergic agonists (Omote et al, 1991; Ossipov et al, 1990; Ossipov et al, 1989; Sherman et al, 1988; Wilcox et al, 1987; Nalda and Gonzalez, 1986). However, the complexity of neurons, neuronal connections and endogenous substances involved at numerous sites in both ascending and descending pain pathways has complicated the understanding of their synergistic mechanisms. As a result, several hypotheses have been generated in an attempt to explain the observed synergism.

It has been proposed that the pharmacokinetic parameters of one agent may be altered by the co-administration of another. In other words, an overall increase in drug levels at an effector site could prolong or enhance the ability of both agents to mediate pain (Solomon and Gebhart, 1994).

Some investigators have suggested that analgesic synergy between morphine and alpha 2 adrenergic agonists could result from a common anatomic site of action, such as the locus coeruleus (Andrade and Aghajanian, 1985; Ossipov and Gebhart, 1983) or the spinal cord (Ossipov et al, 1989; Sullivan et al, 1987; Wilcox et al, 1987; Hylden and Wilcox, 1983; Yaksh and Reddy, 1981). Conversely, it has been implied that alpha 2 adrenergic agonists may be active at adrenergic receptor sites distal to opioid receptor sites (Ossipov et al, 1989), producing alpha 2 receptor-mediated inhibition of ascending pain transmission at the spinal cord level concurrent with opioid-mediated activation of descending modulatory pathways. A greatly multiplied inhibitory effect on pain impulse

transmission would therefore be possible.

At the neuronal level, location of opioid and alpha 2 adrenergic receptors has been implicated in their synergistic interaction. Both pre and post-synaptic sites have been described for opioid (mu) as well as alpha 2 adrenergic receptors (Simon and Hiller, 1994; Pertovaara, 1993; Daunt and Maze, 1992; Kamisaki et al, 1992; Calvillo and Guignone, 1986; Zieglgansberger, 1984; Carstens et al, 1979). It has been suggested that simultaneous activation of mu and alpha 2 adrenergic receptors at both pre and post-synaptic locations could enhance the degree of pain modulation produced by activation of 1 receptor type at only 1 site (Solomon et al, 1994; Wilcox et al, 1987).

At the cellular level, investigators have speculated that a common G protein-mediated mechanism of action, such as neuronal hyperpolarization, may be responsible for the synergistic interaction between morphine and alpha 2 adrenergic agonists (Ossipov et al, 1990; Sullivan et al, 1987; Wilcox et al, 1987; Andrade and Aghajanian, 1985). Alternatively, it has been suggested that co-administration of morphine and alpha 2 agonists could result in activation of different G protein-coupled effects by each receptor type (Ossipov et al, 1990). Generation of multiple G protein-mediated effects could then yield a greater inhibitory effect on pain transmission than that achieved by generation of a single G protein-mediated effect through coupling with only 1 receptor type.

Although the exact mechanism of synergy remains elusive, clinical and laboratory experience in humans and animals has consistently demonstrated supra-additive analgesia with co-administration of epidural morphine and alpha 2 adrenergic agonists. The synergistic action of these agents is important therapeutically, as potential development of undesirable side effects may be decreased through use of lower dosages of each drug without compromising analgesic efficacy.

Systemic Side Effects Associated With Epidural Morphine Use

Although epidural morphine is popular for its analgesic effects for many types of

pain, its use in some species has been associated with several side effects including respiratory depression, urinary retention, pruritus, nausea and vomiting, decreased gastrointestinal motility, sedation and tolerance. Reports of epidural morphine use in horses are few. The following discussion highlights the effects documented in human patients after epidural morphine injection, and indicates potential effects that could be observed in horses.

Respiratory Depression Early respiratory depression in humans can occur in the first 2 hours after epidural morphine injection, and is believed to result from rapid vascular uptake and redistribution of the drug to the respiratory center in the brain (Littrell, 1991; Cousins and Mather, 1984). More commonly, however, onset of respiratory depression in humans is delayed by as much as 6 to 24 hours after epidural morphine injection (Stenseth et al, 1985; Rawal and Wattwil, 1984; Gustafsson et al, 1982; Nielsen et al, 1981). Because morphine is poorly lipid soluble, its passage from the epidural space through the dura mater and into the cerebrospinal fluid is prolonged (Gourlay et al, 1987). Slow uptake of morphine from the epidural space and passive flow in the cerebrospinal fluid to the respiratory center in the brain are thought to account for the delay in onset of respiratory depression (Gourlay et al, 1985; Cousins and Mather, 1984).

Morphine is believed to decrease the responsiveness of the respiratory center to increases in carbon dioxide tension, as well as to depress pontine and medullary centers involved in regulation of respiratory rhythmicity (Ready, 1992; Short, 1987; Gourlay et al, 1985). The observed clinical effect is a mild decrease in ventilatory rate and a slight increase in arterial carbon dioxide tension (Pascoe and Dyson, 1993; Weddel and Ritter, 1981). Respiratory depression has been reported to occur in fewer than 1 percent of human patients after epidural morphine injection (Weddel and Ritter, 1991; Gustafsson et al, 1982; Reiz and Westberg, 1980). Interestingly, this effect is reported to be reversible with intramuscular or intravenous administration of naloxone without affecting

the analgesic response (Ready et al, 1991; Weddel and Ritter, 1981). Administration of epidural morphine at varying dosages has not been noted to cause clinical evidence of respiratory depression in dogs (Pascoe and Dyson, 1993; Popilskis et al, 1991), goats (Pablo, 1993) or pigs (Kytta et al, 1986).

Urinary Retention Up to 39 percent of humans receiving epidural morphine have been reported to develop urinary retention (Weddel and Ritter, 1991; Driessen et al, 1989; Lanz et al, 1982; Rawal et al, 1982; Bromage et al, 1980; Reiz and Westberg, 1980). Although the mechanisms underlying this effect are not well understood, urinary retention appears to result from depression of sacral parasympathetic preganglionic neurons, which may decrease pelvic nerve activity and depress cholinergic activation of the smooth muscle of the bladder (Dray, 1988; Gustafsson et al, 1982). Current evidence suggests that this urodynamic effect of epidural morphine is not dose-related (Rawal et al, 1983; Martin et al, 1982). While not formally evaluated, clinical manifestation of urinary retention was not reported in dogs receiving epidural morphine (Pascoe and Dyson, 1993; King et al, 1984).

Pruritus The incidence of pruritus secondary to epidural morphine administration appears to be variable. While some studies have documented development of pruritus in up to 91 percent of patients receiving epidural morphine (Rosaeg and Lindsay ,1994; Ready, 1991; Weddel and Ritter, 1991; Daley et al, 1990; Motsch et al, 1990; Driessen et al, 1989; Arner et al, 1988; Glynn et al, 1988; Bromage et al, 1980; Reiz and Westberg, 1980) other studies have reported that pruritus was not observed (Rosen and Rosen, 1989; Rawal et al, 1982).

Some investigators have attributed epidural morphine-induced pruritus to release of histamine following injection (Weddel and Ritter, 1991). Although morphine is known to cause histamine release from mast cells by an action unrelated to opioid receptors (Rang et al, 1995c), other clinical symptoms of histamine release, such as

bronchoconstriction, have not been observed in affected patients (Bromage et al, 1982). As well, use of antihistamines has not been consistent in alleviation of clinical signs (Reiz and Westberg, 1980). Other investigators have attributed development of pruritus to presence of preservatives in the injectate (Reiz and Westberg, 1980). However, use of preservative-free morphine has not been noted to inhibit development of pruritus after epidural injection (Bromage et al, 1982).

Naloxone and nalbuphine are potent opioid receptor antagonists that have been shown to completely reverse morphine-induced pruritus. This finding suggests that development of pruritus is most likely due to disruption of sensory input at opiate-sensitive receptors in the brain (Littrell, 1991).

In dogs, pruritus was not documented following epidural morphine administration (Pascoe and Dyson, 1993; King et al, 1984). However, one study in horses reported development of perineal wheals secondary to caudal epidural injection of various dosages of morphine (Robinson et al, 1994).

Nausea and Vomiting Between 7 and 60 percent of human patients experience nausea and vomiting following epidural injection of morphine (Rosaeg and Lindsay, 1994; Ready, 1991; Daley et al, 1990; Motsch et al, 1990; Rosen and Rosen, 1989; Glynn et al, 1988; Bromage et al, 1982; Gustafsson et al, 1982; Lanz et al, 1982; Rawal et al, 1982; Reiz and Westberg, 1980). Development of nausea and vomiting has been attributed to cranial spread of morphine via the cerebrospinal fluid to the vomiting center and chemoreceptor trigger zone in the brain (Cousins and Mather, 1984; Bromage et al, 1982). Vomiting was not reported as a side effect following epidural injection of morphine in dogs (King et al, 1984). It is unknown whether a chemoreceptor trigger zone exists in the central nervous system of horses that may be affected by epidural morphine administration.

Decreased gastrointestinal motility Although a comparatively infrequent effect,

epidural administration of morphine has been observed to disrupt gastrointestinal motility in some human patients (Thorn et al, 1992; Motsch et al, 1990; Driessen et al, 1989; Thoren, Tanghoj et al, 1989; Thoren, Sundberg et al, 1989). The exact mechanism for this morphine-induced effect after epidural injection has not been well evaluated. One study in humans demonstrated that while epidural morphine induced premature migrating motor complexes in the small intestine, periodic motor activities in the jejunum were recovered within 32 hours in all patients (Shibata et al, 1994). Epidural morphine injection in dogs (King et al, 1984) and goats (Pablo, 1993) was not associated with development of gastrointestinal ileus. Studies in ponies have demonstrated dose-related colonic inhibition, delayed defecation and fecal drying in association with intramuscular and intravenous administration of morphine and the mu agonist, fentanyl (Roger et al, 1994; Roberts and Argenzio, 1986). Whether similar effects would occur in horses after epidural morphine injection is unknown.

Sedation Two categories exist into which all species may be subdivided based on their response to morphine-like drugs. Sedation in response to parenteral administration of morphine is observed in species including humans, dogs, rabbits, guinea pigs and rats (Brunaud, 1986). In contrast, parenteral morphine administration is known to exert excitatory effects in horses, cows, small ruminants, pigs, cats, bears, mice and fish (Short, 1987; Brunaud, 1986).

Varying degrees of sedation have been documented in human patients secondary to epidural morphine administration (Weddel and Ritter, 1991; Daley et al, 1990; Motsch et al, 1990; Driessen et al, 1989; Petit et al, 1989; Bromage et al, 1980). Sedation after epidural injection is suggested to be a result of vascular uptake of morphine and delivery to supraspinal sites (Littrell, 1991).

Interestingly, sedation has also been observed following epidural morphine injection in species considered to normally respond to systemic morphine in an excitatory manner. One study in horses demonstrated dose-dependent sedation and head drooping

between 6 and 8 hours after caudal epidural injection of morphine (Robinson et al, 1994). As well, goats receiving epidural morphine after hindlimb orthopedic surgery were more sedate and struggled less during recovery than goats that received epidural saline solution (Pablo, 1993). The reason for the marked difference in mentation between parenterally and epidurally applied morphine in these species is not known.

Tolerance Tolerance is defined as an increase in dose needed to produce a given pharmacological effect, such as that of analgesia. Studies in rats (Tung et al, 1981; Yaksh et al, 1977), cats (Tung and Yaksh, 1981) and primates (Yaksh and Reddy, 1981) have documented rapid loss of effectiveness of a fixed dose of morphine with repeated epidural or intrathecal administration. Numerous reports in humans have documented escalation in morphine dosages during long-term treatment of both cancer and non-cancer pain (Stamer and Maier, 1992; Gourlay et al, 1991; Driessen et al, 1989; Arner et al, 1988), although 1 study reported more stable dosages of morphine in patients with non-cancer pain (Plummer et al, 1991).

Development of tolerance has been poorly correlated with duration of epidural morphine treatment. In other words, patients receiving the highest dosages of morphine are not necessarily those who have been treated for the longest periods of time (Plummer et al, 1991; Arner et al, 1988). Additionally, results of 1 study suggested that there were no differences in dose requirements over time for treatment of either neurogenic, somatic or osseous pain (Driessen et al, 1989). Clinical observations have suggested that previous parenteral use of opioids, changes in pain mechanisms, progression of the disease process causing pain or development of additional sources of pain may be responsible for escalations in required dosages of morphine (Crul and Delhaas, 1991; Driessen et al, 1989; Arner et al, 1988).

Some investigators have speculated that rate of tolerance development is proportional to agonist concentration at opioid receptor sites (Cousins and Mather, 1984; Yaksh and Reddy, 1981). According to this hypothesis, high local levels of agonists

achieved by bolus injections may lead to excessive opioid receptor activation. It has been suggested that continuous administration of morphine, such that infusion rate matches clearance rate, would maintain only adequate amounts of the drug at receptor sites. In this way, intermittent exposure of the opioid receptors to high concentrations of morphine from bolus doses would be avoided, and result in slower development of tolerance (Cousins and Mather, 1984; Yaksh and Reddy, 1981). Unfortunately, this theory has not been supported clinically, as a significantly greater degree of dose escalation has been documented in patients receiving continuous infusion compared to patients receiving repeated bolus doses of epidural morphine (Plummer et al, 1991).

More recent work has demonstrated that there is no association between tolerance and increased metabolic degradation, reduced receptor affinity or receptor down-regulation (Rang et al, 1995c). Current thinking is that changes in gene expression may contribute to development of tolerance. It has been shown that expression of G proteins and adenyl cyclase are increased in certain areas of the brain following opioid stimulation, and that these changes show the same time course as development of tolerance (Rang et al, 1995c). It is believed that initial opioid-mediated reduction in cAMP concentrations may reduce phosphorylation not only of target regulatory proteins but of certain transcription factors as well (Rang et al, 1995c). Decreased levels of these transcription factors may subsequently enhance transcription of specific genes, including those coding for adenyl cyclase and various G proteins (Rang et al, 1995c). A secondary rise in adenyl cyclase production ensues, and cAMP production recovers in the presence of morphine (Rang et al, 1995c). In effect, the G_i protein-mediated decrease in adenyl cyclase levels and cAMP production, which inhibits pain impulse transmission, causes self-reversal over time.

Despite escalations in dose, epidural morphine has been used to treat pain in humans for periods of up to 1215 days (Plummer et al, 1991). In 1 report in the horse, epidural morphine was used at a dose of 0.1 mg/kg for 4 days to treat pain following hindlimb digit amputation (Valverde et al, 1990). No signs of tolerance were observed

in this horse, as there was satisfactory pain relief after each dose. Development and clinical significance of tolerance with chronic epidural use in horses has not been studied.

Chronic Epidural Morphine Use

Development of side effects such as those listed above would appear to decrease the attractiveness of epidural morphine for use in pain management. Interestingly enough, however, these effects, with the exception of tolerance, have been reported to be either absent or very transient in human patients treated with epidural morphine for prolonged periods (Stamer and Maier, 1992; Hassenbusch et al, 1990; Driessen et al, 1989; Arner et al, 1988). This phenomenon has been attributed to various factors including desensitization to side effects through previous oral or parenteral opioid administration (Arner et al, 1988; Cousins and Mather, 1984; Zenz et al, 1981) and to development of brain tolerance to side effects (Cousins and Mather, 1984). Because long-term studies in animal species, including horses, are lacking, incidence and severity of side effects secondary to chronic epidural morphine injection is unknown.

Systemic Side Effects Associated With Epidural Alpha 2 Agonist Use

Because epidural alpha 2 adrenergic agonists have been investigated in horses as a means of achieving surgical anesthesia of the perineal region (Skarda and Muir, 1996; Skarda and Muir, 1994a; Skarda and Muir, 1992; Skarda and Muir, 1983), more is known about side effects associated with epidural injection of these agents. Side effects reported following epidural administration of alpha 2 adrenergic agonists in humans and animals have included bradycardia, decreased blood pressure, decreased respiratory rate and sedation. Development of these side effects has been shown to vary between species, as well as with the dose and type of alpha 2 adrenergic agonist applied.

Bradycardia Significant decreases in heart rate have been observed following epidural injection of the alpha 2 adrenergic agonist, clonidine, in humans (Klimscha et al, 1995;

Rockemann et al, 1995; Eisenach et al, 1993; Motsch et al, 1990; Eisenach, Lysak et al, 1989; Eisenach, Rauck et al, 1989), sheep (Eisenach, Castro et al, 1989), goats (Smith et al, 1992), pigs (Gordh et al, 1986) and dogs (Yaksh et al, 1994). Decreased heart rate has also been reported to occur after epidural injection of medetomidine in cats (Duke et al, 1994b), dexmedetomidine in dogs (Sabbe et al, 1994), detomidine in horses (Skarda and Muir, 1994a; Skarda and Muir, 1992) and xylazine in horses and cattle (Skarda and Muir, 1996; Skarda and Muir, 1992). Atrioventricular and sinoatrial heart block were observed in conjunction with bradycardia in horses after epidural administration of either detomidine or xylazine (Skarda and Muir, 1996; Skarda and Muir, 1994a; Skarda and Muir, 1992). However, these disturbances in cardiac rhythm were reported to be transient, appeared to have no ill effect on horses and were able to be abolished with either intravenous, epidural or intrathecal administration of alpha 2 adrenergic antagonists (Skarda and Muir, 1992).

Degree of bradycardia that develops after epidural injection may be related to the specific alpha 2 agonist used (Skarda and Muir, 1994b; Smith et al, 1992) or to the dosage of drug administered (Sabbe et al, 1994; Yaksh et al, 1994). Epidural injection of alpha 2 agonists is thought to produce bradycardia through both peripheral and spinal mechanisms, which are dependent upon the lipid solubility of the agonists. Alpha 2 adrenergic agonists, unlike morphine, are highly lipid soluble drugs. When administered epidurally, these drugs are thought to rapidly penetrate the dura mater and enter the cerebrospinal fluid (Duke et al, 1994a; Yaksh et al, 1994). Alternatively, they may be taken up by the extradural vessels and lymphatics and redistributed through peripheral vasculature to several body systems, including the brain (Duke et al, 1994b; Skarda and Muir, 1994a; Durant and Yaksh, 1986). The lipophilic nature of these drugs may also cause them to be distributed into the adipose tissue of the epidural space, which can subsequently delay uptake (Duke et al, 1994a). To a large extent, distribution and onset of effects after epidural injection of alpha 2 agonists are dependent on the quantity of fat in the epidural space as well as the extradural circulation (Moore et al, 1982).

Development of bradycardia has been attributed to both central and peripheral redistribution of alpha 2 agonists from the epidural space. Suggested mechanisms for development of bradycardia include decreased sympathetic outflow from the central nervous system, increased parasympathetic tone triggered by baroreceptor-mediated responses to blood pressure increases, and depression of cardiac pacemaker and conduction tissues (Duke et al, 1994b; Skarda and Muir, 1992). Clinically, decreases in heart rate have not required corrective therapeutic measures in human patients (Motsch et al, 1990; Eisenach, Rauck et al, 1989). While not formally evaluated, studies in horses have shown onset and duration of bradycardia to be similar to onset and duration of analgesia (Skarda and Muir, 1996; Skarda and Muir, 1994a).

Decreased Blood Pressure The alpha 2 adrenergic agonist, clonidine, was originally developed for use in human medicine as an antihypertensive drug (Van Essen et al, 1992). Injection of clonidine by the epidural route has been reported to produce a decrease in mean arterial pressure in both humans (Klimscha et al, 1995; Rockemann et al, 1995; Eisenach et al, 1993; Van Essen et al, 1992; Motsch et al, 1990; Eisenach, Lysak et al, 1989; Eisenach, Rauck et al, 1989; Penon 1989; Glynn et al, 1988) and animals (Yaksh et al, 1994; Smith et al, 1992; Gordh et al, 1986). In cats, horses and cattle, epidural injection of alpha 2 agonists including medetomidine (Duke et al, 1994b), detomidine (Skarda and Muir, 1994a; Skarda and Muir, 1994b; Skarda and Muir, 1992) and xylazine (Skarda and Muir, 1996; Skarda and Muir, 1992) has been associated with a transient increase in mean arterial blood pressure, followed by a longer-lasting decrease in blood pressure. More severe changes such as decreases in cardiac output and increases in systemic vascular resistence, which have been documented after intravenous and intramuscular use of xylazine and detomidine in horses (Wagner et al, 1991), have not been demonstrated following epidural xylazine administration (Skarda and Muir, 1996).

As with bradycardia, effects on blood pressure may depend on the type of alpha 2 adrenergic agonist administered (Skarda and Muir, 1994b) or the dosage of agonist

used (Yaksh et al, 1994; Eisenach, Lysak et al, 1989; Eisenach et al, 1987; Gordh et al, 1986). Species variation may also be an important factor, as epidural clonidine administration has been shown to have no significant effect on blood pressure in sheep (Eisenach, Castro et al, 1989; Eisenach and Grice, 1988).

Transient increases in blood pressure observed after epidural administration of alpha 2 agonists have been attributed to rapid stimulation of alpha 2 receptors on vascular smooth muscle, resulting in both arteriolar and venular constriction (Muir and Hubbell, 1991). Subsequent decreases in blood pressure have been suggested to occur as a result of inhibition of preganglionic sympathetic nerve activity in the spinal cord (Guyenet and Cabot, 1981), inhibition of sympathetic outflow from the brainstem (Jarrott et al, 1987), enhancement of brainstem parasympathetic activity (Jarrott et al, 1987) and vagally-mediated bradycardia (Skarda and Muir, 1992). Decreases in blood pressure may occur despite persistent vasoconstriction (Wagner et al, 1991). In human patients, decreased blood pressure subsequent to epidural clonidine administration has reportedly been well tolerated and has necessitated corrective therapy in only isolated cases (Van Essen et al, 1992; Eisenach, Rauck et al, 1989; Glynn et al, 1988). Decreased mean arterial pressure following epidural injection of detomidine and xylazine in horses was not treated and was not reported to result in adverse consequences (Skarda and Muir, 1996; Skarda and Muir, 1994a; Skarda and Muir, 1992).

Decreased Respiratory Rate Although development of respiratory depression is suggested to be a contraindication for epidural alpha 2 agonist use in humans, several studies have demonstrated little to no respiratory depression associated with epidural injection of the alpha 2 agonist, clonidine (Eisenach et al, 1993; Bailey et al, 1991; Eisenach, Lysak et al, 1989). Respiratory depression is manifested by an increase in arterial carbon dioxide tension, and may be accompanied by decreases in respiratory rate and arterial oxygen tension. Studies in animals have documented increases in arterial carbon dioxide tension in conjunction with decreased respiratory rate following epidural

administration of various alpha 2 adrenergic agonists (Duke et al, 1994b; Skarda and Muir, 1994a; Smith et al, 1992). However, a more recent study in horses failed to demonstrate any significant change in arterial carbon dioxide or oxygen tensions after epidural xylazine adminstration, despite a reduction in respiratory rate (Skarda and Muir, 1996). This finding correlates with results that have been reported following intravenous or intramuscular administration of alpha 2 adrenergic agonists in horses (Lavoie et al, 1992; Wagner et al, 1991), and is possible by means of a concurrent tidal volume increase.

The mechanisms underlying depression of respiratory frequency after epidural injection of alpha 2 agonists are not well understood. There is evidence that the respiratory center in the brain may be inhibited by a number of local receptor systems, including those for both opioid and alpha 2 adrenergic agonist receptors (Burton et al, 1990; Moss et al, 1986). In contrast to morphine, it is thought that depression of respiratory rate secondary to epidural alpha 2 agonist injection occurs rapidly by redistribution of the agonist through a systemic route rather than through a spinal one (Sabbe et al, 1994). Therefore, development of decreased respiratory rate following epidural injection of alpha 2 adrenergic agonists is not observed clinically as a delayed effect as it is after epidural morphine administration. Epidural co-administration of clonidine and morphine in humans has not been shown to potentiate respiratory depression (Bailey et al, 1991).

Sedation Sedation arising from epidural alpha 2 agonist administration in many species has been described as ranging from mild ((Skarda and Muir, 1996; Duke et al, 1994a; Sabbe et al, 1994) to severe (Eisenach et al, 1993; Penon et al, 1989) in intensity. While some studies have shown that development of sedation is not dose-dependent (Eisenach, Lysak et al, 1989), results of other studies provide evidence that the opposite may be true (Yaksh et al, 1994). Onset of sedation has been shown to occur within the first 15 minutes after epidural alpha 2 agonist injection (Skarda and Muir, 1994; Duke et al,

1994a; Penon et al, 1989). Duration of alpha 2 agonist-induced sedation appears to be more variable, and has been reported to range from 60 minutes (Duke et al, 1994a; Gordh et al, 1984) to 6 hours (Eisenach et al, 1993) following epidural administration. In several instances, duration of sedation has paralleled duration of analgesia, with both effects waning at a similar rate (Skarda and Muir, 1996; Skarda and Muir, 1994a; Skarda and Muir, 1992).

Development of sedation has been attributed to interaction of alpha 2 adrenergic agonists with brainstem alpha 2 receptor sites involved in the mediation of arousal and sleep (Sabbe et al, 1994). In horses, mild ataxia has been reported to accompany sedation after epidural injection of xylazine (0.25 mg/kg; 0.35 mg/kg) or detomidine (60 ug/kg), and has not been associated with recumbency at these dosages (Skarda and Muir, 1996; Skarda and Muir, 1994a; Skarda and Muir, 1994b; Skarda and Muir, 1992; Fikes et al, 1989).

Other Epidural injection of medetomidine in cats (Duke et al, 1994b), detomidine in horses (Skarda and Muir, 1994; Skarda and Muir, 1992) and xylazine in cattle (Skarda and Muir, 1992) has been associated with increased urine output. In horses and cattle, duration of frequent urination was shown to coincide with duration of analgesia (Skarda and Muir, 1992). Numerous explanations for this effect have been offered, including an alpha 2 agonist-mediated decrease in production and release of the antidiuretic hormone vasopressin (Gasthuys et al, 1987), as well as a decrease in alpha 2 agonist-mediated regulation of insulin, resulting in hyperglycemia and osmotic diuresis (Hsu et al, 1981). The significance of increased urine production following epidural alpha 2 agonist administration in these species is unknown.

Transient penile prolapse secondary to epidural xylazine administration was reported in 2 geldings of one study (Grubb et al, 1992). To date, most studies evaluating epidural alpha 2 adrenergic agonist-mediated effects in horses have been conducted in mares. Therefore, incidence and significance of this potential side effect in male horses

is unknown.

Chronic Use of Epidural Alpha 2 Agonists

Studies evaluating the systemic effects of chronically administered epidural alpha 2 adrenergic agonists are scarce. The majority of information regarding this subject has originated from results of one project examining the effects of continuous epidural infusion of the alpha 2 agonist, clonidine, in dogs. Results of this study revealed that while side effects such as bradycardia, hypotension, sedation and decreased respiratory rate were maximal between days 1 and 3, progressive adaptation to these effects occurred over the 28 day study period with the exception of respiratory rate, which remained depressed (Yaksh et al, 1994). These results imply that adaptation to side effects, similar to that observed with chronic epidural morphine use, may occur following long-term epidural alpha 2 agonist administration. Although systemic effects associated with short-term epidural alpha 2 agonist administration have been studied in horses, occurrence of adverse side effects secondary to chronic epidural alpha 2 agonist use has not been investigated in horses.

Chronic Use of an Epidural Morphine and Alpha 2 Agonist Combination in Humans

Various systemic effects have been documented in human and animal species with independent epidural administration of morphine and alpha 2 adrenergic agonists. While these agents appear to interact synergistically with regard to analgesia, the possibility of potentiation of systemic side effects with their co-administration is of concern. Although adaptation to side effects has been described with long-term independent use of each agent, studies evaluating the effects associated with chronic epidural administration of a combination of these agents are rare.

One report has documented the combined use of epidural morphine and the alpha 2 adrenergic agonist, clonidine, for a period of up to 5 months in 7 human patients suffering from metastatic cancer pain (Eisenach, Rauck et al, 1989). These patients had

previously become tolerant to either oral or epidural opioids and were experiencing intractable pain at the onset of the report. Clonidine was combined with morphine and provided by continuous infusion plus demand bolus via indwelling epidural catheters. Morphine and clonidine infusions were administered until the time of death. Several patients reported improved pain relief with less nausea and sedation compared with the period prior to epidural morphine-clonidine infusion. Only one of the 7 patients experienced severe pain, which occurred for 2 days prior to death. Overall, patients reported good analgesia during treatment with no or minimal escalation in morphine or clonidine dose. No adverse side effects requiring supplemental treatment were documented.

Although this report does not represent a controlled study with sufficient number of patients to draw statistical conclusions, its findings support the idea that concomitant administration of morphine and an alpha 2 adrenergic agonist may produce profound long-term analgesia with minimal systemic side effects. This clinical finding, along with investigations that have identified a synergistic analgesic interaction between morphine and alpha 2 adrenergic agonists, provide the rationale for research into an epidural combination of these agents for long-term treatment of pain in horses.

Local Safety of Epidural Drugs

An important aspect to consider in the epidural use of morphine and alpha 2 adrenergic agonists is the compatibility of these agents with tissues of the epidural space and surrounding neural tissues. Virtually all reports in the literature support the local safety of these agents for epidural administration, although some documented observations deserve mention.

One of the first studies to examine the effects of morphine applied to the epidural space was conducted in dogs in 1984 (King et al, 1984). This fact is somewhat surprising, since epidural morphine had been introduced for use in human medicine approximately 5 years previously (Behar et al, 1979). Results of the early study in dogs

showed no adverse tissue reaction either grossly or microscopically from a single epidural injection of morphine. Later work carried out in guinea pigs demonstrated no neurotoxic effects of morphine when applied epidurally once daily for up to 14 days (Edwards et al, 1986). Interestingly, both of these studies evaluated morphine solutions which contained preservatives including formaldehyde sulfoxylate, phenol and sodium metabisulfite. While presence of these preservatives had no apparent local effects, one case was subsequently reported in the human literature documenting an association between loss of analgesia and development of confusion and disorientation with chronic use of an epidural morphine solution containing formaldehyde and phenol (DuPen et al, 1987). Currently, morphine solutions that contain preservatives carry the label warning "not for epidural or intrathecal use", and preservative-free morphine is used clinically for epidural injections in both humans and animals.

Few reports exist in the human literature on local effects of epidural morphine following long-term clinical use, despite the large number of patients to whom epidural morphine has been administered. Some reports have not documented any local detrimental effects with use of epidural morphine for periods of up to 207 days (Mandaus et al, 1982; Borner et al, 1980). However, autopsy of 6 patients treated with continuous epidural morphine infusion for 6 months showed demyelination and vascularisation of the posterior column of the spinal cord in 2 patients (Meier et al, 1982). Late myelin loss within the posterior columns of the spinal cord was also documented in a study in guinea pigs treated with daily epidural morphine injections for up to 14 days (Edwards et al, 1985). The association between epidural morphine administration and posterior column degeneration, as well as the significance of this finding, is uncertain.

Local effects of alpha 2 adrenergic agonists on the epidural space and surrounding tissues have been examined in only a few studies. Single epidural injections of the alpha 2 agonist, clonidine, produced no histologic evidence of spinal cord damage in sheep (Eisenach and Grice, 1988; Eisenach et al, 1987). Similarly, single epidural injections of xylazine were not associated with histologic changes in the spinal cords of ponies

(Fikes et al, 1989). Daily epidural administration of clonidine for 14 days (Gordh et al, 1984), and continuous epidural clonidine infusion for 28 days (Yaksh et al, 1994), showed no toxic effects on the spinal cords or nerve roots of treated dogs. However, clonidine administered epidurally in pigs (Gordh et al, 1986) and intrathecally in rats (Crosby et al, 1990) was associated with decreased spinal cord blood flow. Reduction in spinal cord blood flow has been attributed to either a local vasoconstrictive effect of the alpha 2 agonists (Gordh et al, 1986), or to decreased spinal metabolic demand (Crosby et al, 1990). To date, no evidence exists to associate low spinal cord blood flow with clinical ischemia, and use of epidural clonidine has not been associated with neurologic deficits. Furthermore, this effect has not been observed in sheep given supramaximal doses of epidural clonidine (Eisenach and Grice, 1988). Therefore, the clinical significance of this finding is questionable.

Long-term epidural administration of morphine and alpha 2 adrenergic agonists has not been reported in horses. While chronic use of these agents has been shown to exert no toxic effects on epidural tissues in a variety of species, information regarding local effects in horses would be important prior to clinical use of morphine and an alpha 2 adrenergic agonist, such as detomidine, on a long-term basis.

Epidural Catheterization

The practice of indwelling catheter placement has become a valuable tool in the administration of potent analgesics to the epidural space for long-term treatment of pain. Indwelling epidural catheters have been used to deliver analgesic agents to human patients for periods ranging from a few days to up to 3 years (Crul and Delhaas, 1991; Plummer et al, 1991; Ready et al, 1991; Driessen et al, 1989; Arner et al, 1988; Meier et al, 1982). Catheterization of the epidural space was first described in horses in 1983 (Skarda and Muir, 1983). Since that time, epidural catheterization has been advocated in horses as a means of providing continuous caudal epidural anesthesia for perineal surgery (Green and Cooper, 1985). However, in such reports, duration of catheterization

has been limited to the intraoperative period. Placement of epidural catheters in horses could facilitate administration of analgesics on a long-term basis for treatment of serious musculoskeletal disorders. Consequences associated with indwelling epidural catheters have not been examined to date in horses.

Epidural Catheter Placement

Epidural catheters have been classified as either *implanted* or *percutaneous*, based on their method of placement. Percutaneous catheters may be of the *tunneled* or *non-tunneled* type. *Implanted* catheters are usually surgically placed through a skin incision into the epidural space. A second incision is then made in the skin of the neck or thorax. The free end of the catheter is passed through the subcutaneous tissues to this incision, where it is attached to a subcutaneous injection port. Incisions are closed, thereby completely burying the catheter. Epidural agents are administered through small gauge needles into the subcutaneous injection port.

Alternatively, *percutaneous* catheters are introduced into the epidural space through the skin directly over the desired vertebral interspace (*non-tunneled*) or may be *tunneled* subcutaneously a short distance before being introduced into the epidural space. The free ends of percutaneous catheters are attached to injection ports, which are secured to the skin surface. Epidural agents are administered directly into these injection ports. Nontunneled percutaneous epidural catheters are the least technically demanding catheters to insert and therefore could be routinely placed for clinical use in horses.

Technical Complications and Local Effects Associated With Epidural Catheters

The incidence of infection associated with long-dwelling epidural catheters in humans is low. Increased risk of infection has not been associated with any of the described methods of catheter placement. In humans, catheter-related infections have been localized to the skin and subcutaneous tissues at the catheter insertion point (DeJong and Kansen, 1994; Crul and Delhaas, 1991; Driessen et al, 1989). Local infections have

been reported to resolve with catheter removal and institution of antibiotic therapy (Plummer et al, 1991). Because the equine environment is more contaminated than the hospital or home setting in human medicine, horses would possibly be more prone to catheter-related infections. However, incidence of infection associated with indwelling epidural catheters has not been investigated in horses.

As well, long-term use of epidural catheters is not without risk of technical complications. In a retrospective study of human patients receiving epidural morphine through indwelling catheters, complications including dislocation, obstruction, injectate leakage and pain on injection rose to 55 percent between days 20 and 366 of treatment (Crul and Delhaas, 1991). Complications such as these have been attributed to development of epidural fibrosis in response to the presence of the catheter, a reaction capable of occurring within a 20 day period. Development of complications could limit the functional use of an epidural catheter for extended treatment of pain. Because long-term epidural catheterization has not been evaluated in horses, incidence of complications in unknown. The following discussion outlines technical complications and local effects associated with epidural catheter placement in other species, and indicates potential complications that might be observed with indwelling epidural catheter placement in horses.

Dislocation Catheter dislocation has been cited as a complication in up to 24 percent of patients with indwelling percutaneous catheters (De Jong and Kansen, 1994; Crul and Delhaas, 1991; Ready et al, 1991; Driessen et al, 1989). While some investigators have reported that non-tunneled percutaneous catheters were most likely to dislocate (Crul and Delhaas, 1991), others have demonstrated similar incidences of dislocation with both tunneled and non-tunneled percutaneous catheters (DeJong and Kansen, 1994). Percutaneous catheters appear to be at a greater risk of movement as they are usually held in place by only an adhesive dressing or a few skin sutures (DeJong and Kansen, 1994). Results of retrospective studies have suggested that attachment of epidural

catheters to implanted injection ports may prevent catheter displacement (DeJong and Kansen, 1994; Arner et al, 1988).

Dislocation of epidural catheters is thought to be due to catheter manipulation upon injection, leakage of injected fluid around the catheter causing adhesives to dissolve and detach, or development of epidural fibrosis (DeJong and Kansen, 1994; Crul and Delhaas, 1991; Arner et al, 1988). Dislodgement of epidural catheters was not reported as a complication in ewes, dogs, rabbits, pigs or goats with indwelling catheters, placed in a variety of ways, for periods of up to 180 days (Coombs et al, 1994; Yaksh et al, 1994; Madsen et al, 1993; Kytta et al, 1986; Larsen et al, 1986; Gordh et al, 1984).

Obstruction and Injection Resistance Occlusion has been reported to occur in up to 45 percent of patients with indwelling epidural catheters (Crul and Delhaas, 1991; Plummer et al, 1991; Ready et al, 1991; Driessen et al, 1989). A retrospective study in humans demonstrated that non-tunneled catheters were twice as likely to become obstructed as those that were tunneled (Crul and Delhaas, 1991). Obstruction secondary to kinking of the catheter has been reported to occur (DeJong and Kansen, 1994; Plummer et al, 1991). Occlusion of the catheter lumen by the fibrotic process was ruled out in one report on autopsy of human cancer patients with indwelling epidural catheters for up to a 6 month period (Meier et al, 1982). However, development of fibrosis in the region of the catheter tip is thought to contribute to injection resistance (Crul and Delhaas, 1991). Obstruction to injection was not reported in chronic catheterization studies in dogs (Yaksh et al, 1994; Gordh et al, 1984), ewes (Coombs et al, 1994), goats (Larsen et al, 1986), pigs (Kytta et al, 1986) or rabbits (Madsen et al, 1993).

Leakage of Injectate Between 2 and 49 percent of patients with epidural catheters in place for periods of up to 3 years experience backflow or leakage of solution upon injection (DeJong and Kansen, 1994), Crul and Delhaas, 1991; Plummer et al, 1991; Driessen et al, 1989). Backflow of injectate has been reported in both implanted and

percutaneous catheters (DeJong and Kansen, 1994; Crul and Delhaas, 1991; Plummer et al, 1991) and in both tunneled and non-tunneled percutaneous catheters (Crul and Delhaas, 1991; Driessen et al, 1989). Injectate leakage has been implicated as a contributing factor in dose escalation (Plummer et al, 1991), and early detection has been made difficult by implanted low flow continuous infusion systems (Crul and Delhaas, 1991; Driessen et al, 1989).

Leakage of injected solution with indwelling catheters has been attributed to development of a fibrotic sheath around the catheter tip, preventing normal epidural spread of solution and inducing injectate reflux (Arner et al, 1988). Backflow of injected solutions has not been associated with primary catheter obstruction, as injection of radio-opaque dye through affected catheters has confirmed their patency and revealed the trajectory of leakage to be from the catheter tip to the tissues outside of the epidural space (Crul and Delhaas, 1991; Driessen et al, 1989). Leakage of injected solutions was not found to be a complication of long-dwelling epidural catheters in studies in ewes and dogs (Coombs et al, 1994; Yaksh et al, 1994).

Pain on Injection In humans, the nature of pain that may occur secondary to epidural injection has been described as ranging from dull, ill-localized discomfort to excruciating unilateral or bilateral radicular pain (Buscher and Chedel, 1992). This side effect has been documented in up to 35 percent of human patients with long-term epidural catheters (DeJong and Kansen, 1994; Crul and Delhaas, 1991; Plummer et al, 1991; Ready et al, 1991). Injection pain has been reported in patients with both cancer (DeJong and Kansen, 1994; Crul and Delhaas, 1991; Plummer et al, 1991) and non-cancer (Plummer et al, 1991; Ready et al, 1991) pain, and appears to be independent of level of catheter insertion (Buscher and Chedel, 1992) or catheter type (DeJong and Kansen, 1994).

Pain upon injection has been attributed to development of a fibrous sheath around the catheter tip, leading to potential alteration in compliance of the epidural space (Crul and Delhaas, 1991; Plummer et al, 1991). Injection of large volumes of solution under

increased pressure is suspected to produce swelling of the fibrous sheath and to place pressure on adjacent nerves (Buscher and Chedel, 1992; Plummer et al, 1991). Injection pain in humans may be alleviated through decreased volume and rate of injection, instigation of continuous infusion therapy, addition of local anesthetic to the injectate or repositioning of the catheter tip at a different level in the epidural space (Buscher et al, 1992; Plummer et al, 1991; Arner et al, 1988). Not infrequently, pain on injection in humans has been reported to decrease or spontaneously disappear after a few days or weeks of treatment (Buscher and Chedel, 1992). Pain was documented in rabbits during daily injections of meptazinol, a mu receptor agonist, through indwelling epidural catheters (Madsen et al, 1993). While the exact cause for injection pain was not identified, an excitotoxic effect of meptazinol itself was suggested (Madsen et al, 1993). Injection pain was not documented with daily morphine, bupivicaine or saline injections in pigs, goats or dogs for up to 14 days (Kytta et al, 1986; Larsen et al, 1986; Gordh et al, 1984), nor was it observed with chronic epidural infusion of the alpha 2 agonist, clonidine, in dogs (Yaksh et al, 1994).

Epidural Fibrosis Development of catheter-associated inflammation and fibrosis has been documented in virtually every study evaluating effects of chronic epidural catheterization (Coombs et al, 1994; Yaksh et al, 1994; Madsen et al, 1993; Cherry and Gourlay, 1992; Edwards et al, 1986; Kytta et al, 1986; Larsen et al, 1986; Edwards et al, 1985; Gordh et al, 1984; Meier et al, 1982). Several studies have documented this epidural reaction to be most severe in the region of the catheter tip (Yaksh et al, 1994; Madsen et al, 1993; Edwards et al, 1986; Meier et al, 1982).

Progression of events during development of epidural fibrosis after catheter placement was documented in 1 study in guinea pigs (Edwards et al, 1986). This study showed that within 2 days of catheter insertion, epidural fat cells began to disintegrate and variable amounts of hemorrhage and chronic inflammatory cells, including lymphocytes, plasma cells and foreign body giant cells, were present within the epidural

space. At 7 days, extravasated red blood cells had been resorbed, and the mononuclear cell infiltrate was replaced by loose networks of spindle-shaped cells admixed with collagen and newly formed blood vessels. By 14 days, the connective tissue reaction was organized into dense fibrous granulation tissue with new blood vessels.

Although presence of epidural fibrous tissue has been shown to cause local deformation of the spinal cord (Coombs et al, 1994; Madsen et al, 1993; Cherry and Gourlay, 1992; Driessen et al, 1989; Edwards et al, 1986; Gordh et al, 1984) and stretching of the dorsal roots (Edwards et al, 1986), gross neurological deficits have been observed only in isolated cases (Driessen et al, 1989). Chronic inflammation of the dura mater and ligamentum flavum secondary to long-term catheterization has been reported by some investigators (Coombs et al, 1994; Yaksh et al, 1994; Kytta et al, 1986; Edwards et al, 1985), while others have identified no inflammation of the dura or overlying periosteum or bone in association with epidural catheters (Edwards et al, 1986). It has been suggested that dural reaction may be minimal when catheters are embedded within the epidural fat (Coombs et al, 1994).

Type of epidural catheter has been implicated as an inciting factor in the development of epidural inflammation and fibrosis (Crul and Delhaas, 1991). However, fibrotic responses have been reported with use of nylon (Edwards et al, 1986; Kytta et al, 1986), polyamide (Larsen et al, 1986), polyethylene (Yaksh et al, 1994), polyurethane (Cherry and Gourlay, 1992), polyvinyl (Lebeaux, 1973), silastic (Coombs et al, 1994; Meier et al, 1982) and hydrogel elastomer blend (Coombs et al, 1994) catheters, making it unlikely that development of fibrosis is determined solely by catheter composition. While some investigators have suggested that the presence of preservatives or low pH of injected solutions may induce epidural fibrosis (Crul and Delhaas, 1991), development of similar inflammatory reactions in catheterized animals receiving physiologic saline solutions does not support this theory (Madsen et al, 1993; Edwards et al, 1986; Kytta et al, 1986). It is thought that epidural fibrosis may represent a foreign body reaction to the catheter by local epidural fat and connective tissues (Yaksh et al, 1994). This theory

is supported by a study in pigs which documented only minimal inflammatory changes remaining in the epidural space 3 weeks following epidural catheter removal (Kytta et al, 1986). Therefore, although development of fibrosis appears to be an unavoidable consequence of epidural catheterization, long-term significance of this effect may be limited to technical complications with the catheter. Occurrence of local inflammation and fibrosis requires investigation in horses prior to use of indwelling epidural catheters for management of chronic pain.

AIMS OF THE STUDY

Epidural administration of agents including morphine and alpha 2 adrenergic agonists has been shown to produce profound analgesia in a variety of species. Recent work has demonstrated that both intensity and duration of analgesia may be potentiated by the epidural co-administration of these agents. In humans, administration of such drugs through indwelling epidural catheters has been shown to be an effective means of providing long-term analgesia. This form of analgesia would be valuable for long-term treatment of musculoskeletal pain in horses and would avoid side effects associated with chronic use of high dosages of nonsteroidal anti-inflammatory drugs.

Evaluation of analgesia induced by an epidural combination of morphine and an alpha 2 adrenergic agonist has not been conducted in horses. Whereas systemic and local effects of long-term epidural catheterization and epidural morphine administration have been evaluated in some species, these effects have not been characterized in horses. Furthermore, studies of systemic and local effects of chronic epidural detomidine administration are lacking. The aims of the study reported here were as follows:

1. to evaluate the efficacy of an epidural combination of morphine and the readily available alpha 2 adrenergic agonist, detomidine, in alleviating experimentally-induced hindlimb musculoskeletal pain in horses (Part 1)

2. to study in horses the local and systemic effects associated with long-term (14 day) epidural morphine and detomidine administration (Part 2)

3. to assess technical complications and local effects associated with long-term (14 day) epidural catheterization in horses (Part 2)

MATERIALS AND METHODS

Both parts of this study were approved by the Virginia Polytechnic Institute and State University Animal Care Committee.

Part 1

Eleven horses (9 mares and 2 geldings) free from lameness and systemic disease based on physical examination were studied. Identification numbers of all horses included in the study are listed in Appendix 1, and signalment data are given in Appendix 2. Breeds represented were 9 Thoroughbreds, 1 Quarterhorse and 1 Appaloosa. Horses ranged in age from 5 to 23 years (median, 15.5 years) and ranged in weight from 427 to 536 kg (median, 490 kg). Horses were housed in 12 foot square box stalls during the study and were offered water and a mixture of alfalfa and grass hay ad libitum.

A protocol for amphotericin B-induced synovitis was adapted from a previous study (Peloso et al, 1993) and was used to create a hindlimb lameness in all horses. On day 1, horses were sedated with a combination of detomidine hydrochloride (Dormosedan, SmithKline Beecham, West Chester, PA; 6 ug/kg, intravenously [IV]) and butorphanol tartrate (Torbugesic, Fort Dodge Laboratories Inc., Fort Dodge, IA; 6 ug/kg, IV). The left tarsocrural region was clipped and aseptically prepared. Twenty-five mg of amphotericin B (Fungizone, E.R. Squibb & Sons Inc., Princeton, NJ) in 5 mL sterile water were injected into the left tarsocrural joint and the hock was then bandaged. Phenylbutazone (Phenylzone Paste, Coopers Animal Health Inc., Kansas City, KS; 2 mg/kg orally) was administered to all horses to decrease pain associated with the acute onset of synovitis. Horses were visually assessed for pain every 3 hours for the first 12 hours following intra-articular injection, and then every 12 hours until the conclusion of the study. It was determined that any horse which developed a nonweight-bearing lameness would be withdrawn from the study and treated as necessary to alleviate discomfort.

Forty-eight hours after the first intra-articular injection of amphotericin B, horses were again sedated with a combination of detomidine hydrochloride (6 ug/kg, IV) and butorphanol tartrate (6 ug/kg, IV). The left tarsocrural region was aseptically prepared, a second injection of 25 mg of amphotericin B in 5 mL sterile water was administered and the hock was rebandaged. Horses were immediately moved into stocks and epidural catheters were placed to facilitate injection to multiple horses during the study, as well as to mimic projected clinical use.

To place the epidural catheters, the sacrocaudal and caudal vertebral areas were clipped and aseptically prepared. Two mL of 2% lidocaine (Lidocaine 2% Injectable, Butler Co., Columbus, OH) were placed subcutaneously over the first palpably movable joint space caudal to the sacrum. After further aseptic preparation, a 16 gauge, 1.5 inch needle was introduced through the desensitized skin into the epidural space (Figure 7) at an angle of approximately 45 degrees to the horizontal plane. Placement of the needle into the epidural space was verified by palpable penetration of the ligamentum flavum, disappearance of a drop of sterile physiologic saline solution (Normal Saline Solution, VEDCO Inc., St. Joseph, MO) from the needle hub (i.e., hanging drop technique), ease of injection of sterile physiologic saline solution and ease of catheter advancement. In two horses with tissue mass that exceeded 1.5 inches over the first movable joint space caudal to the sacrum, the needle was instead introduced into the epidural space through the next caudally movable joint space in a similar manner. A 20 gauge, 91.5 cm long, open-tipped teflon epidural catheter (Safetrak, Kendall Healthcare Products Co., Mansfield, MA) was advanced through the needle into the epidural space and threaded cranially to the lumbosacral region. Placement of the catheter tip at the lumbosacral region was determined by measuring the distance between the epidural needle and the lumbosacral region, and advancing the catheter that distance. The 16 gauge needle was removed from the epidural space, leaving the catheter in place, and the catheter was cut so that a 7.5 cm length remained exiting the skin. An adapter was fitted to the end of the epidural catheter and the catheter was flushed with 1 mL heparinized saline (Heparin

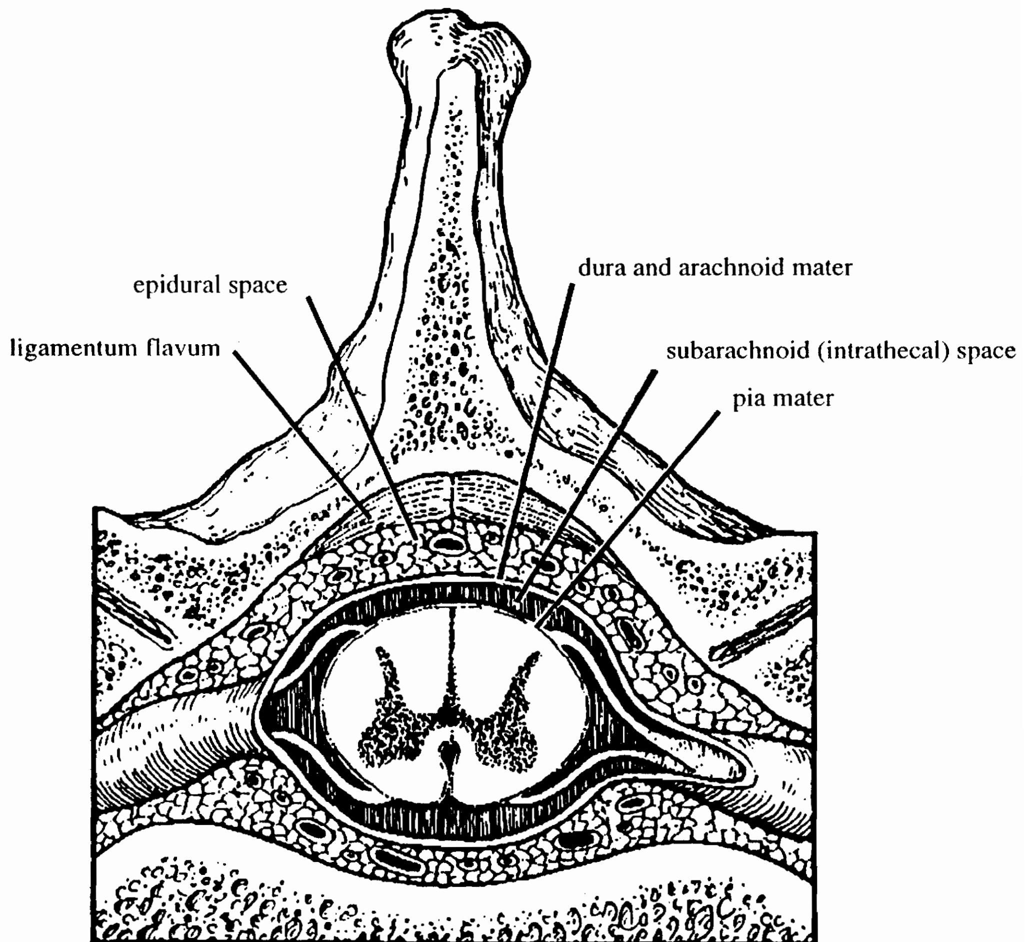

Figure 7. Transverse section of the lumbar spinal cord and related structures. (Adapted from Littrell, 1991)

Sodium Injection, USP, Elkins-Sinn Inc., Cherry Hill, NJ; 10 U/mL in physiologic saline solution). The catheter was sutured in place with 2-0 nylon (Dermalon, Davis & Geck, American Cyanamid Co., Manati, PR) and covered with a nylon patch (Shut-Eye, American Animal Health Inc., Wisner, NE) that was glued circumferentially except over the tailhead to allow access to the catheter.

Twenty-four hours later, resting baseline heart and respiratory rates were obtained on all 11 horses. Horses were walked for a 5 minute warm-up period and a baseline videotape was made of each horse at the walk and trot using front, rear and side views. A grade 3 out of 4 lameness (obvious at both the walk and trot) (Stashak, 1987) was considered necessary for inclusion into the study. Three additional horses underwent the study protocol, received epidural injections and were videotaped, but were excluded from Part 1 of the project for various reasons: 1 horse did not develop a grade 3 lameness, a second horse (Tennessee Walking Horse) could not be made to consistently trot and a third horse displayed gradual interference of the lameness by a pre-existing chronic left hindlimb fetlock injury. These 3 horses were, however, used for Part 2 of the project.

Horses were randomly assigned to one of two groups. Twenty-four hours after the second intra-articular injection of amphotericin B and epidural catheter placement, treated horses (n = 8) received 0.2 mg/kg morphine sulfate (Morphine Sulphate Injection, USP, Elkins-Sinn Inc., Cherry Hill, NJ; 15 mg/mL) followed by 30 ug/kg detomidine hydrochloride (10 mg/mL) through the epidural catheter. An equivalent volume (0.017 mL/kg) of sterile physiologic saline solution was administered to control horses (n = 3) through the catheter. All epidural catheters were flushed with 1 mL sterile heparinized saline. At hourly intervals after epidural injection, resting heart and respiratory rates were recorded, horses were walked for 5 minutes and were videotaped as described. Horses were informally observed for development of sedation and ataxia.

Once taping was completed, all video recordings were scrambled in random order onto a master tape. Ten percent of recordings were randomly displayed twice in order to assess grading consistency. Lameness recordings on the master tape were scored by

3 investigators blinded to group allotment and treatment time. Lamenesses were scored on a scale of 0 to 4 as follows: 0 = no evident lameness; 1 = not lame at the walk but recognizably lame at the trot; 2 = altered gait present at the walk and obviously lame at the trot; 3 = obviously lame at both the walk and trot; 4 = nonweight-bearing lame (Stashak, 1987).

The lameness grade used for analysis of each horse at each hour was the median value of the 3 lameness scores assigned by the videotape reviewers. The effect of treatment on change in lameness grades and heart and respiratory rates over time were analyzed using repeated measures of variance (SAS/STAT, 1990). Comparison of mean lameness grades between groups at each hour was done using a Mann-Whitney test (SAS/STAT, 1990). Two-sample t tests were used to compare mean heart and respiratory rates between groups at each hour (SAS/STAT, 1990). Results with P values less than 0.05 were considered significant.

At the end of Part 1, 7 horses (2 control, 5 treated) were immediately entered into Part 2 of the study. The remaining 4 horses (1 control, 3 treated) were used for surgical instruction laboratories and were euthanatized while under general anesthesia. Phenylbutazone (2 mg/kg orally q 12 hours) was administered to these horses as needed until the time of euthanasia to provide relief from transient synovitis-associated pain.

Part 2

The 7 horses transferred from Part 1 of the study, as well as the 3 horses excluded from Part 1, were used in Part 2 of the project. Identification numbers for all horses are listed in Appendix 1, and signalment data are given in Appendix 2. The study population of horses for Part 2 consisted of 9 mares and 1 gelding. Breeds represented were 8 Thoroughbreds, 1 Quarterhorse and 1 Tennessee Walking Horse. Horses ranged in age from 5 to 18 years (median, 14.5 years) and ranged in weight from 427 to 536 kg (median, 490 kg). Horses were housed in 12 foot square box stalls during the study and were offered water and a mixture of grass and alfalfa hay ad libitum.

Epidural catheters placed for Part 1 of the project were left in place and used in Part 2. The epidural injection used for analysis of effect on lameness in Part 1 occurred 24 hours after epidural catheter placement, and was also considered to be the first injection in the protocol of Part 2 of the project.

Horses had been randomly assigned to 1 of 2 groups for Part 1 of the project. Horses remained in their respective groups for Part 2. Treated horses (n = 7) were given 0.2 mg/kg morphine sulfate and 30 ug/kg detomidine hydrochloride through the epidural catheter every 12 hours for 14 days. Control horses (n = 3) were given an equivalent volume (0.017 mL/kg) of sterile physiologic saline solution through the catheter every 12 hours for 14 days. Epidural catheters were flushed with 1 mL heparinized saline following each injection of morphine and detomidine or physiologic saline solution. Horses were visually assessed every 12 hours. It was determined that any horse which exhibited adverse effects from epidural catheterization or injection would be withdrawn from the study and humanely euthanatized.

Systemic Effects

Systemic effects were evaluated in both control and treated horses. Body weights were recorded on days 1 and 14. Rectal temperature, heart rate, respiratory rate and gastrointestinal motility were recorded twice daily during the 14 day observation period. Variables were recorded immediately before morning epidural injections and 3 hours before evening injections. Gastrointestinal motility was ausculted bilaterally in the dorsal and ventral regions of the abdomen. Motility in each quadrant was scored by one investigator over a 1 minute period on a scale of 0 to 3 as follows: 0 = no gastrointestinal sounds ausculted; 1 = 1 to 2 progressive sounds heard; 2 = more than 2 progressive sounds present; 3 = continuous gastrointestinal sounds heard over a 1 minute period. The sum of the scores assigned to each quadrant was used as the gastrointestinal motility grade for each horse at each recording session. Hay intake (weight of hay consumed per 24 hour period as a percentage of average body weight) and

water intake (volume of water consumed per 24 hour period as a percentage of average body weight) were recorded daily for each horse throughout the 14 day observation period.

At the end of the study period, horses were euthanatized with sodium pentobarbital (Fatal Plus Powder, Vortech Pharmaceuticals, Dearborn, MI; 0.15 g/kg IV). Gross necropsy examinations were performed and representative samples from lung, heart, adrenal gland, kidney, spleen, liver, stomach, small intestine, cecum and colon were collected. Tissue samples were fixed in 10% buffered formalin and embedded in paraffin. Five micron thick sections were cut and stained with hematoxylin and eosin. Sections were examined histologically for presence of pathologic lesions.

Weight change was compared between control and treated horses using a two-sample t test. Temperature, heart rate, respiratory rate, gastrointestinal motility grades and hay and water consumption were compared between control and treated groups using repeated measures analysis of variance (SAS/STAT, 1990). Results with P values less than 0.05 were considered significant.

Local Effects

Immediately after death, the atlanto-occipital region of all horses was clipped and aseptically prepared. With the horse in lateral recumbency and the head ventroflexed, an 18 gauge, 3.5 inch spinal needle was inserted into the atlanto-occipital space. Cerebrospinal fluid was collected and distributed onto Columbia agar plates with 5% sheep blood as well as MacConkey agar plates for bacteriologic evaluation. Five drops of cerebrospinal fluid from each horse were placed into a cytofunnel and processed on a Shandon Cytospin II. The resultant slides were stained with Wright's stain and examined cytologically. Additional cerebrospinal fluid was plated directly onto a hemocytometer and a 1 mm^3 area was used to count both nucleated and red cells. Protein and glucose concentrations were determined by centrifuging cerebrospinal fluid samples at 12,000 rotations per minute for 15 seconds. The resulting supernatant was analyzed

with a Johnson & Johnson Ektachem 700, employing a biuret reaction to establish protein concentrations and a glucose oxidase test to determine glucose concentrations.

Cutaneous catheter entry sites were visually evaluated for evidence of gross abnormalities. The spinal column was examined grossly, then was dissected from each horse. Representative samples of the spinal cord and surrounding tissues were taken from the cervicothoracic, thoracolumbar, lumbosacral, sacral and from catheter entry point regions. Tissue samples were fixed in 10% buffered formalin and embedded in paraffin. Five micron thick sections were cut and stained with hematoxylin and eosin. Spinal tissue sections were graded histologically for degree of inflammation by two investigators, unaware of group assignment, on a scale of 0 to 3 as follows: 0 = no evidence of inflammation; 1 = mild inflammation characterized by the presence of few scattered nucleated cells; 2 = moderate inflammation with the occasional presence of nucleated cells; 3 = diffuse inflammation with nucleated cells consistently present throughout the section. Spinal tissue sections were also graded for degree of fibrosis on a scale of 0 to 3 as follows: 0 = no evidence of fibrosis; 1 = mild fibrosis characterized by the presence of a small focus of fibroblastic activity; 2 = moderate fibrosis with scattered, focally intense areas of fibrous tissue production; 3 = severe diffuse fibrosis.

To enable comparison of cerebrospinal fluid values and spinal segment inflammation and fibrosis grades between epidurally catheterized and uncatheterized horses, 6 horses euthanatized for reasons unrelated to neurologic disease served as an uncatheterized group of horses. Identification numbers of these horses are listed in Appendix 1, and signalment data are given in Appendix 2. Immediately after euthanasia, cerebrospinal fluid samples from 3 of these horses were collected and examined as described previously. Spinal tissue samples were obtained from the remaining 3 horses and histological sections were prepared and graded as described above.

Cerebrospinal fluid values and spinal tissue segment inflammation and fibrosis grades were compared between control and treated horses. Control and treated groups of horses were then pooled together to form a catheterized group of horses.

Cerebrospinal fluid values and spinal tissue segment inflammation and fibrosis grades were compared between catheterized and uncatheterized groups of horses. Statistical comparisons were made using a Mann-Whitney rank sum test (SAS/STAT, 1990). Results with P values less than 0.05 were considered significant.

Efficacy of an Epidural Combination of Morphine and Detomidine in Alleviating Experimentally-Induced Hindlimb Lameness in Horses

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ABSTRACT

Amphotericin B-induced synovitis of the left tarsocrural joint was used to create a grade 3 of 4 lameness in eleven horses. Caudal epidural catheters were advanced to the lumbosacral region. Baseline heart and respiratory rates were recorded and horses were videotaped at a walk and trot. Morphine sulphate (0.2 mg/kg) and detomidine hydrochloride (30 ug/kg) were administered to treated horses (n = 8) through the epidural catheter; an equivalent volume of physiologic saline solution was administered to control horses (n = 3) through the catheter. At hourly intervals after epidural injection for a total of 6 hours, heart and respiratory rates were recorded and horses were videotaped walking and trotting. At the end of the observation period, video recordings were scrambled onto a master videotape. Lamenesses were scored by three investigators unaware of group assignment or treatment time. Lameness grades, heart rates and respiratory rates were compared between groups using repeated measures analysis of variance. There was a significant decrease in lameness grade after treatment with epidural morphine and detomidine (P = .0003); average lameness grades of treated horses were less than grade 1 at each hourly observation for 6 hours after drug administration. Early in the observation period, heart rates significantly increased in control horses and decreased in treated horses (P = .03). A similar trend occurred for respiratory rates (P = .07). Results of this study demonstrate that epidural administration of a combination of morphine and detomidine is capable of providing profound hindlimb analgesia in horses.

INTRODUCTION

Musculoskeletal disorders such as fractures, tendon injuries and septic arthritides occur frequently in horses. Conventional methods for providing analgesia during convalescence after either surgical repair or conservative management of such injuries have been the use of nonsteroidal anti-inflammatory drugs. However, high doses or chronic use of these drugs has been associated with serious side effects including oral, gastric and duodenal ulceration, colonic ulceration and necrosis, renal crest necrosis and hematologic changes.[1,2] An alternate method of analgesia with few to no side effects would therefore be valuable in the long-term management of pain associated with musculoskeletal injuries.

Epidural morphine administered through indwelling catheters has been used in humans to provide potent long-term analgesia to postoperative patients,[3,4] terminally ill cancer patients[5,6,7] and patients with chronic pain that has failed to respond to other therapies.[6] Epidural administration of morphine has been used successfully in dogs to provide pain relief during the perioperative period[8,9] and in goats after abdominal surgery[10] and hindlimb orthopedic surgery.[11] Administration of caudal epidural morphine has been reported to provide cutaneous analgesia in horses as far cranially as the ninth thoracic dermatome[12] and in one horse, deep analgesia to the hindlimb after digit amputation.[13]

Recent work in humans and dogs has shown that intensity and duration of epidural morphine analgesia may be potentiated by the co-administration of an alpha 2 adrenergic agonist such as clonidine[14-16] or medetomidine.[17] Evaluation of analgesia induced by an epidural combination of morphine and an alpha 2 adrenergic agonist has not been conducted in horses. The purpose of the present study was to determine the efficacy of an epidural combination of morphine and a readily available alpha 2 adrenergic agonist, detomidine, to alleviate experimentally-induced hindlimb lameness in horses.

MATERIALS AND METHODS

Eleven horses (9 mares and 2 geldings) free from lameness and systemic disease based on physical examination were studied. Breeds represented were 9 Thoroughbreds, 1 Quarterhorse and 1 Appaloosa; horses were 5 to 23 years old (median, 15.5 years) and ranged in weight from 427 to 536 kg (median, 490 kg). Horses were housed in 12 foot square box stalls during the study and were offered water and a mixture of alfalfa and grass hay ad libitum.

A protocol for amphotericin B-induced synovitis was used to create hindlimb lameness in all horses.[18] On day 1, phenylbutazone (Phenylzone Paste, Coopers Animal Health Inc., Kansas City, KS; 2 mg/kg, orally) was administered to all horses to decrease pain associated with the acute onset of synovitis. Horses were sedated with a combination of detomidine (Dormosedan, SmithKline Beecham, West Chester, PA; 6 ug/kg, intravenously [IV]) and butorphanol (Torbugesic, Fort Dodge Laboratories Inc., Fort Dodge, IA; 6 ug/kg, IV). The left tarsocrural region was clipped and aseptically prepared. Twenty-five mg of amphotericin B (Fungizone, E.R. Squibb & Sons Inc., Princeton, NJ) in 5 mL sterile water was injected into the left tarsocrural joint and the hock was then bandaged. Forty-eight hours later, horses were again sedated with a combination of detomidine (6 ug/kg, IV) and butorphanol (6 ug/kg, IV). Phenylbutazone was not administered. The left tarsocrural region was aseptically prepared, another 25 mg of amphotericin B in 5 mL sterile water was injected and the hock was re-bandaged. Horses were immediately moved into a stocks and epidural catheters were placed to facilitate later drug administration. To place the epidural catheters, the sacrocaudal and caudal vertebral areas were clipped and aseptically prepared. Two mL of 2% lidocaine (Butler Co., Columbus, OH) were placed subcutaneously over the first palpably moveable joint space caudal to the sacrum. After further aseptic preparation, a 16 gauge, 1.5 inch needle was introduced through the desensitized skin into the epidural space at 45 degrees to the horizontal plane. Placement of

the needle into the epidural space was verified by palpable penetration of the ligamentum flavum, disappearance of a drop of sterile physiologic saline solution (VEDCO Inc., St. Joseph, MO) from the needle hub (hanging drop technique), ease of injection of sterile physiologic saline solution and ease of catheter advancement. In two horses with tissue mass greater than 1.5 inches over the first moveable joint space caudal to the sacrum, the needle was instead introduced into the epidural space through the next caudally moveable joint space in a similar manner. A 20 gauge, 36 inch open-tipped teflon epidural catheter (Safetrak, Kendall Healthcare Products Co., Mansfield, MA) was advanced through the needle into the epidural space and threaded cranially to the lumbosacral region. Placement of the catheter tip at the lumbosacral region was determined by measuring the distance between the epidural needle and the lumbosacral region, and advancing the catheter that distance. The 16 gauge needle was removed from the epidural space, leaving the catheter in place, and the catheter was cut so that a 3 inch length remained exiting the skin. An adapter was fitted to the end of the epidural catheter and the catheter was flushed with 1 mL heparinized saline (Heparin Sodium Injection, USP, Elkins-Sinn Inc., Cherry Hill, NJ; 10 U/mL in physiologic saline solution). The catheter was sutured in place with 2-0 nylon and was covered with a nylon patch (Shut-Eye, American Animal Health Inc., Wisner, NE) that was glued circumferentially except over the tailhead to allow access to the catheter.

Twenty-four hours later, baseline heart and respiratory rates were obtained on all eleven horses. All horses were walked for a 5 minute warm-up period and a baseline videotape was made of each horse at the walk and trot using front, rear and side views. A grade 3 lameness (noticeable at both the walk and trot)[19] was considered necessary for entry into the study. A twelfth horse was excluded from the study because it did not develop a grade 3 lameness.

Horses were randomly assigned to one of two groups. Twenty-four hours after the second intra-articular injection of amphotericin B, 0.2 mg/kg morphine sulphate (Elkins-Sinn Inc., Cherry

Hill, NJ) followed by 30 ug/kg detomidine hydrochloride was administered to treated horses (n = 8) through the epidural catheter. An equivalent volume (0.017 mL/kg) of sterile physiologic saline solution was administered to control horses (n = 3) through the catheter. All epidural catheters were flushed with 1 mL sterile heparinized saline solution. At hourly intervals after epidural injection, heart and respiratory rates were recorded, horses were walked for 5 minutes and were videotaped as described. Horses were informally observed for development of sedation and ataxia.

Once taping was completed, all video recordings were scrambled in random order onto a master tape. Ten percent of recordings were randomly displayed twice in order to assess grading consistency. Lameness recordings on the master tape were scored by 3 investigators unaware of group assignment and treatment time. Lamenesses were scored on a scale of 0 to 4 as follows: 0 = no evident lameness; 1 = not lame at the walk but recognizably lame at the trot; 2 = altered gait present at the walk and obviously lame at the trot; 3 = obviously lame at both the walk and trot; 4 = nonweight-bearing lame.[19]

The lameness grade used for analysis of each horse at each hour was the median value of the three lameness scores assigned by the videotape reviewers. The effect of treatment on change in lameness grades and heart and respiratory rates over time were analyzed using repeated measures analysis of variance.[20] Comparison of mean lameness grades between groups at each hour was done using a Mann-Whitney test.[20] Two-sample t tests were used to compare mean heart and respiratory rates between groups at each hour.[20] Results with *P* values less than .05 were considered significant.

Horses were observed for 4 days to 5 weeks until euthanatized. Phenylbutazone (2 mg/kg orally every 12 hours) was administered as needed to provide relief from transient synovitis-associated pain.

RESULTS

Duplicate video recordings were assigned a lameness score identical to their initial score, indicating that there was no individual observer variance. Throughout the study, all control horses remained grade 3 lame in the left hind limb (Fig 1). Before epidural injection all treated horses were grade 3 lame in the left hind limb (Fig 1), whereas after epidural administration of morphine and detomidine, there was a significant decrease in lameness grades (P = .0003); average lameness grades for treated horses was less than grade 1 at each hourly observation for 6 hours.

Treatment with epidural morphine and detomidine had a significant effect on change in heart rate during the observation period (P = .03). Initially following epidural injection, average heart rate of treated horses decreased, whereas average heart rate of control horses increased (Fig 2). However, towards the end of the observation period, differences between treated and control horses diminished. There was a similar trend for average respiratory rate to decrease in treated horses and to increase in control horses early in the observation period (P = .07) (Fig 3).

Informal observation of study horses revealed signs of marked sedation and mild ataxia in treated horses within 15 minutes after epidural injection of morphine and detomidine. Sedation was characterized by lowering of the head, drooping of the eyelids and lower lips, lack of interest in hay or water and a mild decrease in arc of foot flight. During the period of sedation, all horses retained sufficient coordination to walk and trot at each videorecording session. Sedation gradually decreased and was not evident by 3 hours after epidural morphine and detomidine injection.

DISCUSSION

In this study, epidural catheters were advanced to the lumbosacral region to ensure that epidural agents reached the pelvic nerve plexus, thereby eliminating factors such as volume of infusion and effects of redistribution that may have affected cranial spread of the drugs. It is not known whether the results observed in this study would have been similar had catheter tips been left in the epidural space near their point of entry.

Control horses remained grade 3 lame throughout the study period, indicating that neither the presence of an epidural catheter nor epidural injection of physiologic saline solution had any effect on lameness. The significant decline in observable lameness in treated horses by 1 hour after epidural morphine and detomidine injection, and failure to return to the original degree of lameness by 6 hours after injection, suggested that the epidural combination of morphine and detomidine was responsible for the dramatic improvement in hindlimb lameness. These results are consistent with results from studies in humans and dogs that have demonstrated the potential for an epidural combination of morphine and an alpha 2 adrenergic agonist to provide potent analgesia.[14-17]

The dosages of morphine and detomidine used in this study were selected as a starting point to evaluate the efficacy of this combination of drugs in alleviating hindlimb lameness. The dosage of morphine used in this study was based on results of pilot studies conducted in our laboratory, which indicated minimal analgesic effects of epidural morphine on hindlimb lameness up to 6 hours after injection. The dosage of morphine used in this study was therefore doubled to 0.2 mg/kg from the dosage currently used in small animals and horses (0.1 mg/kg)[8,9,13] in anticipation of a limited clinical response. The dosage of detomidine used in this study was halved to 30 ug/kg from the dosage reported to provide perineal analgesia in horses (60 ug/kg)[21,22] in order to minimize the sedative effects shown to occur subsequent to epidural

detomidine administration.[21,22] Based on the significant results of the present study, it is possible that lower dosages of each drug could have been used to produce the same degree of analgesia.

In horses, analgesia associated with epidural morphine administration has been reported to occur as early as 20 minutes[13] and as late as 8 hours[12] after epidural injection, and to last for periods ranging from 8 hours[13] to 19 hours.[12] In contrast, epidural detomidine-induced analgesia has been demonstrated in horses as early as 5 minutes after epidural injection[21] but with an average duration of only 2.5 hours.[21,22] A possible advantage of an epidural combination of morphine and detomidine could therefore be analgesia of rapid onset and prolonged duration. It is possible that epidural detomidine was responsible for the early onset of analgesia in treated horses of this study, and that the analgesic effects of epidural morphine occurred later in the study period. However, because morphine and detomidine were not administered as independent epidural treatments in this study, the true contribution of each drug to the onset of analgesia is speculative. With respect to duration, evaluation of lameness was conducted hourly for 6 hours after epidural injection. A 6 hour observation period was selected based on constraints with number of horses to be videotaped at each hour and daylight limitations. Research in dogs demonstrated that epidural morphine alone produced analgesia for an average of 6.3 hours; however, when combined with the alpha 2 adrenergic agonist medetomidine, duration of analgesia increased to an average of 13.1 hours.[17] It is therefore possible that the epidural combination of morphine and detomidine could have produced analgesia in treated horses of the present study for a period of time exceeding the 6 hour observation period.

It is known that a complex array of interactions occurs both in the brain and within the spinal cord that affects pain pathways and modulates pain transmission. Numerous studies have suggested that spinal opioid and alpha 2 adrenergic receptor-mediated mechanisms act synergistically to modulate pain, enhancing the degree of modulation achieved when either

receptor is independently stimulated.[23-26] The mechanism of synergistic interaction that is believed to occur between epidurally administered opioids and alpha 2 adrenergic agonists still remains unclear. It has been suggested that the pharmacokinetic parameters of one drug may be altered by the co-administration of another.[27] In other words, an overall increase in drug levels at the spinal cord effector site could prolong or enhance the ability of both agents to mediate pain. A second proposed mechanism of synergy involves simultaneous activation of common second messenger guanine nucleotide protein (G protein)-coupled mechanisms.[27] Ligand binding of both opioid and alpha 2 adrenergic receptors, followed by activation of different G proteins, has been shown to cause altered potassium conductance leading to hyperpolarization of spinal cord neurons,[28-30] decreased intraneuronal calcium levels with subsequently decreased neurotransmitter release,[31-35] and inhibition of adenyl cyclase activity resulting in disrupted phosphorylation of target regulatory proteins and altered transmembrane voltages.[34,36,37] The overall effect of any one of these processes is a greatly multiplied inhibition of pain impulse transmission. A third possible synergistic mechanism concerns the functional location of opioid and alpha 2 adrenergic receptors.[27] Evidence suggests that these receptors may differ with respect to their primary site of action (ie. pre vs post synaptic).[38] Therefore, simultaneous stimulation of pre and post synaptic receptors by opioids and alpha 2 adrenergic agonists may magnify the effects produced by either drug acting independently at one site.[27]

Specific location, density and subtypes of spinal opioid and alpha 2 adrenergic receptors have not been elucidated in the horse, nor has the selectivity of morphine and detomidine for these receptors been investigated. Therefore it is difficult to speculate on the actions and interactions of these epidural agents in this species. Regardless of the mechanism of action, results from this study indicate that an epidural combination of an opioid such as morphine, with an alpha 2 adrenergic agonist such as detomidine, can induce profound hindlimb analgesia in the horse.

Several factors may explain the observed trend for heart and respiratory rates to initially decrease in treated horses and increase in control horses after epidural injection. The initial decrease in heart and respiratory rates in treated horses may have been because of the analgesic effect of epidural morphine and detomidine. However, heart and respiratory rate values in treated horses eventually approached those of control horses. If this trend was linked to onset and duration of analgesia, it would seem that a similar trend would have been observed in lameness scores as well. In contrast to heart and respiratory rates, lameness scores in treated horses never approached those of control horses after epidural injection. Therefore it is difficult to explain the initial decrease in heart and respiratory rates in treated horses based on analgesia alone.

The initial decrease in heart and respiratory rates of treated horses could also possibly be explained by cardiopulmonary depression secondary to epidural detomidine injection. One study conducted in mares demonstrated a significant decrease in mean heart rate 5 minutes after epidural injection of detomidine, which persisted for at least 3 hours, the length of the observation period.[21] In the same study, epidural detomidine caused mean respiratory rate to decrease significantly 15 minutes after epidural injection and to persist for the length of the observation period.[21] These cardiopulmonary effects are similar to the dose-dependent effects observed in horses after intravenous or intramuscular administration of detomidine.[39] Bradycardia induced by detomidine has been attributed to a decrease in central sympathetic output and a parasympathetic-mediated baroreceptor reflex initiated by increases in mean arterial pressure.[40] Respiratory depression after detomidine administration has been linked to central nervous system depression.[39] Detomidine, a lipid soluble agent, would be capable of penetrating and exiting the epidural space relatively easily.[41] Therefore, the initial cardiopulmonary depressive effects observed in treated horses in this study may have occurred following rapid vascular or lymphatic absorption, or both processes, of detomidine from the

epidural space, resulting in these systemic effects. Morphine, a polar drug with a low lipid coefficient, would not be capable of penetrating and exiting the epidural space as quickly as detomidine, making it less likely that morphine was responsible for these early effects.[42] This explanation does not account for the initial increase in heart and respiratory rates observed in control horses.

Heart and respiratory rates may have increased initially in control horses after epidural injection either because of pain from the previous videotaping session or in anticipation of another videotaping experience. However, whereas heart and respiratory rates in control horses eventually decreased and approached those of treatment horses, lameness scores remained consistently high. Therefore it seems unlikely that the initial increase in heart and respiratory rates was simply because of a lack of analgesia. Initial apprehension of the videotaping process may have elevated heart and respiratory rates in all horses in the study, but was masked initially in treated horses by the previously discussed cardiopulmonary effects of epidural detomidine. Whereas the cause for the observed effects of epidural injection on heart and respiratory rates in this study may be because of a combination of these or several undefined factors, it is important to note that these effects were transient.

Redistribution of detomidine from the epidural space was most likely responsible for the apparent development of sedation in treated horses shortly after injection. It is important to note that these horses were still able to walk and trot during the period of sedation. However, judicious use of an epidural combination of morphine and detomidine would be advocated in an unsteady or depressed horse.

Placement of an epidural catheter is an easily learned technique that could facilitate administration of epidural morphine and detomidine on a long-term basis for treatment of serious musculoskeletal disorders. However, before this combination can be recommended for routine clinical use, several issues must be addressed. First, efficacy of this combination for

different types of acute and chronic musculoskeletal pain requires evaluation. Second, local and systemic effects of epidural catheterization, and epidural morphine and detomidine administration must be investigated before their use can be advocated clinically on a long-term basis. Third, dose-response studies are necessary to determine appropriate dosages of each agent necessary to produce acceptable analgesia, as well as the dosing interval required to make this epidural combination of agents applicable in a clinical setting.

In summary, results of the present study indicate that an epidural combination of morphine and detomidine provides profound analgesia for equine hindlimb pain. While results of this study are encouraging, further studies need to be conducted before this combination can be recommended for routine use in clinical cases.

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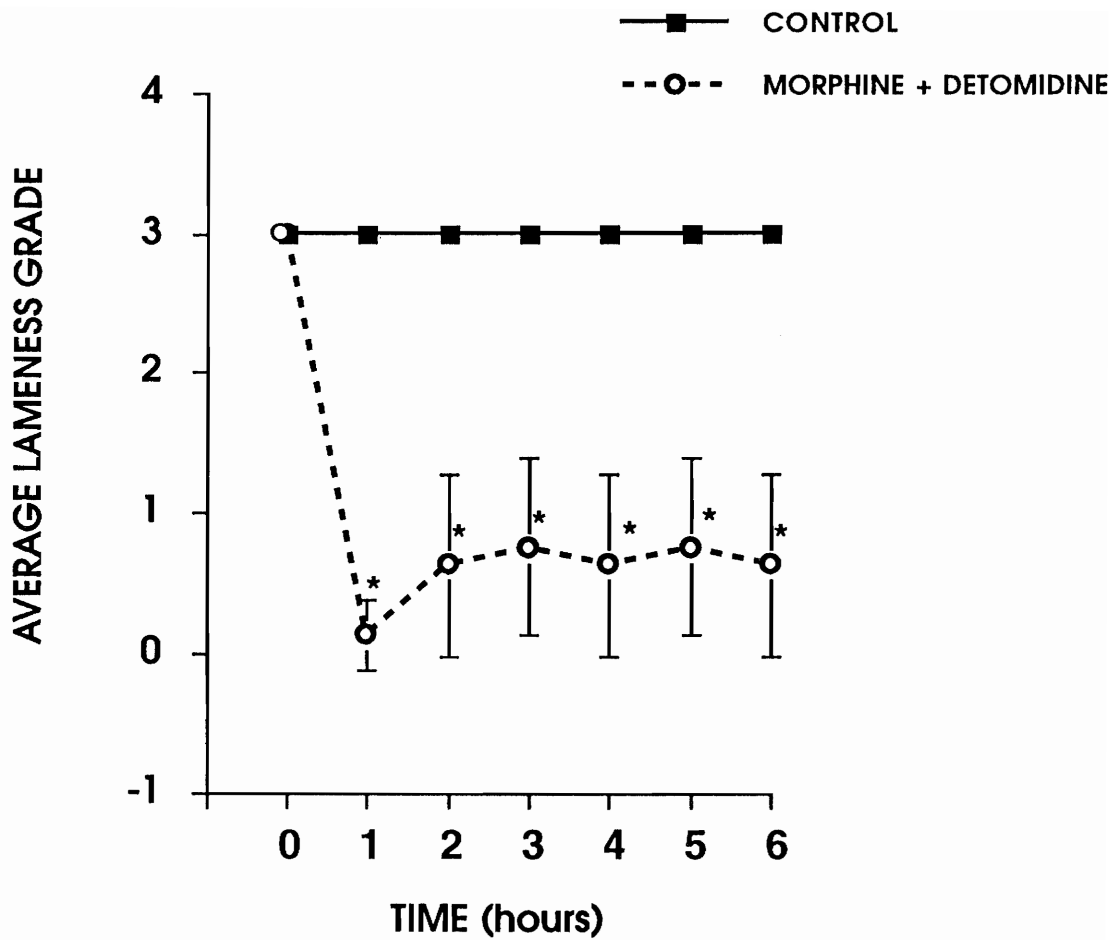
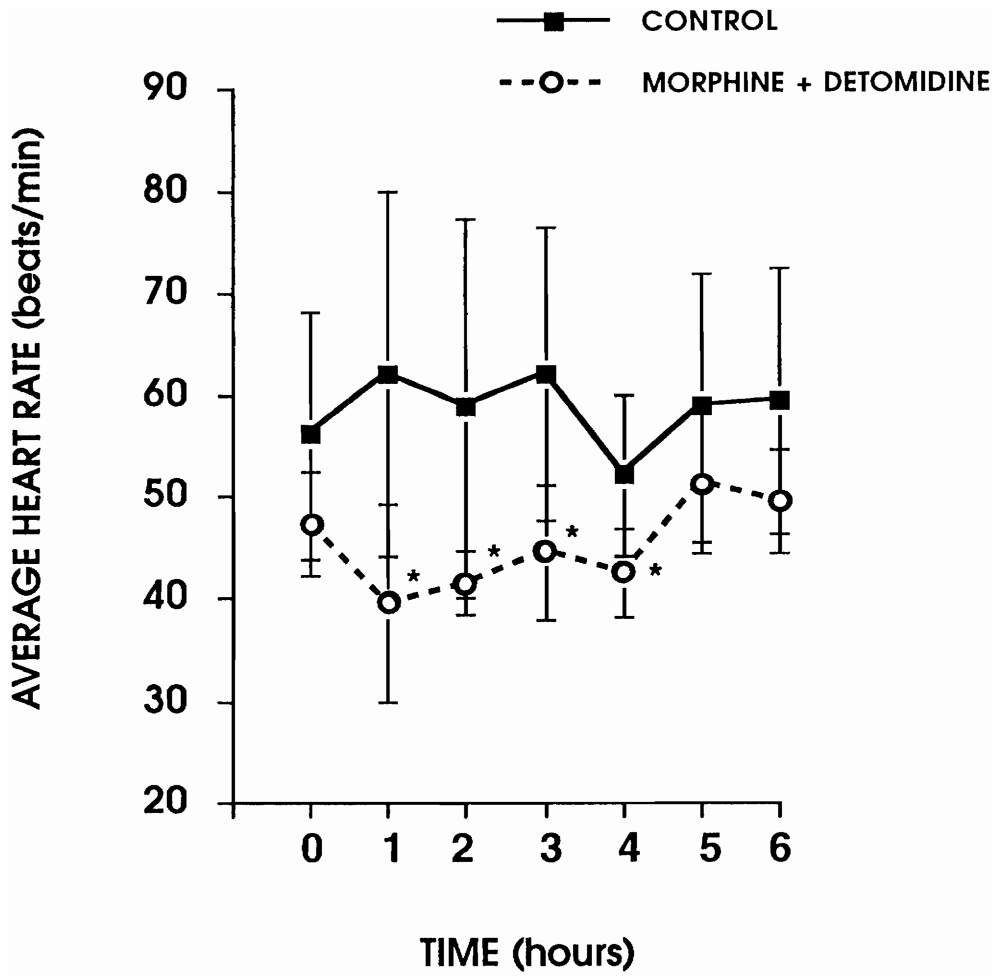
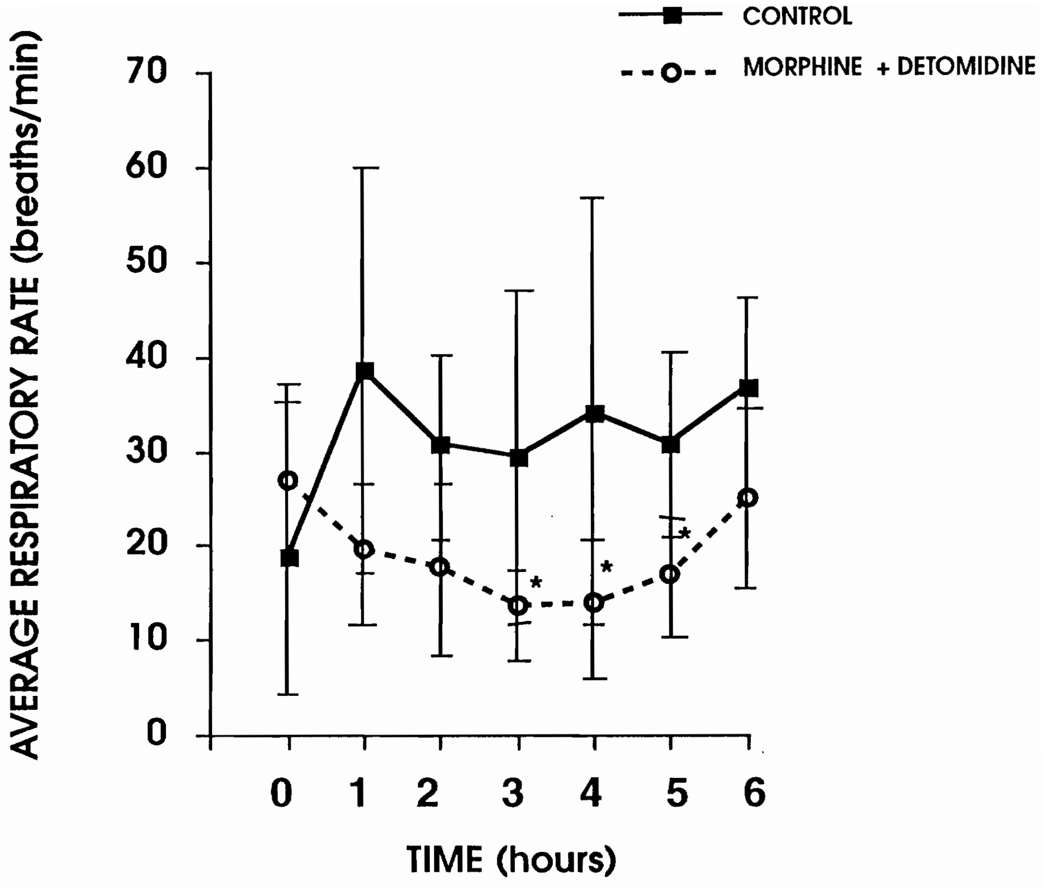
Fig 1. Average lameness grades of control and treated horses at baseline (time 0) and at hourly intervals after epidural injection with physiologic saline solution and morphine and detomidine respectively. Error bars indicate mean values +/- 2 standard errors of the mean. * indicates a value significantly different ($P < .05$) from the control value.

Fig 2. Average heart rates of control and treated horses at baseline (time 0) and at hourly intervals after epidural injection with physiologic saline solution and morphine and detomidine respectively. Error bars indicate mean values +/- 2 standard errors of the mean. * indicates a value significantly different ($P < .05$) from the control value.

Fig 3. Average respiratory rates of control and treated horses at baseline (time 0) and at hourly intervals after epidural injection with physiologic saline solution and morphine and detomidine respectively. Error bars indicate mean values +/- 2 standard errors of the mean. * indicates a value significantly different ($P < .05$) from the control value.


CONTROL
MORPHINE + DETOMIDINE
AVERAGE LAMENESS GRADE
4
3
2
1
0
-1
0
1
2
3
4
5
6
TIME (hours)
*


CONTROL
MORPHINE + DETOMIDINE
AVERAGE HEART RATE (beats/min)
90
80
70
60
50
40
30
20
0
1
2
3
4
5
6
TIME (hours)


CONTROL
MORPHINE + DETOMIDINE
AVERAGE RESPIRATORY RATE (breaths/min)
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
TIME (hours)

Systemic and Local Effects Associated With Long-Term Epidural Catheterization and Morphine-Detomidine Administration in Horses

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ABSTRACT

Objective: The purpose of this study was to determine the systemic and local effects associated with long-term epidural catheterization and epidural morphine-detomidine administration in horses.

Study Design: Development of systemic or local effects was assessed by placing caudal epidural catheters in study horses and administering injections through the catheters every 12 hours for 14 days.

Animals: 10 horses with epidural catheters that received daily injections; 6 uncatheterized horses presented for euthanasia.

Methods: Horses received either 0.2 mg/kg morphine sulfate and 30 mg/kg detomidine hydrochloride or an equivalent volume of physiologic saline solution through epidural catheters. Systemic effects were compared between control and treatment horses by measuring physical parameters and hay and water consumption, as well as by evaluating major organs following euthanasia. Local effects were studied by examining cerebrospinal fluid and by grading representative samples of the spinal cord and surrounding tissues histologically for inflammation and fibrosis. Local effects were compared between control and treatment horses as well as between catheterized (control plus treatment) horses and uncatheterized horses.

Results: No significant difference was identified in daily variables or hay and water consumption between control and treatment horses. No growth was obtained from cerebrospinal fluid cultures. No significant difference in cerebrospinal fluid values or spinal tissue inflammation or fibrosis grades was demonstrated between control and treatment horses. However, when compared to uncatheterized horses, cerebrospinal fluid red blood cell values were marginally higher and protein concentrations were significantly higher in the catheterized group. As well, lumbosacral and sacral spinal tissue segment inflammation grades, and sacral

segment fibrosis grades were significantly higher in catheterized horses.

Conclusions: Long-term epidural administration of a morphine-detomidine combination is not associated with apparent adverse systemic effects in horses. Localized inflammation and fibrosis appear to be catheter-related.

Clinical Relevance: Potential systemic and local effects are important considerations with long-term administration of a morphine-detomidine combination through an indwelling epidural catheter for alleviation of chronic musculoskeletal pain in horses.

INTRODUCTION

Administration of epidural morphine for treatment of pain in humans was first described in 1979.[1] Because of its ability to selectively block pain while leaving sensory, motor and sympathetic function intact,[2] morphine administered through an indwelling epidural catheter has become a popular means of providing analgesia to terminally-ill cancer patients[3-5] and to patients with chronic pain unresponsive to other therapies.[4] Epidural morphine has been used recently in veterinary medicine to provide pain relief in dogs after forelimb and hindlimb orthopedic surgery and after thoractomy.[6-8] Epidural morphine has been administered to goats for analgesia after abdominal and orthopedic surgeries,[9,10] and to a horse after hindlimb digit amputation.[11]

Shortly after the introduction of epidural morphine analgesia into human medicine, the analgesic properties of epidurally-administered alpha 2 adrenergic agonists such as clonidine,[12,13] detomidine,[14] medetomidine,[15] and xylazine[16] were reported in various species. Results of studies in humans and dogs revealed that duration and intensity of epidural morphine analgesia could be enhanced by the co-administration of an alpha 2 adrenergic agonist.[15,17,18] A combination of morphine and detomidine, administered through an indwelling epidural catheter, provided analgesia for experimentally-induced hindlimb lameness in horses.[19]

Nonsteroidal anti-inflammatory drugs are commonly used to provide analgesia for musculoskeletal injuries in horses. However, high doses or prolonged use of these drugs may result in serious side effects.[20,21] An alternative or supplemental form of analgesia, such as an epidural morphine-detomidine combination, that produces few to no side effects would be valuable for long-term treatment of equine musculoskeletal pain.

Whereas systemic and local effects of long-term epidural catheterization and epidural

morphine administration have been evaluated in some species,[4,5,22-29] these effects have not been characterized in horses. Furthermore, studies of systemic and local effects of repeated epidural detomidine administration are lacking. The purpose of the study reported here was to identify systemic and local effects associated with long-term (14 day) epidural catheterization and morphine-detomidine administration in the horse in order to evaluate the safety of this method of analgesia for routine treatment of chronic musculoskeletal pain.

MATERIALS AND METHODS

Ten horses (9 mares and 1 gelding), without clinical evidence of neurologic disease, were studied. Breeds represented were 8 Thoroughbreds, 1 Quarterhorse and 1 Tennessee Walking Horse; horses were 5 to 18 years old (median, 14.5 years) and ranged in weight from 427 to 536 kg (median, 490 kg). Horses were housed in 12 foot square box stalls during the study and were offered a mixture of grass and alfalfa hay and water ad libitum.

On day 1, horses were weighed and then sedated with a combination of detomidine hydrochloride (6.0 ug/kg intravenously [IV], Dormosedan, Smithkline Beecham, West Chester, PA) and butorphanol tartrate (6.0 ug/kg IV, Torbugesic, Fort Dodge Laboratories Inc., Fort Dodge, IA). Sacrocaudal and caudal vertebral areas were clipped and aseptically prepared for caudal epidural catheter placement. Two mL of 2% lidocaine (Lidocaine 2% Injectable, Butler Co., Columbus, OH) were deposited subcutaneously over the first palpably movable joint space caudal to the sacrum. After further aseptic preparation, a 16 gauge, 1.5 inch needle was introduced through the anesthetized area into the epidural space at an angle of approximately 45 degrees to the horizontal plane. Placement of the needle into the epidural space was confirmed by palpable penetration of the ligamentum flavum, disappearance of a drop of sterile physiologic saline solution (Normal Saline Solution, VEDCO Inc., St. Joseph, MO) from the needle hub (hanging drop technique), ease of injection of sterile saline solution and ease of catheter advancement. In two horses with tissue mass greater than 1.5 inches over the first movable joint space caudal to the sacrum, the needle was instead introduced into the epidural space through the next caudally movable joint space in a similar manner. A 20 gauge, 36 inch open-tipped teflon epidural catheter (Safetrak, Kendall Healthcare Products Co., Mansfield, MA) was inserted through the needle into the epidural space and advanced cranially to the

lumbosacral region. Lumbosacral placement was determined by measuring the distance between the sacrocaudal vertebral space and the lumbosacral region and advancing the catheter that distance. The 16 gauge needle was removed from the epidural space, leaving the catheter in place, and the catheter was cut so that a 3 inch length remained external to the skin. An adapter was fitted to the end of the catheter, and the catheter was flushed with 1 mL heparinized saline (Heparin Sodium Injection, USP, Elkins-Sinn Inc., Cherry Hill, NJ; 10 U/mL physiologic saline solution). The catheter was sutured in place with 2-0 nylon and was covered with a nylon patch (Shut-Eye, American Animal Health Inc., Wisner NE) that was glued circumferentially except over the tailhead to permit access to the catheter adapter.

Horses were randomly assigned to one of two groups. Treatment horses (n = 7) were given 0.2 mg/kg morphine sulfate (Morphine Sulfate Injection, USP, Elkins-Sinn Inc., Cherry Hill, NJ) and 30 ug/kg detomidine hydrochloride through the epidural catheter every 12 hours for 14 days. Control horses (n = 3) were given an equivalent volume (0.017 mL/kg) of sterile physiologic saline solution through the catheter every 12 hours for 14 days. Epidural catheters were flushed with 1 mL heparinized saline after each injection of morphine-detomidine or physiologic saline solution.

Systemic Effects

Systemic effects were evaluated in both control and treatment horses. Body weights were recorded on days 1 and 14. Rectal temperature, heart rate, respiratory rate and gastointestinal motility were recorded twice daily during the 14 day observation period. Variables were recorded immediately before morning epidural injections and 3 hours before evening injections. Gastrointestinal motility was ausculted bilaterally in the dorsal and ventral regions of the abdomen. Motility in each quadrant was scored by one investigator over a 1 minute period on a scale of 0 to 3 as follows: 0 = no gastrointestinal sounds ausculted; 1 = 1 to 2 progressive

sounds heard; 2 = more than 2 progressive sounds present; 3 = continuous gastrointestinal sounds heard over a 1 minute period. The sum of the scores assigned to each quadrant was used as the gastrointestinal motility grade for each horse at each recording session. Hay intake (weight of hay consumed per 24 hour period as a percent of average body weight) and water intake (volume of water consumed per 24 hour period as a percent of average body weight) were recorded daily for each horse throughout the 14 day observation period.

At the end of the study period, horses were euthanatized with sodium pentobarbital (Fatal Plus Powder, Vortech Pharmaceuticals, Dearborn, MI; 0.15 g/kg IV). Gross necropsy examinations were performed and representative samples from lung, heart, adrenal gland, kidney, spleen, liver, stomach, small intestine, cecum and colon were collected for histopathologic evaluation.

Weight change was compared between control and treatment horses using a 2 sample t-test.[30] Temperature, heart rate, respiratory rate, gastrointestinal motility grades and hay and water consumption were compared between control and treatment groups using repeated measures analysis of variance.[30] Results with *P* values less than .05 were considered significant.

Local Effects

Immediately after death, the atlanto-occipital region of all horses was clipped and aseptically prepared. With the horse in lateral recumbency and the head ventroflexed, an 18 gauge, 3.5 inch spinal needle was inserted into the atlanto-occipital space. Cerebrospinal fluid was collected and submitted for bacteriologic and cytologic evaluation, as well as determination of white and red blood cell counts and protein and glucose concentrations.

Cutaneous catheter entry sites were visually evaluated for evidence of gross abnormalities. The spinal column was examined grossly, then was dissected from each horse. Representative

samples of the spinal cord and surrounding tissues were taken from the cervicothoracic, thoracolumbar, lumbosacral and sacral regions and from catheter entry point regions and processed for histologic evaluation. Spinal tissue sections were graded for degree of inflammation by two investigators, unaware of group assignment, on a scale of 0 to 3 as follows: 0 = no evidence of inflammation; 1 = mild inflammation characterized by the presence of few scattered nucleated cells; 2 = moderate inflammation with the occasional presence of nucleated cells; 3 = diffuse inflammation with nucleated cells consistently present throughout the section. Spinal tissue sections were also graded for degree of fibrosis on a scale of 0 to 3 as follows: 0 = no evidence of fibrosis; 1 = mild fibrosis characterized by the presence of a small focus of fibroblastic activity; 2 = moderate fibrosis with scattered, focally intense areas of fibrous tissue production; 3 = severe diffuse fibrosis.

To enable comparison of cerebrospinal fluid values and spinal segment inflammation and fibrosis grades between epidurally catheterized and uncatheterized horses, six horses killed for reasons unrelated to neurologic disease served as an uncatheterized group of horses. Immediately after euthanasia, cerebrospinal fluid samples from three of these horses were collected and examined as described previously. Spinal tissue samples were obtained from the remaining three horses and sections were prepared and graded for inflammation and fibrosis as described above.

Cerebrospinal fluid values and spinal tissue segment inflammation and fibrosis grades were compared between control and treatment horses. Control and treatment groups of horses were then pooled together to form a catheterized group of horses. Cerebrospinal fluid values and spinal tissue segment inflammation and fibrosis grades were compared between catheterized and uncatheterized groups of horses. Statistical comparisons were made using a Mann-Whitney rank sum test.[30] Results with *P* values less than .05 were considered significant.

RESULTS

No problems were encountered with maintainance of epidural catheters over 14 days. Catheter adapters occasionally became disconnected but the catheters themselves remained patent and secure; new adapters were easily reconnected. Neither injection resistance, leakage of solution around the catheter, nor pain on injection were observed.

Systemic Effects

No significant difference was identified in body weight change, daily temperature, heart rate, respiratory rate, gastrointestinal motility grade or hay or water consumption between control and treatment horses over the 14 days.

No gross or histologic abnormalities were identified in the heart, adrenal gland, spleen, cecum or colon in control or treatment horses. Pulmonary congestion was noted in the lungs of five treatment horses. Mild glomerulonephrosis, characterized by thickened glomerular tufts, was observed in one control horse and in one treatment horse. Mild renal tubular necrosis, evidenced by scattered tubules with attenuated epithelium and necrotic epithelial cells, was observed in another control horse. Atrophy of the right hepatic lobe was evident in one control horse. Vacuolation of hepatocytes was observed histologically in one control horse and in two treatment horses. Mild hyperplasia of the bile ducts was noted in one treatment horse. Hyperemia of the gastric mucosa was found in one treatment horse. Mild superficial gastric erosions were identified in two control and two treatment horses. Gastric ulceration was evident at the margo plicatus in two treatment horses and in the squamous portion of the stomach in one control and one treatment horse. Gastric ulcers showed evidence of mild inflammation histologically and were underlain by granulation tissue. Mucosal hyperemia was

identified in the duodenum of one treatment horse. Focal areas of hyperemia were visualized in the jejunum of five treatment horses, but these areas appeared normal histologically.

Local Effects

Cutaneous catheter insertion sites had no gross abnormalities. Epidural catheter tips were identified in the region between the fifth lumbar vertebra and the lumbosacral junction in catheterized horses. All cerebrospinal fluid bacteriologic cultures were negative for growth. A cerebrospinal fluid sample from one catheterized control horse was contaminated by iatrogenic hemorrhage at the time of collection. Therefore statistical analysis of cerebrospinal fluid characteristics among all groups was performed using samples from two, instead of three, control horses (Table 1). When cerebrospinal fluid values were compared between control and treatment horses, no significant difference was found in white blood cell counts or protein or glucose concentrations between groups. Treatment horses tended to have higher cerebrospinal fluid red blood cell counts than did control horses, although this difference was not significant (P = .111). When cerebrospinal fluid values were compared between catheterized horses and uncatheterized horses, white blood cell counts and glucose concentrations were not significantly different. However, there was a marginally significant trend for cerebrospinal fluid red blood cell counts to be higher in the catheterized horses than in uncatheterized horses (P = .05). As well, cerebrospinal fluid protein concentrations were significantly higher in all catheterized horses than in uncatheterized horses (P = .009).

Histologic evidence of inflammation and fibrosis was most obvious in lumbosacral, sacral and catheter entry point spinal tissue segments of catheterized horses. Inflammation was characterized by localized infiltration with a combination of lymphocytes, neutrophils, plasma cells, macrophages and eosinophils. Inflammatory foci were identified within the peridural fat of both control and treatment horses. Foci of inflammation were also seen around nerve roots

and extradural vessels, and within the meninges and dura in treatment horses. A localized area of inflammation was identified in the sacral spinal cord itself in one treatment horse. Epidural fat necrosis was evident in sacral tissue segments of four treatment horses. Fibrous tissue was present at the catheter's point of entry into the epidural space in all control and treatment horses. Fibrous tissue was observed to adhere the epidural catheter to the cauda equina in one treatment horse. Fibrous tissue was also present along the catheter tract in sacral segments of one control horse and one treatment horse. In thoracolumbar segments, fibrous tissue was identified in the leptomeninges of one treatment horse. Focal hemorrhage was evident at catheter entry point segments of one control and six treatment horses. Hemorrhage was present along the catheter tract of sacral segments in one control and one treatment horse. Focal hemorrhage was also present in lumbosacral segments in two treatment horses.

When spinal tissue inflammation grades for each segment were compared between control and treatment horses, no significant difference in inflammation grade was identified between groups in any segment (Table 2). However, when inflammation grades were compared between catheterized and uncatheterized groups, catheterized horses had significantly higher lumbosacral (P = .007) and sacral (P = .004) spinal segment inflammation grades.

When fibrosis grades for each segment were compared between control and treatment horses, no significant difference in fibrosis grade was identified between control and treatment groups in any segment (Table 3). Lumbosacral fibrosis grades tended to be higher in catheterized vs uncatheterized horses, although this difference was not significant (P = .108). However, sacral segment fibrosis grades were significantly higher in catheterized as compared to uncatheterized horses (P = .039).

DISCUSSION

Problems associated with long-term epidural catheter maintenance in humans have included dislocation, catheter obstruction with subsequent injection resistance, leakage of injected fluid at the site of catheter entrance through the skin and pain during injection.[4,5,22,24] None of these complications were encountered in the horses in this study. It is possible that the 14 day observation period was short enough that such problems did not develop. In a retrospective study of human patients receiving epidural morphine through indwelling catheters, only 8% of patients experienced technical complications with epidural catheters during the first 20 days of treatment; however, the frequency of complications rose to 55% between days 20 and 366 of treatment.[24] It is unknown whether complications would have occurred in horses had epidural catheters been maintained longer than 14 days.

No significant difference in body weight, temperature, heart rate, respiratory rate, gastrointestinal motility, hay or water consumption was noted between control and treatment horses. This finding indicates that long-term epidural morphine-detomidine administration had no apparent adverse effects on any of these variables. Whereas short-term postoperative epidural catheterization and morphine administration in humans has been associated with side effects including delayed respiratory depression,[2] nausea and vomiting,[2,31] urinary retention,[2,5,31] pruritus,[2,5,31] dysphoria,[2] sedation,[2,5,31] delayed gastric emptying,[32] and constipation,[5] these effects have not been identified in patients treated with epidural morphine for prolonged periods.[2,5] This phenomenon in humans has been attributed to various factors including desensitization to side effects through previous oral or parenteral opioid administration and development of brain tolerance to side effects.[2,33] A similar finding has been reported with chronic epidural infusion of the alpha 2 adrenergic agonist, clonidine, in dogs. Whereas side

effects including decreased heart rate, respiratory rate, blood pressure, and increased sedation were maximal between days 1 and 3, progressive adaptation was observed over the 28 day study period with the exception of respiratory rate, which remained depressed.[34] To our knowledge, none of the horses in this study had previously been exposed to regular opioid or alpha 2 agonist administration. Whether the absence of systemic side effects in study horses was due to some form of adaptation or central tolerance over the 14 day observation period is unknown.

Gross and histologic examination did not reveal evidence of adverse systemic effects of long-term epidural morphine-detomidine administration. Certain findings were attributed to either acute death (eg, pulmonary congestion) or age-related changes (eg, glomerulonephrosis, renal tubular necrosis, hepatic atrophy, hepatocellular vacuolation, bile duct hyperplasia). Either gastric erosion or ulceration was identified in all control and in five of seven treatment horses. The presence of gastric erosions or ulcers in horses before the onset of the study was not determined. As erosions or ulcers were present in both control and treatment horses, their development was probably not linked to the long-term administration of epidural morphine-detomidine. As well, it is unlikely that the presence of epidural catheters was responsible for ulcer development. While emotional stress has been implicated as a cause of ulcers in both humans and horses, studies in humans have indicated that there is no relationship between phychological stress and development of gastric ulcers.[35] Research has shown that horses on pasture which are brought into stall confinement frequently develop gastric lesions within one week, even though free-choice hay is available.[36,37] It is thought that because stalled horses spend less time eating, there are periods of time when the stomach is empty, and hydrochloric acid may contact both glandular and nonglandular regions of the stomach and induce lesions.[36] Eight of the 10 horses in this study were known to have been on pasture prior to commencement of the study. Therefore, stall confinement may have played a role in inducing

gastric erosion or ulcer formation.

Cerebrospinal fluid cultures were negative for bacteriologic growth in all horses. These results correlate with those of human studies that have documented a low incidence of infection associated with long-dwelling epidural catheters.[4,5,22,24,29] Catheter-related infections in humans are most often localized to the skin and subcutaneous tissues at the catheter insertion point.[4,5,22,24] Although the skin and subcutaneous tissues surrounding the catheter entry site of horses in this study were not cultured, clinical evidence of infection was not observed.

There was a trend for cerebrospinal fluid red blood cell counts to be higher in horses with epidural catheters when compared to uncatheterized horses. As well, some degree of hemorrhage was identified in the epidural space of lumbosacral and sacral regions and catheter entry point sites in catheterized horses. In goats receiving a daily injection of saline through an epidural catheter for eight days, occasional focal hemorrhages were documented in the epidural space.[26] Similarly, a study conducted in guinea pigs documented the appearance of epidural hemorrhage within two days of placement of nylon epidural catheters.[27] However, studies in various other species have not demonstrated the development of hemorrhage as a consequence of epidural catheterization or injection, regardless of the type of catheter used or the agent administered.[23-25,27-29,34] Epidural hemorrhage in some of the control and treatment horses of this study may have occurred as a result of trauma induced by either the needle or catheter at the time of insertion. Epidural hemorrhage may also have originated from continued local tissue disruption caused by the volume of agents administered, which was an average of 8 mL per injection.

A significant elevation in cerebrospinal fluid protein concentrations and the presence of significantly higher lumbosacral and sacral inflammation grades and sacral segment fibrosis grades in epidurally catheterized horses is consistent with the development of epidural

inflammation and fibrosis related to catheterization. Since no significant difference in these values was observed between control and treatment horses, inflammation and fibrosis did not likely develop as a result of epidural morphine- detomidine administration. Studies conducted in other species have shown that epidural administration of morphine or the alpha 2 adrenergic agonist, clonidine, is not associated with adverse local tissue reactions.[25,27,28,34,38,39] Studies in animals and humans have shown, however, that chronically implanted epidural catheters can produce a fibrous reaction in the epidural space in the region of the catheter.[5,23-27,29,34,39] Epidural fibrosis has been cited as the cause of technical complications associated with long-term epidural catheter maintenance, including dislocation, obstruction, leakage of injected fluid and injection pain.[5,24] The type of epidural catheter inserted has been implicated as an inciting factor in the development of epidural inflammation and fibrosis. Teflon epidural catheters were used in this study as they were rigid enough to permit advancement to the lumbosacral region. However, epidural fibrosis has been also documented after use of polyamide, polyurethane, nylon, polyethylene, polyvinylchloride and silicone rubber catheters. [24-27,29,34,40]

Epidural catheters of all horses were advanced to the lumbosacral junction from their point of entry into the epidural space. The most noticeable histologic signs of inflammation and fibrosis occurred in spinal tissue segments through which the catheter ran. A recent report in the human literature recommended that the tip of an epidural catheter not be advanced more rostrally than necessary for desired segmental analgesic cover.[41] It has been suggested that the rostral epidural spread of agents from caudally placed catheters may be achieved by increasing injection volume.[42,43] However, effective distal epidural morphine analgesia without the use of large injection volumes or catheter advancement was demonstrated in children after open heart surgery.[44] Whereas the extent of local epidural inflammation and fibrosis may be decreased by leaving the epidural catheter tip near its point of entry into the epidural space, it is unknown whether analgesia to the equine hindlimb would be possible using a large injection volume from

such a caudal location.

The significance of localized epidural inflammation and fibrosis has yet to be determined. None of the horses in this study showed clinical effects or technical catheter complications related to the development of inflammation or fibrosis. In a study conducted in pigs to evaluate effects of continuous epidural administration of bupivicaine, morphine or saline solution through a catheter, only minimal inflammatory changes remained in the spinal tissues in one of two pigs 3 weeks after catheter removal.[25] It is possible that the inflammatory reaction attributable to the presence of an epidural catheter would subside after catheter removal, making the development of epidural inflammation and fibrosis significant only as an impediment to long-term catheter maintenance. The significance of adhesions between the epidural catheter and the cauda equina in one treatment horse in this study is unknown.

Administration of a morphine and an alpha 2 agonist combination through an indwelling epidural catheter has been shown to be a safe and effective means of providing long-term analgesia in human patients. This form of analgesia would be valuable for long-term treatment of musculoskeletal pain in the horse and would avoid the side effects that could develop with chronic use of high doses of nonsteroidal anti-inflammatory drugs. The study reported here has demonstrated that long-term epidural administration of a morphine-detomidine combination does not adversely affect weight, temperature, heart rate, respiratory rate, gastrointestinal motility, hay or water consumption in the horse. As well, long-term epidural administration of a morphine-detomidine combination does not appear to have adverse effects on the epidural tissues of the horse. While inflammation, fibrosis and occasional hemorrhage have been shown to occur in tissues in proximity to long-dwelling epidural catheters, further studies are required to determine the cause and significance of these catheter-related changes. Results of this study suggest that long-term epidural catheterization and epidural morphine-detomidine administration may be clinically applicable for the routine treatment of chronic musculoskeletal pain in horses.

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Table 1. Median Cerebrospinal Fluid Values

Group	White blood cells (cells/μL)	Red blood cells (cells/μL)	Protein (mg/dL)	Glucose (mg/dL)
Control (n=2)	1.5 (1-2)*	1.5 (0-3)	64.5 (58-71)	48.5 (44-53)
Treatment (n=7)	2.0 (0-25)	25.0 (0-2780)	69.0 (48-207)	52.0 (45-60)
Catheterized[a] (n=9)	2.0 (0-25)	11.0[b] (0-2780)	69.0[c] (48-207)	52.0 (44-60)
Uncatheterized (n=3)	0 (0-5)	0[b] (0-1)	46.0[c] (39-55)	52.0 (49-64)

*ranges are shown in parentheses

[a]catheterized group consists of pooled values for control plus treatment horses

[b]denotes a marginally significant difference between catheterized and uncatheterized horses (P=.05)

[c]denotes a significant difference between catheterized and uncatheterized horses (P=.009)

Table 2. Median Inflammation Grades of Spinal Tissue Segments

Group	Spinal Tissue Segments				
	Cervicothoracic	Thoracolumbar	Lumbosacral	Sacral	Catheter Entry Point
Control (n=3)	0 (0-1)*	0 (0-1)	1 (1-2)	2 (1-3)	2 (1-3)
Treatment (n=7)	1 (0-1)	0 (0-1)	2 (0-3)	2 (1-3)	2 (0-3)
Catheterized[a] (n=10)	0.5 (0-1)	0 (0-1)	2[b] (1-3)	2[c] (1-3)	2 (0-3)
Uncatheterized (n=3)	0	0	0[b]	0[c]	/

* ranges are shown in parentheses; where ranges are not indicated, grades for horses within the group are identical

[a]catheterized group consists of pooled grades for all control plus treatment horses

[b]denotes a significant difference between catheterized and uncatheterized horses (*P*=.007)

[c]denotes a significant difference between catheterized and uncatheterized horses (*P*=.004)

Table 3. Median Fibrosis Grades of Spinal Tissue Segments

Group	Spinal Tissue Segments				
	Cervicothoracic	Thoracolumbar	Lumbosacral	Sacral	Catheter Entry Point
Control (n=3)	0	0	1 (0-2)	0 (0-3)	2 (1-3)
Treatment (n=7)	0 (0-1)*	0 (0-1)	2 (0-2)	2 (0-2)	2 (0-3)
Catheterized[a] (n=10)	0 (0-1)	0 (0-1)	1.5 (0-2)	2[b] (0-3)	2 (0-3)
Uncatheterized (n=3)	0	0	0 (0-1)	0[b]	/

* ranges are shown in parentheses; where ranges are not indicated, grades for horses within the group are identical

[a]catheterized group consists of pooled grades for all control plus treatment horses

[b]denotes a significant difference between catheterized and uncatheterized horses (*P*=.039)

SUMMARY

The dosages of morphine and detomidine used in Part 1 of the study were selected as a starting point to evaluate the efficacy of this combination of drugs in alleviating hindlimb lameness in horses. The dosage of morphine used was based on results of unpublished research (Ewing, 1995) and results of our pilot studies, which indicated minimal analgesic effects of epidural morphine on different types of experimentally-induced hindlimb lameness. Therefore, in anticipation of a limited clinical response, the dosage of morphine administered to treated horses in this study was doubled to 0.2 mg/kg from the dosage of 0.1 mg/kg that has been reported in small animals and horses (Pascoe and Dyson, 1993; Valverde et al, 1993; Valverde et al, 1990). The dosage of detomidine administered to treated horses in this study was halved from 60 ug/kg, the dosage reported to provide perineal analgesia in horses (Skarda and Muir, 1994; Skarda and Muir, 1992), to 30 ug/kg in order to minimize sedative effects which might have led to significant ataxia. Because the dosages used for Part 1 appeared to alleviate hindlimb lameness in treated horses, identical dosages were continued twice daily for 14 days during Part 2 to assess systemic or local effects associated with these agents at clinically analgesic dosages.

In this study, epidural catheters were advanced to the lumbosacral region in all horses to ensure that epidural agents reached the pelvic nerve plexus supplying the hindlimbs. In this way, variables such as volume of infusion and effects of redistribution, which might have affected craniad spread of drugs, were eliminated. While studies in humans and animals have documented thoracic (Robinson et al, 1994; Pascoe and Dyson, 1993; Popilskis et al, 1991; Rosen and Rosen, 1989) and forelimb (Duke et al, 1994a; Valverde et al, 1993; Valverde et al, 1989) analgesia following caudal epidural injection of morphine or alpha 2 agonists, it is not known whether the profound hindlimb analgesia observed in horses in Part 1 of this study would have been possible had catheter tips been left near their point of entry into the epidural space.

Intra-articular amphotericin B was administered to the left tarsocrural joint of all horses. The decision to inject the left tarsocrural joint, rather than randomly inject right and left joints, was done prospectively. This decision was made in order that subtle changes in gait could be detected in the affected limb. All videotape reviewers were aware of the left hindlimb designation at the time of grading of lameness videorecordings.

A protocol for amphotericin B-induced synovitis was adapted from a previously reported study and was used to create a hindlimb lameness in all horses. During our initial pilot studies, an adjustable heartbar shoe had been used as a model to create a temporary hindlimb lameness. However, problems such as loosening of the allen screw, loosening of the shoe clinches and possible acclimation by the horse to the shoe diminished the ability of the heartbar shoe to produce a consistent lameness over a 6 hour period. It therefore became difficult to separate epidural drug-induced improvement in lameness from improvement due to the inconsistent nature of the heartbar shoe. Amphotericin B, a polyene antibiotic, has been shown to induce acute traumatic synovitis and create consistent lameness in horses for 2 weeks following a series of intra-articular injections (Peloso et al, 1993). Injection with amphotericin B would avoid the problem of primary cartilage destruction as has been observed with historic models of joint inflammation including intra-articular filipin (McIlwraith et al, 1979), monoiodoacetate (Yovich et al, 1987; Gustafson et al, 1992) and cartilaginous particles (Hurtig, 1988). Furthermore, horses could be spared from the severe systemic endotoxin-induced side effects reported to occur with intra-articular lipopolysaccharide injection (Palmer and Bertone, 1994). While amphotericin B created a transient hindlimb lameness in horses of the study, no horse became so painful as to necessitate withdrawal from the study.

Amphotericin B-induced synovitis produced a consistent grade 3 hindlimb lameness in all but 1 horse. Evaluation of lameness videorecordings of this horse by investigators 1 and 2 indicated no obvious lameness, while investigator 3 determined the horse to be grade 1 lame in the left hindlimb. Because this horse did not meet the

criterion for inclusion into Part 1 of the study (ie. an initial grade 3 lameness), it was excluded from Part 1 and used only in Part 2 of the study. Inadvertent periarticular injection may potentially explain failure to develop grade 3 lameness following 2 intra-articular injections of amphotericin B. However, gross and histopathological examination of the left tarsocrural joint of this horse revealed the presence of fibrin and granulation tissue within the joint, indicating evidence of intra-articular inflammation similar to that seen in other horses of the study. The amphotericin B itself used for intra-articular injection would not account for the lack of development of obvious lameness, as a different bottle of the drug was used for each of the 2 injections and other horses of the study, which became grade 3 lame, received injections from the same bottles. Individual variation in pain tolerance levels may have been a contributing factor to this horse's mild clinical pain response to intra-articular amphotericin B injection.

Two additional horses were excluded from Part 1 of the study. One horse, a Tennessee Walking Horse, could not be made to consistently trot throughout the videotaping process. The second horse had a pre-existing chronic exostosis associated with the left hind fetlock, which did not appear to cause a significant lameness on initial physical examination but which may have become exacerbated by walking and trotting on pavement for several hours during the videotaping process. Therefore, these 2 horses were evaluated only in Part 2 of the study.

Lameness scores assigned by each videotape reviewer are listed in Appendices 3(i) to 3(iii). Grading of lamenesses was consistent for each reviewer, although scores did vary slightly among reviewers. Lack of individual observer variance with viewing of duplicate videorecordings indicated that the grading scale was well-defined and that lamenesses were critically evaluated by each reviewer.

Median lameness grades used for statistical analysis are listed in Appendix 4. Lameness grades of control and treated groups are plotted against time in Appendix 15. Control horses remained grade 3 lame throughout the study period, indicating that neither the presence of the epidural catheter nor epidural injection of physiological saline had an

affect on lameness. The significant decline in observable lameness in treated horses by 1 hour after epidural morphine-detomidine injection, and failure to return to the original degree of lameness by 6 hours after injection, suggests that the epidural combination of morphine and detomidine was responsible for the dramatic improvement in hindlimb lameness. These results are consistent with reports in humans (Motsch et al, 1990; Eisenach, Rauck et al, 1989; Petit et al, 1989; Nalda and Gonzalez, 1986; Tamsen and Gordh, 1984) and dogs (Branson et al, 1993) that have demonstrated the potential for an epidural combination of morphine and an alpha 2 adrenergic agonist to provide potent analgesia.

A number of investigations have documented a synergistic interaction between morphine and alpha 2 adrenergic agonists in the modulation of pain transmission (Plummer et al, 1992; Omote et al, 1991; Ossipov et al, 1990; Ossipov et al, 1989; Sherman et al, 1988; Wilcox et al, 1987; Yaksh and Reddy, 1981). Whether or not a synergistic interaction occurred between morphine and detomidine in this study is unknown, as separate study groups for each epidural agent did not exist to enable comparison. However, our pilot studies did not reveal profound relief from hindlimb lameness with independent epidural injections of morphine or detomidine. These observations, in combination with findings of this study, suggest that some degree of interaction may occur between these two agents to initiate the profound clinical analgesia seen.

In horses, dermatomal and hindlimb analgesia associated with epidural morphine administration at a dosage of 0.1 mg/kg has been reported to occur as early as 20 minutes (Valverde et al, 1990) and as late as 6 hours (Robinson et al, 1994) after injection, and to last for periods ranging from 8 hours (Valverde et al, 1990) to 19 hours (Robinson et al, 1994). These findings correlate well with those that have been observed in humans following epidural morphine injection (Petit et al, 1989; Glynn et al, 1988; Rawal et al, 1982; Bromage et al, 1980), although duration following a single injection has been reported to be as long as 96 hours (Weddel and Ritter, 1991). Results of our

pilot studies demonstrated minimal analgesic efficacy of 0.1 mg/kg and 0.2 mg/kg epidural morphine during a 6 hour observation period on various types of induced hindlimb lameness in horses. These findings may have been a result of minimal drug effect on pain modulation or may have represented a prolonged (ie. greater than 6 hour) onset of action. Delay in onset of action and prolonged duration of analgesia are presumably related to morphine's hydrophilic nature, which slows uptake of the drug through the dura mater and hinders redistribution through the cerebrospinal fluid. In horses, onset and duration of analgesia have been suggested to be dose related (Robinson et al, 1994).

Perineal analgesia in horses after epidural injection of 60 ug/kg of detomidine has been reported to occur within 10 to 25 minutes of injection (Skarda and Muir 1994a; Skarda and Muir, 1992) and to last between 114 and 180 minutes (Skarda and Muir, 1994a; Skarda and Muir, 1992). Results of our pilot studies in horses with amphotericin B-induced synovitis demonstrated onset of analgesia within 5 to 15 minutes of epidural detomidine injection and a duration of 2.5 to 3 hours. Duration of analgesia following epidural injection of the alpha agonist, clonidine, has been reported to be dose dependent in both humans (Eisenach, Lysak et al, 1989) and sheep (Eisenach et al, 1987). As well, evidence exists to suggest that duration of analgesia may be dependent on the alpha adrenergic agonist administered (Skarda and Muir 1994b, Smith et al, 1992). The more rapid onset of analgesia and the shorter duration of action of epidural alpha 2 agonists, as compared to morphine, is most likely due to the lipophilic character of these agents and their ability to be quickly absorbed from the epidural space and redistributed through the cerebrospinal fluid and peripheral vasculature. In horses of this study, it is possible that detomidine was responsible for early onset of analgesia in treated horses, and that analgesic effects of morphine occurred later during the study to extend the duration of analgesia. This phenomenon could be one advantage to using an epidural morphine-detomidine combination for alleviation of pain. However, because morphine and detomidine were not administered as independent epidural treatments in this study, the

contribution of each drug to onset and duration of observed hindlimb analgesia is speculative.

Evaluation of lameness was conducted hourly for 6 hours after epidural injections. A 6 hour observation period was selected based on constraints with number of horses to be videotaped at each hour, as well as daylight limitations. At the end of Part 1, 7 of the 11 horses (2 control, 5 treated) were immediately entered into Part 2 of the study. These 7 horses received their second epidural injection (as part of the 14 day q 12 hour series) 12 hours after the first epidural injection, with the exception of 3 treated horses, whose second epidural morphine-detomidine injection was withheld until 24 hours after the first injection. The 4 horses from Part 1 which were not used for Part 2 (1 control, 3 treated) were used for surgical instruction laboratories between 4 days and 5 weeks after the conclusion of Part 1. Informal evaluation of lameness beyond Part 1 of the study in all 11 horses indicated that control horses remained grade 3 lame for an average of 7 to 10 days, after which time the left hindlimb lameness became less pronounced at a walk. None of the 3 horses whose second epidural morphine-detomidine injection was withheld for 24 hours were grade 3 lame at that time. Since control horses were still grade 3 lame 24 hours after epidural injection of saline, these informal observations suggest that synovitis-associated pain had not decreased and that epidural morphine and detomidine provided analgesia for up to 24 hours after injection. As well, none of the treated horses that were used in Part 1 but not in Part 2 (and therefore received no additional epidural morphine-detomidine injections) ever returned to a grade 3 lameness. This finding was unexpected and suggests that a single epidural injection may have extended analgesia for a period of time sufficient for synovitis-associated pain to noticeably diminish, which based on lameness observations of control horses may have been between 7 and 10 days. It is also conceivable that epidural administration of morphine and detomidine exerted an early anti-inflammatory effect which decreased the overall degree of tarsocrural synovitis that developed in treated horses and minimized the amount of pain that they experienced.

Although anti-inflammatory activity of epidural opioids and alpha 2 adrenergic agonists is not well documented, several characteristics of their mechanisms of action in pain modulation suggest that they also be involved in mediation of the inflammatory process. G protein-mediated effects, including inhibition of substance P release and decreased phospholipase A_2 production, may be involved.

Substance P is an 11 amino acid polypeptide neurotransmitter that is released from synaptic terminals of afferent fibers following peripheral nociceptive stimulation (Fields, 1987b). Elevated synovial fluid concentrations of substance P have been observed in both humans (Marshall et al, 1990) and horses (Caron et al, 1992) with arthropathies. In addition to serving as an excitatory neurotransmitter to propagate nociceptive impulses at the dorsal horn level, discharge of substance P from nerve fiber terminals is associated with release of histamine from mast cells and with production of cardinal signs of inflammation including vasodilation and edema (Fields et al, 1987b). Opioid (mu) and alpha 2 receptor coupling to the G_o protein has been shown to decrease calcium concentrations within afferent nerve fiber terminals (Nestler and Duman, 1994; Hescheler et al, 1987) and to reduce fusion of substance P-containing synaptic vesicles with synaptic cleft membranes (Daunt and Maze, 1992; Jessell and Kelly, 1991; Jessell and Dodd, 1989). The resulting decrease in substance P release following administration of morphine and alpha 2 adrenergic agonists may therefore not only disrupt pain transmission but may minimize clinical signs of inflammation as well. Evaluation of substance P concentrations in synovial fluid of horses both before and after epidural injection of morphine and detomidine may prove valuable in assessing effects of these drugs on release of this neurotransmitter at the joint level, as well as their potential involvement in anti-inflammatory mechanisms.

Phospholipase A_2 is the enzyme responsible for release of arachidonic acid from phospholipids in cell membranes following cellular injury. Within tissues, arachidonic acid is transformed into various inflammatory mediators, including prostaglandins, thromboxanes and leukotrienes. Decreased availability of phospholipase A_2 therefore

prohibits production of arachidonic acid and its subsequent conversion into mediators of inflammation. Corticosteroids are known to exert their effects early in the inflammatory cascade through inhibition of phospholipase A_2 activity (Kallings, 1993). Evidence also exists to suggest that inhibition of phospholipase A_2 may be mediated through receptor coupling with G_o or G_i proteins (Nestler and Duman, 1994). Since both opioid (mu) and alpha 2 adrenergic receptors are known to couple to these G proteins, it is possible that agonists such as morphine and detomidine may activate coupling of these receptors to the G protein involved and disrupt the inflammatory cascade at the same level as systemically administered corticosteroids.

Specific location, density and subtypes of opioid and alpha 2 adrenergic receptors have not been elucidated in horses, nor has the selectivity of morphine and detomidine for these receptors been investigated. Although several hypotheses have been extrapolated from human and animal studies, description of the actions and interactions of these epidural agents on pain modulation and inflammation in horses is speculative. Regardless of the mechanisms that may be involved, results from this study indicate that an epidural combination of an opioid such as morphine, with an alpha 2 adrenergic agonist such as detomidine, can induce profound hindlimb analgesia in horses, possibly as long as 24 hours or more after injection.

Heart and respiratory rate values of horses for Part 1 are listed in Appendices 5 and 6. There was a trend for heart and respiratory rates to initially decrease in treated horses and to increase in control horses after epidural injection. These trends are illustrated graphically in Appendices 16 and 17. Initial decrease in heart rates and respiratory rates of treated horses may have been a result of the analgesic effect of epidural morphine and detomidine. However, heart and respiratory rate values in treated horses eventually approached those of control horses. If this trend were linked to onset and duration of analgesia, it would seem that a similar trend would have been observed in lameness scores as well. In contrast to heart and respiratory rates, however, lameness scores in treated horses never approached those of control horses after epidural injection.

Therefore, it becomes difficult to explain initial decrease in heart and respiratory rates in treated horses based on analgesia alone.

Cardiopulmonary depression secondary to epidural detomidine injection may have participated in these observed trends in heart and respiratory rates. One study conducted in mares demonstrated a significant decrease in mean heart rate 5 minutes after epidural injection of 60 ug/kg detomidine, as well as a significant decrease in mean respiratory rate 15 minutes following injection (Skarda and Muir, 1994a). These cardiopulmonary effects are similar to the dose-dependent effects observed in horses after intravenous or intramuscular administration (Muir et al, 1992), and may be attributed to rapid redistribution of detomidine from the epidural space.

Initial increase in heart and respiratory rates in control horses may have been related to pain from the previous videorecording session or to anticipation of another videotaping experience. However, whereas heart and respiratory rates in control horses eventually decreased and approached those of treated horses, lameness scores remained consistently high. Therefore, it seems unlikely that initial increase in heart and respiratory rates was simply due to lack of analgesia. Initial apprehension of the videorecording process may have elevated heart and respiratory rates in all horses of the study, but was masked initially in treated horses by the cardiopulmonary effects of epidural detomidine. While the cause of the observed effects of epidural injection on heart and respiratory rates in this study may have occurred as a result of a combination of these or several undefined factors, it is important to note that these effects were transient.

Rapid redistribution of detomidine from the epidural space to brainstem sites was most likely responsible for apparent development of sedation in treated horses shortly after injection. While some horses developed signs of mild ataxia concurrent with sedation, all horses retained sufficient co-ordination to walk and trot at each videorecording session. Informal observations indicated dissipation of sedation and ataxia within 3 hours after epidural morphine-detomidine injection, while the analgesic effect

was maintained for at least 6 hours. This finding implies that epidural morphine-detomidine injection produced a modulatory effect on pain transmission and that the decrease in lameness scores of treated horses was not simply due to decreased awareness of pain.

Sedation was apparent in treated horses during Part 2 of the study following each epidural morphine-detomidine injection. Onset and duration of sedation did not appear to vary with continued injection over the 14 day period. No special precautions were necessary with treated horses following epidural morphine-detomidine injection. Haynets and water pails were left in the stalls at all times, and horses typically did not consume hay or water while sedated. No episodes of choke or recumbency occurred as a result of sedation. We have used an epidural morphine-detomidine combination in a small number of clinical cases of severe hindlimb lameness in horses and have found development of sedation to be an advantage for management of inciting injuries. Daily bandage changes, joint lavage or wound debridement is possible during periods of sedation with minimal stress and discomfort to patients. While judicious use of an epidural combination of morphine and detomidine would be advocated in an unsteady or depressed horse, sedation observed in horses of this study, as well as in clinical cases, was not considered to be an adverse complication and, in clinical cases, was therapeutically useful.

Daily parameters of all horses are listed in Appendices 8(i) to 8(xiv). Morning (am) and evening (pm) parameters of control and treated horses are individually plotted against time in Appendices 18 to 26. Average hay and water consumption by group are plotted against time in Appendices 28 to 29. No significant difference in body weight, temperature, heart rate, respiratory rate, gastrointestinal motility, hay or water consumption was noted between control and treated horses during 14 days of epidural treatment. Water consumption, expressed as a percentage of body weight, seemed higher on average for both groups of horses, but may have occurred secondary to the high ambient temperatures present during the study period. No clinical evidence of respiratory compromise, urinary retention, pruritus, abdominal discomfort or abnormal fecal output

was noted in either group of horses. Furthermore, gross and histologic examination of all organ systems did not reveal evidence of adverse systemic effects of long-term epidural morphine-detomidine administration. These findings indicate that long-term epidural morphine-detomidine administration had no apparent adverse systemic effects.

Short-term epidural administration of morphine and alpha 2 adrenergic agonists in humans and animals has been associated with various side effects including bradycardia, hypotension, respiratory depression, urinary retention, pruritus, nausea, vomiting, decreased gastrointestinal motility, sedation and tolerance. These effects, with the exception of tolerance, and respiratory depression in one case, have not been identified in humans or dogs treated with these agents for prolonged periods (Yaksh et al, 1994; Stamer and Maier, 1992; Hassenbusch et al, 1990; Driessen et al, 1989; Arner et al, 1988). Adaptation to side effects has been suggested to occur, and has been attributed to various factors including desensitization through previous oral or parenteral administration of the agents (Arner et al, 1988; Cousins and Mather, 1984; Zenz et al, 1981) and development of brain tolerance (Cousins and Mather, 1984). To our knowledge, none of the horses in this study had previously been exposed to regular opioid or alpha 2 agonist administration. Whether absence of systemic side effects in study horses was due to some form of adaptation or central tolerance over the 14 day observation period is unknown.

Certain post-mortem findings were attributed to either acute death (ex. pulmonary congestion) or age-related changes (ex. glomerulonephrosis, renal tubular necrosis, hepatic atrophy, hepatocellular vacuolation, bile duct hyperplasia). While either gastric erosion or ulceration was identified in all control and in five of seven treated horses in Part 2 of the study, the presence of gastric erosions or ulcers in horses prior to the onset of the study was not determined. As erosions or ulcers were present in both control and treatment horses, their development was probably not linked to long-term administration of epidural morphine-detomidine. As well, it is unlikely that the presence of epidural catheters was responsible for ulcer development. While emotional stress has been

implicated as an important cause of ulcers in both humans and horses, studies in humans have indicated that there is no relationship between psychological stress and development of gastric ulcers (Feldman and Sabovich, 1980). Research has shown that horses on pasture which are brought into stall confinement frequently develop gastric lesions within one week, even though free-choice hay is available (Murray, 1996; Sellnow, 1996). It is thought that because stalled horses spend less time eating, there are periods of time when the stomach is empty, and hydrochloric acid may contact both glandular and nonglandular regions of the stomach and induce lesions (Murray, 1996). Eight of the 10 horses in Part 2 of the study were known to have been on pasture prior to commencement of the project. Therefore, stall confinement may have played a role in inducing gastric erosion or ulcer formation in horses of this study.

In all horses, cerebrospinal fluid cultures were negative for bacteriologic growth. These results correlate with those of human studies that have documented a low incidence of infection associated with indwelling epidural catheters (DeJong and Kansen, 1994; Crul and Delhaas, 1991; Plummer et al, 1991; Driessen et al, 1989; Meier et al, 1982). Catheter-related infections in humans are most often localized to the skin and subcutaneous tissues at the catheter insertion point (DeJong and Kansen, 1994; Crul and Delhaas, 1991; Plummer et al, 1991; Driessen et al, 1989). Although the skin and subcutaneous tissues surrounding the catheter entry site of horses in Part 2 of the study were not cultured, clinical evidence of infection was not observed.

Cerebrospinal fluid parameters for all horses are listed in Appendix 9. Median values for all groups are listed in Appendix 10. There was a trend for cerebrospinal fluid red blood cell counts to be higher in horses with epidural catheters when compared to uncatheterized horses. In 1 treatment horse, the cerebrospinal fluid red blood cell count was markedly higher than in all other horses. The cerebrospinal fluid obtained from this horse at necropsy did not grossly appear abnormal, and the cause for such a high red blood cell count is unknown. Cerebral trauma at the time of euthanasia or laboratory error may have been contributing factors. Because a non-parametric test using ranks for

analysis was used to compare cerebrospinal fluid values between groups of horses, the test was not sensitive to outliers, and this horse was therefore not responsible for the observed trend in cerebrospinal fluid red blood cell counts between catheterized and uncatheterized horses.

Some degree of hemorrhage was identified in the epidural space of lumbosacral and sacral regions and catheter entry point sites in catheterized horses. In goats receiving a daily injection of saline through an epidural catheter for 8 days, occasional focal hemorrhages were evident in the epidural space (Larsen et al, 1986). Similarly, epidural hemorrhage was documented in guinea pigs within 2 days of placement of nylon epidural catheters (Edwards et al, 1986). However, studies in various other species have not reported the development of hemorrhage as a consequence of epidural catheterization or injection, regardless of the type of catheter used or the agent administered (Coombs et al, 1994; Yaksh et al, 1994; Madsen et al, 1993; Crul and Delhaas, 1991; Edwards et al, 1986; Kytta et al, 1986; King et al, 1984; Meier et al, 1982). Epidural hemorrhage in control and treated horses of this study may have occurred as a result of trauma induced by either the needle or catheter at the time of insertion. Epidural hemorrhage may also have originated from continued local tissue disruption caused by the volume of agents administered, which was an average of 8 mL per injection.

Problems associated with long-term catheter maintenance in humans have included dislocation, catheter obstruction with injection resistance, leakage of injectate and pain on injection (DeJong and Kansen, 1994; Buscher and Chedel, 1992; Crul and Delhaas, 1991; Plummer et al, 1991; Ready et al, 1991; Driessen et al, 1989). None of these complications were encountered in horses of this study. It is possible that the 14 day observation period was short enough that such problems did not develop. A retrospective study of human patients showed that technical complications associated with epidural catheters were minimal for the first 20 days after placement, but that the complication rate rose to 55 percent of patients between days 20 and 366 of treatment (Crul and Delhaas, 1991). It is unknown whether technical complications would have occurred in

horses had epidural catheters been maintained for longer than 14 days.

Spinal tissue segment inflammation and fibrosis grades for all horses are listed in Appendices 11 and 13. Median values for all groups are given in Appendices 12 and 14. The presence of significantly higher lumbosacral and sacral inflammation grades and sacral segment fibrosis grades in epidurally catheterized horses, in conjunction with a significant elevation in cerebrospinal fluid protein concentrations, is consistent with the development of epidural inflammation and fibrosis related to catheterization. Since no significant difference in these values was observed between control and treated horses, inflammation and fibrosis did not likely develop as a result of epidural morphine-detomidine administration. Studies in humans and animals have shown that chronically implanted epidural catheters can produce a fibrous reaction in the epidural space in the region of the catheter (Coombs et al, 1994; Yaksh et al, 1994; Madsen et al, 1993; Cherry and Gourlay, 1992; Edwards et al, 1986; Kytta et al, 1986; Larsen et al, 1986; Edwards et al, 1985; Gordh et al, 1984; Meier et al, 1982). Although epidural fibrosis has been cited as the cause of technical complications associated with long-term epidural catheter maintenance (DeJong and Kansen, 1994; Crul and Delhaas, 1991; Plummer et al, 1991; Arner et al, 1988), such complications were not evident in catheterized horses of this study despite the development of epidural fibrosis.

The type of epidural catheter used has been implicated as an inciting factor in the development of epidural inflammation and fibrosis (Crul and Delhaas, 1991). Catheter stiffness and catheter surface characteristics, including smoothness, antigenicity and release of degradation products or plasticizers, have been suggested to play a role in tissue response within the epidural space (Coombs et al, 1994). Polytetrafluoroethylene (Teflon[R]) epidural catheters were used in this study as they were rigid enough to permit advancement to the lumbosacral region. Studies examining incidence of jugular vein inflammation and thrombus formation associated with various catheter materials have shown teflon catheters to induce more inflammation than the softer silastic, polyurethane, nylon or polyvinyl chloride catheters (Spurlock and Spurlock, 1990; Spurlock et al,

1990). While epidural fibrosis was observed with teflon catheters in this study, epidural fibrosis has also been documented after use of nylon (Edwards et al, 1986; Kytta et al, 1986), polyamide (Larsen et al, 1986), polyethylene (Yaksh et al, 1994), polyurethane (Cherry and Gourlay, 1992), polyvinyl chloride (Lebeaux, 1973), silicone rubber (Silastic[R]) (Meier et al, 1982) and hydrogel elastomer blend (Coombs et al, 1994) catheters. Whether degree of epidural inflammation and fibrosis observed in catheterized horses of this study would have been less marked with use of a different type of catheter is unknown.

Presence of preservatives or low pH of injected solutions have also been cited as causative factors in the development of epidural fibrosis (Crul and Delhaas, 1991). The morphine sulfate solution used in this study had a pH ranging from 2.5 to 6.5, and contained the preservatives sodium formaldehyde sulfoxylate and phenol. The detomidine hydrochloride solution used had a pH of between 4.0 and 5.5, and contained the preservative methylparaben. Investigators have advocated the use of additive-free solutions with a pH of approximately 5.5 for epidural injections (Crul and Delhaas, 1991). However, development of epidural fibrosis in animals receiving preservative-free physiological saline solutions (Madsen et al, 1993; Edwards et al, 1986; Kytta et al, 1986), including the control horses of this study, make it unlikely that the character of injected solutions contributes significantly to the development of epidural fibrosis.

Epidural catheters were advanced to the lumbosacral junction from their point of entry into the epidural space in all horses to eliminate variables that may have affected craniad flow of injectate. The most noticeable histologic signs of inflammation and fibrosis occurred in spinal tissue segments in which the catheter was located. A report in the human literature has recommended that the tip of the epidural catheter not be advanced more rostrally than necessary for the desired segmental analgesic cover (Chrubasik et al, 1993). Effective epidural morphine analgesia to the thorax has been documented from caudal injections without the use of large injection volumes or catheter advancement (Rosen and Rosen, 1989). Therefore, extent of local epidural inflammation

and fibrosis may be decreased by leaving the catheter tip near its point of entry into the epidural space. However, whether analgesia to the equine hindlimb would be possible from such a caudal location is unknown.

The significance of localized epidural inflammation and fibrosis has yet to be determined. Although the presence of epidural fibrous tissue has been shown to cause local deformation of the spinal cord (Coombs et al, 1994; Madsen et al, 1993; Cherry and Gourlay, 1992; Driessen et al, 1989; Edwards et al, 1986; Gordh et al, 1984) and stretching of the dorsal roots in some species (Edwards et al, 1986), horses of this study did not exhibit similar changes on histologic examination of epidural tissues, nor did they display clinical neurological deficits related to development of inflammation and fibrosis. Furthermore, technical complications were not encountered secondary to epidural inflammation and fibrosis. In a study conducted in pigs evaluating effects of continuous epidural administration of bupivicaine, morphine and saline, epidural catheters were left in place for 7 days (Kytta et al, 1986). In 2 pigs, epidural catheters were removed at the end of 7 days and the pigs were allowed to recover for 3 weeks. Histologic examination of the epidural space after the 3 week recovery period was normal with the exception of minimal inflammation at the catheter tip site in one pig. It is therefore possible that the inflammatory reaction attributable to the presence of an epidural catheter would subside after catheter removal, making the development of epidural inflammation and fibrosis significant only as an impediment to long-term catheter maintenance. The significance of adhesions between the epidural catheter and the cauda equina in one treated horse in this study is unknown.

Results of this study demonstrated that an epidural combination of morphine and detomidine provided profound analgesia for acute hindlimb pain in horses. Long-term administration of a morphine-detomidine combination did not appear to produce adverse systemic effects in horses, nor did long-term epidural administration of this combination of drugs result in toxic effects on the epidural tissues. Localized inflammation and fibrosis appeared to be catheter related, and produced no complications clinically.

Placement of an epidural catheter is an easily learned technique that could facilitate administration of morphine and detomidine to horses on a long-term basis for treatment of serious musculoskeletal disorders, while avoiding side effects that could develop with chronic use of high doses of nonsteroidal anti-inflammatory drugs. However, before this combination can be recommended for routine clinical use, several issues must be addressed. First, dose-response studies are necessary to determine appropriate dosages of each agent necessary to produce acceptable analgesia, as well as the dosing interval required to make this epidural combination applicable in a clinical setting. Second, efficacy of this combination of agents for forelimb pain, as well as for different types of acute and chronic musculoskeletal pain, requires evaluation. Third, while inflammation, fibrosis and occasional hemorrhage have been shown to occur in tissues in proximity to long-dwelling epidural catheters, further studies are required to determine the cause and significance of these catheter-related changes.

> "...ailments will at times baffle the most skilled veterinarian, and leave our burden bearing servants to succumb to the inevitable, and suffer and perish in unrelieved distress" (Liautard, 1903).

It was with this thought in mind that we were prompted to conduct the studies reported here. Results of this study suggest that long-term epidural catheterization and epidural morphine-detomidine administration may be clinically applicable for the treatment of severe, chronic musculoskeletal pain in horses. It is hoped that these findings may in some way make a small contribution to the vast field of equine analgesia and stimulate further research into this ongoing and sometimes overlooked subject.

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APPENDICES

Appendix 1. Horse Identification Chart

Horse Name	Study Part Number	Group Assignment	Clinic Number	Cytology Number	Histopathology Number
Countess Petite	1	C	03 66 13	/	/
Bones	1,2	C	03 51 43	94-2810	94-2818
Blue Barflower	1,2	C	03 53 26	94-3556	94-3564
Ramerigo	1,2	T	03 50 93	94-2755	94-2781
Dallsitter	1,2	T	03 51 44	94-2811	94-2820
Covert	1,2	T	03 52 15	94-2868	94-2874
Heart's Ransom	1,2	T	03 52 14	94-2866	94-2875
Sheaf	1,2	T	03 51 94	94-2863	94-2876
Snowball	1	T	03 65 37	/	/
Dajera's Delight	1	T	03 65 11	/	/
Maverick	1	T	03 52 61	/	/
Sally	2	C	01 71 19	94-2754	94-2782
Blue	2	T	03 24 50	94-275	94-2780
Gay Racine	2	T	03 51 42	94-2791[a]	94-2819
Mickey	2	U (CSF)	03 75 94	95-790	/
Notorg	2	U (CSF)	03 79 28	95-1182	/
Night Watch	2	U (CSF)	03 82 58	95-1053	/
Impressive Gal	2	U (ST)	03 74 01	/	94-5319
Larry	2	U (ST)	03 72 92	/	94-5279
Star Created Skip	2	U (ST)	03 08 55	/	94-5251

C = control group (epidural saline)

T = treated group (epidural morphine + detomidine)

U = uncatheterized group

CSF = cerebrospinal fluid collection only

ST = spinal tissue segment collection only

[a] antemortem lumbosacral cerebrospinal fluid collection

Appendix 2. Signalment Data

Horse	Age (years)	Breed	Sex	Initial Weight (kg)	Reason for Donation// Elective Euthanasia
Countess Petite	15	TB	F	455	Reproductive cull
Bones	5	TB	F	512	Reproductive cull
Blue Barflower	13	QH	MC	532	Blindness
Ramerigo	18	TB	F	427	Reproductive cull
Dallsitter	17	TB	F	527	Reproductive cull
Covert	17	TB	F	536	Reproductive cull
Heart's Ransom	7	TB	F	450	Reproductive cull
Sheaf	16	TB	F	495	Reproductive cull
Snowball	23	APP	F	530	Blindness
Dajera's Delight	23	TB	F	435	Chronic weight loss
Maverick	15	TB	MC	514	Behavior
Sally	17	QHX	F	484	Old age
Blue	11	TWH	F	417	Behavior
Gay Racine	12	TB	F	469	Reproductive cull
Mickey[a]	7	TB	MC	540	Chronic colic
Notorg[a]	18	TB	F	511	P_3 osteomyelitis
Night Watch[a]	20	TB	MC	600	Old age
Impressive Gal[b]	7	QH	F	432	Large colon torsion
Larry[b]	18	TB	F	/	Chronic lameness
Star Created Skip[b]	6	QH	M	534	Chronic subsolar abscessation

TB = Thoroughbred
QH = Quarter Horse
APP = Appaloosa
TWH = Tennessee Walking Horse
X = mixed breed

F = female
M = intact male
MC = castrated male

[a] cerebrospinal fluid collection only
[b] spinal tissue segment collection only

Appendix 3 (i). Part 1: Investigator 1 Lameness Score Data (0-4)

Horse	Group	T_0	T_1	T_2	T_3	T_4	T_5	T_6
Countess Petite	C	3	3 (3)[a]	3	3	3	3	3
Bones	C	3	3	3	3	3	3	3
Blue Barflower	C	3 (3)	3	3	3	3	3	3
Ramerigo	T	3	0	0	0	0	0	0
Dallsitter	T	3	0	0 (0)	0	0	0	0
Covert	T	3	0	0	0	0 (0)	0	0
Heart's Ransom	T	3	0	0	0	0	0 (0)	0
Sheaf	T	3	0	0	0	0	0	0 (0)
Snowball	T	3	0	0	1	1	1	1 (1)
Dajera's Delight	T	3	2	2	2	2	2	2
Maverick	T	3	0	1 (1)	1	2	1	1

T_0 = baseline prior to epidural injection
T_1 = 1 hour following epidural injection; T_2 = 2 hours following epidural injection, etc.

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)

0 = no evident lameness
1 = not lame at the walk but recognizably lame at the trot
2 = altered gait present at the walk and obviously lame at the trot
3 = obviously lame at both the walk and trot
4 = nonweight-bearing lame

[a] values in parentheses represent lameness scores assigned to randomly duplicated video recordings

Appendix 3 (ii). Part 1: Investigator 2 Lameness Score Data (0-4)

Horse	Group	T_0	T_1	T_2	T_3	T_4	T_5	T_6
Countess Petite	C	3	3 (3)[a]	3	3	3	3	3
Bones	C	3	3	3	3	3	3	3
Blue Barflower	C	3 (3)	3	3	3	3	3	3
Ramerigo	T	3	0	0	0	0	0	0
Dallsitter	T	3	0	0 (0)	0	0	1	0
Covert	T	3	0	0	1	0 (0)	0	0
Heart's Ransom	T	3	0	0	0	0	0 (0)	0
Sheaf	T	3	0	1	0	0	0	0 (0)
Snowball	T	3	0	1	1	1	1	1 (1)
Dajera's Delight	T	3	1	1	1	1	1	1
Maverick	T	3	0	2 (2)	2	2	2	2

T_0 = baseline prior to epidural injection
T_1 = 1 hour following epidural injection; T_2 = 2 hours following epidural injection, etc.

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)

0 = no evident lameness
1 = not lame at the walk but recognizably lame at the trot
2 = altered gait present at the walk and obviously lame at the trot
3 = obviously lame at both the walk and trot
4 = nonweight-bearing lame

[a] values in parentheses represent lameness scores assigned to randomly duplicated video recordings

Appendix 3 (iii). Part 1: Investigator 3 Lameness Score Data (0-4)

Horse	Group	T_0	T_1	T_2	T_3	T_4	T_5	T_6
Countess Petite	C	3	3 (3)[a]	3	3	3	3	3
Bones	C	3	3	3	3	3	3	3
Blue Barflower	C	3 (3)	3	2	3	3	2	2
Ramerigo	T	1	1	1	1	1	0	0
Dallsitter	T	2	1	0 (0)	0	1	1	1
Covert	T	3	0	0	1	0 (0)	0	0
Heart's Ransom	T	3	0	0	0	1	0 (0)	0
Sheaf	T	3	2	1	0	0	1	1 (1)
Snowball	T	3	0	2	2	2	2	2 (2)
Dajera's Delight	T	3	1	2	2	2	2	2
Maverick	T	3	0	2 (2)	2	2	2	2

T_0 = baseline prior to epidural injection
T_1 = 1 hour following epidural injection; T_2 = 2 hours following epidural injection, etc.

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)

0 = no evident lameness
1 = not lame at the walk but recognizably lame at the trot
2 = altered gait present at the walk and obviously lame at the trot
3 = obviously lame at both the walk and trot
4 = nonweight-bearing lame

[a] values in parentheses represent lameness scores assigned to randomly duplicated video recordings

Appendix 4. Part 1: Median Lameness Grade Data (0-4)

Horse	Group	T_0	T_1	T_2	T_3	T_4	T_5	T_6
Countess Petite	C	3	3	3	3	3	3	3
Bones	C	3	3	3	3	3	3	3
Blue Barflower	C	3	3	3	3	3	3	3
Ramerigo	T	3	0	0	0	0	0	0
Dallsitter	T	3	0	0	0	0	1	0
Covert	T	3	0	0	1	0	0	0
Heart's Ransom	T	3	0	0	0	0	0	0
Sheaf	T	3	0	0	0	0	0	0
Snowball	T	3	0	1	1	1	1	1
Dajera's Delight	T	3	1	2	2	2	2	2
Maverick	T	3	0	2	2	2	2	2

T_0 = baseline prior to epidural injection
T_1 = 1 hour following epidural injection; T_2 = 2 hours following epidural injection, etc.

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)

0 = no evident lameness
1 = not lame at the walk but recognizably lame at the trot
2 = altered gait present at the walk and obviously lame at the trot
3 = obviously lame at both the walk and trot
4 = nonweight-bearing lame

Appendix 5. Part 1: Heart Rate Data (beats/minute)

Horse	Group	T_0	T_1	T_2	T_3	T_4	T_5	T_6
Countess Petite	C	48	54	56	58	48	52	56
Bones	C	52	52	44	52	48	52	50
Blue Barflower	C	68	80	76	76	60	72	72
Ramerigo	T	46	40	42	60	36	60	60
Dallsitter	T	44	28	36	36	40	40	44
Covert	T	40	40	40	36	44	44	44
Heart's Ransom	T	48	32	40	40	40	46	48
Sheaf	T	44	36	32	36	40	40	40
Snowball	T	60	52	52	50	48	56	56
Dajera's Delight	T	56	56	46	54	48	80	56
Maverick	T	40	32	44	44	44	44	48

T_0 = baseline prior to epidural injection
T_1 = 1 hour following epidural injection; T_2 = 2 hours following epidural injection, etc.

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)

Appendix 6. Part 1: Respiratory Rate Data (breaths/minute)

Horse	Group	T_0	T_1	T_2	T_3	T_4	T_5	T_6
Countess Petite	C	8	28	28	40	32	28	40
Bones	C	16	60	40	36	54	40	42
Blue Barflower	C	32	28	24	12	16	24	28
Ramerigo	T	20	12	8	12	16	32	12
Dallsitter	T	14	16	40	24	36	24	48
Covert	T	20	28	8	8	8	8	16
Heart's Ransom	T	36	20	10	8	12	24	44
Sheaf	T	36	8	12	8	12	12	24
Snowball	T	48[a]	40	32	20	12	16	20
Dajera's Delight	T	12	12	12	12	8	12	12
Maverick	T	28	20	20	16	8	8	24

T_0 = baseline prior to epidural injection
T_1 = 1 hour following epidural injection; T_2 = 2 hours following epidural injection, etc.

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)

[a] respiratory rate at 17 minutes post epidural injection = 100 bpm; respiratory rate at 33 minutes post injection = 56 bpm

Appendix 7. Part 2: Body Weight Data (kg)

Horse	Group	Day 1 Body Weight	Day 14 Body Weight	Average Body Weight	Body Weight Change
Bones	C	512	500	506	-12
Blue Barflower	C	532	507	520	-25
Sally	C	484	470	477	-14
Ramerigo	T	427	400	414	-27
Dallsitter	T	527	477	502	-50
Covert	T	536	514	525	-22
Heart's Ransom	T	450	441	446	-9
Sheaf	T	495	457	476	-38
Blue	T	417	404	411	-13
Gay Racine	T	469	453	461	-16

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)

Appendix 8 (i). Part 2: Day 1 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	39.0	39.0	52	50	16	42	0+0+2+2 4	1+1+1+1 4	7 1.3	29 2.6
Blue Barflower	C	38.8	38.3	68	72	32	28	2+2+2+2 8	2+2+2+2 8	8 1.5	17 1.5
Sally	C	37.6	38.2	42	60	12	24	/	1+2+1+2 6	7 1.4	49 4.7
Ramerigo	T	37.2	38.5	46	42	20	26	/	2+2+2+2 8	11 2.6	48 5.3
Dallsitter	T	38.2	38.0	44	44	14	48	1+1+2+2 6	1+2+2+2 7	5 1.1	/
Covert	T	36.7	38.0	40	44	20	16	2+2+0+2 6	2+2+2+2 8	8 1.6	47 4.1
Heart's Ransom	T	38.3	38.6	48	48	36	44	1+2+1+1 5	2+2+2+2 8	7 1.6	28 2.9
Sheaf	T	38.1	37.8	44	40	36	24	2+2+2+1 7	2+2+1+2 7	7 1.5	39 3.7
Blue	T	37.4	38.9	42	48	36	64	/	1+2+2+2 7	5 1.3	43 4.8
Gay Racine	T	37.7	39.0	56	60	16	36	0+1+1+2 4	2+2+2+2 8	5 1.2	36 3.6

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm): RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (ii). Part 2: Day 2 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	38.0	37.7	36	36	16	20	2+2+2+2 8	2+2+2+2 8	10 2.0	48 4.3
Blue Barflower	C	37.8	38.6	48	54	24	32	2+2+2+2 8	2+2+2+2 8	9 1.8	28 2.5
Sally	C	37.4	37.9	40	48	14	12	1+2+1+2 6	1+1+1+2 5	13 2.8	40 3.8
Ramerigo	T	37.3	38.2	48	72	16	40	2+2+1+2 7	3+2+2+2 9	10 2.3	38 4.2
Dallsitter	T	37.4	36.9	36	44	16	60	2+2+2+2 8	2+2+2+2 8	5 1.0	36 3.3
Covert	T	37.0	37.4	36	36	16	8	1+2+2+2 7	/	10 1.9	50 4.3
Heart's Ransom	T	37.7	37.7	36	36	20	10	2+1+2+2 7	/	5 1.0	31 3.2
Sheaf	T	38.1	37.8	36	40	36	8	2+2+1+2 7	/	5 1.0	39 3.7
Blue	T	37.6	38.2	45	48	14	46	1+2+2+2 7	2+2+2+2 8	7 1.7	38 4.0
Gay Racine	T	38.0	37.3	42	40	14	40	1+2+1+3 7	1+1+1+2 5	4 0.8	36 3.7

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (iii). Part 2: Day 3 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	38.1	38.2	44	36	20	28	1+2+2+2 7	2+2+1+1 6	12 1.6	33 3.0
Blue Barflower	C	38.1	38.0	40	48	12	18	2+2+2+2 8	2+2+2+2 8	8 1.8	15 1.3
Sally	C	37.2	37.5	48	48	14	20	2+2+2+2 8	1+1+2+2 6	9 2.6	42 4.0
Ramerigo	T	37.8	38.1	48	60	14	52	2+2+2+2 8	2+1+2+2 7	11 2.6	41 4.5
Dallsitter	T	37.7	37.8	36	40	10	40	2+2+1+2 7	1+1+1+1 4	7 1.4	48 4.3
Covert	T	37.7	37.5	36	32	16	24	1+0+0+1 2	1+2+2+2 7	9 1.6	46 4.0
Heart's Ransom	T	38.2	38.2	36	32	40	36	1+2+2+2 7	2+2+2+2 8	9 2.0	35 3.6
Sheaf	T	37.9	37.7	36	40	12	16	1+1+2+2 6	2+2+2+2 8	9 1.8	46 4.4
Blue	T	37.5	38.0	48	52	20	48	2+2+2+2 8	1+1+2+2 6	8 1.9	40 4.4
Gay Racine	T	37.9	38.2	44	40	10	22	1+2+1+1 5	2+2+2+2 8	8 1.8	31 3.1

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (iv). Part 2: Day 4 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.6	37.9	48	42	12	12	2+1+2+2 7	2+2+2+2 8	14 2.8	50 4.5
Blue Barflower	C	37.8	38.1	44	48	12	/	2+2+2+2 8	2+2+2+2 8	9 1.7	33 2.9
Sally	C	36.8	37.5	40	44	14	16	1+1+2+2 6	2+2+2+2 8	10 2.0	32 3.0
Ramerigo	T	37.6	37.7	44	48	16	40	1+1+2+2 6	2+1+2+2 7	9 2.2	30 3.3
Dallsitter	T	37.5	37.8	40	76	18	34	1+1+1+2 5	1+1+2+1 5	5 1.1	53 4.8
Covert	T	38.2	38.0	36	36	16	12	1+2+1+2 6	0+1+1+2 4	7 1.4	34 2.9
Heart's Ransom	T	37.7	38.2	36	44	24	20	1+2+2+2 7	0+1+1+2 4	7 1.5	29 3.0
Sheaf	T	38.1	38.2	36	44	12	20	1+1+2+2 6	2+2+2+2 8	8 1.7	42 4.0
Blue	T	38.0	38.0	42	46	44	60	1+2+1+1 5	2+2+2+2 8	9 2.1	32 3.5
Gay Racine	T	/	38.1	48	52	18	42	1+1+1+1 4	2+2+2+2 8	8 1.8	38 3.7

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (v). Part 2: Day 5 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.0	37.8	36	40	10	12	2+2+2+2 8	2+2+2+2 8	12 2.4	47 4.2
Blue Barflower	C	38.0	38.1	40	48	10	36	2+2+2+2 8	2+2+2+2 8	10 2.0	26 2.3
Sally	C	37.6	37.8	42	42	10	18	1+2+1+2 6	1+1+1+2 5	7 1.5	37 3.5
Ramerigo	T	37.6	38.1	48	52	26	39	2+2+2+2 8	2+2+2+2 8	11 2.6	40 4.4
Dallsitter	T	37.0	37.6	28	36	6	8	/	1+2+2+2 7	5 0.9	46 4.2
Covert	T	37.5	37.8	48	32	24	24	1+1+2+2 6	1+1+2+2 6	15 2.9	51 4.4
Heart's Ransom	T	38.1	37.7	40	44	16	36	1+1+1+2 5	1+2+2+2 7	8 1.8	24 2.4
Sheaf	T	38.1	38.0	32	36	40	36	1+1+2+2 6	2+2+2+2 8	7 1.5	44 4.2
Blue	T	37.6	38.2	46	50	30	44	2+2+1+2 7	2+2+2+2 8	10 2.4	28 3.1
Gay Racine	T	37.2	37.6	40	36	8	10	/	1+1+0+0 2	8 1.8	31 3.1

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (vi). Part 2: Day 6 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.4	37.7	40	36	16	24	2+2+2+2 8	1+2+2+2 7	13 2.5	44 4.0
Blue Barflower	C	37.7	37.9	46	48	20	24	1+2+2+2 7	1+2+2+2 7	8 1.6	26 2.3
Sally	C	37.3	37.6	42	40	16	24	1+1+2+2 6	2+2+2+2 8	12 2.6	44 4.2
Ramerigo	T	37.8	37.8	54	50	28	24	2+2+2+2 8	2+2+2+2 8	10 2.4	36 4.0
Dallsitter	T	37.3	36.9	34	36	8	16	1+1+1+1 4	1+2+1+2 6	7 1.4	52 4.7
Covert	T	37.7	37.8	32	36	16	42	1+1+0+2 4	0+2+2+2 6	9 1.7	26 2.3
Heart's Ransom	T	37.9	37.8	36	36	28	20	1+2+2+2 7	1+2+2+2 7	9 2.0	32 3.3
Sheaf	T	38.2	37.8	36	44	16	36	1+1+2+2 6	2+1+2+2 7	8 1.7	51 4.9
Blue	T	37.9	37.6	42	48	22	48	1+2+2+1 6	1+1+2+2 6	12 3.0	35 3.9
Gay Racine	T	36.9	37.8	36	36	12	20	1+2+1+2 6	1+2+2+2 7	10 2.2	35 3.5

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (vii). Part 2: Day 7 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.4	37.4	36	36	12	20	2+2+2+2 8	2+2+2+2 8	12 2.4	58 5.2
Blue Barflower	C	37.4	37.8	40	40	12	12	2+2+2+2 8	2+2+2+2 8	9 1.7	20 1.8
Sally	C	37.2	37.6	44	40	12	8	1+1+1+2 5	2+2+2+2 8	15 3.0	33 3.1
Ramerigo	T	37.1	37.8	40	44	24	14	/	2+2+2+2 8	16 2.6	36 4.0
Dallsitter	T	37.3	37.1	36	44	8	12	1+2+2+2 7	1+2+1+2 6	6 1.2	38 3.4
Covert	T	37.0	38.0	28	40	12	32	1+1+1+2 5	1+2+2+2 7	11 2.1	56 4.8
Heart's Ransom	T	37.9	37.8	32	36	28	64	0+1+2+2 5	1+1+1+1 4	5 1.2	28 2.9
Sheaf	T	38.7	38.6	36	40	20	36	0+1+1+1 3	1+2+2+2 7	7 1.4	34 3.2
Blue	T	37.6	37.8	40	36	21	10	/	2+2+2+2 8	12 2.9	33 3.7
Gay Racine	T	36.8	37.3	36	40	10	12	2+2+2+2 8	2+2+2+2 8	10 2.1	34 3.4

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (viii). Part 2: Day 8 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.6	37.6	40	36	20	20	2+2+1+1 6	/	12 2.4	47 4.2
Blue Barflower	C	37.5	37.7	42	40	16	24	2+2+2+2 8	2+2+2+2 8	10 1.9	41 3.6
Sally	C	37.3	37.1	36	36	20	24	2+2+2+2 8	1+2+0+2 5	11 2.4	31 3.0
Ramerigo	T	37.2	37.1	36	40	12	28	2+2+2+2 8	1+1+2+2 7	8 2.0	43 4.7
Dallsitter	T	37.7	37.3	36	40	20	32	2+1+2+2 7	/	6 1.3	46 4.1
Covert	T	37.4	37.3	40	32	16	12	1+2+2+2 7	1+1+2+2 6	9 1.7	46 4.0
Heart's Ransom	T	37.8	37.7	36	36	12	16	0+2+2+2 6	1+2+1+2 6	8 1.8	42 4.3
Sheaf	T	38.0	38.1	36	36	8	16	1+1+2+2 6	2+2+2+2 8	7 1.5	41 3.9
Blue	T	37.7	38.0	36	40	8	28	1+2+2+2 7	1+1+2+2 6	7 1.7	35 3.9
Gay Racine	T	37.7	37.8	36	40	16	20	1+2+1+2 6	/	9 1.9	28 2.8

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (ix). Part 2: Day 9 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.4	37.4	36	36	12	20	1+2+2+2 7	2+2+2+2 8	14 2.7	51 4.6
Blue Barflower	C	37.6	37.9	40	36	22	24	1+1+2+2 6	2+2+2+2 8	10 1.9	31 2.7
Sally	C	37.2	37.6	38	48	12	20	2+2+1+2 7	2+2+2+2 8	16 3.4	52 5.0
Ramerigo	T	37.1	37.7	36	40	10	56	2+2+2+1 7	2+2+2+2 8	13 3.1	34 3.7
Dallsitter	T	37.2	37.4	32	36	20	24	2+2+2+2 8	1+2+2+2 7	5 0.9	41 3.7
Covert	T	37.2	38.1	36	40	12	48	/	1+1+1+1 4	6 1.2	32 2.8
Heart's Ransom	T	37.8	37.9	32	36	32	32	/	2+2+2+2 8	3 0.7	36 3.7
Sheaf	T	37.7	38.0	42	36	10	40	/	2+1+1+2 6	5 1.1	30 2.9
Blue	T	37.5	38.0	36	44	12	36	2+2+2+2 8	2+2+2+2 8	15 3.8	30 3.3
Gay Racine	T	37.5	37.6	36	40	12	12	1+2+1+2 6	1+2+2+2 7	10 2.3	41 4.0

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (x). Part 2: Day 10 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.2	38.0	32	44	12	20	2+2+2+2 8	2+2+2+2 8	7 1.4	37 3.3
Blue Barflower	C	37.7	/	42	/	16	/	2+2+2+2 8	/	11 2.2	31 2.7
Sally	C	37.2	37.5	40	36	24	8	2+2+2+2 8	/	10 2.2	39 3.7
Ramerigo	T	37.5	37.5	36	40	20	24	2+1+2+2 7	/	12 2.9	34 3.7
Dallsitter	T	37.7	37.6	40	44	12	16	1+2+1+2 6	0+1+2+2 5	5 0.9	50 4.5
Covert	T	36.7	37.6	33	38	15	24	1+2+2+2 7	2+2+2+2 8	11 2.1	47 4.1
Heart's Ransom	T	37.7	37.7	33	45	16	54	2+2+2+3 9	1+2+2+2 7	9 2.0	34 3.5
Sheaf	T	37.5	38.1	30	44	15	40	2+2+2+2 8	2+2+2+2 8	12 2.6	41 3.9
Blue	T	37.6	37.7	40	40	20	44	2+2+2+2 8	/	10 2.4	31 3.4
Gay Racine	T	37.8	38.4	36	44	12	16	2+2+1+1 6	2+2+2+2 8	10 2.2	35 3.5

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (xi). Part 2: Day 11 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.6	37.7	44	42	16	20	2+2+2+2 8	2+2+2+2 8	9 1.7	36 3.2
Blue Barflower	C	37.3	38.1	36	42	16	28	2+2+2+2 8	2+2+2+2 8	11 2.2	28 2.5
Sally	C	37.5	37.6	36	44	12	20	1+1+2+2 6	1+2+2+2 7	13 2.7	46 4.4
Ramerigo	T	37.2	37.7	36	36	9	16	2+2+2+2 8	1+2+2+2 7	9 2.1	26 2.9
Dallsitter	T	37.5	37.6	36	44	20	40	0+1+1+1 3	1+2+2+2 7	5 0.9	37 3.3
Covert	T	36.6	37.9	36	45	16	25	2+2+2+2 8	2+2+2+2 8	12 2.3	54 4.7
Heart's Ransom	T	37.3	/	34	/	18	/	2+2+2+2 8	1+2+2+2 7	8 1.8	29 3.0
Sheaf	T	37.4	37.5	36	45	9	50	2+2+2+2 8	2+2+2+2 8	7 1.5	34 3.2
Blue	T	37.7	37.7	36	36	20	28	2+2+2+2 8	2+2+2+2 8	9 2.2	28 3.1
Gay Racine	T	37.5	37.8	36	36	14	16	1+1+1+2 5	1+1+2+2 6	7 1.6	33 3.3

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (xii). Part 2: Day 12 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.8	37.4	48	40	16	20	2+2+2+2 8	2+2+2+2 8	9 1.8	42 3.8
Blue Barflower	C	37.7	38.2	36	46	12	16	1+2+2+2 7	2+2+2+2 8	10 2.0	28 2.5
Sally	C	37.3	37.6	44	44	12	16	1+2+2+2 7	1+2+2+2 7	10 2.0	49 4.7
Ramerigo	T	37.0	38.0	36	44	12	36	2+2+2+2 8	2+2+2+2 8	12 3.0	50 5.5
Dallsitter	T	37.9	37.7	44	36	12	40	1+2+1+2 6	2+2+2+2 8	5 1.1	44 4.0
Covert	T	37.0	38.3	36	40	12	36	2+2+2+2 8	2+2+2+2 8	11 2.2	32 2.8
Heart's Ransom	T	37.3	38.0	36	44	16	24	2+2+2+2 8	2+2+2+2 8	12 2.7	49 5.0
Sheaf	T	37.6	38.1	36	46	16	51	2+2+2+2 8	2+2+2+2 8	9 1.9	33 3.2
Blue	T	37.4	37.7	32	40	16	20	2+2+2+2 8	2+2+2+2 8	10 2.3	36 4.0
Gay Racine	T	37.1	37.8	48	40	16	20	1+2+1+2 6	1+1+2+2 6	9 2.0	47 4.6

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (xiii). Part 2: Day 13 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.4	37.4	36	32	24	40	0+2+1+2 5	2+2+2+2 8	12 2.3	41 3.7
Blue Barflower	C	37.6	37.8	40	44	12	12	2+2+2+2 8	2+2+2+2 8	12 2.3	28 2.5
Sally	C	37.5	37.6	42	36	14	20	2+2+1+2 7	2+2+2+2 8	11 2.4	55 5.2
Ramerigo	T	37.6	37.8	40	44	16	24	3+2+2+2 9	2+2+2+2 8	11 2.7	36 4.0
Dallsitter	T	37.0	37.6	40	36	20	28	0+2+1+2 5	2+2+1+2 7	6 1.2	41 3.7
Covert	T	37.0	38.7	32	40	12	16	1+2+2+2 7	1+2+1+2 6	7 1.4	24 2.1
Heart's Ransom	T	38.0	38.4	36	36	12	16	1+2+2+2 7	1+2+2+2 7	7 1.6	28 2.9
Sheaf	T	37.6	38.2	40	40	12	16	2+2+2+2 8	1+2+2+2 7	6 1.2	29 2.8
Blue	T	37.3	37.5	40	40	12	48	2+2+2+2 8	2+2+2+2 8	9 2.2	30 3.3
Gay Racine	T	37.8	37.4	36	32	20	24	1+1+1+2 5	1+2+2+2 7	8 1.7	28 2.8

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 8 (xiv). Part 2: Day 14 Parameters

Horse	Group	Ta	Tp	HRa	HRp	RRa	RRp	GMa	GMp	Hay	Water
Bones	C	37.1	37.3	36	40	12	20	2+2+2+2 8	2+2+2+2 8	14 2.8	42 3.8
Blue Barflower	C	37.6	38.1	36	40	16	20	2+2+2+2 8	2+2+2+2 8	11 2.1	26 2.3
Sally	C	37.3	37.5	42	44	16	24	1+2+1+1 5	2+2+2+2 8	11 2.3	56 5.3
Ramerigo	T	37.6	37.3	46	44	14	24	2+2+2+2 8	2+2+2+2 8	9 2.1	41 4.5
Dallsitter	T	37.0	37.0	36	36	8	12	1+2+1+2 6	1+2+1+2 6	5 1.1	28 2.5
Covert	T	37.8	38.1	36	40	20	32	2+2+2+2 8	2+2+2+2 8	13 2.4	59 5.1
Heart's Ransom	T	38.1	38.3	32	40	12	32	1+2+2+3 8	2+2+2+2 8	10 2.2	41 4.2
Sheaf	T	37.9	37.4	40	36	24	20	1+2+2+3 8	2+2+1+2 7	9 1.9	35 3.3
Blue	T	37.4	37.6	44	36	14	44	2+2+2+2 8	2+2+2+2 8	8 1.9	34 3.8
Gay Racine	T	37.7	37.7	36	36	12	12	1+2+2+2 7	2+2+2+2 8	12 2.7	36 3.6

C = control group (epidural saline); T = treated group (epidural morphine + detomidine); Ta = am temperature (°C); Tp = pm temperature (°C); HRa = am heart rate (bpm); HRp = pm heart rate (bpm); RRa = am respiratory rate (bpm); RRp = pm respiratory rate (bpm); GMa = am gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; GMp = pm gastrointestinal motility scores from left ventral, left dorsal, right dorsal, and right ventral abdominal quadrants (0-3) and cumulative grade; Hay = pounds of hay consumed and pounds of hay consumed as a percentage of average body weight; Water = liters of water consumed and liters of water consumed as a percentage of average body weight

Appendix 9. Part 2: Atlanto-Occipital Cerebrospinal Fluid Data

Horse	Group	White Blood Cells (cells/μl)	Red Blood Cells (cells/μl)	Protein (mg/dl)	Glucose (mg/dl)
Bones	C	2	3	71	44
Blue Barflower	C	1	0	58	53
Sally[a]	C	/	/	7600	88
Ramerigo	T	1	0	48	47
Dallsitter	T	0	2780	207	52
Covert	T	1	1	74	45
Heart's Ransom	T	11	58	65	53
Sheaf	T	3	25	69	47
Blue	T	25	131	69	55
Gay Racine[b]	T	2	11	56	60
Mickey	U	0	0	46	64
Notorg	U	0	0	39	49
Night Watch	U	5	1	55	52

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)
U = uncatheterized group

[a] iatrogenic hemorrhage induced at time of cerebrospinal fluid aspiration; cell counts not possible
[b] antemortem lumbosacral cerebrospinal fluid collection

Appendix 10. Part 2: Median Atlanto-Occipital Cerebrospinal Fluid Data

Group	White blood cells (cells/µl)	Red blood cells (cells/µl)	Protein (mg/dl)	Glucose (mg/dl)
C (n=2)	1.5	1.5	64.5	48.5
T (n=7)	2.0	25.0	69.0	52.0
C + T (n=9)	2.0	11.0	69.0	52.0
U (n=3)	0	0	46.0	52.0

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)
C + T = catheterized group (pooled values for control + treated horses)
U = uncatheterized group

Appendix 11. Part 2: Spinal Tissue Segment Inflammation Grades (0-3)

Horse	Group	Spinal Tissue Segments				
		Cervio-thoracic	Thoraco-lumbar	Lumbo-sacral	Sacral	Catheter Entry Point
Bones	C	0	1	1	2	1
Blue Barflower	C	1	0	1	1	3
Sally	C	0	0	2	3	2
Ramerigo	T	1	0	2	3	0
Dallsitter	T	0	1	3	3	1
Covert	T	1	1	3	3	2
Heart's Ransom	T	1	0	2	2	3
Sheaf	T	0	0	2	2	3
Blue	T	0	0	0	1	2
Gay Racine	T	1	0	1	1	0
Impressive Gal	U	0	0	0	0	/
Larry	U	0	0	0	0	/
Star Created Skip	U	0	0	0	0	/

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)
U = uncatheterized group

0 = no evidence of inflammation
1 = mild inflammation (few scattered nucleated cells)
2 = moderate inflammation (occasional presence of nucleated cells)
3 = diffuse inflammation (nucleated cells consistently present throughout the section)

Appendix 12. Part 2: Median Spinal Tissue Segment Inflammation Grades (0-3)

Group	Spinal Tissue Segments				
	Cervicothoracic	Thoracolumbar	Lumbosacral	Sacral	Catheter Entry Point
C (n=3)	0	0	1	2	2
T (n=7)	1	0	2	2	2
C + T (n=10)	0.5	0	2	2	2
U (n=3)	0	0	0	0	/

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)
C + T = catheterized group (pooled grades for control + treated horses)
U = uncatheterized group

0 = no evidence of inflammation
1 = mild inflammation (few scattered nucleated cells)
2 = moderate inflammation (occasional presence of nucleated cells)
3 = diffuse inflammation (nucleated cells consistently present throughout the section)

Appendix 13. Part 2: Spinal Tissue Segment Fibrosis Grades (0-3)

Horse	Group	Spinal Tissue Segments				
		Cervio-thoracic	Thoraco-lumbar	Lumbo-sacral	Sacral	Catheter Entry Point
Bones	C	0	0	1	0	1
Blue Barflower	C	0	0	0	0	2
Sally	C	0	0	2	3	3
Ramerigo	T	1	0	2	2	0
Dallsitter	T	0	1	2	2	2
Covert	T	0	0	1	2	3
Heart's Ransom	T	0	0	2	2	3
Sheaf	T	0	0	2	2	3
Blue	T	0	0	0	0	2
Gay Racine	T	0	0	0	1	2
Impressive Gal	U	0	0	0	0	/
Larry	U	0	0	0	0	/
Star Created Skip	U	0	0	1	0	/

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)
U = uncatheterized group

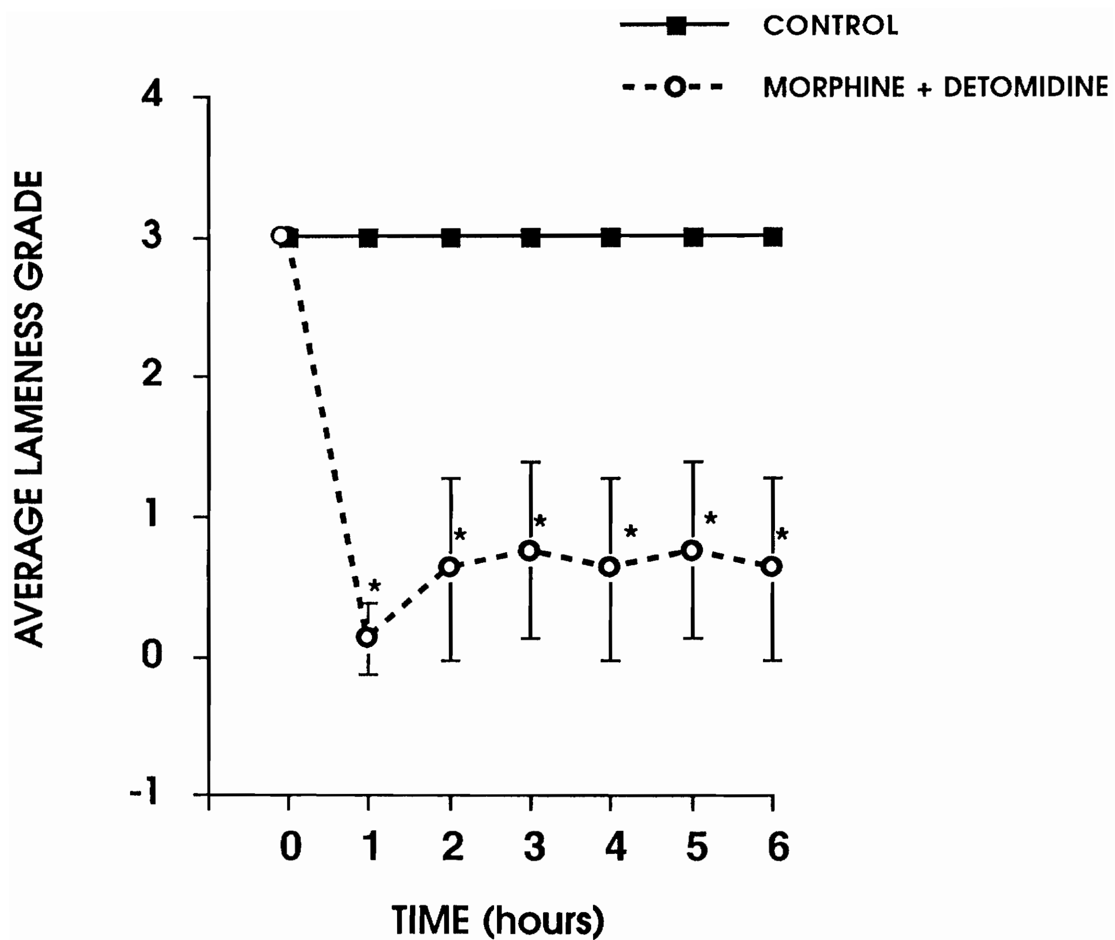
0 = no evidence of fibrosis
1 = mild fibrosis (small focus of fibroblastic activity)
2 = moderate fibrosis (scattered, focally intense areas of fibrous tissue production)
3 = severe, diffuse fibrosis

Appendix 14. Part 2: Median Spinal Tissue Segment Fibrosis Grades (0-3)

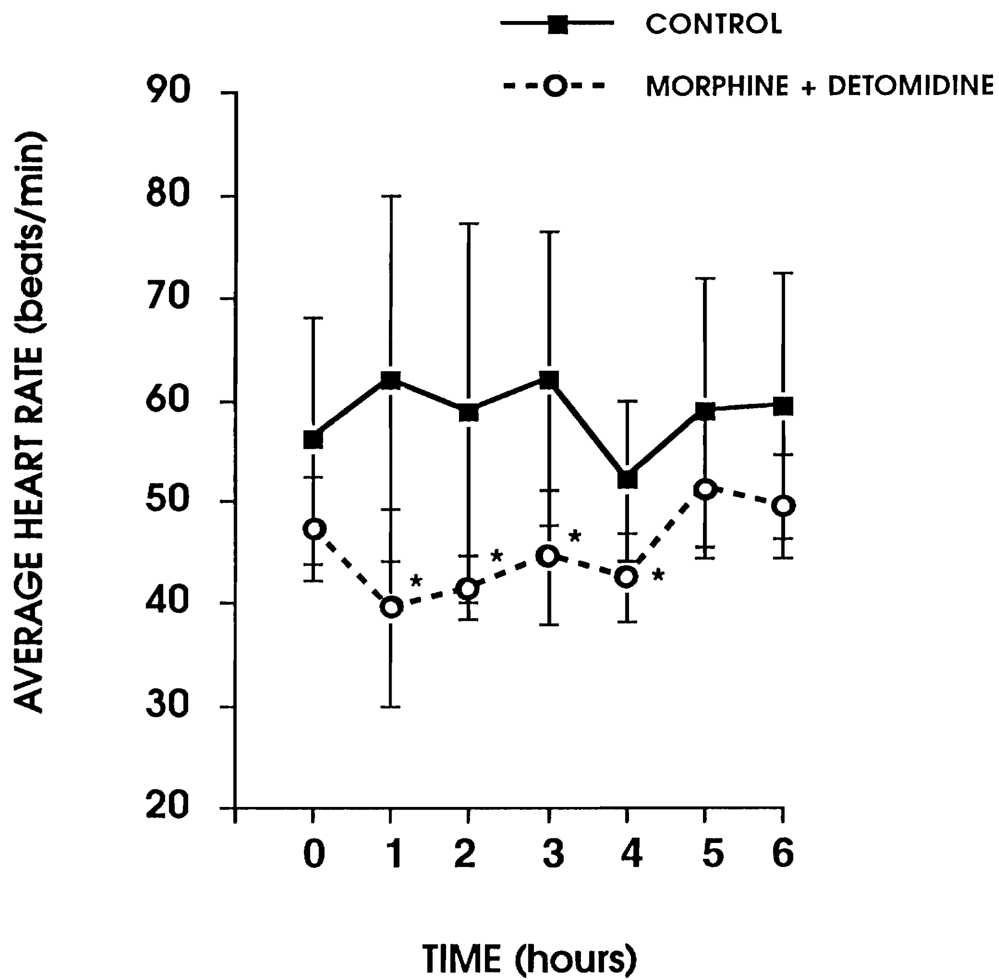
Group	Spinal Tissue Segments				
	Cervicothoracic	Thoracolumbar	Lumbosacral	Sacral	Catheter Entry Point
C (n=3)	0	0	1	0	2
T (n=7)	0	0	2	2	2
C + T (n=10)	0	0	1.5	2	2
U (n=3)	0	0	0	0	/

C = control group (epidural saline)
T = treated group (epidural morphine + detomidine)
C + T = catheterized group (pooled grades for control + treated horses)
U = uncatheterized group

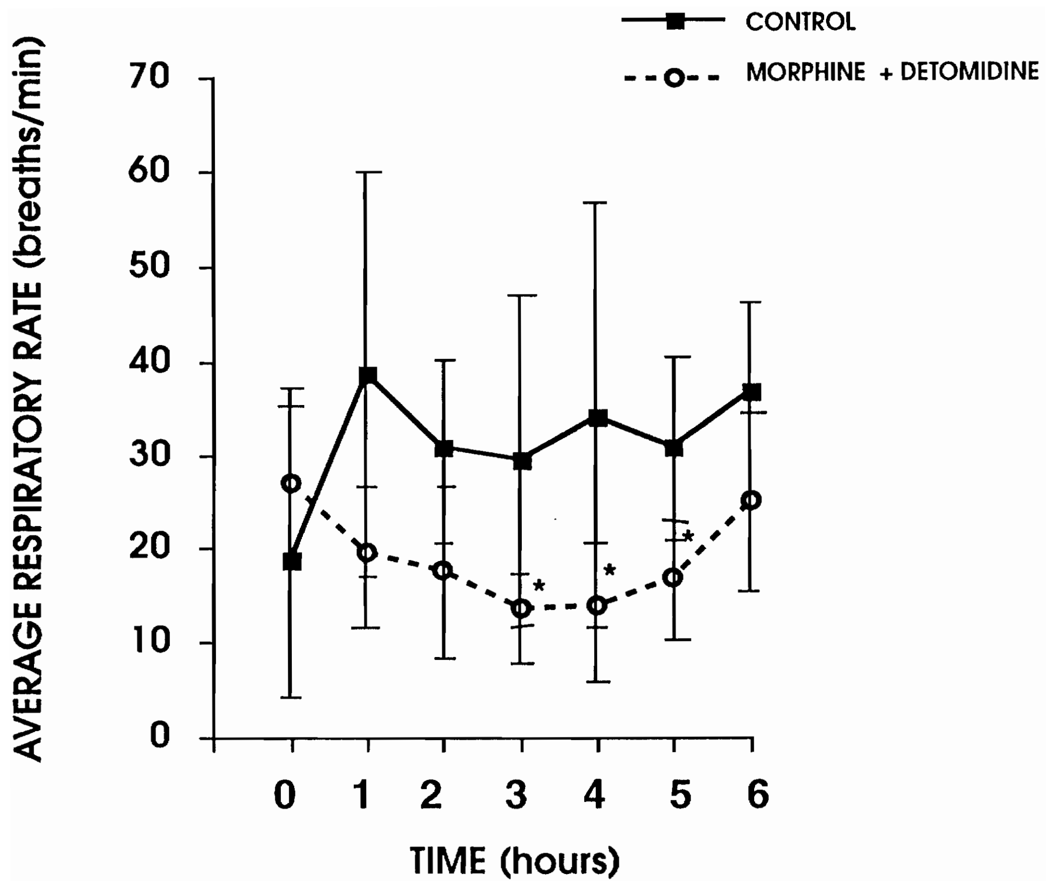
0 = no evidence of fibrosis
1 = mild fibrosis (small focus of fibroblastic activity)
2 = moderate fibrosis (scattered, focally intense areas of fibrous tissue production)
3 = severe, diffuse fibrosis



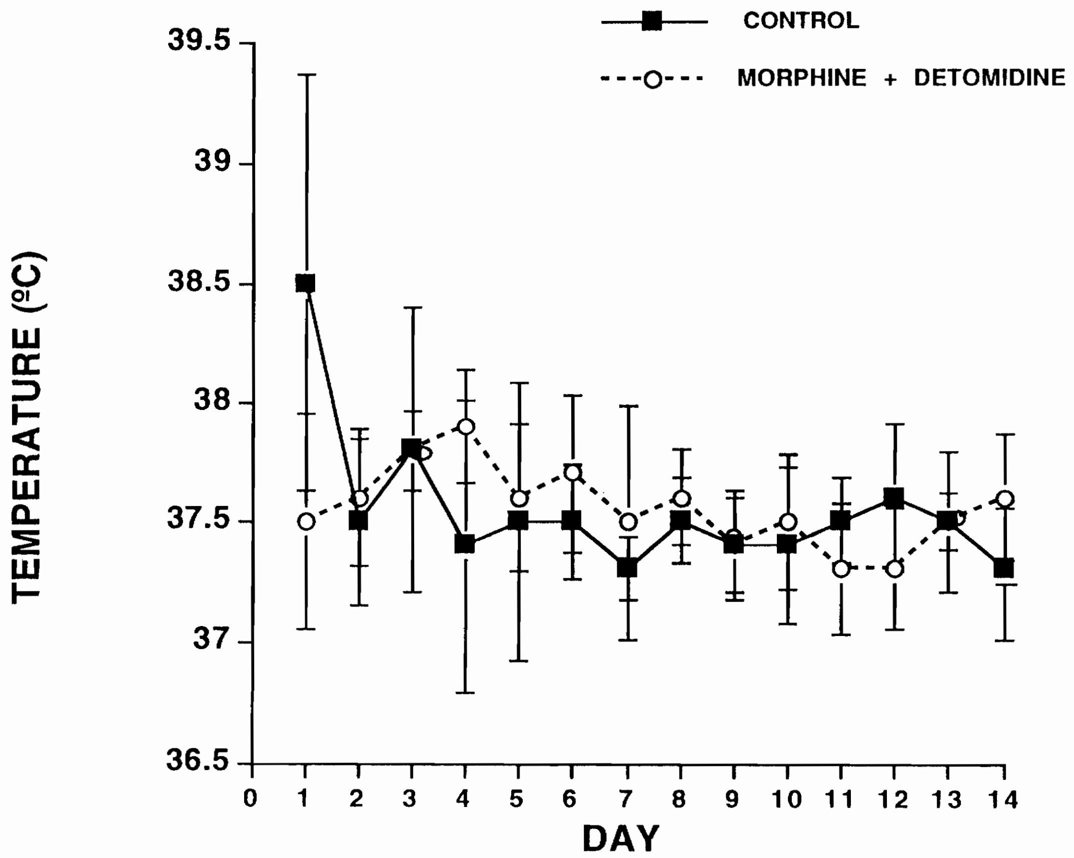
Appendix 15. Part 1: Average Lameness Grade



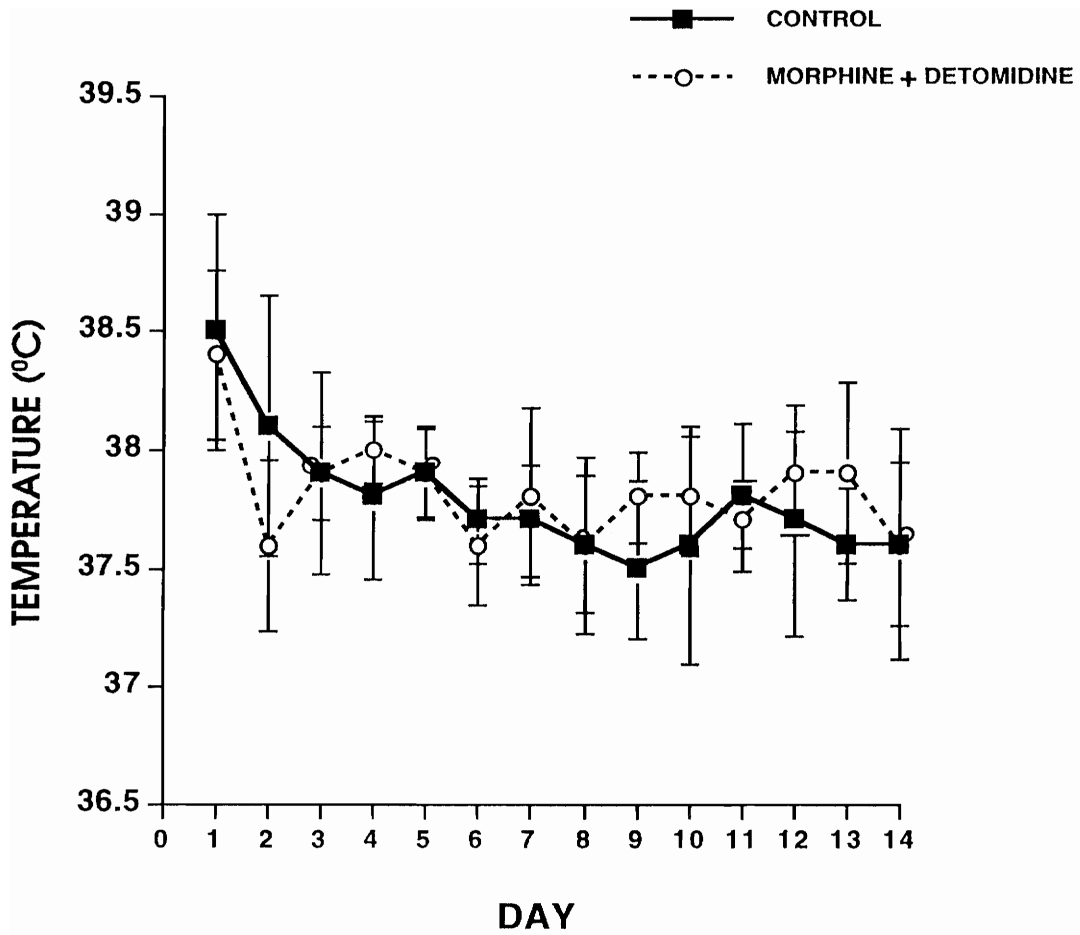
Appendix 16. Part 1: Average Heart Rate



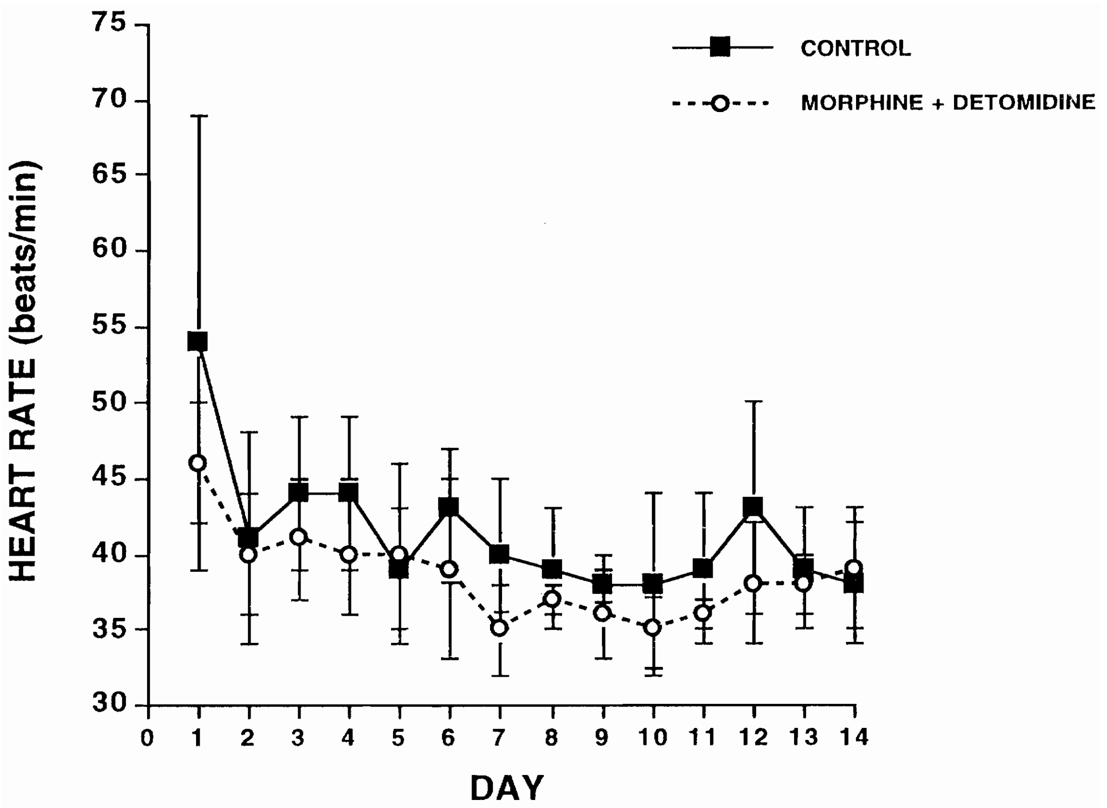
Appendix 17. Part 1: Average Respiratory Rate



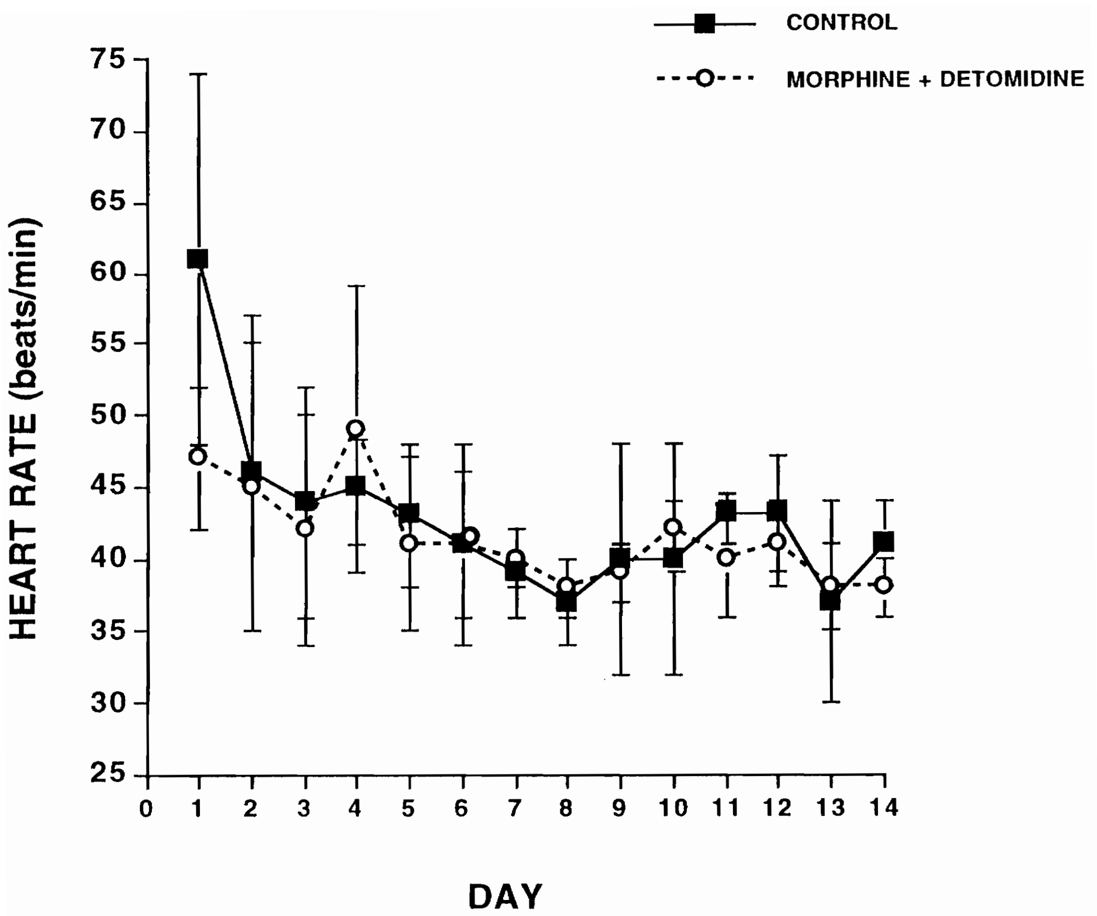
Appendix 18. Part 2: Average Daily AM Temperature



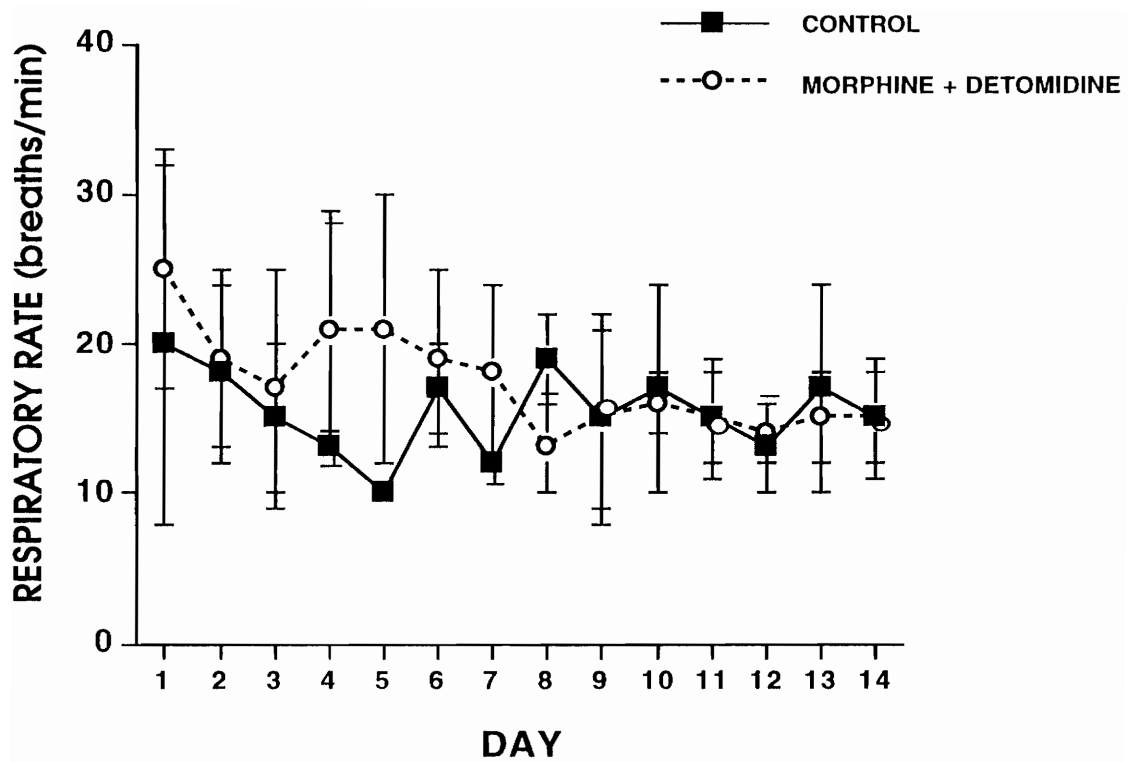
Appendix 19. Part 2: Average Daily PM Temperature



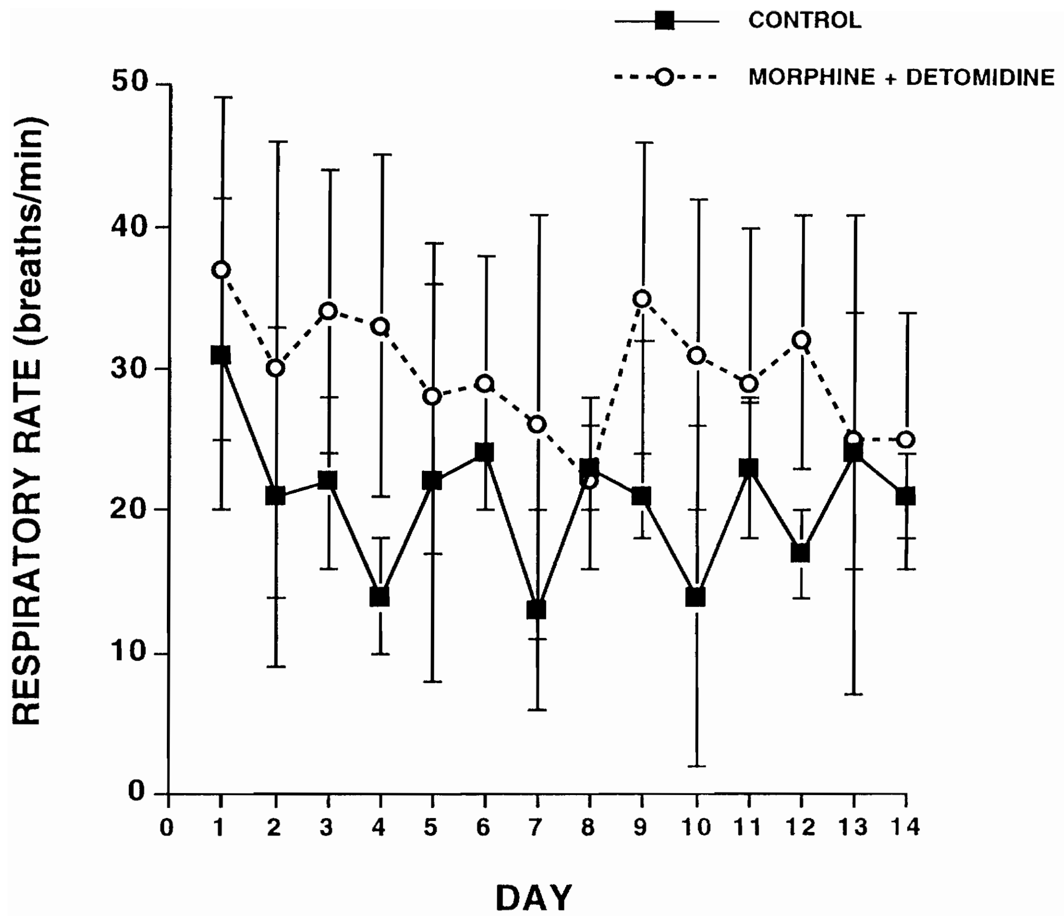
Appendix 20. Part 2: Average Daily AM Heart Rate



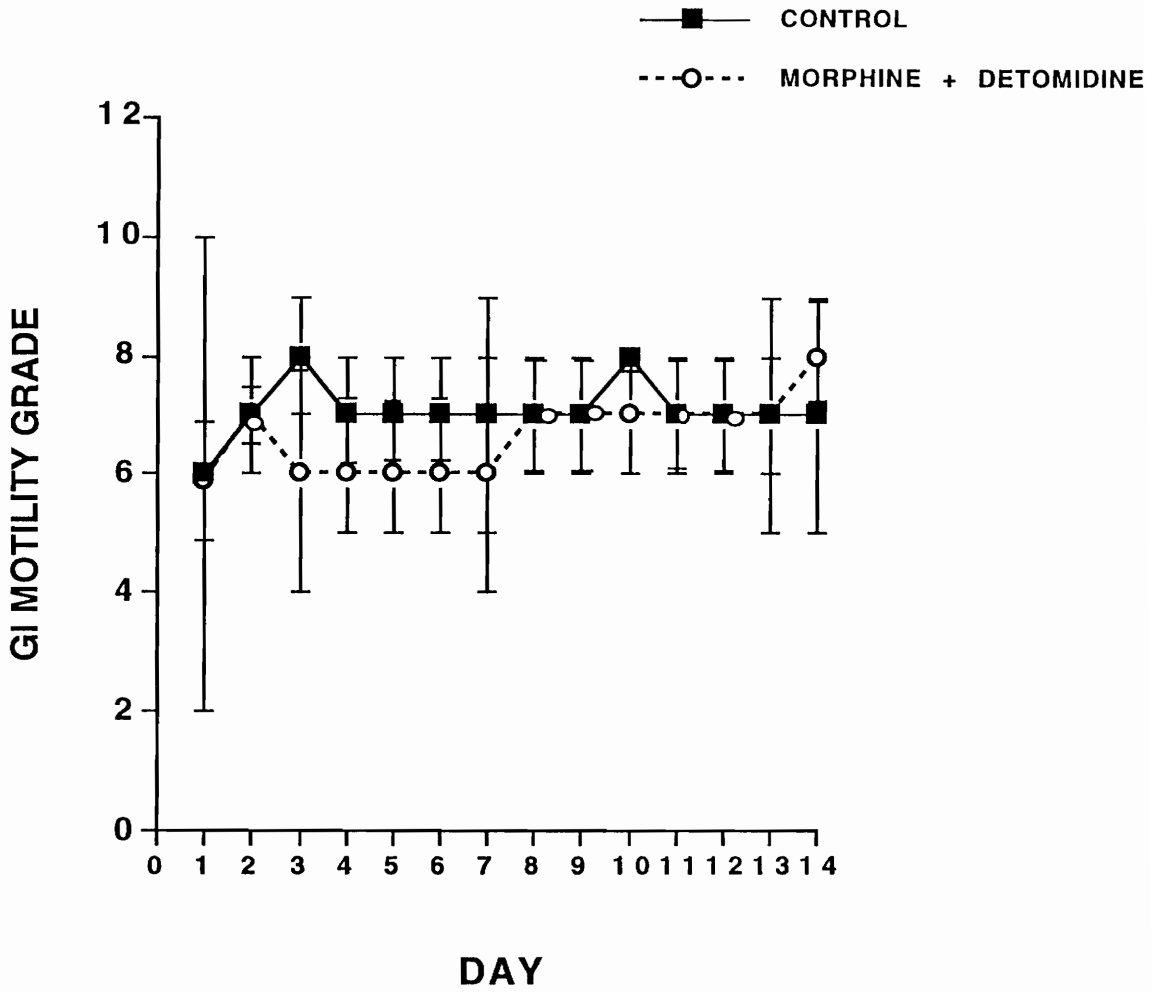
Appendix 21. Part 2: Average Daily PM Heart Rate



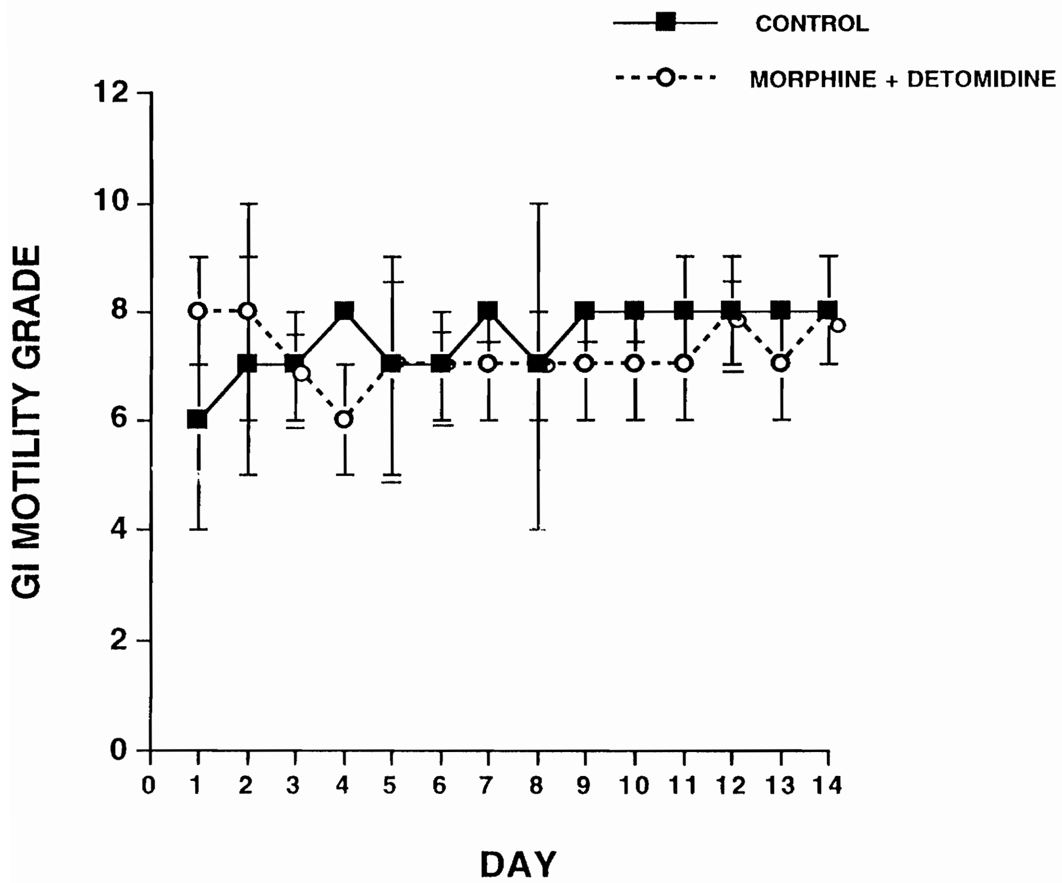
Appendix 22. Part 2: Average Daily AM Respiratory Rate



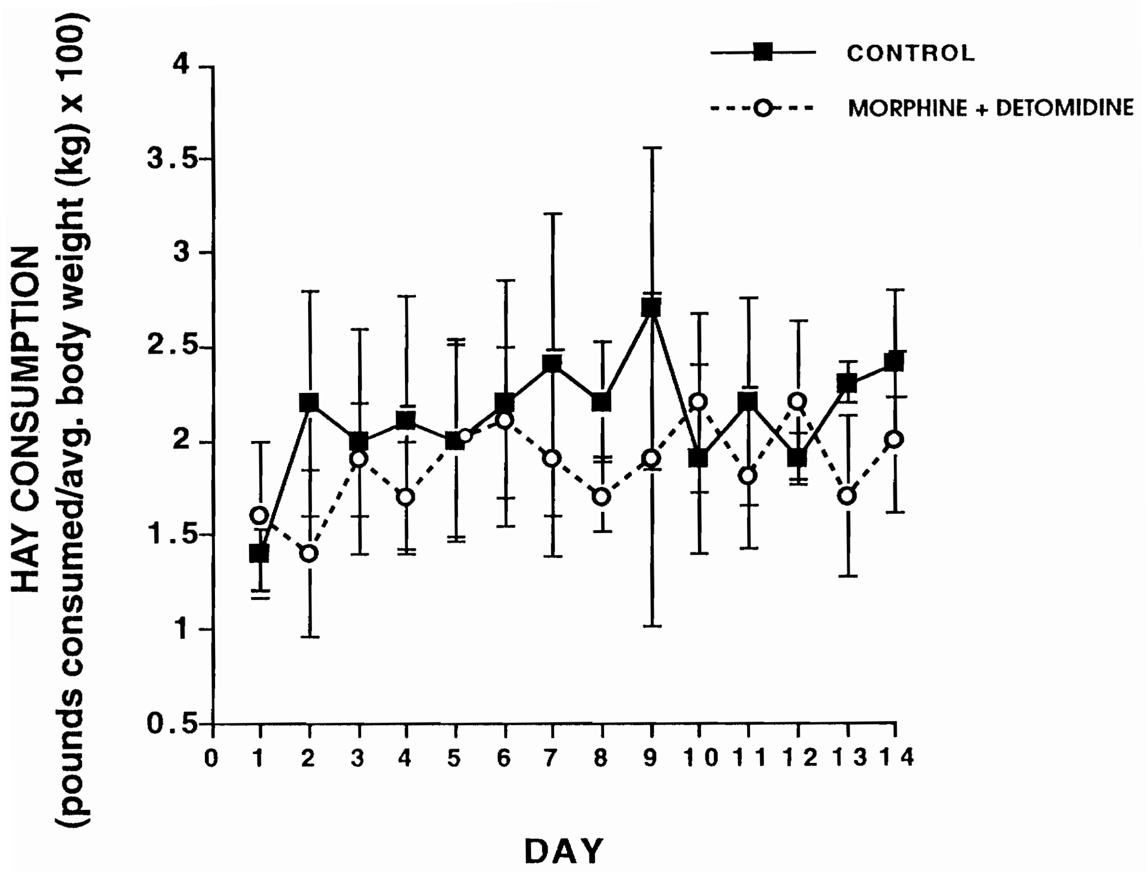
Appendix 23. Part 2: Average Daily PM Respiratory Rate



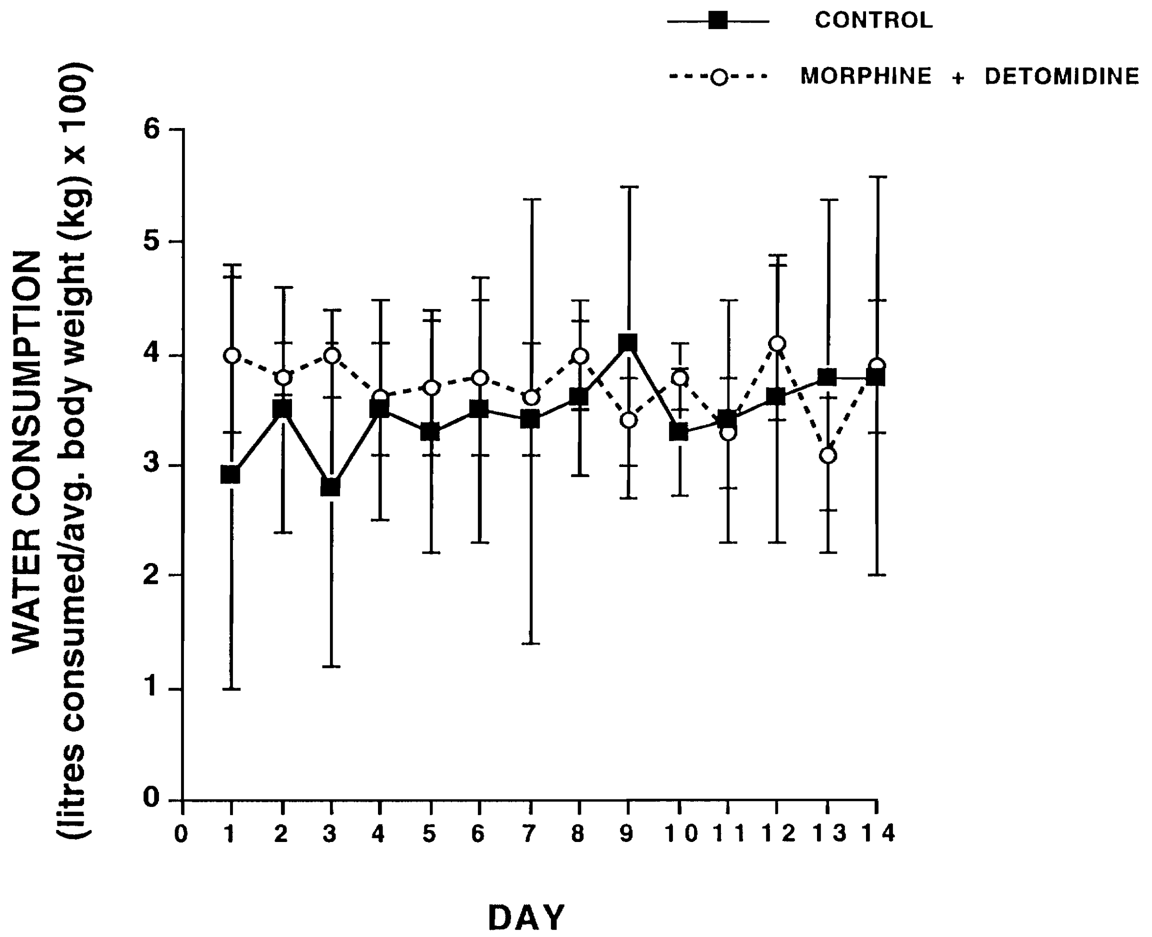
Appendix 24. Part 2: Average Daily AM Gastrointestinal Motility Grade



Appendix 25. Part 2: Average Daily PM Gastrointestinal Motility Grade



Appendix 26. Part 2: Average Daily Hay Consumption

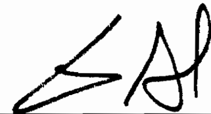


Appendix 27. Part 2: Average Daily Water Consumption

VITA

Annette M. Sysel was born on February 25, 1964 in Chatham, Ontario and is the daughter of Frank and Helen Sysel. While growing up at home, her accomplishments included completion of Grade 8 piano requirements for the Royal Conservatory of Music and a bronze medal in ballet from the British Association of Dance. After graduating from high school, Annette completed one year of undergraduate study in biological sciences at the University of Western Ontario in London. The following year, she moved to Guelph to complete her undergraduate requirements. Annette spent the summer living in Brasil, and returned to Canada for her veterinary school interview. In the fall of 1986, Annette was accepted into the Ontario Veterinary College. As a veterinary student, she was an active member of various committees and held office in the Veterinary Equine Club and the student chapter of the American Association of Equine Practitioners. As well, she headed the Neonatal Foal Watch Team and assisted in the development of a computer-based management program for equine breeding farms. Annette graduated from the Ontario Veterinary College with honours in May 1991 and was awarded the Samuel Downing Stirk Memorial Award for proficiency in diagnosis and management of large animal diseases.

Annette began her internship program at the Atlantic Veterinary College in Charlottetown, Prince Edward Island in July 1991. She received her Certificate of Internship in June 1992. Her internship helped to define her interest in equine surgery, and in January 1993, she became the first large animal surgery resident at the Virginia-Maryland Regional College of Veterinary Medicine. During her residency, Annette made several presentations at meetings of the American College of Veterinary Surgeons, including one presentation in the Residents' Forum. As well, she received a Graduate Student Clinical Science Research Award in May 1995 and again in June 1996. Two manuscripts originating from her Master's research project have been accepted for publication in *Veterinary Surgery*. Annette now plans to remain "somewhere warm" with Tabitha the cat to pursue her interests in equine surgery and medicine.



Annette M. Sysel, DVM