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EFFECTS OF INTRAVENOUS TRAMADOL IN HORSES

By

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ABSTRACT

EFFECTS OF INTRAVENOUS TRAMADOL IN HORSES

By

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Tramadol is a potential analgesic in horses. The objectives of this study were to determine the effects of tramadol on behavior, heart rate, respiratory rate, and locomotion and to assess the effect of tramadol on the response to a thermal cutaneous stimulus. Six horses were treated every 20 minutes with tramadol (0.1, 0.2, 0.4, 0.8 and 1.6mg/kg), or equal volumes of saline. Ten minutes after dosing heart rate, respiratory rate, step frequency, head height, and sweating, trembling, and head nodding scores were recorded. After the final dose, values were recorded at specific times. Gut sounds also were scored. Blood was drawn for measurement of serum tramadol before treatment, and at predetermined intervals after the final dose. In a second study, hoof withdrawal and skin twitch reflex latencies (HWRL and STRL) to a thermal stimulus were determined before treatment and at several time points after a IV bolus of 2.0 mg/kg tramadol or vehicle. Respiratory rate, head height, trembling and head nodding scores were increased by tramadol. Gut sounds and rectal temperature transiently decreased after tramadol. Baseline HWRL and STRL were not significantly prolonged by tramadol. In the horse, IV tramadol at cumulative doses less than 3.1 mg/kg produces minimal side effects and a bolus of 2.0 mg/kg does not prolong the response to a thermal stimulus.

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INTRODUCTION

Currently, analgesics for horses are limited to mainly two classes of drugs, alpha-2 adrenergic agonists and non-steroidal anti-inflammatory drugs (NSAIDs). Alpha-2 agonists cause considerable sedation at doses used for analgesia. In addition, they are used mostly for acute, visceral pain. NSAIDs are the corner stone for treatment of chronic somatic and orthopedic sources of pain but they can have significant side effects on the gastrointestinal, renal, and coagulation systems. Opioids are not widely used in horses because they can cause CNS excitation, sympathetic stimulation, and stimulate locomotion when given intravenously.

Tramadol is a centrally acting synthetic analog of codeine with analgesic effects resulting from interactions between opiate, adrenergic and serotonin receptor systems. It is widely used for treatment of chronic cancer and orthopedic pain in people and in dogs, and it has the advantage of not being a controlled substance. In people, tramadol has minimal effects on gastrointestinal motility and no significant cardiovascular or respiratory effects. Published reports of tramadol use in veterinary medicine are limited, and these are focused on the pharmacokinetic profile.

Recent advancements in the treatment of pain in people, dogs and cats have been widespread. Many of the advancements include the use of opioids. Due to the side effects of opioids in horses, and the regulatory control on and expense of opioids. the equine clinician is still limited to use of the NSAIDs and alpha 2 agonists for management of pain. It is not known if the effects of intravenous tramadol in horses

include sympathetic stimulation and CNS excitation. If it does not cause opioid related excitation, tramadol has the potential to be useful for analgesic therapy in horses.

The objectives of this study were:

1. To determine the effects of cumulatively increasing doses of intravenous tramadol on behavior, heart rate, respiratory rate, gut sounds, and rectal temperature.
2. To assess the effect of tramadol on the response to a thermal cutaneous stimulus.
3. To correlate these effects with pharmacokinetic data.

The objectives were addressed in two phases. Phase I was a dose finding study to determine the highest dose of tramadol that could be safely administered. In Phase II, a dose based on results from Phase I was evaluated for analgesic efficacy using a thermal stimulus.

CHAPTER 1

LITERATURE REVIEW

Opioids

Opioids are a drug class used for analgesia in many species. These drugs are traditionally considered to be the mainstay for treatment of most types of pain. Opioids are chemically related to a group of compounds that have been isolated from the juice of *Papaverum somniferum* (the poppy plant). Opium is the unrefined extract and it is comprised of nearly twenty active compounds, including codeine and morphine. The purified natural agents are referred to as opiates, while the term opioid includes all drugs that are chemical derivatives of compounds purified from opium.

Endogenous receptor ligands

Endogenous opioid peptides are natural products of the central nervous system, pituitary gland, and adrenal glands. There are three families and distinct precursors for the endogenous opioid peptides. They are the enkephalins (proenkephalin), the dynorphins (prodynorphin), and beta-endorphin (proopiomelanocortin). The presence of endogenous peptides has been confirmed in both the central and peripheral nervous systems. None of the three families bind only to one receptor. While the roles of the peptides are not completely understood, they seem to function as neuromodulators, neurotransmitters, and neurohormones. They are also involved in mediation of stress-related analgesia and analgesia induced by electrical stimulation of the periaqueductal gray area of the mesencephalon (Inturrisi, 2002).

Specific receptors

Exogenously administered opioids exert their effects by interacting with specific opioid receptors and by behaving like endogenous opioid peptides. The four main types of opioid receptor are mu, kappa, delta, and the nociceptin receptor. Several subtypes of mu, kappa and delta receptors exist. The mu receptor is responsible for most of the clinical analgesic effects, and has been further subdivided to include mu1 and mu2. Mu1 is related to supraspinal analgesia, euphoria, and serenity. Mu2 is related to respiratory depression, pruritis, dependence, sedation, vomiting, anorexia, and urinary retention. The kappa receptor mediates spinal analgesia, sedation, dysphoria, and respiratory depression (Trescot et al., 2008). The delta receptor may modify antinociception mediated by the mu receptor. The nociceptin receptor does not mediate typical opioid analgesia, but instead has pronociceptive effects.

Opioid receptors in horses

Opioid receptors are present in the brain and spinal cord of horses. An autoradiographic study showed that horses had significantly higher binding to mu opioid receptors than dogs in the frontal cortex, somatosensory cortex, mid-brain, and cerebellum (Hellyer et al, 2003). The horse mu opioid receptor has been partially cloned and sequenced, and it has high homology with the cat and pig (94%), and cow (93%) (Wetmore et al, 2003). Another recent study demonstrated that the horse cerebral cortex has a high concentration of high-affinity mu opioid receptors, with a lower density of delta and kappa receptors. The horse cerebellum has a high concentration of high-affinity kappa and mu receptors, and a lower density of delta receptors (Thomasy et al, 2007).

Opioid receptors have been identified in the synovial membranes of horses (Hellyer et al, 2001).

Mechanism of analgesic action

Opioids act at several classes of opioid receptors, which have been shown to be present in the central nervous system and in peripheral tissues. Opioid agonists act at opioid receptors. Opioid antagonists are used to reverse opioid effects. Agonists/antagonists produce morphine like effects but to less of a degree. Generally speaking, there are four main ways that opioids exert their analgesic effect. One is that opioids inhibit transmission of pain in the dorsal horn of the spinal cord. A second is that opioids inhibit somatosensory afferents at supraspinal levels. A third mechanism is by decreasing the release of neurotransmitters. A fourth mechanism is by activation of descending inhibitory pathways (Chahl, 1996).

Opioid receptors are membrane bound receptors coupled to G proteins. Binding of opioids to receptors and activation of G proteins may result in inhibition of adenylyl cyclase activity, suppression of voltage-gated calcium currents, and activation of receptor-operated potassium currents (Inturrisi, 2002). Presynaptically, decreased calcium influx reduces the release of neurotransmitters from primary afferent fibers in the dorsal horn of the spinal cord, and this inhibits the synaptic transmission of nociceptive input. At the postsynaptic level, opioids open voltage sensitive potassium channels and the result is enhanced potassium efflux from neurons in the brain, spinal cord and myenteric plexus. The efflux of potassium inhibits ascending nociceptive pathways via hyperpolarization of spinal cord projection neurons (Chahl 1996). Opioids also may

upregulate supraspinal descending antinociceptive pathways in periaquecductal gray matter (Christie et al, 2000). Opioids are antinociceptive by inhibiting C fiber transmission. They also inhibit substance P release from peptidergic neurons, thus decreasing pain associated with inflammation.

Other effects

Central nervous system

Depending on the species, type of opioid administered, dose, route, and level of pain, the effects on the central nervous system vary between sedation (humans, dogs, and monkeys) and arousal (horses, cats, cows). The excitatory effects are more associated with the mu agonists and tend to be maximal if the animal is pain free. The different response based on species is most likely a result of differing distributions and concentrations of receptors in the brains of different species (Hellyer et al, 2003). Opioids affect the hypothalamic thermoregulatory system, and cause hypothermia in most species. In cats, horses, ruminants, and swine, opioids can cause hyperthermia that may be associated with excitement and increased muscle activity. Opioids directly stimulate the chemoreceptor trigger zone in the area postrema of the medulla and induce emesis in species that can vomit, including humans, dogs and cats. Vomiting does not usually occur if opioids are administered in the immediate postoperative period or if the animal is in pain. Opioids can depress the cough reflex by directly affecting a cough center in the medulla. Codeine, hydrocodone, and butorphanol are better antitussives than other opioids. In species that become sedated with opioids, miosis tends to occur secondary to an excitatory action of opioids on neuronal firing in the oculomotor nucleus

In those species that exhibit CNS excitement with opioid administration, mydriasis tends to occur because the miotic effect is masked by an increased release of catecholamines (Wallenstein et al, 1979).

Respiratory system

Opioids cause a dose-dependent depression of ventilation via a direct depressant effect on respiratory centers in the brainstem. A decreased responsiveness to carbon dioxide develops and the carbon dioxide response curve is shifted to the right as resting arterial PaCO2 increases. The effect of opioids on ventilation is compounded by administration of sedatives and anesthetic agents.

Cardiovascular system

Most opioids have minimal effects on heart rate, rhythm, blood pressure and cardiac output. Bradycardia may result from opioid-induced medullary vagal stimulation, and the bradycardia responds to treatment with an anticholinergic drug. Morphine and meperidine can cause histamine release, especially following rapid intravenous administration, resulting in vasodilation and hypotension (Branson et al, 2001).

Gastrointestinal system

Opioids bind to mu and delta receptors in the myenteric plexus of the gastrointestinal tract. Dogs and cat are stimulated to defecate, and then spasm of smooth muscle in the GI tract result in ileus and constipation. In horses, decreased gastrointestinal sounds and decreased passage of feces may occur (Malone et al, 2002).

Genitourinary system

Opioids can cause urinary retention secondary to a dose-dependent suppression of detrusor muscle contraction and a decreased sensation of urge (Kuipers et al, 2004). This effect is more likely to occur if the opioids have been administered neuraxially. Opioids can also affect urinary production. Mu agonists tend to cause oliguria due to increased antidiuretic hormone release and resultant altered renal tubular function. Kappa agonists tend to have a diuretic effect, possibly by inhibiting release of antidiuretic hormone (Mercadante and Arcuri, 2004).

Specific drug classes: agonists, agonist-antagonists, partial agonists

The following section describes drugs that will be discussed in detail with regards to specific studies in horses.

Mu agonists: morphine, fentanyl, hydromorphone, methadone, tramadol.

Morphine sulfate is the prototypical opioid analgesic with full agonist activity at mu, kappa, and delta receptors. Compared with synthetic agonists, morphine is relatively hydrophilic and crosses the blood brain barrier at a slower rate. This delays the peak effect of morphine even after intravenous administration (Stoelting RK, 2006). Despite the development of numerous synthetic opioids with greater potency than morphine, it is still considered to be an extremely efficacious drug for relief of pain. In dogs and cats, morphine is more likely to induce vomiting than other mu agonists. Morphine has the potential to cause histamine release after intravenous administration, and must be given slowly via this route. Metabolism of morphine is via hepatic conjugation with glucuronic acid. The analgesic effects of a single dose of morphine in the dog lasts from 3 to 4

hours. Enterohepatic recycling of the metabolites can lead to a prolonged duration of the effects in horses. Morphine is typically administered intramuscularly, intravenously or in the epidural space.

Fentanyl citrate is a synthetic mu agonist with high lipid solubility and a short duration of action. A single dose of intravenous fentanyl has a more rapid onset of action than morphine, but also a much shorter duration of action. The peak analgesic effects occur within several minutes and last less than 30 minutes (Stoelting RK, 2006). Fentanyl is rapidly redistributed to inactive tissue sites, and this results in the decrease in plasma concentration that terminates the clinical effects. Large doses or prolonged infusions may cause saturation of inactive tissues, after which termination of effects becomes dependent on hepatic metabolism and renal excretion (Stoelting RK, 2006). Side effects are similar to those from morphine except that intravenous fentanyl is not associated with histamine release but bradycardia may occur after bolus administration. Due to its short duration of action, fentanyl is usually administered intravenously as a constant rate infusion. A transdermal formulation is available and has shown variable plasma levels in different species following application of the patch.

Hydromorphone is a semisynthetic opioid with efficacy and duration of action similar to that of morphine. The intravenous administration of hydromorphone is not associated with a clinically significant release of histamine.

Methadone hydrochloridè is a synthetic mu agonist that is pharmacologically similar to morphine, but with additional activity at the N-methyl-D-aspartate (NMDA) receptor. In people, methadone is highly bioavailable following oral administration, has

high potency and an extended duration of action (Branson et al, 2001). Methadone is being used with increasing frequency for treatment of chronic pain in people.

Tramadol hydrochloride is a synthetic mu agonist with structural similarities to codeine. Tramadol has analgesic potency similar to codeine, which is approximately 50% as potent as morphine (Trescot et al., 2008). Tramadol has weak activity at the mu receptor but has been shown to be efficacious for a variety of acute and chronic pain conditions. The reason for this is that greater than 70% of tramadol's analgesic effect is purported to be secondary to its effects on the monoaminergic system. Tramadol inhibits reuptake of norepinephrine and serotonin. Tramadol should be used with caution in patients with a seizure history and it should not be used concurrently with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors.

Agonist-antagonists and partial agonists

Mixed agonists-antagonists and partial agonists were developed with the goal of producing analgesia with fewer side effects and less addictive potential than the pure mu agonists.

Butorphanol tartarate is a synthetic agonist-antagonist opioid with agonist activity at the kappa receptor and antagonist activity at the mu receptor. It occupies the mu receptor but does not cause a maximal clinical response. Butorphanol does not appear to provide adequate analgesia for moderate to severe pain, and its use in dogs and cats has been replaced with the pure mu agonists. It does have sedative effects, which makes it useful for non-painful procedures. Butorphanol is still widely used in horses because it provides good analgesia for visceral pain.

Buprenorphine is a semisynthetic, highly lipid soluble agent that is a partial mu agonist. Binding of buprenorphine is such that the receptor is partially occupied but in a way that prevents binding of other agonists. The affinity of buprenorphine for the mu receptor is very high, and once bound it can be difficult to antagonize buprenorphine. There is also a ceiling effect after which increasing the dose does not increase the side effects or the analgesia. Buprenorphine has a delayed onset of action, and it takes at least 1 hour to attain maximal effects after intramuscular administration. In most species, the duration of action is 6 to 12 hours. Buprenorphine is well absorbed in cats after transmucosal buccal administration.

Antagonists

Antagonists have high affinities for the opioid receptors, displace opioid agonists from the receptors, and occupy receptors but do not activate them. Antagonists have few clinical effects when given to a patient who has not received exogenous opioids.

Naloxone hydrochloride is a pure opioid antagonist that can reverse all opioid agonist effects. Administration of naloxone produces increased responsiveness, alertness, and coordination, and it can also reverse analgesia secondary to the agonist that is being displaced from the receptor. Unless cardiorespiratory arrest has occurred in a patient that has received opioids, naloxone should be titrated to reverse adverse side effects such as respiratory depression. Titrating the dose to effect will enable preservation of analgesia.

Pharmacokinetics and pharmacodynamics

Pharmacokinetics is the relationship between dose and the resulting concentration in plasma or the effect site, and it can also be described as what happens to a drug once it enters the body: absorption, distribution, metabolism and elimination. Clinical pharmacokinetics is a field that relates the pharmacokinetics of a drug to the therapeutics of that drug. Important terms in pharmacokinetics include clearance, volume of distribution, elimination half-life, maximal plasma concentration and bioavailability. Clearance is a measure of how efficient the body is in eliminating a drug, and is defined as the volume cleared of drug per unit time. The distribution of a drug throughout the plasma and tissues is a process of dilution from the highly concentrated solution to the dilute concentration in the plasma, which results from mixing of the drug into a larger volume. The volume of distribution is a measure of the space in the body that is available to contain drug. The size of the volume of distribution reflects the drug's solubility in tissue relative to plasma. A drug that is more soluble in peripheral tissues relative to plasma has a large volume of distribution. The elimination half life is a measure of the rate of removal of drug from the body. The bioavailability is the fraction of drug absorbed into the systemic circulation, and is a term that is only used when a drug is given by a route other than intravenously. Pharmacodynamics can be described as what happens to the body as a result a drug; it describes the relationship between plasma drug concentration and pharmacologic effect. Pharmacokinetic and pharmacodynamic parameters are important in determining dose and dosing regimens, and avoiding adverse events, drug interactions, and toxicities. Correlations between plasma concentrations of drug and drug effects can also be important for determining dosing interval. However,

once a drug has bound to its receptor, the molecular cascade of events that follows (and the therapeutic effects) may no longer depend on plasma concentrations of drug.

Pharmacokinetics and pharmacodynamics of selected opioids in the horse

Historically, studies of opioids in horses that have investigated analgesic efficacy and other effects have not studied the pharmacokinetics of the drug. Other studies that have reported pharmacokinetic data have not investigated analgesic efficacy. It is therefore not possible to draw conclusions about plasma concentrations and effects of the drug.

Butorphanol

Horses were given butorphanol as a single IV dose of 0.1 to 0.13mg/kg, or a bolus dose of 17.8mcg/kg followed by a CRI of 23.7mcg/kg/hr for 24 hours (Sellon et al, 2001). Following the single dose of 0.1 to 0.13mg/kg, several horses became ataxic and staggered for up to 20 minutes after dosing. Butorphanol treated horses had decreased borborygmi for 60 minutes compared to pretreament auscultation scores. These horses also had an increased duration of time to passage of feces and passed fewer piles of feces in the first 24 hours after dosing compared to saline treated horses. The adverse effects on the gastrointestinal tract were less in the horses given a loading dose of 17.8mcg/kg followed by a CRI of 23.7mcg/kg/hr. In this experiment, butorphanol treated horses passed fewer fecal piles than saline treated horses in the first 6 hours and first 24 hours. Auscultation scores were not different from pretreatment scores. Following a single IV injection, the terminal half-life of butorphanol was 44 minutes and clearance was

21ml/kg/min. The volume of distribution was greater than 1 L/kg, consistent with a wide distribution to tissues. Following the loading dose and CRI for 2 hours, terminal half-life was 34 minutes, clearance was 18.5ml/kg/min, and volume of distribution was 1.1 L/kg. This suggests that butorphanol does not accumulate after a CRI at the dose studied.

Morphine

In horses given 0.1 mg/kg of morphine intravenously, morphine was detected in serum for up to 48 hours and in urine for up to 144 hours after dosing (Combie et al, 1981). Computer analysis indicated that data were consistent with a three compartment open model. Serum half-life was 87.9 minutes and urine half-life was 101.1 minutes.

Tramadol

In one study, horses were given 5mg/kg of one of four preparations and serum levels of tramadol and several of its metabolites were measured (Giorgi et al, 2007). Horses received tramadol intravenously, oral immediate release capsules following a 10-hour fasting period, oral immediate release capsules with access to food, or oral sustained release capsules after a 10-hour fasting period. All oral doses were administered through a nasogastric tube, which was flushed with 100cc of water after dosing. Following IV tramadol, serum half-life was 0.69 $\pm$ 0.1 hours, Cmax was 3.59 $\pm$ 0.2 mcg/ml, volume of distribution (Vd) was 1.42 $\pm$ 0.08 L/kg, and clearance (Cl) was 1.16 $\pm$ 0.1 ml/kg/min. Half-life in fasted horses treated with immediate release capsules was 1.54 $\pm$ 0.23 hours, compared to 1.92 $\pm$ 0.27 hours in fed horses treated with immediate release capsules. Vd and Cl were 1.86 $\pm$ 0.25 and 1.35 $\pm$ 0.12 L/kg, and 1.8 $\pm$ 0.22 and 1.44 $\pm$ 0.27 ml/kg/min

respectively for fasted versus fed horses. Cmax was 1.77 ± 0.22 mcg/ml in fasted horses and 3.61 ± 0.5 mcg/ml in fed horses. Bioavailability in fasted horses was 64.5 ± 8.36% versus 84.6 ± 18.35% in fed horses. In fasted horses that were treated with the sustained release capsules, half-life was 3.43 ± 0.51 hours, Cmax was 0.057 ± 0.07 mcg/ml, and bioavailability was 10.5 ± 2.41%.

In another pharmacokinetic study of tramadol in the horse, a dose of 2mg/kg was given in one of four ways: intramuscularly, intravenously over 10 minutes, orally as an aqueous suspension of crushed immediate release capsules, or orally as intact sustained release tablets. Horses were fasted for 12 hours before drug administration. Oral dosing was done via a nasogastric tube and was followed with 500 cc of water (Shilo et al, 2007). After IV dosing half-life was 82 ± 10 minutes, Vd at steady state was 2.17 ± 0.52 L/kg, and Cl was 26 ± 3 ml/kg/min. After IM dosing, half-life was 92 ± 14 minutes and bioavailability was 111 ± 39%. Oral tramadol was poorly bioavailable (3±2% for the immediate release capsules).

The major metabolite of tramadol in the horse appears to be the M2 metabolite, N-desmethyltramadol. The production of the active metabolite M1 (O-desmethyltramadol) is very low in the horse. This is similar to the dog. In people it is the M1 metabolite that is purported to be responsible for tramadol's activity at the mu receptor. The M1 metabolite has a 200 times greater affinity for the mu receptor than tramadol. Even though M1 is a minor metabolite in the dog, tramadol has analgesic efficacy in this species.

Fentanyl

In one study, adult horses were treated with a single transdermal fentanyl dose (two 10 mg patches) and several transdermal doses over a period of 8 to 9 days (Maxwell et al, 2003). Patches were applied to shaved skin on the lateral or medial antebrachium or gaskin region, and covered with a nonadherent bandage. Blood was collected serially while the patches were in place and up to 24 hours after patch removal for evaluation of serum fentanyl concentrations. By three hours after application of the patch in the single dose phase, serum concentrations of fentanyl exceeded 1 ng/ml in all horses. Serum levels were greater than 1 ng/ml for 32 hours but declined to 0.6 ± 0.18 ng/ml by 48 hours after being applied. The serum levels followed a similar pattern after multiple dosing regardless of whether patches were changed every 48 or 72 hours.

A second study evaluating transdermal fentanyl and pharmacokinetics in horses indicated that there is a large amount of variability concerning transdermal absorption of fentanyl (Orsini et al, 2006). Three transdermal fentanyl patches, each containing 10mg of fentanyl, were applied to the mid-thoracic area of adult horses and were left in place for 72 hours. Blood was collected periodically while the patches were in place and for 12 hours after patch removal. The authors reported that there was an initial delay of approximately 2 hours, after which the plasma concentrations of fentanyl increased rapidly in a linear fashion. The initial delay ranged from 0 to 5.1 hours, the time to Cmax ranged from 8.5 to 14.5 hours, and Cmax ranged from 0.67 to 5.12 ng/ml. Plasma concentrations did not reach 1ng/ml in two out of six horses, but they exceeded 1ng/ml for at least 40 hours in the other four horses. There were no adverse effects reported in the study.

In another study, four different stepwise continuous rate infusions of fentanyl were evaluated for analgesic efficacy and pharmacokinetic data in horses (Sanchez et al, 2007). The different doses were administered in a stepwise manner in 5-minute increments for 15 minutes, followed by a CRI for 105 minutes. The doses were as follows. For the F1 group, infusions of 64ng/kg/min, 32ng/kg/min, 16ng/kg/min were administered each for 5 minutes, followed by a CRI of 8ng/kg/min for 105 minutes. For the F2 group: 192, 96, 48ng/kg/min each for 5 minutes, then 24ng/kg/min for 105 minutes. For the F3 group: 320, 160, 80ng/kg/min each for 5 minutes, then 40ng/kg/min for 105 minutes. For the F4 group: 640, 320, 160ng/kg/min each for 5 minutes, then 80ng/kg/min for 105 minutes. Mean serum concentrations of fentanyl did not exceed 0.5ng/ml in the F1 group. In the F2 group, mean serum concentrations were 0.75 to 1.5ng/ml. In the F3 group, mean serum concentrations were 2 to 2.5ng/ml and in the F4 group they were 5 to 6ng/ml. In the F4 group, two horses became tachycardic and agitated within the first 15 minutes of the infusion, associated with a peak serum concentration of 7.8ng/ml. The behavior resolved without intervention.

Studies documenting analgesic efficacy of opioids in horses

Parenteral administration

Kappa agonists

In horses, the kappa agonists tend to be used more than the mu agonists for systemic administration because the former drugs cause less locomotor and sympathetic stimulation than the latter (Kamerling et al, 1986). In horses, the greater the selectivity

for kappa receptors, the more favorable the ratio of analgesia to locomotor effects (Kamerling et al, 1988).

U-50,488H

Horses were treated intravenously with U-50,488H at 160mcg/kg, 80mcg/kg, 40mcg/kg and 0.9 % NaCl (Kamerling et al, 1988). Nociception was evaluated using an intense radiant heat stimulus over the skin of the fetlock and the skin of the withers and the latency to withdrawal of the hoof or skin twitch was measured. Twenty minutes following the highest dose of U-50,488H, the hoof withdrawal reflex latency (HWRL) nearly doubled from pretreatment values. This effect lasted for 40 minutes, after which measurements were no longer taken. Skin twitch reflex latency (STRL) increased by almost 100 percent within 5 minutes after 160mcg/kg of U-50,488H, and remained greatly increased for the 60 minutes of the study. The HWRL and STRL were also significantly different from control following 80mcg/kg of U-50,488H. In a separate study, four of the six horses were treated with the highest dose of U-50,488H, pretreated with 0.02 mg/kg of naloxone IV 5 minutes before the highest dose U-50,488H, and 0.02mg/kg of naloxone followed by saline. The STRL was measured for 200 minutes, and it was more that doubled for 120 minutes after the highest dose of U-50,488H. Pre-treatment with naloxone blocked the analgesic effect of U-50,488H. The STRL values were similar for naloxone + U-50,488H and naloxone + saline. The frequency of yawning was increased in a dose-dependent manner following treatment with U-50,488H. Other effects included lowering of the head and hindlimb relaxation. At high doses of U-50,488H, horses were drowsy and ataxic and would take small steps to maintain balance.

This is in clear difference from the locomotor response seen with pure mu opioid agonists, in which the horses stall walk compulsively (Combie et al, 1979).

Butorphanol

Butorphanol has analgesic efficacy in several models. In one study the authors assessed the analgesic effect of 4 doses (0.05, 0.1, 0.2, and 0.4 mg/kg) of intravenous butorphanol in the face of superficial and visceral pain (Kalpravidh et al, 1984). Superficial pain was induced using an intense thermal stimulus over the skin of the fetlock. Visceral pain was induced by balloon distention of the cecum via a surgically implanted cecal cannula. Analgesia for superficial pain was significantly greater than the control at 15 minutes after 0.1 mg/kg of butorphanol and for up to 30 minutes after 0.4 mg/kg of butorphanol. None of the doses produced significant analgesia for superficial pain after 30 minutes. Analgesia for visceral pain was significantly greater than the control at 15 minutes following all doses except 0.1 mg/kg of butorphanol. The 0.4 mg/kg dose produced analgesia for up to 90 minutes after injection. Treated horses displayed ataxia, restlessness and shivering, and the magnitude and duration of these side effects was dose related. Based on the results of this study, the authors suggested a dose of 0.2 mg/kg of butorphanol IV for analgesia. In another study, butorphanol (0.22mg/kg) was given to ponies intramuscularly and the analgesic effect was compared to morphine (0.66mg/kg) and xylazine 2.2mg/kg given IM. The same techniques for assessment of superficial and visceral pain as described above were used (Kalpravidh et al, 1984). For visceral pain, butorphanol resulted in an increased pain threshold at 30, 60, 120, 180 and 240 minutes after dosing. Only xylazine produced better analgesia than butorphanol for

visceral pain. Butorphanol had a mild effect on superficial pain at 60 minutes after dosing. Behavioral effects included shivering, pacing, pawing, and head shaking. A model of colic pain using balloon distention of the cecum via a cecal cannula was used to evaluate the effect of intravenous xylazine (1.1mg/kg), butorphanol (0.2mg/kg), and meperidine (1.0mg/kg) in horses (Muir et al, 1985). Butorphanol produced analgesia that lasted for approximately 60 minutes. Three out of the nine horses were ataxic for 5 minutes after butorphanol administration. Meperidine's analgesic effect lasted only 30 minutes, and horses were restless, hyperresponsive to stimuli, and shivered for 5 to 10 minutes.

A combination of xylazine and butorphanol was evaluated for chemical restraint for a standing surgical approach to the abdomen in six horses (Robertson, JT and Muir, WW 1983). Horses were given IV xylazine 1.1mg/kg, and five minutes later a 2cm skin incision was made in the left flank, a towel clamp was applied and the response was noted. Butorphanol 0.1mg/kg was given intravenously and five minutes later, a skin drape was applied and secured with 4 towel clamps. A 15cm vertical skin incision and muscle separation was performed in the left flank. The musculature, subcutaneous tissue and skin were each sutured. The entire surgical procedure took approximately 30 minutes to perform. The absence of kicking, switching of the tail, turning of the head to look at the left flank, or vigorous movement in response to surgical stimulation defined acceptable analgesia. All horses reacted to the initial skin incision. Following butorphanol administration, there was only slight flinching after the longer incision, and the surgical procedure was completed with an acceptable level of analgesia in four of the six horses. The other two horses were treated with infiltration of local anesthetic at 15

and 20 minutes after start of the surgical procedure. The authors concluded that the combination studied produced synergistic analgesia and good chemical restraint for a standing surgical approach to the left flank.

In 93% of colic cases, butorphanol at a dose of 0.1mg/kg intravenously was determined to provided good to excellent analgesia (Stout et al, 1986). However when the same dose of butorphanol was compared to detomidine (20 and 40mcg/kg IV), butorphanol was considered to be unsatisfactory as an analgesic 90% of the time in colic cases (Jochle et al, 1989). In a randomized, controlled, blinded clinical trial, horses that presented for colic were treated with either flunixin meglumine (1.1mg/kg IV every 12 hours) plus a saline continuous rate infusion (CRI) or the same dose of flunixin meglumine plus a butorphanol CRI (13mcg/kg/hr) for the first 24 hours after abdominal surgery (Sellon et al, 2004). Horses in the butorphanol treatment group had improved behavior scores and lower plasma cortisol concentrations compared to horses in the other group. The time to first passage of feces after surgery was delayed and the total number of times feces was passed was decreased in the butorphanol treatment group. This difference from the control group was no longer present after 24 hours. Horses in the butorphanol treatment group had a shorter hospital stay than control group horses.

The analgesic effects of intravenous butorphanol (25mcg/kg) combined with detomidine (10mcg/kg) were compared to detomidine alone using electrical stimulation and a pneumatic pressure model for somatic pain (Schatzmann et al, 2001). The electrical stimulation consisted of a constant current delivered via two electrodes on the skin above the coronary band. The pressure device was a pneumatically operated piston that pressed a sharp-ended steel pin onto the horse's leg at the level of the dorsal aspect

of the cannon bone. Detomidine alone increased the nociceptive threshold to constant current with a maximum at 15 minutes and a return to baseline within 45 minutes. The addition of butorphanol increased the nociceptive threshold significantly for 15 to 75 minutes and the return to baseline was within 90 minutes of dosing. Detomidine alone increased the nociceptive threshold to pressure after 15 minutes to the cut off point and this returned to baseline after 60 minutes. The addition of butorphanol resulted in a significant difference from detomidine alone at 60 minutes after dosing and a return to baseline after 90 minutes from dosing. This study confirmed the clinical experience that the use of butorphanol in addition to alpha 2 agonists has synergistic analgesic effects.

The effects of a single intravenous dose of butorphanol (0.1mg/kg) on the nociceptive withdrawal reflex using threshold, suprathreshold, and repeated subthreshold electrical stimuli in conscious horses has been reported (Spadavecchia et al, 2007). The nociceptive withdrawal reflex (NWR) was tested using single transcutaneous electrical stimulation of the palmar digital nerve. Repeated stimulations were used to evoke temporal summation. The responses of the common digital extensor to stimulation were recorded and quantified with surface electromyography. Behavioral reactions were recorded as well. The use of the NWR and temporal summation in this model attempt to identify somatic phasic pain mediated by Aδ fibers. Observation of and analysis of electromyographic activity in different post stimulation time frames enables the separation of reflex components according to their latency (Spadavecchia et al 2002, 2003). Five minutes after butorphanol administration, all horses exhibited excitation, shivering, stepping, restlessness and ataxia lasting for about 1 hour. The NWR, temporal summation thresholds, and behavioral reaction scores were not altered. However, at

temporal summation threshold intensity, there was significantly decreased electromyographic activity within specific post stimulation time frames, indicating changes in nociceptive gain. The authors conclude that butorphanol has minimal effect on immediate Aδ mediated pain but it may influence spinal processing and reduce delayed sensations.

Mu agonists

Morphine

Kalpravidh and coworkers (1984) assessed the analgesic potency of morphine (0.66mg/kg) intramuscularly in ponies. Superficial pain was induced using an intense thermal stimulus over the skin of the fetlock. Visceral pain was induced by balloon distention of the cecum via a surgically implanted cecal cannula. Morphine produced good analgesia for superficial pain but was less potent than xylazine for visceral pain. This dose of morphine stimulated locomotor activity for almost 5 hours, while the analgesic effects lasted only about 1 hour. Heart rate and respiratory rate were significantly increased for four hours after dosing. Behavioral changes included apprehension, headshaking, shivering, and pawing. Similar effects on behavior have been observed following IV administration of 0.66mg/kg morphine in horses (Kalpravidh et al 1984, Combie et al 1981).

Methadone

The analgesic effects of intravenous levomethadone (100mcg/kg) combined with detomidine (10mcg/kg) were compared to detomidine alone using electrical stimulation and a pneumatic pressure model for somatic pain (Schatzmann et al, 2001). The electrical stimulation consisted of a constant current delivered via two electrodes on the skin above the coronary band. The pressure device was a pneumatically operated piston that pressed a sharp-ended steel pin onto the horse's leg at the level of the dorsal aspect of the cannon bone. Detomidine alone increased the nociceptive threshold to constant current with a maximum at 15 minutes and a return to baseline within 45 minutes. The addition of levomethadone increased the nociceptive threshold significantly for 15 to 75 minutes and the return to baseline was within 90 minutes of dosing. Detomidine alone increased the nociceptive threshold to pressure after 15 minutes to the cut off point and this returned to baseline after 60 minutes. The addition of levomethadone resulted in a significant difference from detomidine alone at 75 minutes after dosing and a return to baseline after 90 minutes from dosing. This study demonstrated that the use of levomethadone in addition to alpha 2 agonists has synergistic analgesic effects.

Fentanyl

The antinociceptive effects of intravenous fentanyl in horses have been reported (Kamerling et al, 1985). The following 3 doses were administered: 2.5, 5 and 10mcg/kg. There were dose dependent increases in the STRL as determined by the method described above. No effects on HWRL were appreciated, but horses also displayed dose dependent

increases in spontaneous locomotor activity, which may have interfered with evaluation of HWRL.

In a small clinical study of eight horses, it was shown that transdermal fentanyl offered consistent and significant improvement in visceral pain in horses (Wegner et al, 2002). Somatic pain was only slightly improved or unchanged. These horses were already being treated with maximal doses of NSAIDs, or NSAID use was contraindicated. The dose used was one 10mg patch for 150kg body weight, applied every 48 to 72 hours. Analgesic assessment was a subjective evaluation based on changes in vital signs, appetite, attitude, and mobility. Examples of cases that had a significant improvement included peritonitis, colitis, and pleuritis. Cases of laminitis showed minimal improvement of pain levels. Undesirable side effects were not observed in any of the treated horses.

In another clinical study, the authors evaluated the efficacy of transdermal fentanyl in nine horses with moderately to severely painful soft tissue or orthopedic conditions that had not responded to treatment with NSAIDs alone (Thomasy et al, 2004). The application of one to two 10mg fentanyl patches significantly improved pain scores in horses that were already being treated with phenylbutazone or flunixin meglumine. Analgesic efficacy was judged to be better in cases of visceral pain than in cases of orthopedic pain. There were no adverse effects on behavior or gastrointestinal motility. Pharmacokinetic analysis revealed that mean serum concentrations were greater than 1ng/ml for at least 18 hours.

In a recent study, the effects of fentanyl on somatic and visceral nociception in horses were evaluated (Sanchez et al, 2007). Somatic nociception was evaluated by

measuring thermal threshold. A probe with a heater and temperature sensor was attached to a shaved area over the withers and the probe was connected to a threshold testing device. The temperature was increased and the horse's response was measured. A positive response was defined as twitching of the skin or if the horse turned its head to look at the test site. Visceral nociception was evaluated by use of colorectal and duodenal distention. Four different doses of fentanyl were administered intravenously in a stepwise manner in 5 minute increments for 15 minutes, followed by a CRI for 105 minutes. Mean serum concentrations of fentanyl ranged from 0.5ng/ml with the lowest dose up to 5 to 6ng/ml with the highest dose. There were no significant antinociceptive effects in any of the groups, and two horses in the highest dose group became agitated for 15 minutes after drug infusion began.

Agonist-antagonists

Buprenorphine

The effects of buprenorphine on nociception in horses have been reported. Horses randomly received each of the following treatments: intravenous saline, 5mcg/kg buprenorphine, and 10mcg/kg buprenorphine (Carregaro et al, 2007). The antinociceptive effects of the treatments were evaluated by assessment of latency to response to a heat lamp. The hoof withdrawal reflex latency (HWRL) was defined as the amount of time that elapsed between focusing of the lamp on the fetlock and limb withdrawal. The skin twitch reflex latency (STRL) was defined as the amount of time that elapsed between focusing the lamp at the withers and skin twitching. Following

10mcg/kg of buprenorphine, there was a significant increase in the STRL for up to 6 hours and the HWRL for up to 11 hours. The 5mcg/kg dose did not produce antinociception in this study. All horses were excited for 5 to 10 minutes after both doses of buprenorphine. Characteristic behaviors included continuous head nodding, shifting of limbs, trotting, digging, and restlessness. Spontaneous locomotor activity (SLA) was significantly increased for 6 and 14 hours after 5 and 10mcg/kg buprenorphine, respectively.

Epidural administration

Epidural administration of opioids in horses is a valuable and clinically useful route because systemic side effects from opioids can be minimized while providing long lasting analgesia for pelvic limb, perineal, and caudal abdominal pain.
Epidural administration of drugs in the horse is usually performed at the interspace between the first and second coccygeal vertebrae. Positive aspects of epidural administration of opioids include a lack of excitement and increased locomotor activity associated with systemic administration of these same drugs, the analgesic effects are long lasting, and there are fewer systemic side effects compared with systemic administration. Negative aspects of epidural administration of opioids include the potential for the horse to develop pruritis, a slow onset of action (45 minutes to 2 hours) depending on drugs used, restraint and sedation of the patient is needed to perform the epidural, and it may require preservative free drug or a filter.

The effects of epidurally administered alfentanil, butorphanol, morphine, tramadol, U50488H, meperidine and hydromorphone in horses have been reported. In a

study comparing alfentanil (0.02mg/kg), butorphanol (0.08mg/kg), morphine (0.1mg/kg), tramadol (1mg/kg), U50488H (0.08mg/kg) or sterile water in volumes of 20mls, only tramadol and morphine resulted in a significantly increased threshold to avoidance of electrical stimulation of sacral, perineal, lumbar and thoracic dermatomes (Natalini and Robinson 2000). The increase in avoidance threshold in the sacral and perineal areas following tramadol occurred within 20 minutes and lasted for 6.5 hours. The increase in avoidance threshold in the lumbar and thoracic areas following tramadol occurred after 3 hours and lasted for 5 hours. With morphine administration, the increase in avoidance threshold in the perineal area occurred after 5 hours and lasted for 6 hours. The increase in avoidance threshold in the sacral area occurred at 4 hours and lasted for 6 hours. In the lumbar and thoracic areas, increases in avoidance threshold were 6 hours and 8 hours, and duration was 5 hours and 3 hours, respectively. Tramadol and morphine have a similar structure, protein-binding fraction and volume of distribution. Tramadol had a faster onset of action than morphine and this was attributed to its greater affinity for tissues than morphine.

The hemodynamic, analgesic and respiratory effects of 0.8mg/kg of epidural meperidine hydrochloride in horses has been reported (Skarda and Muir, 2001). There was no significant difference from saline with respect to heart rate, respiratory rate, and rectal temperature. Analgesia was assessed by measuring the avoidance response to noxious electrical and thermal stimuli at the perineal dermatome, and needle-prick stimuli from coccygeal to S1 dermatomes. Meperidine treatment resulted in bilateral analgesia of dermatomes from the coccygeal area to S1. The onset of analgesia was 12 minutes and the duration was from 240 to 300 minutes. The degree of sedation, determined by

position of the head and the eyelids, was mildly increased after meperidine but this difference from saline was not significant. Following treatment with meperidine, one of the mares exhibited buckling of one pelvic limb and leaning on the stocks. All treated mares displayed dilatation of the rectum and relaxation of genitalia, indicating blockade of parasympathetic fibers of the pelvic nerves. Meperidine is a synthetic opioid that is structurally similar to local anesthetics. It is speculated that the analgesia from epidural meperidine is the result of a regional analgesia. The local anesthetic effects of in vitro meperidine on mammalian peripheral nerves and nerve conduction cannot usually be reversed by naloxone (Power et al, 1991).

The analgesic effect of 0.04 mg/kg of epidural hydromorphone in horses has been described (Natalini and Linardi, 2006). Analgesia was assessed using electrical stimulation of sacral, perineal, lumbar and thoracic dermatomes. By 20 minutes post injection of hydromorphone, there was a significant increase in the avoidance threshold in all dermatomes evaluated. The increase in avoidance threshold lasted for 250 minutes after injection. There was no change in avoidance threshold after injection of sterile water. Although sedation was not objectively evaluated in this study, horses did appear to become sedated and there was no ataxia noted.

Epidurally administered opioids must cross the dura mater and enter the subarachnoid space in order to contact spinal tissue and nerves. Opioids interfere with nociceptive neural transmission in the central nervous system via their action on receptors in dorsal horn of spinal cord and mesolimbic system, thalamic and hypothalamic nuclei, and periaqueductal gray matter in midbrain (Cousins and Mather, 1984). Different physiochemical properties of opioids may impact their onset and duration of action when

administered epidurally. After crossing the dura mater, lipid solubility of a drug influences how rapidly it binds to spinal cord receptors and takes effect. The duration of effect of epidurally administered opioids is affected by the number of molecules retained in the cerebrospinal fluid and spinal tissue, and the drug's dissociation kinetics (Cousins and Mather, 1984).

Classical opioid effects in horses

The classical responses of horses following intravenous high doses of opioids consist of central nervous system stimulation, increased sponataneous locomotor activity (SLA), incoordination, and agitation. Depending on the drug and dose administered, ataxia and collapse have occurred. Physiologic changes have included tachycardia, hyperthermia and increased blood pressure (Kamerling et al, 1985, 1988; Pascoe et al, 1991; Mama et al, 1993). As little as 5mcg/kg of intravenous fentanyl results in a doubling of SLA above baseline. Increasing doses result in a greater increase in SLA (Kamerling et al, 1985). If the dose of intravenous fentanyl in the 450kg horse is increased from 1 to 2 to 4 to 8mg, the steps/2 minutes increase from less than 5 to approximately 100 steps/2 minutes (Tobin, 1981). The increase in step frequency occurs in a smooth, predictable dose-dependent manner. The peak effect occurs with 4 to 6 minutes of IV dosing and then rapidly declines. Horses are back to control values by one hour after dosing. If the same horses are given a dose of 16mg, they become incoordinated, stagger and may fall down (Tobin, 1981). Following intravenous morphine at 0.1 and 0.3 mg/kg, there were no substantial increases in step frequency (steps/2 minutes). A dose of 0.6mg/kg causes a gradual increase in SLA to about 60

steps/2 minutes, and this response declines back to control values after 4 hours. A dose of 1.2mg/kg increases SLA to 80 steps/2 minutes and 2.4mg/kg increases SLA to 120 steps/2 minutes. At the highest dose, the increase in SLA is maintained for almost 8 hours and takes almost 14 hours to return to control values (Combie et al, 1979). Low doses of opioids (0.1mg/kg morphine, 2.2mcg/kg fentanyl) stimulate eating behavior, with the horses standing at the hay rack and consuming large amounts of hay. Once the dose becomes high enough to stimulate locomotion, the horse snatches at a piece of hay as it is trotting around its stall, but won't actually eat until SLA declines (Tobin, 1981; Combie et al, 1979). At high doses, horses are ataxic and bump into the walls of their stalls as they compulsively trot. The locomotor response has also been induced with kappa agonists, but the response is not as marked as that seen following mu agonists (Kamerling et al, 1985).

Other effects in horses

Effects on behavior

Behavioral changes that have occurred following administration of opioids such as morphine, butorphanol, and fentanyl to pain free horses include restlessness, shivering, pacing, tremors, and head shaking (Kalpravidh et al, 1984; Kamerling et al, 1985; Spadavecchia et al, 2007; Sanchez et al, 2007; Carregaro et al, 2007). These effects are likely mediated by dopamine release. Dopamine is the immediate precursor of norepinephrine. The midbrain contains cell bodies of many dopaminergic neurons. These cell bodies are localized in an area related to motor function, the nigrostriatal system.

Effects on GI motility

Opioids cause an increase in segmental intestinal contraction but an overall depression of intestinal propulsion. In addition, in humans and rats, morphine reduces intestinal secretory activity while increasing fluid absorption. The overall effect is usually a decrease in gastrointestinal motility. An intravenous bolus dose of butorphanol (0.1mg/kg) decreases both mean borborygmus score for up to one hour after treatment and number of fecal piles passed in the first 24 hours, compared with a saline control. The adverse effects on the gastrointestinal tract are to a lesser degree in the horses given a loading dose of 17.8mcg/kg followed by a CRI of 23.7mcg/kg/hr (Sellon et al, 2001). Horses given intravenous buprenorphine (10mcg/kg) have decreased borborgymus scores compared to saline treated horses for 4 hours after treatment (Carregaro et al., 2006). Intravenous morphine (0.5mg/kg) in horses every 12 hours for 6 days resulted in decreased gastrointestinal motility and fecal moisture content for 4 to 6 hours after dosing. (Boscan et al, 2006). The doses listed above are higher than those that are used clinically, and lower doses of opioids have been administered to horses without causing clinically relevant decreases in GI motility.

Cardiopulmonary effects

Opioids tend to cause bradycardia and respiratory depression in most species. Cardiopulmonary effects in the horse are variable. Butorphanol at doses up to 0.4mg/kg intravenously does not alter cardiorespiratory function in horses. In horses given 0.1 or 0.2mg/kg of butorphanol, there was no change in PaO2 and PaCO2 values (Robertson

and Muir, 1981). Following intramuscular administration of 0.66mg/kg morphine in ponies, heart rate and respiratory rate were significantly increased for four hours after dosing (Kalpravidh et al, 1984). Administration of 10mcg/kg of buprenorphine intravenously to horses causes significant increases in heart rate, cardiac index, and blood pressure. Respiratory rates were significantly increased without significant differences in PaCO2, PaO2 and SaO2 (Carregaro et al., 2006).

Implications for opioid use in the horse

Opioid agonists may induce increased locomotor activity and excitement in horses, especially if they are pain-free. Pure kappa agonists tend to cause less disruption of normal gastrointestinal motility when compared to pure mu agonists such as morphine and fentanyl. Early reports of administration of opioids studied doses that would now be considered to be excessive by clinical standards. However, the actual analgesic plasma concentrations of opioids in the horse are not documented. In a paper published in 1984 referring to how people are reluctant to use morphine in horses: "Morphine has not received wide acceptance for use in horses because of their unpredictable responses; many horses show excitement...It has been recommended that no more than 60mg, 120mg, or 200mg be given to the horse" (Kalpravidh et al, 1984 Feb). Subsequent investigation into opioid use in horses has revealed that the negative side effects are related to dose and the rate of increase in plasma concentration. Finally, clinical reports of the use of opioids for management of pain in the horse indicate that it is possible to provide efficacy without clinically relevant side effects (Wegner et al, 2002; Thomasy et al, 2004; Sellon et al, 2004).

Tramadol

Tramadol was first synthesized in Germany in 1962, and it has been available for treatment of pain there since 1977. It was registered in the United States in 1995 and in the United Kingdom in 1994. It is classified by the US FDA as a nontraditional centrally acting analgesic. It is currently available in more than 70 countries.

Structurally tramadol is related to morphine and codeine. It is a racemic mixture of two enantiomers – (+) tramadol and (-) tramadol. Both opioid and nonopioid mechanisms act on descending inhibitory pathways in the CNS, resulting in modulation of second order spinal cord neurons.

Mechanism of action

Tramadol works by two distinct and complementary mechanisms. The first is by binding of the parent compound and metabolite (M) to the mu opioid receptor. The second is by inhibition of norepinephrine and serotonin uptake. The (+) enantiomer has a higher affinity for the mu receptor and is more effective at inhibiting serotonin reuptake. The (-) enantiomer is more effective at inhibiting norepinephrine reuptake (Lewis and Han, 1997). Tramadol's overall activity is from the sum of the actions of enantiomers plus the action of the active metabolite (M1), which has a higher affinity for the opioid receptor than does the parent compound (Scott and Perry, 2000). Tramadol is a weak mu agonist with an affinity for the receptor that is 6000 times less than morphine. When given intravenously in people, it is 1/10th as potent as morphine (Raffa et al, 1991). Approximately 30% of the analgesic activity of tramadol can be reversed by the opioid

antagonist naloxone (Grond and Sablotzki, 2004). This suggests that only 1/3 of tramadol's analgesia is due to an opioid mechanism of action. Tramadol inhibits reuptake of serotonin and norepinephrine, resulting in increased concentrations of both of the neurotransmitters at the synaptic level. The dual activity may explain tramadol's analgesic efficacy in treatment of conditions that are traditionally poorly responsive to conventional opioids (neuropathic pain). Also, tramadol's weak activity at the mu opioid receptor probably explains the lack of or low incidence of side effects associated with commonly used opioids.

Pharmacokinetics

Tramadol undergoes extensive first pass hepatic metabolism. Phase I N and O demethylation results in M1 and other metabolites. Phase II conjugation of O-demethylated compounds occurs and tramadol and its metabolites are 90% excreted through the kidney. The bioavailability after a single oral dose is approximately 75% and this increases to 90-100% after multiple doses. In people, absorption is not affected by the presence or absence of food. Following oral dosing, the peak effect is seen in 1-4 hours with analgesia lasting 3-6 hours. The onset of action following parenteral dosing is in the range of minutes. The maximum effect is reached after 15-30 minutes, with peak plasma levels in 2-3 hours and the duration of effect is again 3-6 hours (Grond and Sablotzki, 2004; Lewis and Han, 1997). Anecdotal reports in people suggest that analgesia occurs with serum concentrations of 100 to 300ng/ml, but studies have shown that plasma tramadol concentration is a poor predictor of analgesia (Lewis and Han, 1997).

Tramadol crosses the placental barrier, with umbilical venous concentrations approaching 80% of maternal venous levels. Tramadol has been found in low concentrations of 0.1 % of maternal dose 16 hours after a single dose. Since safety in pregnancy, newborns and infants has not been established, tramadol is not recommended for use in perioperative or postoperative obstetrical procedures.

Analgesic efficacy

Multiple US clinical trials and European postmarketing surveillance studies have shown that tramadol provides better analgesia than placebo for various surgical and nonsurgical pain conditions. Randomized, double-blinded parallel group studies in adults have shown that tramadol provides effective analgesia for moderate to moderately severe postoperative and chronic pain. Tramadol is comparable to morphine for relief of moderate to moderately severe pain following abdominal, gynecological, orthopedic and thoracic surgery (Scott and Perry, 2000). In a prehospital setting, tramadol was considered to provide similar analgesia to morphine for acute traumatic musculoskeletal pain (Vergnion et al, 2001). Many studies in people have shown that tramadol has analgesic efficacy in the treatment of chronic pain conditions such as osteoarthritis, fibromyalgia, diabetic neuropathy, cancer pain, and neuropathic pain (Budd and Langford, 1999). Pain relief from tramadol is comparable to that produced by acetaminophen with codeine or aspirin with codeine (Lewis and Han, 1997). In addition, tramadol has been included as a World Health Organization step 2 recommendation for cancer pain treatment (Nossol S, 1998).

Side effects, drug interactions, and precautions

The most commonly reported side effects in people taking tramadol are dizziness, nausea, sedation, dry mouth, and sweating (Scott and Perry, 2000). To minimize the incidence of adverse effects, start with the lowest dose, increase the dose gradually, and titrate the patient response against the dose. Deaths have been reported in animal studies where tramadol and monoamineoxidase (MAO) inhibitors were administered concurrently. The combination of tramadol and MAO inhibitors, tricyclic antidepressants, or selective serotonin reuptake inhibitors can lower the seizure threshold. Concurrent administration of a P450 enzyme inducer may necessitate increasing the dose of tramadol. Tramadol should be used cautiously or avoided in patients with pre-existing ventilatory problems, head trauma or increased intracranial pressure because it has the potential to cause respiratory depression, subsequent increases in arterial CO2 and elevations in intracranial pressure. Seizures have been reported in patients receiving tramadol within the dose range. Anaphylactoid reactions have been reported after single doses. Tramadol should be avoided in individuals with prior reaction to other opioids (Scott and Perry, 2000).

Summary

This literature review describes opioids and their use in the equine veterinary patient. It also describes the use of tramadol in humans as a unique analgesic. The use of high doses of opioids in horses causes undesirable side effects such as compulsive locomotion, CNS stimulation, and decreased GI motility; this has precluded their routine use. In addition, due to the side effects of opioids in the horse, and other practical

considerations regarding expense and drug administration, opioids will probably never replace the NSAIDs for treatment of equine pain. Judicious dosing and an appreciation for the type of pain that is being treated will enable the incorporation of opioids for pain management in the clinical setting, and perhaps decrease the dose of NSAID required and minimize side effects from that class of drug. Epidural administration of opioids in horses provides analgesia without the typical effects on behavior and the CNS.

Tramadol is a centrally acting synthetic analog of codeine with analgesic effects resulting from interactions between opiate, adrenergic and serotonin receptor systems. It is widely used for treatment of acute pain and chronic cancer and orthopedic pain in people. In people, tramadol has minimal effects on gastrointestinal motility and no significant cardiovascular or respiratory effects. Tramadol has the benefit of not being a controlled substance and potentially being administered orally. Based on tramadol's activity at the mu receptor, it has the potential to have analgesic efficacy in horses. In addition, although the effects of drugs that alter levels of norepinephrine and serotonin have not been studied in horses, it is possible that tramadol's actions on the monoaminergic system will contribute to analgesia in horses. If tramadol does not have the negative side effects that other opioids have, it may play a role in the treatment of pain in the horse. The purpose of the study described in this thesis was to determine the effects of intravenous tramadol in the horse. The effects of tramadol on behavior, heart rate, respiratory rate, gut sounds, and the response to a thermal cutaneous stimulus were evaluated. In addition, serum concentrations of tramadol were measured.

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CHAPTER 2

EFFECTS OF INTRAVENOUS TRAMADOL IN HORSES

Summary

Objective –To determine the optimal dose, serum concentrations and analgesic effects of IV tramadol

Animals – Six horses, three geldings and three mares with a mean age of 21 years and a mean weight of 565kg.

Procedure – In a blinded, randomized dose-response study, 6 horses were treated every 20 minutes with successive doses of tramadol HCl (0.1, 0.2, 0.4, 0.8 and 1.6mg/kg), or with equivalent volumes of saline. Ten minutes after each dose heart rate, respiratory rate, step frequency, head height, and sweating, trembling, and head nodding scores were recorded. After the final dose, values were recorded every 20 min for 1 hour, hourly for 3 hours, and at 6 hours. Gut sounds also were scored. Blood was drawn for GC/MS measurement of serum tramadol before treatment, 20 min after each dose, and 80, 140, 200, and 380 min after the final dose. In a second study, hoof withdrawal and skin twitch reflex latencies (HWRL and STRL, respectively) to a thermal stimulus were determined 5, and 30 min and 1, 2, 4 and 6 hours after a bolus injection of 2.0 mg/kg tramadol or vehicle. HR, RR, temperature, step frequency and head height were analyzed using a 3 factor ANOVA. Trembling, head nodding, excitement, sweating, and gut sounds were analyzed using Wilcoxon Signed-Rank test.

Results – In comparison to saline, tramadol caused no significant change in heart rate, step frequency or sweating score. Trembling and head nodding scores were dose-dependently increased by tramadol. Respiratory rate increased from 18.5 [4.6] (mean

[sem]) to 38.3 [7.1] and head height from 60.0 [3.1] cm to 67.6 [2.1] cm following the highest dose (p 0.01). In all horses, there was a transient decrease in gut sounds after tramadol. Peak serum concentration of tramadol after a cumulative dose of 3.1 mg/kg was 619.5 [60.2] ng/ml. The half-life was 114.3 [19.7] minutes. Baseline HWRL and STRL were 4.16 [0.41] and 3.06 [0.41], respectively and were not significantly prolonged by tramadol.

Conclusion and Clinical Relevance – In the horse, IV tramadol at cumulative doses less than 3.1 mg/kg produces minimal side effects and a bolus dose of 2.0 mg/kg does not prolong the response to a thermal stimulus

Introduction

Currently, analgesics for horses are comprised mainly of two classes of drugs, alpha-2 adrenergic agonists and non-steroidal anti-inflammatory drugs (NSAIDs). Alpha-2 agonists cause considerable sedation at doses used for analgesia. In addition, they are used mostly for acute, visceral pain. NSAIDs are the corner stone for treatment of chronic somatic and orthopedic sources of pain but they can have significant side effects on the gastrointestinal, renal, and coagulation systems. Opioids are not widely used in horses because they can cause CNS excitation, sympathetic stimulation, and stimulate locomotion when given intravenously. These responses are thought to be due to cerebral dopamine and norepinephrine release and activation of opiate receptors (Combie et al., 1981). In addition, the regulatory controls on opiates make their practical use difficult.

Tramadol is a centrally acting synthetic analog of codeine with analgesic effects resulting from interactions between opiate, adrenergic and serotonin receptor systems (Lewis et al., 1997; KuKanich et al., 2004). It is a weak mu-opioid agonist and its action is mostly mediated by inhibiting neuronal norepinephrine and serotonin reuptake (Lewis et al., 1997). In humans, administration of the opioid antagonist naloxone can reverse approximately 30% of the analgesic effect of tramadol (Raffa et al., 1992; Besson et al., 1994). It is widely used for treatment of chronic cancer and orthopedic pain in people and in dogs, and it has the advantage of not being a controlled substance. In people, tramadol has minimal effects on gastrointestinal motility and no significant cardiovascular or respiratory effects (Scott et al., 2000) yet has the same analgesic effects

for mild to moderate pain as equipotent doses of morphine, but with less respiratory depression (Lewis et al., 1997; Mastrocinque et al., 2003).

Published reports of tramadol use in veterinary medicine are limited, and these are focused on the pharmacokinetic profile. One study in dogs undergoing ovariohysterctomy following pyometra showed that the analgesic effects of preoperative IV tramadol (2mg/kg) or morphine (0.2mg/kg) were similar when assessed in the early postoperative period (Mastrocinque et al., 2003). In dogs, the following doses have been suggested: 1 to 4 mg/kg PO every 6 hours for cancer pain (Lascelles 2003) and 1 to 2 mg/kg PO every 12 hours for degenerative joint disease and other chronic pain (Parker 2004). In one report, five hundred milligrams of tramadol was given IV to a 7 year old Standardbred gelding to evaluate urine metabolites but there was no report of the effects of the drug on the horse (Russo et al., 2000). Two recent reports of the pharmacokinetics in horses following IV tramadol administration evaluated doses of 2mg/kg (Shilo et al., 2007) and 5mg/kg (Giorgi et al., 2007).

The optimal dose of tramadol for use in horses has not been established. Epidural injection of 1mg/kg tramadol in horses has been shown to produce a moderate analgesic effect for approximately six hours, with no adverse effects on behavior (Natalini et al., 2003). It is not known if the effects of IV tramadol in horses include the typical opioid-induced sympathetic stimulation, increased locomotion, and CNS excitation. If it does not cause excitation, tramadol has the potential to be useful for analgesic therapy in horses.

The three objectives of this study were to determine the effects of cumulatively increasing doses of intravenous tramadol on behavior, heart rate, and respiratory rate, to

assess the effect of tramadol on the response to a thermal stimulus, and to correlate these effects with pharmacokinetic data. The objectives were addressed in two phases. Phase I was a dose finding study to determine the highest dose of tramadol that could be safely administered. In Phase II, a dose based on results from Phase I was evaluated for analgesic efficacy using a thermal stimulus.

Materials and methods

Animals

The study was approved by the Michigan State University Institutional Animal Care and Use Committee. Sixteen horses were screened for inclusion in the study group based on the latency of their response to a thermal pain stimulus (methods described below). The six selected horses - three geldings and three mares with a mean age of 21 years (range 7-29) and a mean weight of 565kg (490 –623), were studied in two experiments. Physical examination, packed cell volume, and total solids were within normal limits. Horses were brought in from pasture and housed in box stalls bedded with shavings for at least 12 hours prior to each study. They had free access to fresh water and were fed a pelleted diet. Horses were restrained with a halter and lead rope during data collection.

Screening process

Horses were positioned in the middle of a large quiet room and held with a halter and lead rope. The latency response to the thermal stimulus was determined at the withers and the fetlock. A 6 x 6 cm area over the left withers was clipped and blackened

with stamp pad ink and a 2 x 3 cm area over the left front lateral fetlock was similarly prepared. Blinders were placed on the horses so that they could not see the light of the lamp. The heat lamp was provided by the Gluck Equine Research Center at the University of Kentucky (courtesy T. Tobin). Horses were excluded if they demonstrated a response time of 6 seconds or greater to the thermal stimulus. This was done since it was anticipated that tramadol would result in a prolongation of the baseline response time and the cut off time of exposure would be 10 seconds to prevent tissue damage.

Response to a thermal stimulus: Hoof withdrawal and skin twitch reflex latencies were measured in response to a thermal stimulus using the method first published by Kamerling et al (1985). The skin over the left withers and left front fetlock was clipped and blackened with stamp pad ink to promote uniform absorption of light. The heat lamp was always operated by the same investigator (JD). Before each use, the lamp was pointed away from the horse, turned on for 5 seconds, and was then allowed to cool for 1 minute before it was used again. The lamp was held approximately 11cm from the horse and the intense stimulus was applied to a focal area. The heat lamp had an automatic timer that was activated when the heat lamp was turned on, and shut off when the lamp was turned off. A sham light was randomly activated so as not to condition horses to expect the heat stimulus. Positive responses were skin twitch at the left wither or shoulder and withdrawal of the left front foot. Latency to response was determined at each site in triplicate and sites were alternated with at least 1 minute between readings at a site.

Instrumentation

On the morning of study, blinders were placed on the horse and it was fed as usual. After a period of 30 minutes, horses were instrumented. Each jugular vein was catheterized aseptically with a 5 ¼ inch 14 gauge catheter (BD Angiocath). The left jugular catheter was used for administration of treatment and the right jugular catheter was used for blood sampling. Each injection was followed with 10mls of sterile heparinized saline.

A stepcounter (Cyma StepWatch Activity Monitor SAM3) was placed on the lateral side of the left lower forelimb, just proximal to the fetlock. It was secured in place using the Velcro strap provided by the manufacturer, and was covered with a light bandage. At the end of each study day, the step counter was removed from the horse, and docked to a computer using the equipment and software provided by the company.

The haircoat was clipped over the left side of the body at the withers, the neck and caudal to the elbow for application of ECG patches. A receiver for the telemetric heart rate monitor (Hewlet Packard M1401A model) was secured to the horse's neck using a Velcro strap and the leads were attached to the ECG patches. The monitor for the unit was kept outside of the stall. Respiratory rate was obtained by counting thoracic cage excursion for one minute. A digital thermometer was used to measure rectal temperature.

Level of sedation was judged by the height of the horse's head from the ground. A bright orange piece of tape was affixed to the mane on the poll. After the horse had been instrumented and allowed to stand undisturbed in the stall for at least 15 minutes, baseline head height was determined from the height of the head tape against a tape measure applied to a wall of the stall.

To evaluate gut sounds, the right upper, right lower, left upper and left lower abdominal quadrants were each ausculted for 30 seconds and gut sounds were scored using a modification of a previously published scale (Sellon et al., 2001). More than 2 sounds in 30 seconds scored 2, 1 to 2 sounds scored 1 and no sounds scored 0. The cumulative score from all four quadrants could therefore range from 0 to 8. The number of fecal piles also was counted.

Sweating, excitement, trembling (Derksen et al, 1999), and head nodding were scored using numerical rating scales. Sweating was scored as follows: no sweat, cool flanks = 0; warm humid flanks = 1; flanks warm, hand wet after stroking = 2; flanks visibly wet = 3; sweat dripping from flanks = 4. Level of excitement was scored as follows: calm, no change from pretreatment = 0; restless = 1; anxious appearance, pinnae retracted back, eyes wide open = 2; kicking and pawing, distressed = 3; uncontrollable, kicking violently, biting flanks = 4. Trembling was scored as follows: none = 0; intermittent trembling of flanks = 1; constant trembling of flanks = 2; sustained trembling of flanks and some shaking of whole body = 3; sustained shaking of whole body = 4. Head nodding was scored as follows: none = 0; intermittent subtle nodding of head = 1; constant mild nodding of head = 2; obvious constant nodding of head = 3.

Tramadol

A stock solution of 5 % tramadol was provided by Dr. Tobin (Gluck Equine Reasearch Center, University of Kentucky). Heparinized saline was prepared by adding 1 unit/ml of heparin to 0.9% NaCl. Coded syringes containing tramadol or vehicle were

prepared on the morning of each study by a technician who was not involved in data collection.

Sample handling

Ten mls of waste was drawn out of the right jugular catheter before the 20ml sample was collected and placed into two 10 ml vacutainer tubes (BD). Tubes were spun for 15 minutes at 1700g in a Jouan CR4-12 centrifuge. The serum was removed and stored at -20 C until analysis.

Tramadol assay

Tramadol was analyzed by GC/MS after extraction with dichloromethane followed by introduction of a pentazaocine internal standard and derivatization with BSTFA-1%TMCS. The limit of detection is 2ng/ml with an estimated lower limit of quantitation of approximately 4ng/ml.

Experimental design

Phase I (Dose-response)

In a blinded, randomized cross over design, all horses were treated with 5% tramadol intravenously or with a similar volume of IV saline at each treatment time point. The treatments were separated by at least 36 hours. See figure 1.1. Following baseline (time zero) measurements of heart rate, respiratory rate, rectal temperature, steps taken, level of sedation (head height), sweating, excitement, trembling, and head nodding, dosing began. The first dose was tramadol (0.1mg/kg) or an equivalent volume of saline.

Subsequent doses of tramadol were serially doubled (0.2, 0.4, 0.8 and 1.6mg/kg) and administered every 20 minutes. Ten minutes after each dose, measurements were taken. After the final dose, data were collected every 20 minutes for 1 hour, hourly for 3 hours, and then at 6 hours. Gut sounds were scored at time 0, and at the times indicated after the final dose of tramadol or saline. The number of fecal piles were counted at time zero, at each data collection time point, and then 24 hours after time zero. Blood was collected for measurement of serum tramadol concentration at time 0, 20 minutes after each dose, and 80, 140, 200 and 380 minutes after the final dose of tramadol or saline. Horses were monitored for signs of colic and other potential adverse effects (excitement, restlessness) for a further 24 hours and then returned to pasture.

Phase II (analgesic efficacy)

In a blinded, randomized cross over design, 6 horses were treated IV with a single dose of 2mg/kg of 5% tramadol or with a similar volume of 16% sodium acetate trihydrate, and the responses to a thermal stimulus were evaluated (described above). The treatments were separated by at least 7 days. Phase II began one month after completion of Phase I. All but one horse from Phase I was studied in this phase, and the study environment was the same. Horses were instrumented with bilateral jugular catheters and blinders as in Phase I. The same observer unaware of treatment status collected all the data. Horses were restrained by use of halter and lead rope and a single handler at data collection time points. In addition, horses were restrained randomly throughout the study period to prevent the association of being handled with the thermal

stimulus. Baseline readings were taken, horses were dosed, and then readings were taken 5, 30, 60, 120, 240, and 360 minutes following dosing.

Statistical analysis

Heart rate, respiratory rate, temperature, step frequency, and head height were analyzed by means of a three factor analysis of variance. Fixed factors were treatment and time and horse was a random factor. Bonferroni's correction was used for multiple measurements over time. Within specific time points and between groups, trembling, head nodding, excitement, sweating, and gut sounds were analyzed using Wilcoxon Signed-Rank test. Significance was determined at a p value of less than 0.05. Data are presented as mean [standard error of the mean].

Results

Phase 1

Tramadol had no effect on heart rate (35 bpm), step frequency (3 steps over 2 minutes), sweating (0.18) and excitement (0.35) scores, and fecal output. Tramadol caused an increase in respiratory rate, head height, trembling and head nodding, and a decrease in gut sounds and rectal temperature.

Temperature

Following tramadol, there was significant decrease in rectal temperature during the recovery phase. Starting with 40 minutes after the highest dose, rectal temperature in tramadol treated horses was significantly lower than rectal temperature in saline treated

horses. Mean temperature for saline treated horses during recovery was 99.34 [0.16] degrees Fahrenheit. Mean temperature for tramadol treated horses during recovery was 98.86 [0.17] degrees Fahrenheit. This difference was statistically significant but is not likely to be clinically significant.

Respiratory rate

Following tramadol, there was a dose dependent increase in respiratory rate. Respiratory rate increased from 18.5 [4.6] at baseline to 38.3 [7.1] breaths per minute after the highest dose. (Figure 1.2) Respiratory rate decreased after the highest dose and it approached baseline values at the end of the measurement period.

Trembling

Following tramadol, there was a dose dependent increase in trembling score from 0 to 1 [0.52] after 0.8mg/kg, and to 2.5 [0.67] after 1.6mg/kg. This increase resolved by 20 minutes after the highest dose. (Table 1.1) Trembling was pronounced in neck muscles, pectorals, triceps, and gluteal muscles.

Head nodding

Following tramadol, there was a dose dependent increase in head nodding score from 0 to 2.5 [0.34] after 1.6mg/kg. Head nodding was still detectable for 40 minutes after the highest dose, but then resolved. (Figure 1.3)

Borborymus score

There was a transient decrease in borborygmus score from 4.16 [2.22] to less than 2 for forty minutes after the highest dose of tramadol. A significant difference from saline was no longer present after that time and there was no difference in the number of fecal piles between saline and tramadol treatments. (Figure 1.4)

Head height

The characteristic appearance of a horse following tramadol is seen in the photograph on the right. The same horse following saline is seen in the photograph on the left. (Figure 1.5) Head height was 67.6 [2.1] cm following the highest dose of tramadol, compared to 60.0 [3.1] cm after the corresponding dose of saline. (Figure 1.6)

Pharmacokinetics

The peak serum concentration of tramadol following a cumulative dose of 3.1mg/kg was 619.5 [60.2] ng/ml with an elimination half life of 114.3 [19.7] minutes. (Figure 1.7)

Phase II

A single bolus dose of 2 mg/kg of tramadol IV did not prolong the hoof withdrawal or skin twitch reflex latencies to a thermal stimulus. Baseline HWRL and STRL were 4.16 [0.41] and 3.06 [0.41], respectively and were not significantly prolonged by tramadol. (Figures 1.8 and 1.9) Following the 2mg/kg dose of tramadol, trembling

score increased from 0 to 2.2 [0.3] and head nodding score increased from 0 to 2.5 [0.34]. These scores were back to baseline values of 0 by 30 minutes after dosing.

Discussion

Tramadol does not appear to produce the classical opiate effects in the horse. Behavioral effects that have been reported with opioids such as morphine, fentanyl, buprenorphine and butorphanol include pacing, pawing and ataxia (Boscan et al 2006, Sellon et al 2001). These effects did not occur in horses given tramadol. Following tramadol, horses tended to adopt a basewide stance and seemed to plant their feet. No ataxia was noted when the horses were moved laterally.

Tramadol has central nervous system (CNS) stimulant effects. Horses appeared to be more excited, more alert (head held higher), and more sensitive to noise and stimulation. Trembling was displayed by 5 out of the 6 horses treated with tramadol, and all of the horses treated with tramadol exhibited head nodding. Head nodding or shaking has been reported with butorphanol, buprenorphine and other non-opioid drugs such as alpha 2 agonists.

Although tramadol caused a short-lived and significant decrease in borborygmus score, this did not have an effect on fecal output. By comparison, an IV bolus dose of butorphanol (0.1mg/kg) was shown to decrease both mean borborygmus score for up to one hour after treatment and number of fecal piles passed in the first 24 hours, compared with a saline control (Sellon et al, 2001); horses given buprenorphine (10mcg/kg) IV had decreased borborgymus scores compared to saline treated horses for 4 hours after treatment (Carregaro et al., 2006); and intravenous morphine (0.5mg/kg) every 12 hours for 6 days resulted in decreased gastrointestinal motility and fecal moisture content for 4

to 6 hours after dosing (Boscan et al, 2006). Compared to other opioids, tramadol affected gut sounds for a shorter amount of time and did not decrease fecal output.

Respiratory rate was increased following tramadol. Assessment of ventilation was not performed so it is not possible to comment on the presence of a respiratory acidosis. The increase in respiratory rate may have been secondary to CNS stimulation from tramadol's effects on the monoaminergic system. The return of respiratory rate to baseline followed a similar time course as the other variables that were changed. In a study in which horses were treated with IV buprenorphine (10mcg/kg) or an equivalent volume of saline, buprenorphine treated horses had significantly increased respiratory rates without significant differences in PaCO2, PaO2 and SaO2 (Carregaro et al., 2006).

The results of our study indicate that following cumulative IV dosing of 3.1 mg/kg, the peak serum concentration is 619.5 [60.2] ng/ml and the elimination half life is 114.3 [19.7] minutes. The most pronounced effects on head nodding, trembling, respiratory rate and gut sounds correlated with serum concentrations around 600 ng/ml. Less pronounced effects were detectable with serum concentrations around 300 ng/ml. In another study in horses, following a single 2mg/kg dose, the half-life was 82 $\pm$ 10 minutes (Shilo et al., 2007). In research beagles, the elimintation half-life is 0.8 $\pm$ 0.12 hours after a single intravenous dose of 4.4mg/kg of tramadol (KuKanich et al., 2004). In cats, the terminal half-life is 134 $\pm$ 18 minutes after a single intravenous dose of 2mg/kg of tramadol (Pypendop et al., 2007).

Tramadol at the dose studied did not prolong the response to an intense thermal stimulus. The heat lamp model has been used extensively in horses to test the antinociceptive activity of alpha 2 agonists and buprenorphine. Xylazine, detomidine and

buprenorphine prolong the response to the heat lamp but with different effects depending on the drug, dose, and the site studied (Kamerling et al., 1988; Queiroz-Neto et al., 1998; Carregaro et al., 2007). In horses, epidural tramadol at a dose of 1mg/kg resulted in increased avoidance thresholds to electrical stimulation of various dermatomes lasting several hours (Natalini et al., 2003). Tramadol has been shown to have antinociceptive efficacy in thermal models of pain in mice (Raffa et al, 1992).

It is possible that the dose of tramadol studied was not high enough to blunt the response to the heat lamp, but the first phase of the study elucidated a ceiling dose above which the observed effects on behavior and respiratory rate were deemed undesirable. We decided that effects seen after a cumulative dose of 1.5mg/kg were acceptable, and wanted to evaluate a dose of 2mg/kg, a dose that has been evaluated for analgesia in dogs. In Phase II, moderate trembling and head nodding were appreciated for up to 10 minutes after a single dose of 2mg/kg of tramadol. With regard to higher doses, one study that administered 5mg/kg IV to horses reported nausea, tremor, confusion, agitation and tachycardia 3 to 5 minutes after the dose with maximum effects at 15 to 20 minutes following dosing (Giorgi et al., 2007). Another study reported muscle twitching of the pectorals in two horses receiving 2mg/kg IV but the authors attribute this to the rate of administration because they did not see this effect when the dose was given over 10 minutes versus 5-6 minutes (Shilo et al., 2007). In the present study, tramadol was administered as a bolus dose over less than one minute, and this rate of administration may have contributed to the degree of trembling exhibited by the horses.

Intravenous tramadol does not induce sedation in horses and it in fact causes stimulation of the central nervous system. Data presented as an abstract indicated that

two horses receiving 1mg/kg tramadol after 1mg/kg xylazine for sedation for dental procedures had adverse reactions such as rearing up and falling over in the stocks (Roscoe et al., 2006).

While intravenous tramadol at 2mg/kg does not prolong the response to a thermal stimulus, other models of analgesia should be evaluated. Two studies have indicated that tramadol is bioavailable in horses following oral dosing but with conflicting results. Long-term effects on gastrointestinal function in horses have not been evaluated. Single dose IV administration of tramadol does not cause mania, increased spontaneous locomotor activity and has no adverse effects on fecal output. The incidence of trembling and muscle twitching may be decreased if intravenous tramadol is given slowly over at least 10 minutes, as opposed to a bolus dose. Future studies should consider tramadol's potential role for treatment of chronic pain in the equine patient.

Table 1.1

Mean trembling score. Trembling score was 0 for all times after saline. Trembling score after tramadol was 1 following the 0.8 mg/kg dose and 2.5 following the 1.6 mg/kg dose.

Table 1.1 Mean Trembling score

Elapsed time(min)	0	20	40	60	80	110	130	150	210	270	330	450
Dose mg/kg	0.1	0.2	0.4	0.8	1.6	recovery ----------→						
tramadol	0	0	0	0	1	2.5	0	0	0	0	0	0
saline	0	0	0	0	0	0	0	0	0	0	0	0

Figure 1.1

Diagram outlining protocol for Phase 1. Time in minutes is on the horizontal axis. Data were collected at each of the numbered time points. Gut sounds were scored at times indicated by the black diamonds. The first dose was 0.1mg/kg, subsequent doses were serially doubled and injections were made every 20 minutes as indicated by the broken arrows. Ten minutes after each dose, measurements were taken. After the final dose, data were collected every 20 minutes for 1 hour, hourly for 3 hours, and then at 6 hours. Blood was collected at times indicated by the solid arrows into glass tubes.

Figure 1.1

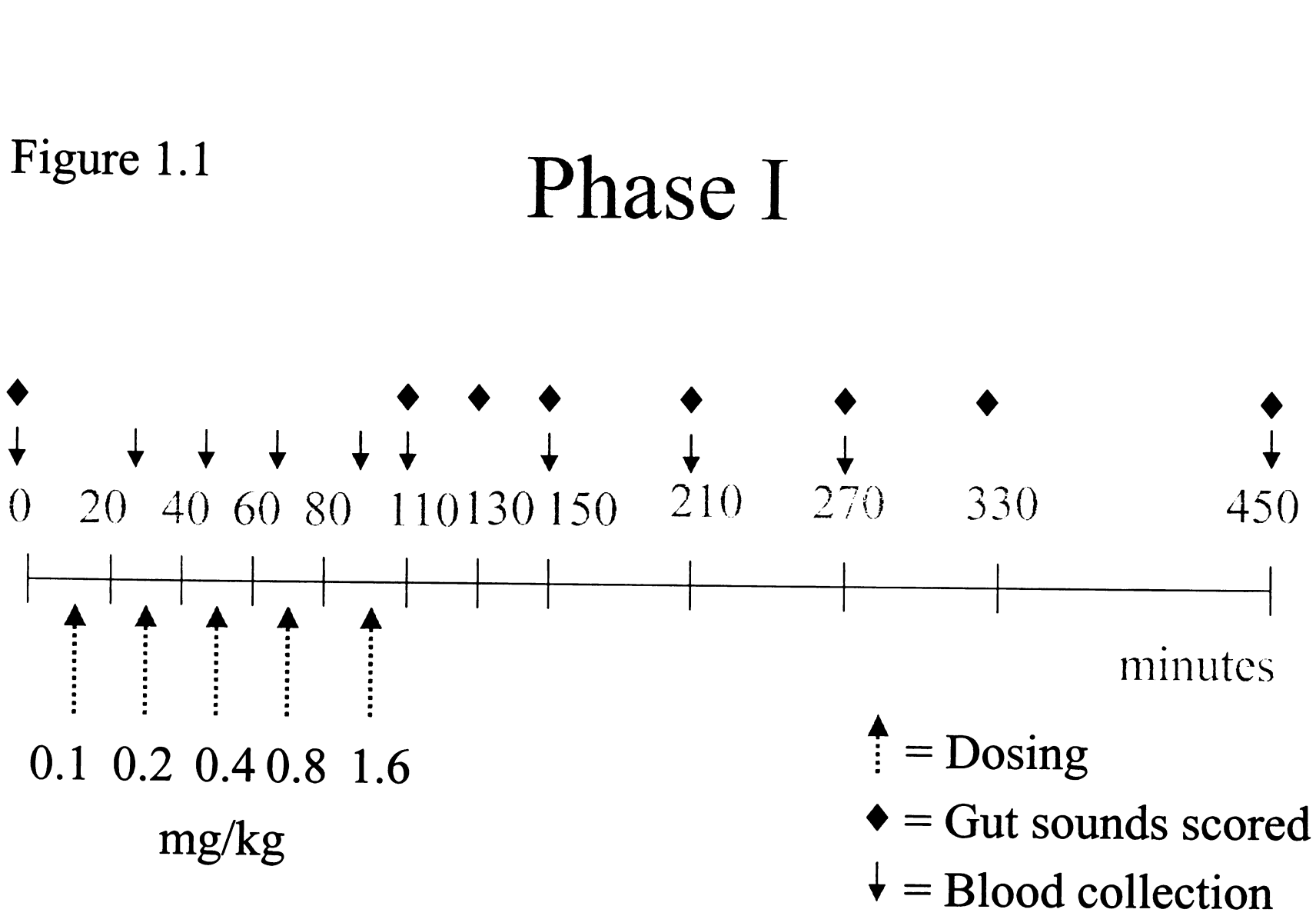

Phase I
0 20 40 60 80 110 130 150 210 270 330 450
minutes
0.1 0.2 0.4 0.8 1.6
mg/kg
= Dosing
= Gut sounds scored
= Blood collection

Figure 1.2

Effect of tramadol and saline on respiratory rate. Elapsed time in minutes is on the x axis, breaths per minute are on the y axis. Doses indicated at bottom. Black bars = tramadol, gray bars = saline. Data are mean $\pm$ sem. There was a dose dependent increase in respiratory rate following treatment with tramadol and the differences were significant (* = $p < 0.05$) at 20 and 40 minutes after the highest dose of tramadol.

Figure 1.2

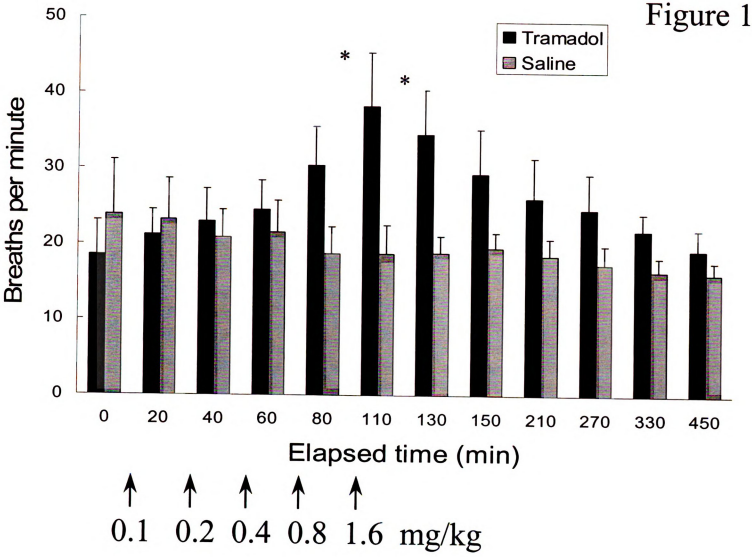

Tramadol
Saline
Breaths per minute
50
40
30
20
10
0
*
*
0
20
40
60
80
110
130
150
210
270
330
450
Elapsed time (min)
0.1
0.2
0.4
0.8
1.6
mg/kg

Figure 1.3

Effect of tramadol and saline on head nodding. Elapsed time in minutes is on the x axis, head nodding score is on the y axis. Doses indicated at bottom. Black bars = tramadol, gray bars = saline. Data are mean $\pm$ sem. There was a dose dependent increase in head nodding after tramadol.

* = significant ($p < 0.05$)

Figure 1.3

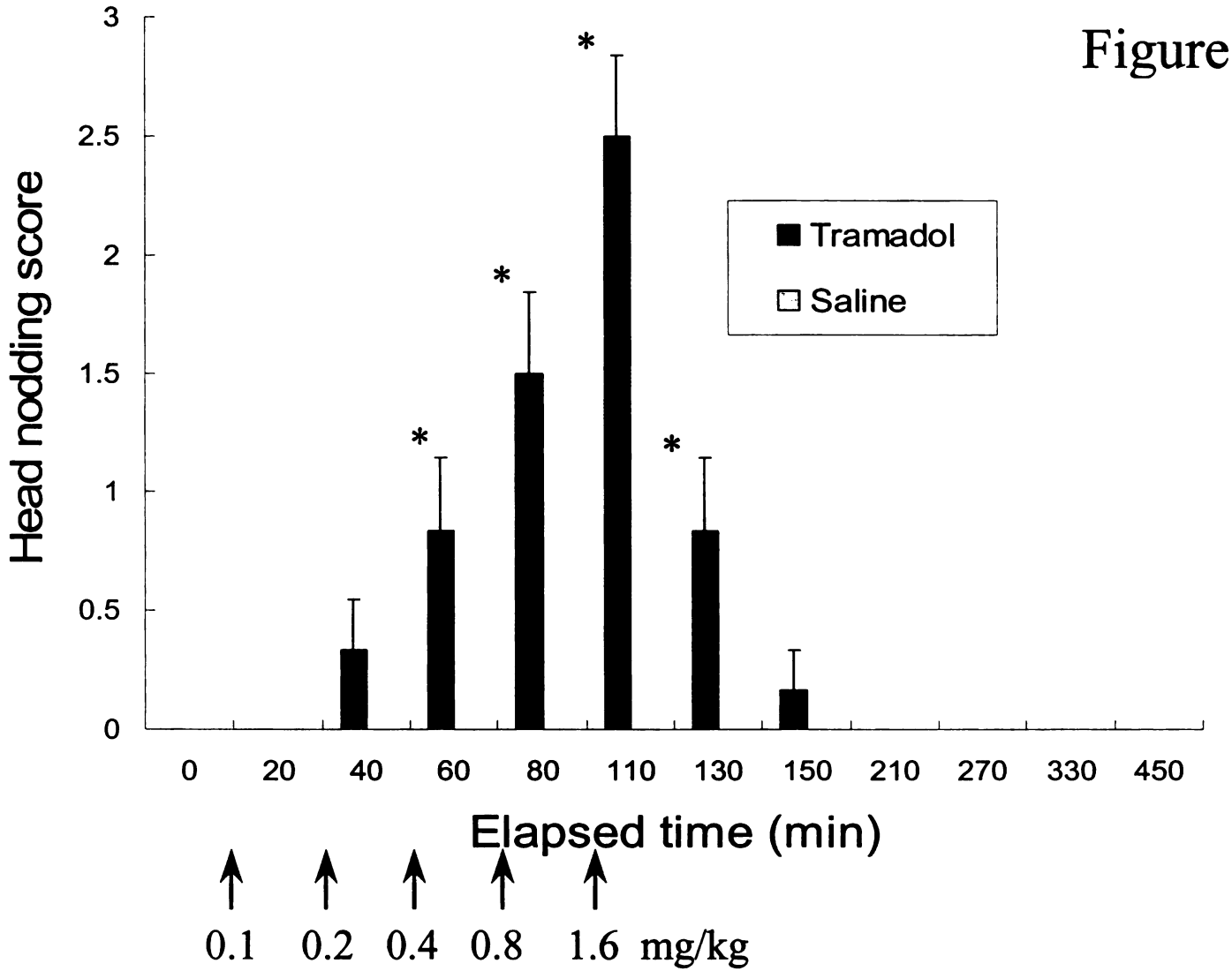

Head nodding score
3
2.5
2
1.5
1
0.5
0
*
*
*
*
Tramadol
Saline
0
20
40
60
80
110
130
150
210
270
330
450
Elapsed time (min)
0.1
0.2
0.4
0.8
1.6 mg/kg

Figure 1.4

Effect of tramadol and saline on gut sounds. Elapsed time in minutes is on the x axis, gut sounds score is on the y axis. Doses indicated at bottom. Black bars = tramadol, gray bars = saline. Data are mean $\pm$ sem. There was a transient decrease in gut sounds score after tramadol. * = significant ($p < 0.05$)

Figure 1.4

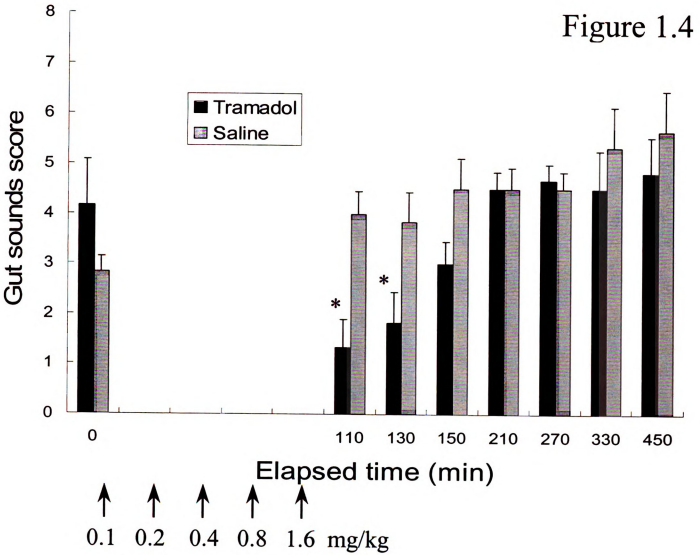

Gut sounds score
Tramadol
Saline
0
1
2
3
4
5
6
7
8
*
*
0
110
130
150
210
270
330
450
Elapsed time (min)
0.1
0.2
0.4
0.8
1.6
mg/kg

Figure 1.5

The photograph on the left is of a horse after treatment with saline, and the photograph on the right is the same horse after treatment with tramadol. The horse is wearing blinders to minimize visual stimulation. Note that following tramadol, the horse is holding his head higher and appears to be more alert.

Figure 1.5

Saline

Tramadol

Figure 1.6

Effect of tramadol and saline on head height. Elapsed time in minutes is on the x axis, head height in cm is on the y axis. Doses indicated at bottom. Black bars = tramadol, gray bars = saline. Data are mean $\pm$ sem. There was a significant (* = $p < 0.05$) increase in head height after the highest dose of tramadol.

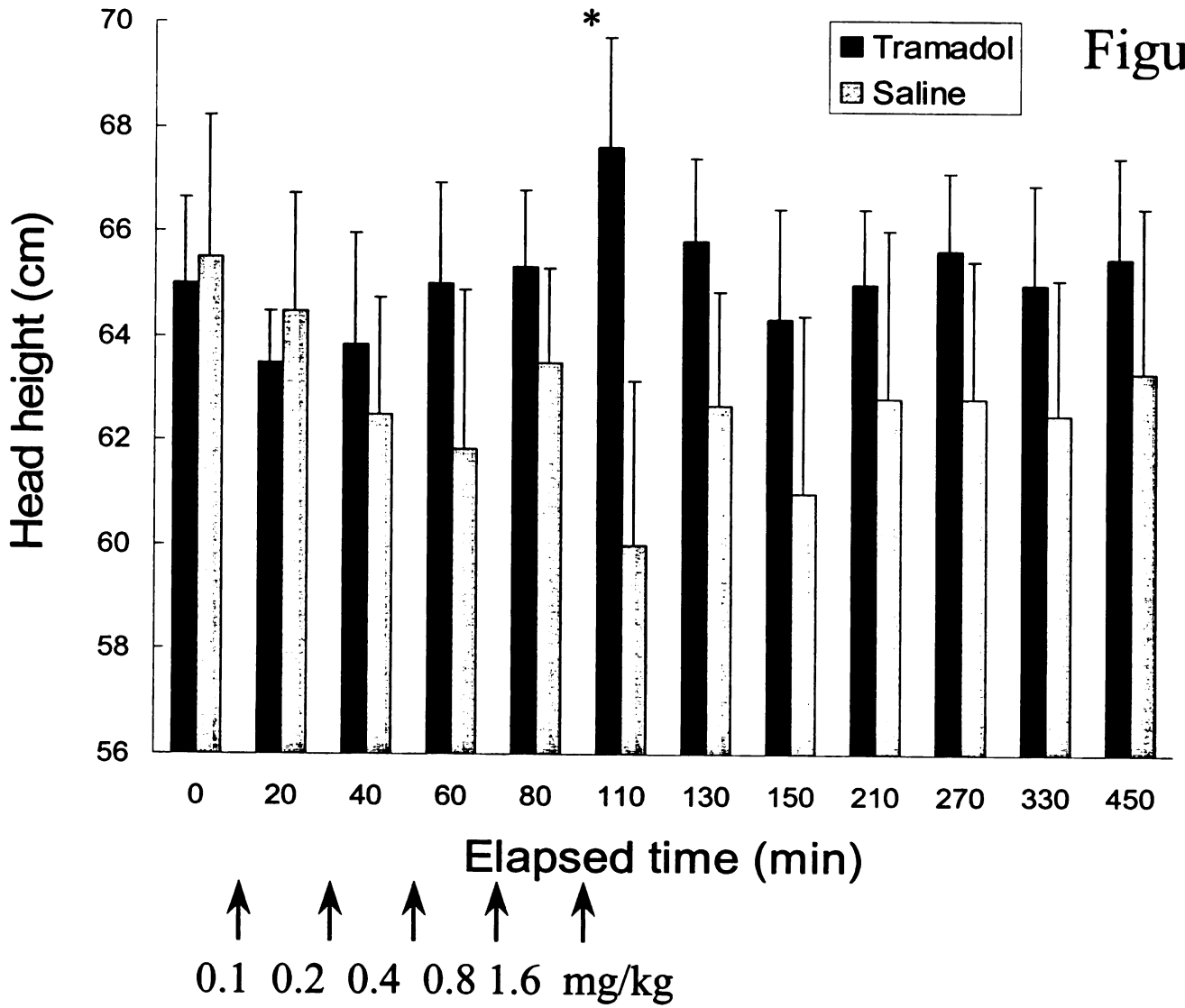

Tramadol
Saline
*
Head height (cm)
70
68
66
64
62
60
58
56
0
20
40
60
80
110
130
150
210
270
330
450
Elapsed time (min)
0.1 0.2 0.4 0.8 1.6 mg/kg

Figure 1.6

Figure 1.6

Effect of tramadol and saline on head height. Elapsed time in minutes is on the x axis, head height in cm is on the y axis. Doses indicated at bottom. Black bars = tramadol, gray bars = saline. Data are mean $\pm$ sem. There was a significant (* = $p < 0.05$) increase in head height after the highest dose of tramadol.

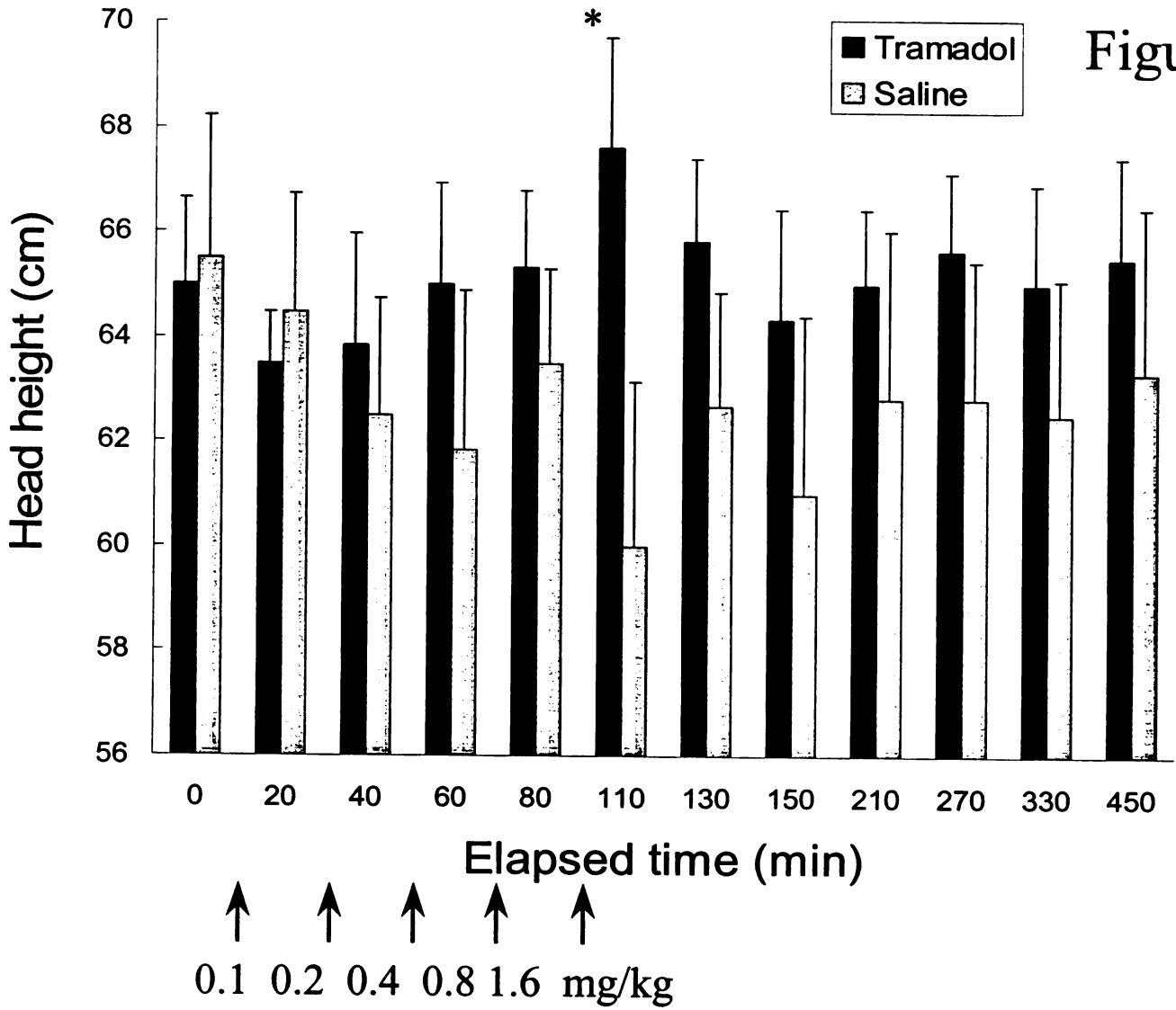

Tramadol
Saline
*
Head height (cm)
70
68
66
64
62
60
58
56
0
20
40
60
80
110
130
150
210
270
330
450
Elapsed time (min)
0.1 0.2 0.4 0.8 1.6 mg/kg

Figure 1.6

Figure 1.7

Serum concentrations of tramadol. Elapsed time in minutes is on the x axis, tramadol concentrations are ng/ml on the y axis. Doses indicated at bottom. The peak serum concentration of tramadol following a cumulative dose of 3.1mg/kg was 619.5 [60.2] ng/ml with an elimination half life of 114.3 [19.7] minutes.

Figure 1.7

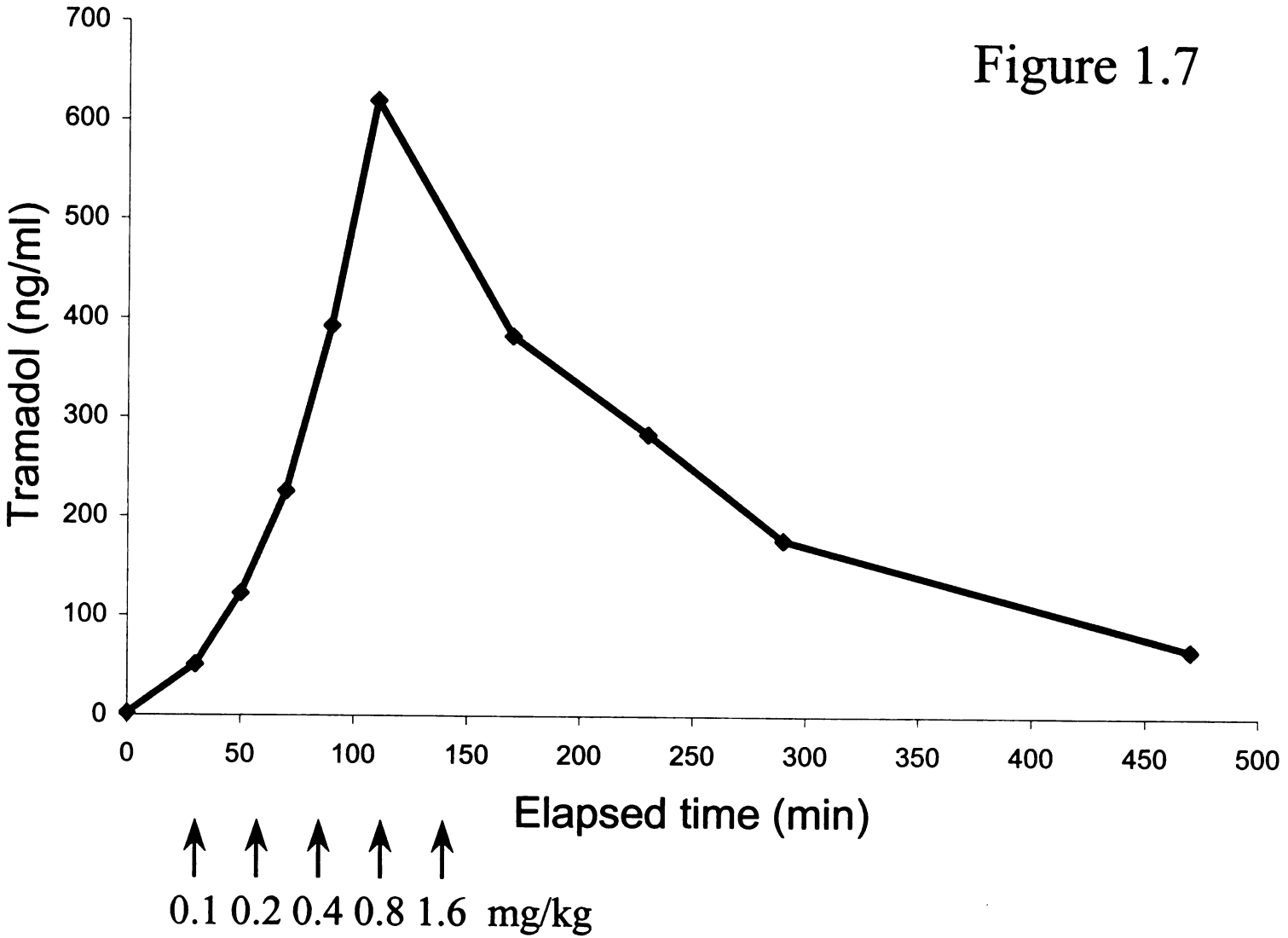

Tramadol (ng/ml)
700
600
500
400
300
200
100
0
0
50
100
150
200
250
300
350
400
450
500
Elapsed time (min)
0.1 0.2 0.4 0.8 1.6 mg/kg

Figure 1.8

Hoof withdrawal reflex latency (HWRL). Elapsed time in minutes is on the x axis, response time in seconds is on the y axis. Baseline readings were taken at time 0 and then 2mg/kg of tramadol or an equivalent volume of vehicle was administered. Readings were taken again at 5, 30, 60, 120, 240, and 360 minutes after dosing. Mean values are depicted with error bars representing standard error of the mean. Baseline HWRL was 4.16 [0.41] seconds and this was not significantly prolonged by tramadol.

Figure 1.8

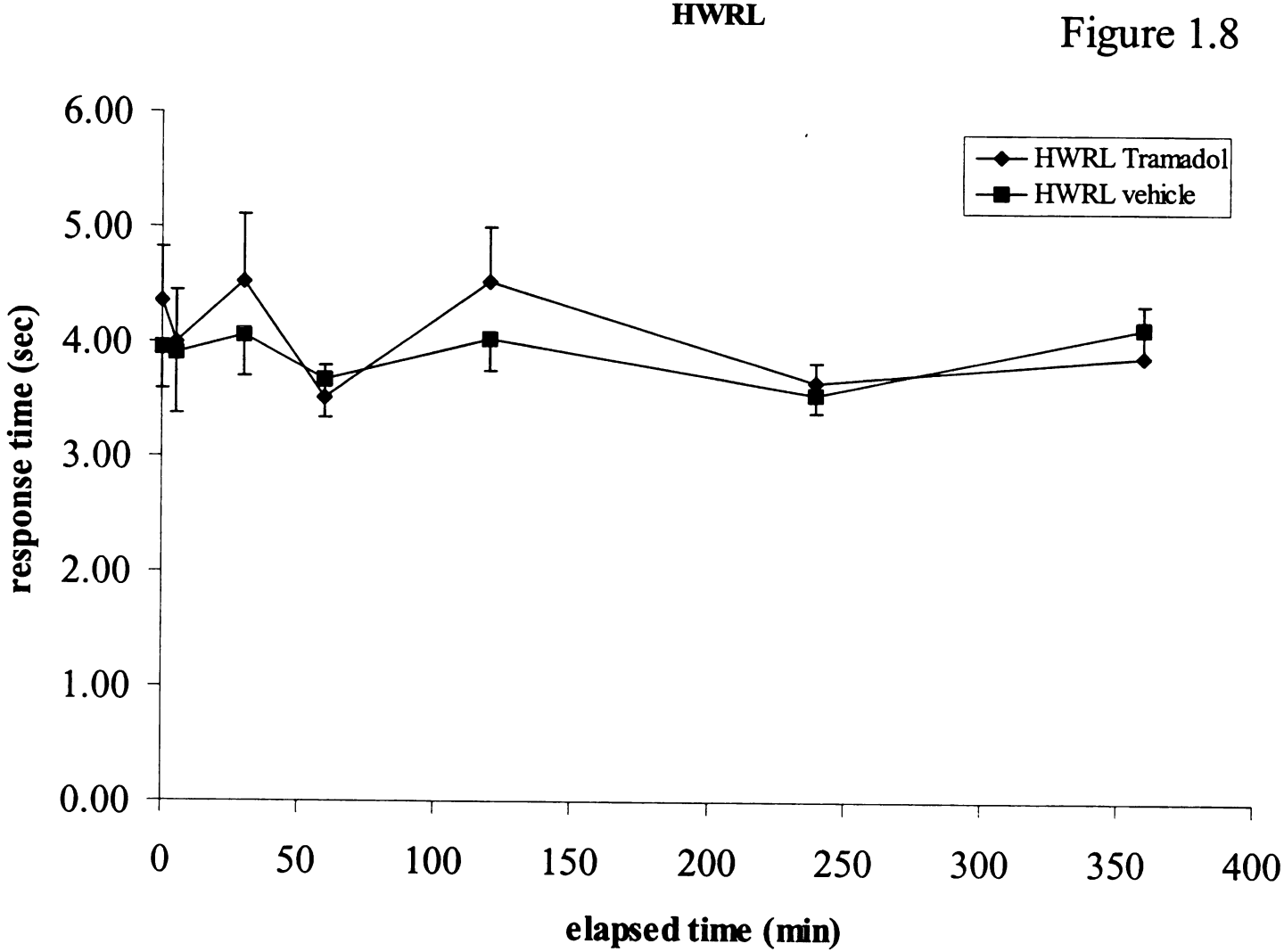
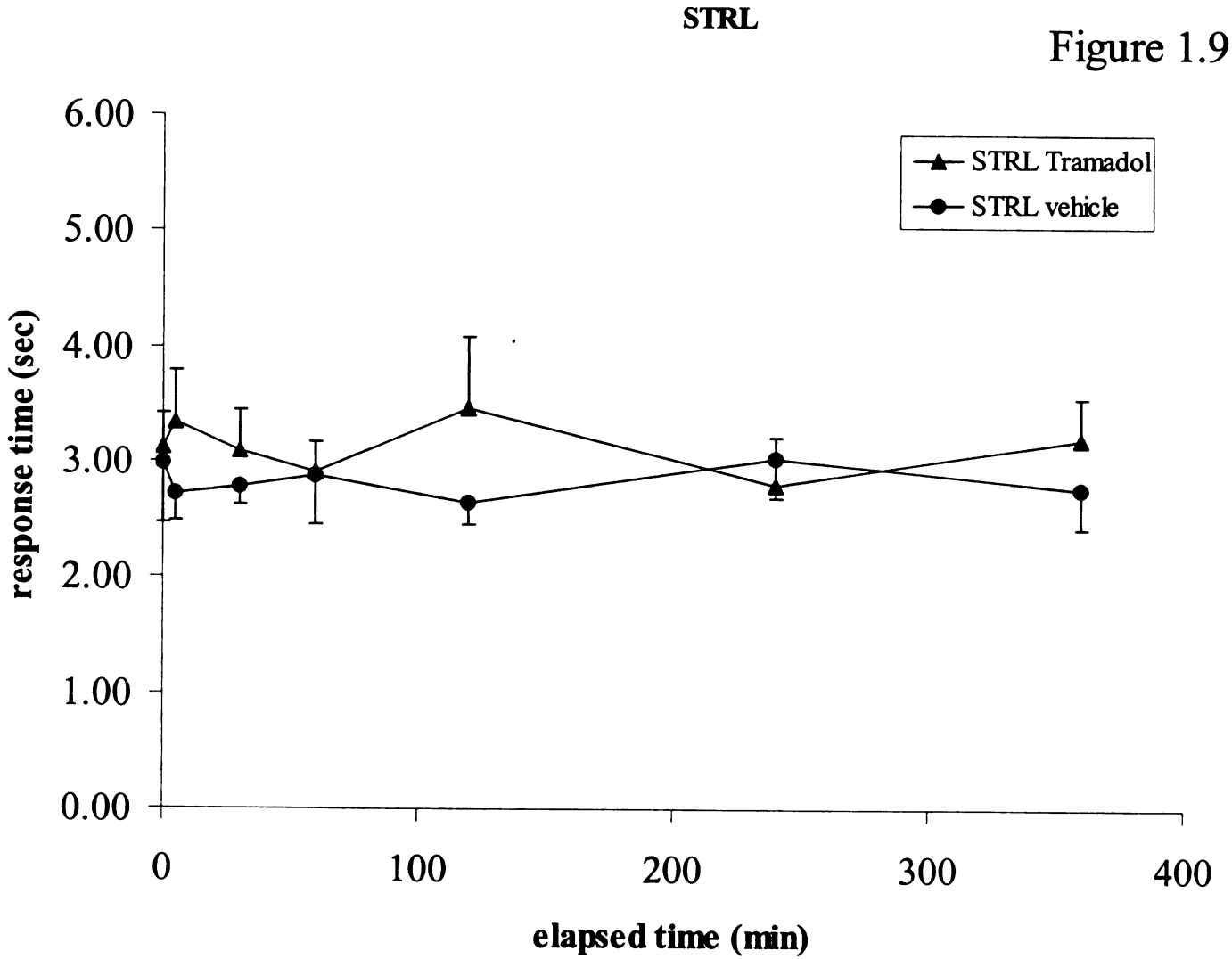

HWRL
HWRL Tramadol
HWRL vehicle
response time (sec)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0
50
100
150
200
250
300
350
400
elapsed time (min)

Figure 1.9

Skin twitch reflex latency (STRL). Elapsed time in minutes is on the x axis, response time in seconds is on the y axis. Baseline readings were taken at time 0 and then 2mg/kg of tramadol or an equivalent volume of vehicle was administered. Readings were taken again at 5, 30, 60, 120, 240, and 360 minutes after dosing. Mean values are depicted with error bars representing standard error of the mean. Baseline STRL was 3.06 [0.41] seconds and this was not significantly prolonged by tramadol.

Figure 1.9


STRL
STRL Tramadol
STRL vehicle
response time (sec)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
0
100
200
300
400
elapsed time (min)

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SUMMARY, CONCLUSIONS, AND FUTURE INVESTIGATIONS

This research demonstrated that in the adult horse, intravenous tramadol at cumulative doses less than 3.1 mg/kg produces dose dependent increases in respiratory rate, head height, head nodding, and trembling. In addition, gut sounds and rectal temperature decreased. The most pronounced effects on head nodding, trembling, respiratory rate and gut sounds correlated with serum concentrations around 600 ng/ml. Less pronounced effects were detectable with serum concentrations around 300 ng/ml.

Tramadol does not cause classical opioid effects such as mania or increased spontaneous locomotor activity. It does cause central nervous stimulation, manifested as horses looking more alert and holding their heads higher. Compared to other opioids, tramadol affected gut sounds for a shorter amount of time and did not decrease fecal output. A single bolus dose of 2mg/kg produced minimal side effects but did not increase the skin twitch reflex latency or hoof withdrawal reflex latency to a thermal stimulus. The safety of the study warrants further investigation using the same dose but other models of pain.

Two other studies have reported similar effects on behavior following tramadol administration to horses. A larger dose (5mg/kg) intravenously caused agitation, confusion, and tachycardia. A second study reported muscle twitching in their horses when 2mg/kg was given quickly, but twitching did not occur when the dose was given over about 5 minutes.

Horses possess opioid receptors and they are capable of feeling pain. Opioids are an effective class of drug for treatment of painful conditions in many species. However,

they are not routinely used in horses because of their association with negative side effects such as excitation, increased spontaneous locomotor activity, and decreased gastrointestinal motility. Early studies of the classical effects of opioids in horses evaluated high doses in pain-free subjects. It is now known that these effects are dose related. While opioids will not be the first line choice for treating pain in the horse, it is possible to use them appropriately for pain management in this species. The epidural route is especially promising because of the long duration of effect and the low incidence of typical adverse effects. However, not every cause of pain will be amenable to treatment with epidural opioids.

At least one study has shown that tramadol is bioavailable following administration of capsules in non-fasted horses. Additional work on the bioavailability of oral tramadol should be carried out. Further studies need to be pursued to investigate the role of the different metabolites of tramadol in the horse. Future investigations regarding tramadol in the horse should evaluate other models of pain, such as a thermal threshold model, cecal distention model, or a model for chronic pain such as that which occurs with laminitis.