



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Opioid Analgesia in Horses

Citation for published version:

Clutton, RE 2010, 'Opioid Analgesia in Horses', *Veterinary Clinics of North America, Equine Practice*, vol. 26, no. 3, pp. 493-514. <https://doi.org/10.1016/j.cveq.2010.07.002>

Digital Object Identifier (DOI):

[10.1016/j.cveq.2010.07.002](https://doi.org/10.1016/j.cveq.2010.07.002)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Early version, also known as pre-print

Published In:

Veterinary Clinics of North America, Equine Practice

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Opioid Analgesia in Horses

R. Eddie Clutton, BVSc, MRCVS, DVA, MRCA

KEYWORDS

• Opioid • Analgesic • Anesthesia • Horses

Opioid analgesics have been the foundation of human pain management for centuries, and their value in animals has increased since Yoxall¹ proposed that it was the veterinarian's duty to alleviate pain whenever it may occur. Compared with other domesticated species, the horse has benefitted less from the increased understanding of opioid pharmacology in animals. This situation has occurred because early literature was overlooked, whereas later work, which examined adverse side effects rather than analgesia, concluded that analgesic and excitatory doses were irreconcilably close. More recent studies have indicated a widening role for opioid analgesics in equine pain management, and radioligand studies have revealed a basis for the equine response pattern to opioid analgesics.²

MORPHINE AND OPIOID ANALGESICS: EXCITATORY EFFECTS

The excitatory effects of morphine (fear of which is an important factor limiting the veterinary use of opioid drugs in horses³) were first described in 1899.⁴ In 1917 Milks⁵ reported that 2 to 5 grains of morphine provided "maximal analgesia with a minimum of excitement." Fröhner⁶ reported that excitement combined with sensory and motor depression characterized all cases when morphine doses of 0.4, 0.75, 1.5, and 10 g were given to horses. These early reports omitted body mass data for the animals described, but an assumption that test animals weighed 600 kg indicates the doses studied were considerably greater than those used in contemporary practice. Amadon and Craigie⁷ described minimal analgesic and excitant morphine doses of 0.2 and 0.5 mg/kg, respectively in pain-free horses, and ensured that veterinary scientists thereafter focused on the excitatory and locomotor side effects of the drug rather than its analgesic properties. To complicate matters, the term excitation when applied to opioid-induced side effects in horses was subsequently used indiscriminately. For example, in one study, excitation involved "continuous head nodding, digging, shifting of limbs, vocalizing, trotting and even galloping",⁸ whereas in another the signs of excitement included muzzle tremors, muscle twitching, head jerks, head pressing, and a raised tail.⁹

Easter Bush Veterinary Centre, University of Edinburgh, Easter Bush, Roslin, Midlothian EH25 9RG, Scotland, UK

E-mail address: e.clutton@ed.ac.uk

Vet Clin Equine 26 (2010) 493–514

doi:10.1016/j.cveq.2010.07.002

vetequine.theclinics.com

0749-0739/10/\$ – see front matter © 2010 Elsevier Inc. All rights reserved.

Morphine, meperidine, pentazocine, methadone, and hydromorphone were studied in varying numbers¹⁻⁹ of pain-free horses in what has probably become the most cited reference on opioid-induced locomotion in horses.¹⁰ The study revealed 3 important points: (1) that opioids induce eating behavior at low doses and dose-dependent locomotor activity with incoordination at high doses; (2) that there is marked individual variation in responses; and (3) that the median effective value for morphine for increasing locomotion in pain-free animals is 0.91 mg/kg. This dose is considerably greater than the doses used to produce analgesia.

The opioid antagonist naloxone (15 μ g/kg) entirely prevented locomotor responses to the μ -agonist fentanyl in pain-free horses, whereas a higher dose (20 μ g/kg) reduced those of morphine by 75%.¹¹ This finding indicates that opioid-induced locomotion is mediated via opioid receptors. The propensity of an opioid analgesic to promote locomotion may be greater with μ - compared with κ -agonists,¹² although κ -agonism more commonly causes ataxia and staggering.^{13,14} However, the evidence is confusing. The κ -agonist butorphanol (50 μ g/kg intravenously [IV]) increased locomotion compared with fentanyl (5 μ g/kg), although given later in the same animals, fentanyl antagonized the locomotor effect of butorphanol.¹⁵ In contrast, another study showed that the κ -agonist U50,488H increased the intensity of fentanyl-induced locomotion.¹⁶ Although the role of opioid receptor subtypes involved in drug-induced locomotion remains unclear, much evidence points to the role of dopamine because dopamine antagonists reduce the locomotor response in most species studied. Acepromazine has antidopaminergic effects and 0.16 mg/kg IV partly blocked the locomotor effects of fentanyl (20 μ g/kg) and morphine (2.4 mg/kg) in horses.¹¹ In another study, acepromazine (0.1 mg/kg) injected IV before etorphine gave better relaxation than xylazine 3.0 mg/kg intramuscularly (IM).¹⁷ However, the participation of dopamine is not straightforward: the dopamine antagonists NNC 01-0756 and eticlopride not only failed to inhibit alfentanil-induced locomotion after 20 μ g/kg IV, but appeared to stimulate locomotion in their own right.¹⁸

Wide dose ranges tested in small study groups make it difficult to determine whether different receptors mediate different types of excitatory behaviors. However, κ -agonism might be associated with yawning, because this was seen with butorphanol (50 μ g/kg IV)¹⁵ and U50,488H (30, 60, and 120 μ g/kg).¹⁶ A sample of the range of side effects produced by high-dose opioid analgesics in pain-free horses is summarized in **Table 1**. This table illustrates a wide variation in response to fixed drug doses between studies, which in turn reflects the variation observed between horses within the same study.¹⁰ Analysis of individual studies further reveals that a given animal frequently reacted differently in response to the same drug given under identical conditions. In one study of buprenorphine²⁶ 3 μ g/kg caused signs of severe excitation, whereas doses of 5 and 10 μ g/kg IV given later produced only hallucinations. Although this might reflect a true dose effect, it raises the question whether some horses and ponies used extensively in opioid research became opioid dependent and/or tolerant, despite reported washout periods between trials.

DO OPIOID DRUGS PRODUCE ANALGESIA IN HORSES?

The use of opioid analgesics in horses can be justified when the benefits of their analgesic and sedative properties outweigh the disadvantages of potential side effects. However, demonstrating the analgesic properties of opioid analgesics is not straightforward (at least under experimental conditions) because of inconsistent results.¹² This finding may indicate biologic variability amongst the animals studied, inconsistent drug effects, or the use of flawed pain models.

Opioid Analgesia: Experimental Studies

Most experimental studies on the analgesic properties of opioid analgesics in horses have tested: (1) superficial analgesia by focusing a radiant light source onto the black painted skin overlying the distal limb or withers; the increasing time taken for the animal to respond by lifting the limb or twitching the skin in response to local heating (the withdrawal reflex latency) is taken to indicate an increasing level of analgesia; (2) visceral analgesia, using accelerometry to detect an animal's reaction to the increasing pressure in a rubber balloon implanted in the cecum; and (3) deep pain, by heating of an element implanted in the lateral surface of the humerus and recording the withdrawal reflex latency.²⁸ An alternative method (dental dolorimetry) involves recording the minimum electrical current applied to the canine tooth pulp nerve that elicits a head-lift or jaw-opening response.²⁹

One or more of these techniques in combination have been used to show and/or compare the analgesic effects of the κ -agonist U50,488H,³⁰ fentanyl (0.22 mg/kg), meperidine (4.4 mg/kg), methadone (0.22 mg/kg), oxymorphone (0.033 mg/kg), pentazocine (2.2 mg/kg), xylazine (2.2 mg/kg),²⁸ butorphanol (0.22 mg/kg), flunixin (2.2 mg/kg), levorphanol (0.033 mg/kg), morphine (0.66 mg/kg), xylazine (2.2 mg/kg),²¹ butorphanol (0.05, 0.1, 0.2, and 0.4 mg/kg IV), and pentazocine (2.2 mg/kg IV)³¹ in small (3–6) groups of horses or ponies. However, the assumption that increasing withdrawal reflex latencies indicate increasing degrees of analgesia alone is flawed. First, an animal's inclination to lift its feet is probably affected by drug-induced ataxia, if present. Alternatively, opioid-induced stepping behavior may complicate the interpretation of limb withdrawal.³¹ Many analgesic studies have incorporated α_2 agonist drugs (eg, xylazine^{21,28} or detomidine^{32,33}) and have concluded that opioid analgesics provide less analgesia than α_2 agonists used alone, or contribute little analgesia to α_2 agonist/opioid combinations. This finding is not surprising. All 3 tests for analgesia rely on motor responses as the experimental end point, which is likely to be delayed, if not by the sedative, then by the widely recognized muscle-relaxing properties of α_2 -agonist drugs. These and other factors may explain the wide variation in drug effects as well as discrepancies between the analgesic properties of opioids identified under experimental, compared with clinical, circumstances.³⁰ Furthermore, both heat and electrical current produce phasic pain of short duration that responds less to analgesics than tonic pain.³⁴ New techniques using electrophysiologic methods to investigate the pharmacologic modulation of nociception (eg, the nociceptive withdrawal reflex [NWR] and temporal summation) have been used in experimental equine pain research.³⁵ The NWR enables the examination of drug effects on evoked activity in A β and A δ fibers, whereas temporal summation provides information on drug-related changes in the gain of the nociceptive system and modulation of central integration mechanisms. These methodologies may reveal the analgesic potential of opioid analgesics more accurately than previous methods.³⁶

Opioid Analgesia: Clinical Studies

Discrepancies between experimental and clinical experiences may also be related to a belief that the risk of adverse opioid-mediated reactions is inversely proportional to the extent of the recipient's pain.³⁷ There is a paucity of literature supporting this subject. In one study, the responses of 66 horses with abdominal pain to butorphanol (0.1 mg/kg IV) were considered to be excellent (a pronounced analgesic effect was produced for a period adequate to permit specific therapy) or good (a noticeable analgesic effect with minor indications of pain).³⁸ In one case report³⁹ sublingual

Table 1			
Behavioral side effects associated with opioid analgesic use in pain-free Equidae			
References	Dose	n	Effect
Morphine			
¹⁹	70 µg/kg ^a	Unstated	Locomotor stimulation during recovery from general anesthesia (unsubstantiated)
¹⁰	100 µg/kg	5 ponies	Sham feeding, drinking and facial grimacing
²⁰	120 µg/kg	Unstated	Dysphoria, then euphoria
¹⁰	0.3 mg/kg	4 horses	1 of 5 showed increased locomotor activity ^b
	0.6 mg/kg	4 horses	4 of 5 showed increased locomotor activity; mean step rate = 30 steps per 2 minutes
²¹	0.66 mg/kg	8 ponies	1 unaffected, 7 were restless
¹⁰	1.2 mg/kg	4 horses	Mean step rate = 50 steps per 2 minutes (mean) Marked propensity to eat from the hay rack; animals swiped at hay as they passed manger, but unable to chew or swallow prehended food
	2.4 mg/kg		Mean step rate = 100 steps per 2 minutes (mean) Loss of coordination; walked as if oblivious to surroundings; played with, rather than drank, offered water; continued to eat large amounts of hay Incoordination and collapse
Meperidine			
¹⁰	1.0 mg/kg	1 horse	No effect
	2.5 mg/kg		Modest increase in locomotor activity
	5.0 mg/kg		Incoordination, shaking, immobility, then a good locomotor response
Pentazocine			
¹⁰	0.25 mg/kg	6 horses	Tendency to eat
	0.5 mg/kg	6 horses	Tendency to eat
	1.0 mg/kg	6 horses	Hay eating increased, incoordination
	2.0 mg/kg	10 horses	Severe incoordination, reluctance to walk
Methadone			
¹⁰	0.1 mg/kg	4 horses	Dose-dependent increase in stepping rate
	0.5 mg/kg		Poor coordination
	1.0 mg/kg		Tended to go down
Fentanyl			
¹⁵	5 µg/kg	4 ponies	Increased locomotion
¹¹	20 µg/kg	3 horses	Increased locomotion
¹⁶	20 µg/kg	6 horses	Head bobbing, food snatching, cribbing
Alfentanyl			
²²	4 and 10 µg/kg	6 horses	No effect
	20 and 40 µg/kg		Box walking, bizarre eating behaviors, head tossing, and shaking
Butorphanol			
¹⁵	50 µg/kg		Yawning
²³	0.1–0.13 mg/kg		Staggering and ataxia
²⁴	0.1 mg/kg		Box walking
²⁵	0.2 mg/kg		Apprehension, increased locomotor activity, ataxia
²¹	0.22 mg/kg		Nodding, pacing, pawing, body swinging, head shaking, shivering

(continued on next page)

References	Dose	n	Effect
Buprenorphine			
²⁶	3 µg/kg	10 horses	Head nodding, pawing, chewing, facial rictus, a violent and potentially dangerous excitation crisis
	5 and 10 µg/kg		Marked ataxia, CN system excitation, or hallucinations in 3 animals
⁸	5 and 10 µg/kg	6 horses	Continuous head nodding, digging, shifting of limbs, vocalizing, trotting, galloping
²⁷	10 µg/kg	6 horses	Continuous head nodding, head shaking, neighing, pawing, shifting of ground support, and restlessness

^a All doses intravenous unless otherwise stated.

^b A statistically significant increase in the number of steps taken in a 2-minute sampling period.

buprenorphine (6 µg/kg) was given twice daily to a filly with traumatic head and neck injuries and in which signs of pain were unresponsive to phenylbutazone. After administration, “the filly became sedated and noticeably more comfortable. The neck muscles relaxed and the filly moved its head and neck more freely. Mild euphoria was displayed by the filly’s tranquil and affectionate temperament. No signs of excitement of the central nervous system were seen.” This report supports the view that opioids are beneficial when given to horses with real (ie, nonexperimental) pain.

OPIOID ANALGESICS AND STANDING SURGICAL ANESTHESIA

Do Opioids Enhance the Sedative Effects of α_2 Agonists?

It seems so. Morphine (0.1 mg/kg), methadone (0.1 mg/kg), butorphanol (50 µg/kg), but not meperidine (1.0 mg/kg) improved the sedative effects of intravenous detomidine (10 µg/kg) in 3 ponies and a thoroughbred and decreased responses to external stimuli.⁹ In another study, the inclusion of butorphanol (50 µg/kg, IV) to one of 2 romifidine doses (40 and 80 µg/kg, IV) reduced responses in 4 pain-free ponies and one thoroughbred when the animals’ coronets were touched, their ears tickled, a cloth was flapped in front, and hands were clapped behind them. However, the height of the muzzle from the ground was not lessened by the addition of butorphanol, which indicates that low-dose romifidine does not measurably relax the cervical muscles.⁴⁰ When the effects of intravenous detomidine (30 µg/kg), xylazine (1.1 mg/kg), and xylazine (1.1 mg/kg) with morphine (0.75 mg/kg up to 300 mg) were compared in 99 horses undergoing bronchoalveolar lavage, no significant differences between treatments were found. However, those assessing the level of sedation considered it to be unnecessarily deep. Opioids conferred no benefit because all animals were overdosed.⁴¹

Do Opioid Analgesics Enhance the Experimentally Determined Analgesic Effects of α_2 Agonists?

Three studies indicate an additive or synergistic effect, although one, using dental dolorimetry, concluded that xylazine (1.1 mg/kg IV) alone prevented motor responses to electrocution equal to that induced with xylazine/morphine (0.75 mg/kg IV), xylazine/butorphanol (0.04 mg/kg IV), or xylazine/nalbuphine (0.75 mg/kg IV) combinations.²⁹ In contrast, observers grading analgesia in the face of electrical and

pressure stimuli applied to the body wall produced by xylazine (0.66 mg/kg IV) combined with one of 2 morphine doses (0.12 or 0.66 mg/kg IV) opined that analgesia was considerably improved when xylazine was combined with the higher morphine dose.²⁰ Detomidine (10 µg/kg IV) alone, or combined with butorphanol (25 µg/kg) or levomethadone (100 µg/kg),³³ caused a significant temporary increase in the nociceptive threshold (established electrically and pneumatically), although butorphanol and levomethadone both increased the threshold and prolonged antinociception compared with detomidine alone. The same results were found in a similar study examining the same drugs³² but these investigators expressed concern that the stimulus applied (electrical or mechanical) might influence the interpretation of drug effects, because although both butorphanol and levomethadone increased the reaction threshold to a similar degree, the threshold increase was more apparent when the coronary band was heated.

Do the Analgesic Properties of Opioids Compare with α_2 Agonists?

The contemporary popularity of multimodal pain therapy challenges the need to compare the analgesic effects of individual α_2 agonist and opioid drugs, because most practitioners now recognize the benefits of using several analgesic drugs in combination. Nevertheless, one study comparing the effects of xylazine (2.2 mg/kg IM), pentazocine (1 mg/kg IM), and meperidine (2.2 mg/kg IM) injected 10 minutes after colic signs had been induced by cecal balloon inflation⁴² concluded that xylazine was the only drug that provided consistent analgesia. A similar tendency to attribute the suppression of colic signs to a pure analgesic, rather than a sedative or muscle-relaxing effect, was apparent in a study comparing butorphanol (0.1 mg/kg) with detomidine (20 or 40 µg/kg), intravenous flunixin (1.0 mg/kg) and xylazine (0.5 mg/kg) in 152 horses presenting with colic.⁴³ Butorphanol was considered unsatisfactory as an analgesic 90% of the time, whereas detomidine was considered to be superior.

OPIOID ANALGESICS AND TOTAL INTRAVENOUS ANESTHESIA

The evidence that the beneficial effects of opioids in standing surgical techniques may extend to those performed under total intravenous anesthesia (TIVA) is not compelling. Love and colleagues⁴⁴ studied the effects of preoperative butorphanol (0.1 mg/kg IV) on postcastration pain in 20 ponies and concluded that a single preoperative dose does not provide adequate postoperative analgesia for open castration in colts. In another study of colt castration (n = 36)⁴⁵ the analgesic effects of butorphanol alone (0.05 mg/kg IM before surgery, then every 4 hours for 24 hours), phenylbutazone alone (4.4 mg/kg IV, before surgery and then 2.2 mg/kg by mouth, every 12 hours for 3 days) or butorphanol and phenylbutazone at the aforementioned dosages were similar. However, every horse in the study received preoperative intratesticular lidocaine, which may have obscured differences between treatments. One study⁴⁶ compared the effects of butorphanol (50 µg/kg IV), morphine (0.1 mg/kg IV), or saline given with romifidine (100 µg/kg IV) in 54 ponies undergoing field castration and found sedation was significantly better in ponies receiving butorphanol compared with saline. Quality of anesthesia was better in the butorphanol group compared with the morphine and control groups. Quality of induction and recovery were not significantly different between groups, nor were recovery time and the number of repeated anesthetic doses required during surgery. This finding indicates that butorphanol at least improves the quality of some TIVA anesthetic techniques.

OPIOID ANALGESICS AND INHALATIONAL ANESTHESIA

The Effects of Opioid Analgesics on Minimum Alveolar Concentration

The sparing effects of morphine (and those of other opioids) on inhalational agents are less obvious in horses compared with other species.¹² The minimum alveolar concentration (MAC) (ie, the end-tidal concentration of inhaled anesthetic preventing purposeful responses to a specified noxious stimulus in 50% of a test population) is lowered by opioid drugs in most species studied. However, in horses most studies reveal opioid drugs exert either a negligible or a MAC-increasing effect and considerable individual variation. For example, in an investigation of the MAC of halothane in 7 ponies⁴⁷ acepromazine (0.05 mg/kg) reduced MAC by 36.9% (mean), whereas butorphanol (0.05 mg/kg) did not significantly change the mean group MAC value, although it increased it in 3 ponies, decreased it in 1, and was without effect in the remaining three. In another study⁴⁸ the MAC of isoflurane was unaffected by low-dose morphine (0.25 mg/kg) but was increased significantly by a higher dose (2.0 mg/kg). Again, the effects were highly variable; MAC was reduced by 19% in one horse, and increased by 56% in another. No significant changes in MAC of halothane were identified before and during the infusion of alfentanil (another opioid-3 agonist) given at 3 constant rate infusions⁴⁹ and the investigators concluded that plasma alfentanil concentrations known to be effective in human beings and dogs did not induce an appreciable change in halothane MAC in horses. In a fourth study⁵⁰ butorphanol (0.022 mg/kg and 0.044 mg/kg) decreased the MAC of halothane by 9% or 10%, depending on the dose; however, this was not a statistically significant effect, and in 2 ponies, MAC increased. These studies suggest that opioid drugs at certain doses stimulate rather than depress CN activity in horses anesthetized with experimental techniques and stimulated electrically.

The Benefits of Opioid Analgesics During Inhalation Anesthesia

Opioids are used in other species during inhalational anesthesia to reduce the requirement for volatile anesthetic, and thus preserve cardiopulmonary function. This situation may not apply in horses given their variable effect on MAC. However, numerous studies show that intraoperative opioids given to horses undergoing surgical procedures have negligible cardiopulmonary effect and improve the quality of recovery (see later discussion), whereas at least 2 studies indicate an analgesic and anesthetic-sparing effect. In one study⁵¹ involving 45 horses anesthetized for arthroscopy with halothane, 31 horses received preoperative butorphanol (50 µg/kg IV), whereas the remainder did not. The mean dose of vaporized halothane, the vaporizer dial setting, and the dose of dobutamine required to correct hypotension were significantly lower in butorphanol recipients, whereas mean arterial blood pressure was significantly higher. In a retrospective study of 82 surgical cases⁵² butorphanol appeared to deepen isoflurane anesthesia without adversely affecting cardiovascular variables. Furthermore, it appeared to obtund sympathetic stimulation arising from surgery.

Opioid Analgesics in Experimental versus Clinical Inhalation Anesthesia

Studies showing MAC increase by opioid analgesics do not confirm the absence of an analgesic effect¹² during inhalation anesthesia for several reasons. First, electrical stimulation is probably qualitatively different from surgical nocistimulation. Second, even under general anesthesia, opioid stimulation may obfuscate more subtle signs of antinociception. Extradural (rather than systemic) morphine (0.1 mg/kg) reduces the MAC of halothane by 14% during pelvic limb stimulation.⁵³ Third, MAC studies

are performed on horses anesthetized with the drug being evaluated and no other, which contrasts with a typical general anesthetic for animals undergoing surgery. Fourth, the use of movement as an index of inadequate CN depression (ie, MAC) has been challenged.⁵⁴

Opioid Analgesics, Recovery from General Anesthesia, and Box-walking

Concerns have been raised¹² that opioid-induced locomotor activity may adversely affect recovery quality from anesthesia, whereas others have warned that opiates may prolong recovery when given before animals have recovered consciousness.⁵⁵ In support of these concerns, Steffey and colleagues⁴⁸ described poor recoveries in horses that had received 2.0 mg/kg morphine characterized by strong running or galloping movements made while horses were still in lateral recumbency; preoperative butorphanol (0.1 mg/kg IV) significantly prolonged recovery from a TIVA technique used for colt castration.⁴⁴

However, several studies have indicated that morphine does not impair recovery quality after general anesthesia in clinical cases. One study, involving 25 horses undergoing minor orthopedic or soft-tissue surgery, found no differences in recovery quality between horses receiving saline, butorphanol (50 µg/kg), or morphine (0.02 or 0.05 mg/kg).¹⁹ A retrospective study of 84 horses undergoing surgery found no significant differences in the incidence of postoperative box-walking between horses receiving (n = 51) and not receiving morphine.⁵⁶ Of the 2 horses that box-walked (one from each group) that which had received morphine (120 µg/kg IV) was identified as a habitual box-walker. In the United Kingdom, one study (n = 8427) revealed that 1.1% of racehorses box-walk spontaneously and without anesthetic and/or surgical provocation.⁵⁷ Furthermore, Mircica and colleagues⁵⁶ found recovery quality was better in horses receiving morphine. Box-walking was similarly absent in a prospective study of 22 horses undergoing elective surgical procedures in which 11 received preinduction morphine (0.15 mg/kg) followed by its infusion (0.1 mg/kg/h) during halothane anesthesia.⁵⁸ In this study, morphine recipients recovered better than those not receiving morphine, with quality differences increasing with the duration of anesthesia. In a fourth study involving 38 thoroughbred horses undergoing upper airway surgery,⁵⁹ no box-walking was observed in any horse but recovery quality was significantly better in horses that received morphine (0.1 [n = 13] and 0.2 [n = 12] mg/kg). Meperidine (2 mg/kg IM) injected at the end of 3 different anesthetic techniques in 128 horses undergoing surgery and/or radiography did not affect recovery scores, nor the time to achieve sternal recumbency or standing.⁶⁰

The use of intraoperative opioids also reduces the need for postoperative analgesics. In one study⁶¹ analgesia was supplemented in 68 of 203 horses anesthetized with halothane using butorphanol (up to 0.1 mg/kg) treated postoperatively with phenylbutazone (4 mg/kg), flunixin (1 mg/kg), or carprofen (0.7 mg/kg). The need for additional postoperative analgesia was significantly reduced in horses receiving butorphanol.

Reconciling Opioid-induced Locomotion Versus Improved Recovery Quality

One explanation for the absence of locomotor activity and improved recovery quality in surgical cases compared with experimental horses is that the former receive sedatives (eg, α_2 agonists), which may obscure any stimulant effects that high-dose morphine or other opioids may exert, whereas drugs with antidopaminergic activity (eg, acepromazine) may depress the neural processes promoting adverse reactions.⁶² Second, α_2 -agonist or phenothiazine drugs may potentiate the sedative and/or analgesic properties of opioid analgesics. Third, opioid doses used in clinical studies

are substantially less than those used in deliberate attempts to experimentally produce side effects. Fourth, surgical pain may reveal the principal pharmacologic quality of morphine (ie, analgesia) more reliably than laboratory nocistimulation (ie, the drug performs better when real pain is present). These possibilities feature in one study⁴⁸ in which 6 pain-free horses anesthetized only with isoflurane had undesirable and dangerous recoveries after receiving high- (2.0 mg/kg) but not low- (0.25 mg/kg) dose morphine. Clinical anecdotes attributing postoperative box-walking to opioid analgesics may have described horses suffering from inadequate analgesia. Increased locomotor activity is a common sign of pain in horses, particularly those with gastrointestinal pain. Postoperative gastrointestinal pain is not uncommon in horses deprived of analgesia. In one study⁶³ horses not receiving phenylbutazone after arthroscopy were more likely to show signs of postoperative abdominal discomfort than those receiving the drug. Such signs could have been attributed to opioid analgesics, had they been given. In another study⁵⁹ 3 (of 12 horses) not receiving morphine showed signs of postoperative abdominal discomfort, whereas 25 (of 25) morphine recipients did not. In a study examining the postoperative effects of morphine⁵⁶ one horse ran obsessively around the recovery box after standing, and could be halted with difficulty only after 5 minutes. In this case, a misdiagnosis of opioid-induced locomotion could not be made because the horse had not received opioid analgesics. One multicenter study examining the role of opioids in controlling colic pain⁴³ graded abdominal discomfort using signs that included sweating, exaggerated body movement, heart and respiratory rates, continuous moving, stomping or pawing, weight-shifting, and exaggerated responses to noise. The same study simultaneously used sweating, excitation, cardiovascular or respiratory abnormalities, instability, and abnormal reactions to sight, sound, or touch as indicators of opioid-induced side effects. This study illustrates the potential to confuse signs of inadequate analgesia and the side effects of an opioid analgesic. The ability of veterinary surgeons to distinguish signs of pain from excitatory opioid effects in horses should not be assumed. The lack of consensus in the UK veterinary profession about whether a horse feels pain after castration suggests that equine pain behaviors are not well recognized or fully appreciated.³

DOES MORPHINE CAUSE POSTOPERATIVE COLIC?

The gastrointestinal effects of morphine that are held to predispose to postanesthetic colic (PAC) have contributed to the unpopularity of opioid analgesics in horses.³ Opioid-induced dysfunction in chronically instrumented bowel loops in small numbers of pain-free Equidae has been convincingly shown, although the clinical relevance of such studies at times seems obscure. For example, morphine (0.5 and 1.0 mg/kg) and fentanyl (10 or 50 µg, IV) initially stimulated, but then inhibited cecocolic electrical and mechanical activity for up to 3 hours in 3 pain-free ponies, whereas naloxone (0.5 mg/kg IV) elicited marked propulsive activity in the colonic segment.⁶⁴ Other opioid drugs behave similarly: meperidine (250 mg) and especially methadone (10 mg) decreased the total electrical activity of a chronically instrumented bowel loop in 3 ponies.⁶⁵ However, effects are often variable, and seem at odds with clinical observations. In one study⁶⁶ butorphanol (0.1 mg/kg) meperidine (1.0 mg/kg) and pentazocine (0.3 mg/kg) increased the duration of migrating myoelectric complexes (MMCs) in the jejunum of 4 pain-free ponies, but although metoclopramide (30 µg/kg) had no effect on MMCs it produced clinical signs of colic, whereas the opioid analgesics did not.

Morphine exerts a constipative effect in normal horses as in other species. In one study⁶⁷ morphine (0.5 mg/kg) given twice daily to 5 pain-free horses for 6 days

decreased propulsive motility and moisture content in the gastrointestinal tract lumen. The investigators concluded that the effects observed may predispose treated horses to ileus and constipation although they did not reveal the medical indications for 6 days of morphine therapy in pain-free animals.

The volume of references to the adverse effects of μ -agonists on equine gastrointestinal function contrasts with that on μ -antagonist activity. Nevertheless, naloxone (0.75 mg/kg IV) produced rapid onset diarrhea, restlessness, abdominal checking, tachycardia, tachypnoea, and diaphoresis in 8 adult previously pain-free thoroughbreds, which the investigators concluded was an acute abdominal distress syndrome similar to spasmodic colic.⁶⁸ This finding confirms the complexity of equine gastrointestinal pharmacology and supports the possibility that inadequate analgesia may have been responsible for signs previously attributed to morphine.

Nonopioid Causes of PAC in Horses

Other causes of gastrointestinal dysfunction may contribute to PAC in horses. Recent changes in management^{69–72} such as exercise, diet, and transport may increase risk in hospitalized horses.⁷³ Prolonged starvation (18 hours) has also been implicated.⁷⁴ Sympathetic nervous stimulation as part of the stress response to anesthesia, surgery, and nocistimulation decreases gastrointestinal motility in human beings⁷⁵ and probably has similar effects in horses.⁷⁶ Many drugs used to ameliorate the stress response also depress gut motility, including α_2 -agonist drugs, which are almost universally used for preanesthetic medication^{77,78} and nonsteroidal antiinflammatory drugs (NSAIDs),⁷⁹ which are commonly used for analgesic and antiendotoxic effects. The combination of xylazine and ketamine (arguably one of the most popular means of inducing anesthesia in horses) produced the longest period of hypomotility in one myoelectrical study of equine intestinal activity.⁸⁰ These findings challenge the justification for implicating opioid drugs as a principal cause of postoperative colic, which is unsupported by epidemiologic studies.

Postoperative Colic: Epidemiologic Studies

One study⁷³ linked morphine with a 4-fold increase in risk of PAC after orthopedic surgery compared with the use of butorphanol, or abstinence from opioid analgesia. In this study, 14 horses develop colic after a total of 496 operations. However, despite a population dose range of 0.08 to 0.3 mg/kg, 13 of the 14 cases that subsequently developed colic received only 0.1 mg/kg. The study also failed to clarify the factors determining morphine dose. It is therefore possible that severe orthopedic pain contributed to postoperative gastrointestinal dysfunction in some of the horses that developed colic. Another link between morphine and an increased prevalence of PAC was identified in a different center,⁸¹ but the association disappeared when analyses were stratified by procedure, indicating that the operation type was a greater risk factor than the opioid analgesic. This study, which examined the anesthetic records of 553 horses (342 undergoing magnetic resonance imaging [MRI]; 211 having nonabdominal [predominantly orthopedic] surgery), found 20 cases developed PAC,⁸¹ representing 7.1% of surgical and 1.5% of MRI cases. Increased risk was associated with isoflurane, and the use of benzyl penicillin and/or ceftiofur for antibiosis. Factors reducing risk were romifidine for preanesthetic medication, prolonged anesthesia, and sedation within 2 days of general anesthesia. Perianesthetic morphine administration was not associated with increased risk. A multicenter case-control study⁸² looking at the prevalence of and risk factors associated with PAC in 861 horses undergoing non-abdominal surgery found that the center involved and the operation type increased risk, nonseptic orthopedic cases being at greatest risk. Preoperative food deprivation

(horses that were not starved were more likely to develop colic) and opioid drugs were confounding factors. In this study, 45 horses developed colic. Although the use of opioid analgesics increased risk when compared with surgeries in which none were used, there were no significant differences between butorphanol or morphine use. The prevalence of PAC in those centers using butorphanol exclusively was the same as those using only morphine. In one study^{60,61} of 38 thoroughbreds undergoing upper airway surgery, the prevalence of decreased appetite for up to 4 postoperative days in horses not receiving morphine (8 of 12) was similar with those receiving morphine at 0.1 mg/kg (7 of 13) or 0.2 mg/kg (7 of 12). However, 3 (of 12) horses not receiving morphine showed signs of postoperative discomfort consistent with colic. No horses receiving morphine developed PAC. Butorphanol also seems to confer benefit. Doses up to 100 µg/kg were used in a proportion of 203 horses undergoing surgery and randomly allocated to receive flunixin, carprofen, or phenylbutazone. Signs of mild colic were observed in 18 horses but were unassociated with use of butorphanol. Butorphanol ensured a reduced requirement for postoperative NSAID therapy.⁵⁹ In another study⁵⁶ there were no significant differences in the incidence of postoperative gastrointestinal complications between horses receiving (n = 51) and not receiving (n = 33) morphine at 100 to 170 µg/kg.

The literature indicates a multifactorial cause for PAC and an equivocal contribution by morphine and other opioid analgesics. However, even unequivocal evidence for an opioid-associated risk would have to be weighed against the better recoveries that opioid analgesics promote. In 5 studies^{56,59,73,81,82} investigating opioid-induced morbidities in a total of 2240 horses, PAC occurred in 100. None of these died directly from postoperative colic and only 2 required surgical treatment. In contrast, fractures in recovery, some of which are related to poor-quality recoveries, are the second greatest cause of postoperative equine mortality.⁸³

Opioid Analgesics in the Control of Gastrointestinal Pain

Some authorities, although acknowledging the efficacy of opioids as analgesics, have condemned their use in equine colic because they cause excitation.²¹ Others have suggested the ability of opioids to stimulate forceful contractions in an already distended bowel supports a relative contraindication for their use in colicky horses with that condition.¹² In 1946 Milks wrote, "Small doses [of morphine] are usually sedative to the horse so that the drug is especially indicated in strong persistent pain such as enteritis. It may often be extremely useful in spasmodic colic and produces its action here by arresting the irregular and violent peristalsis which is the cause of the pain."⁸⁴ Later support for the role of morphine in colic pain emerged in a study that recorded gastrointestinal electrical potentials from 2 ponies that developed colic naturally.⁸⁵ The investigators recommended the use of morphine because "it provided concomitant antispasmodic action on the small bowels while stimulating colonic activity." This recommendation contrasts with the conclusion of a study⁷⁸ examining the effects of xylazine (0.5 mg/kg) detomidine (12.5 µg/kg) and a xylazine (0.5 mg/kg)-butorphanol (0.05 mg/kg) combination on equine duodenal motility that concluded that "the profound suppressive effect of a routine dose of detomidine or xylazine - butorphanol combination on equine duodenal motility must be considered when using these agents for management of colic, especially when encouragement of intestinal motility is desirable."

In the clinical situation, the effective management of pain overrides theoretic concerns with the effects of opioid analgesics on gastrointestinal function for at least 2 reasons: (1) it allows the safer diagnosis of surgical versus medical colic; and (2) it is humane.

CARDIOVASCULAR EFFECTS OF OPIOID DRUGS IN HORSES

The cardiovascular effects of opioid analgesics in horses seem to depend on the drug, dose, administration route, and coadministered drugs, although the recipient's level of consciousness is important because cardiovascular hyperdynamism is often linked with central nervous (CN) stimulation. Morphine can cause hypotension in human beings by initiating histamine release with peripheral vasodilatation and tachycardia. The likelihood of this is said to be greatest when high doses are given rapidly IV. Morphine has caused urticarial lesions in horses, which may be linked to this finding, although associated cardiovascular effects are unreported. This is not the case with meperidine, which has caused severe reactions when given IV (1 mg/kg) in both conscious and unconscious horses.⁸⁶ In general, opioid drugs seem not to depress cardiovascular variables in anesthetized horses to the same (modest) extent that they do in other species,²⁰ although all studies conducted in this area have involved small numbers of pain-free horses or ponies.

Cardiovascular Effects of Opioid Analgesics in Conscious Horses

Intravenous morphine (0.12 mg/kg), meperidine (1.1 mg/kg), oxymorphone (0.03 mg/kg), methadone (0.12 mg/kg), and pentazocine (0.9 mg/kg) caused similar levels of cardiovascular stimulation⁸⁷ linked with dysphoria and euphoria. Heart rate (HR) increased after injection but returned to baseline within 30 minutes. Systolic (SAP), mean (MAP), and diastolic (DAP) arterial pressures increased significantly although transiently. In another study²¹ morphine (0.66 mg/kg IM) caused excitation and increased all cardiovascular variables for at least 4 hours. Buprenorphine (10 µg/kg IV) also stimulated 6 pain-free horses, causing a sustained (120-minute) increase in HR, SAP, MAP, and DAP and cardiac index.²⁷ However, in another buprenorphine study several effects did not coincide with CN system activity: 3 µg/kg IV caused a marked and lasting hypertension without a corresponding HR increase. In one horse that became sedated DAP, but not SAP, increased without a concomitant increase in HR.²⁶

Cardiovascular and CN stimulation are variably linked in horses receiving butorphanol. Intravenous doses of 0.1, 0.2, and 0.4 mg/kg caused predominantly excitatory signs yet did not significantly affect HR, MAP, or DAP.⁸⁸ In another study²³ IV butorphanol (0.1–0.13 mg/kg) caused gross behavioral disturbances although the HR was unaltered in 4 of 7 animals. Although these studies suggest that the depressant effect of butorphanol on HR overcomes the chronotropy of CN stimulation, another study²¹ found 0.22 mg/kg increased HR. Furthermore, neither HR nor MAP changed from pre-injection values when butorphanol (0.05 mg/kg) was injected IV in horses anesthetized with halothane undergoing minor orthopedic or soft-tissue surgery.¹⁹

Cardiovascular Effects of Opioid Analgesics with α_2 Agonists

The cardiovascular effects of opioid/ α_2 agonist combinations are unpredictable because the latter have complex time- and dose-dependent effects, whereas their sedative properties ameliorate any opioid-induced CN stimulation in nonpainful horses. Most studies indicate the hemodynamic effects of α_2 agonists prevail over those of opioid analgesics. For example, in one study, butorphanol (50 µg/kg, IV) added to one of 2 romifidine doses (40 and 80 µg/kg, IV) had no effect on HR and MAP compared with those of romifidine alone.⁴⁰ In another study,²⁰ 2 doses of morphine (0.12 and 0.66 mg/kg) given to horses premedicated with xylazine (0.66 mg/kg) caused similar significant decreases in cardiac output (Qt) and increases in central venous pressure, SAP, MAP, DAP, and pulmonary arterial pressure.

Detomidine (10 $\mu\text{g}/\text{kg}$) seems to ameliorate opioid-induced cardiovascular effects less than xylazine and romifidine.⁹ When morphine (0.1 mg/kg), methadone (0.1 mg/kg), meperidine (1.0 mg/kg), or butorphanol (50 $\mu\text{g}/\text{kg}$) were administered IV to pain-free ponies and a thoroughbred sedated 6 minutes earlier with detomidine (10 $\mu\text{g}/\text{kg}$), marked tachycardia and hypertension followed morphine and meperidine injection, although cardiovascular changes were minimal within 5 minutes. This finding was not associated with excitation except in one pony whose HR rose to 70 beats per minute and MAP to 200 mm Hg. Despite preexisting sedation, meperidine caused marked excitation in one pony and increased HR to 100 beats per minute and MAP to 215 mm Hg.

Cardiovascular Effects of Opioid Analgesics with Inhalant Anesthetics

Opioids seem to have little, if any, cardiovascular effects in anesthetized horses undergoing surgery. Neither HR nor MAP changed when intravenous morphine (20 and 50 $\mu\text{g}/\text{kg}$) or butorphanol (0.05 mg/kg) were given to horses anesthetized with halothane undergoing minor orthopedic or soft-tissue surgery.¹⁹ The incidence of bradycardia, tachycardia, hypertension, and hypotension was similar in 84 horses anesthetized with halothane irrespective of whether morphine (100–170 $\mu\text{g}/\text{kg}$) was given or not ($n = 33$).⁵⁶ In another study⁸⁹ 19 of 38 horses anesthetized with halothane received preoperative morphine (0.15 mg/kg IV) followed by infusion (0.1 mg/kg/h). There were no significant differences in the MAP or HR of these animals compared with those receiving the same anesthetic without morphine. Butorphanol also exerted little measurable effect in horses anesthetized with isoflurane.⁵² A retrospective evaluation of anesthetic records from 76 horses anesthetized for various operations revealed that butorphanol did not affect SAP, MAP, DAP, or HR, causing the investigators to conclude that butorphanol can be administered to horses during isoflurane anesthesia without adverse cardiovascular effects.

Pharmacologic relationships do not seem to allow the prediction of the effect of a drug. In one study of horses anesthetized with halothane not undergoing surgery⁵⁰ infused alfentanil caused dose-dependent increases in blood pressure, although HR did not change. In contrast, the related phenylpiperidine derivative sufentanil (1 and 2 $\mu\text{g}/\text{kg}$ IV) transiently reduced MAP and HR in 6 different animals similarly anesthetized.⁹⁰

It is possible that surgical nocistimulation during inhalation anesthesia offsets any opioid-induced cardiovascular depression, whereas general anesthesia obtunds sympathoadrenal responses arising from opioid-induced CN stimulation.

RESPIRATORY EFFECTS OF OPIOID DRUGS IN HORSES

The respiratory effects of morphine and other opioid drugs in horses also seem to depend on whether recipients are conscious and excitable, or unconscious,⁸⁷ although this is not always predictable.

Respiratory Effects of Opioid Analgesics in Conscious Horses

In one study, butorphanol (0.1, 0.2, and 0.4 mg/kg IV) caused excitatory signs but did not significantly affect respiratory rate (fr), arterial blood gas values, or arterial pH (pHa).²³ In contrast, buprenorphine (10 $\mu\text{g}/\text{kg}$ IV) caused CN stimulation and increased fr although the arterial partial pressure of oxygen (PaO_2) and carbon dioxide (PaCO_2) and hemoglobin saturation (as determined by pulse oximetry [SpO_2]) were unchanged.²⁷ Changes are usually minor and drug dependent. In a comparison of morphine (0.12 mg/kg IV), meperidine (1.1 mg/kg IV), oxymorphone (0.03 mg/kg IV),

methadone (0.12 mg/kg IV), and pentazocine (0.9 mg/kg IV)⁸⁷ fr was unchanged or initially increased and then decreased minimally. Although P_{aCO_2} decreased slightly, arterial and venous O_2 tensions and pH were unchanged. The fr was changed least by morphine, meperidine, and oxymorphone and most by methadone. In general, changes were linked with dysphoria and euphoria. In another study²¹ comparing butorphanol (0.22 mg/kg), flunixin (2.2 mg/kg), levorphanol (0.033 mg/kg), and morphine (0.66 mg/kg), butorphanol, flunixin, and levorphanol produced no effect on fr or blood-gas values, whereas morphine increased fr for 4 hours without affecting blood gas values. One study²⁶ concluded that the modest respiratory effects (increased fr and minute expiratory ventilation with reduced tidal volume) of buprenorphine (3, 5, and 10 μ g/kg IV) were not dose related, nor linked with CN excitation.

Respiratory Effects of Opioid Analgesics with α_2 Agonists

α_2 agonists seem to modestly potentiate the respiratory depressant effects of some, but not all, opioid drugs. Detomidine (10 μ g/kg) given alone or followed with morphine (0.1 mg/kg), methadone (0.1 mg/kg), meperidine (1.0 mg/kg), or butorphanol (50 μ g/kg) was studied in 3 ponies and a thoroughbred. Morphine caused modest falls in P_{aO_2} and rises in P_{aCO_2} , whereas meperidine increased only P_{aCO_2} .⁹ The effect may depend on the α_2 agonist involved: butorphanol (50 μ g/kg IV) had no effect on P_{aO_2} and pHa, but significantly increased P_{aCO_2} for 20 minutes when added to romifidine (40 and 80 μ g/kg, IV).⁴⁰

The dose of opioid involved seems to be unimportant. Two doses of morphine (0.12 and 0.66 mg/kg) given to 9 horses sedated with xylazine (0.66 mg/kg) caused similar and significant decreases in fr whereas P_{aCO_2} , P_{aO_2} , and pHa remained unchanged.²⁰

Respiratory Effects of Opioid Analgesics with Inhalant Anesthetics

Neither low morphine doses (20 and 50 μ g/kg) nor butorphanol (0.05 mg/kg) caused significant changes from preinjection values for fr, P_{aCO_2} , P_{aO_2} and airway occlusion pressure in horses anesthetized with halothane.¹⁹ In another study of horses anesthetized with halothane undergoing elective surgery, the preoperative injection of morphine (0.15 mg/kg IV) followed by infusion (0.1 mg/kg/h) did not cause significant differences in P_{aO_2} or P_{aCO_2} when compared with horses from which morphine was withheld.⁸⁹

These data do not support the widely held view^{9,24} that high doses of intraoperative opioids depress ventilation in unconscious horses, a view to which this author subscribes.

MORPHINE AND PULMONARY EDEMA

Despite its mild cardiopulmonary effects, morphine has been implicated in 2 cases of postoperative pulmonary edema.⁹¹ Although the investigators identified numerous risk factors⁹² in both cases, they concluded that fluid overload was worsened by a "morphine-induced reduction in urine production," and by "potential morphine-induced changes in pulmonary permeability." This reveals the most useful role of morphine in equine anesthesia: to assume responsibility for any untoward perioperative event.

OPIOID ANALGESICS IN HORSES: RECOMMENDATIONS

Recommended doses of opioid analgesics in horses vary widely (**Table 2**) because the effective dose depends on numerous factors. Dosing should follow 4 general rules: (1) the more severe the pain (or the greater the surgical insult), the greater the dose of

	Analgesia	Preoperative	Intraoperative	Postoperative
Morphine	0.05–0.1 mg/kg IV or IM ^a 24,93 0.1–0.3 mg/kg IV ^b	0.15 mg/kg ^{58,59}	0.1 mg/kg/h ^{58,59}	0.1–0.2 mg/kg ^b
Meperidine	0.3–0.6 mg/kg IV ⁹³ 1–2 mg/kg IM only ²⁴			2 mg/kg IM ^{62,63}
Methadone	0.05–0.1 mg/kg ⁹³ 0.1 mg/kg IV or IM ²⁴			
Butorphanol	0.01–0.02 mg/kg ⁹³ 0.05–0.1 mg/kg ²⁴			13 µg/kg/h ^{94,b}
Buprenorphine	10–20 µg/kg IV ⁹³ 60 µg/kg IV or IM ²⁴			

^a All doses intravenous unless stated otherwise.

^b Author's preference.

opioid analgesic required, and the lower the risk of excitatory side effects; (2) in pain-free horses, giving appropriate doses of α_2 agonists matched for duration of action eliminates the risk of excitation; acepromazine reduces, but does not eliminate, risk; (3) although opioid analgesics are described in terms of duration of action, they should be given to effect (ie, when the desired level of analgesia has waned below acceptable levels), and not by the clock; and (4) clinical signs of underdose (ie, pain) may mimic signs of overdosage.

NEW TECHNIQUES FOR PERIOPERATIVE OPIOID ANALGESIA

Extradural Opioid Analgesia

Extradural morphine injection consistently suppresses responses to experimental and clinical nocistimulation in horses without causing sensory, sympathetic nervous, or motor blockade. This subject is discussed elsewhere.

Opioid Analgesics and Intraarticular Analgesia

Opioid receptors have been identified on peripheral terminals of sensory nerves, whereas opioid peptide ligands (principally β -endorphin and met-enkephalin) have been discovered in immune cells from inflamed synovial tissue of human patients undergoing arthroscopic knee surgery.⁹⁵ The identification of opioid receptors in the equine synovia⁹⁶ has stimulated interest in producing intraarticular (IA) opioid analgesia in horses.

Initial studies showed an absence of tissue irritancy or systemic effects after IA morphine. No evidence of adverse local reactions or systemic effects were seen after IA morphine sulfate (1 mg) or buprenorphine hydrochloride (300 µg) injection into the middle carpal joints of 5 ponies. However, the vehicles of each drug were not detailed.⁹⁷ The disposition and local effects (15 mg in 5 mL saline) of morphine were also studied after injection into the tarsocrural joint of normal ponies.⁹⁸ Morphine remained detectable in synovial fluid 24 hours after injection, although systemic levels were unmeasurable after 6 hours. No adverse systemic effects were seen. The injection contained 0.1% w/v sodium metabisulfite but morphine did not irritate the joint any more than saline.

A later study⁹⁹ compared the analgesic efficacy of IA and intravenous morphine (0.05/mg both routes) in horses with experimentally induced radiocarpal synovitis. As might be expected from the predictable differences in effector site drug concentration, IA morphine resulted in significantly less lameness than intravenous morphine, although overall pain scores did not differ between treatments. The results indicate the potential usefulness of IA morphine after arthroscopic surgery, although further studies in clinical cases are needed. The analgesic effects of IA morphine (40 mg) were compared with the local anesthetic ropivacaine (40 mg) and a ropivacaine (20 mg)-morphine (200 mg) mixture injected intraarticularly in 12 horses with experimentally induced radiocarpal synovitis.¹⁰⁰ Ropivacaine produced approximately 3 hours of analgesia after a rapid onset, whereas morphine had a slower onset but a greater analgesic effect of longer duration (>24 hours). The combination combined the advantages of both drugs.

Transdermal Fentanyl Analgesia

The fentanyl transdermal therapeutic system or patches has become popular in small animals and has recently been studied in horses. Plasma fentanyl concentration during transdermal administration depends on the properties of the skin and so may vary with the application site of the patches. An *in vitro*¹⁰¹ study of equine skin from thoracic, inguinal, and dorsal metacarpal areas revealed similar values for fentanyl flux (over 48 hours) for thoracic and inguinal skin, which were greater than those from the dorsal metacarpus. Fentanyl penetration through inguinal skin was significantly slower compared with the other 2 sites. Two 100- $\mu\text{g}/\text{h}$ fentanyl patches applied to the lateral necks of 3 horses weighing 352 to 459 kg¹⁰² resulted in rapid absorption, with plasma fentanyl levels exceeding 2 ng/mL after 4 hours. Peak plasma concentrations (3.85 ng/mL) occurred at 6.7 hours, after which levels declined over 48 hours but remained greater than 1 ng/mL (which is held to represent an analgesic concentration in other species) for 54 hours. Plasma drug levels decreased rapidly after patch removal and no adverse behavioral responses were reported. In another study¹⁰³ 3 10-mg patches (equivalent to 60–67 $\mu\text{g}/\text{kg}$) were applied to the middorsal thorax and resulted, after a 2-hour lag period, in a rapid increase in plasma fentanyl concentration, which was a maximum at 12 hours and declined thereafter in a near-linear fashion. However, there was much individual variation. In 2 horses, plasma concentrations failed to reach 1 ng/mL. In the remaining four it was greater than 1 ng/mL for at least 40 hours and longer than 72 hours in two of these. No adverse effects attributable to fentanyl were observed, indicating that the dose tested was safe in healthy adult horses. However, it failed to achieve plasma fentanyl concentrations generally considered to be analgesic in about one-third of horses. The clinical efficacy of transdermal fentanyl was investigated in 9 horses whose pain was unresponsive to phenylbutazone ($n = 3$) or flunixin ($n = 6$) and which subsequently received between 39 and 110 $\mu\text{g}/\text{kg}$ of transdermal fentanyl.¹⁰⁴ One 10-mg patch was applied per 150 kg of body mass to the lateral cervical and/or lateral or medial proximal antebrachial area. After administration, mean time to serum fentanyl concentrations greater than 1 ng/mL was 14 hours. Serum fentanyl concentrations 1 ng/mL or greater were maintained in all but one horse for at least 18 hours. No adverse effects were observed. Pain scores were significantly decreased after fentanyl and NSAID administration but improvement was minimal in horses with orthopedic disease, and lameness scores did not change in the 3 horses with septic physitis or osteomyelitis. That transdermal fentanyl is less effective at relieving orthopedic pain compared with soft-tissue pain has been observed elsewhere.¹⁰⁵

SUMMARY

A questionnaire-based study of UK equine veterinarians' attitudes to analgesics (which confused the terms potency with efficacy) revealed the most important determinant of choice was the perceived potency of a drug.³ Fears of adverse gastrointestinal and locomotor effects were also important. These fears have been generated by studies that lack external validity, having been conducted on small numbers of pain-free horses or ponies, exposed to artificial, rather than surgical or traumatic, nocistimulation and not receiving the range of drugs that would be the case in the peri-operative or trauma setting. Similarities between equine pain behaviors and opioid side effects make it possible that some adverse reactions attributed to drugs were signs of inadequate analgesia. Despite increasing evidence of their clinical usefulness, unenlightened assertions concerning opioid analgesics continue to be made. The statement "Opioids are not widely used in horses because they can cause CN system excitation, sympathetic stimulation, and can stimulate locomotion" was recently used to justify an experimental study of the analgesic activity of tramadol in pain-free horses.¹⁰⁶ To show that the margin between the analgesic and stimulant effects of opioid analgesics in horses is probably much broader than hitherto proposed requires (1) an improved ability to recognize equine pain; (2) a precise and valid equine pain scoring system; (3) the use of effective, not excessive, opioid doses; (4) a large number of animals with actual, rather than experimentally induced, pain.

REFERENCES

1. Yoxall AT. Pain in small animals—its recognition and control. *J Small Anim Pract* 1978;19:423–38.
2. Hellyer PW, Bai L, Supon J, et al. Comparison of opioid and alpha-2 adrenergic receptor binding in horse and dog brain using radioligand autoradiography. *Vet Anaesth Analg* 2003;30:172–82.
3. Price J, Marques M, Welsh EM, et al. Pilot epidemiological study of attitudes towards pain in horses. *Vet Rec* 2002;151:570–5.
4. Guinard L. *Encyclopedie cadeac veterinaire, "effets apparents du morphinisme chez les solipèdes" thérapeutique et pharmacodynamie*, Tome 1. 401, Paris, 1899.
5. Milks HJ. Opium-morphine. In: *Practical veterinary pharmacology and therapeutics*. New York: The Macmillan Company; 1917. p. 139–46.
6. Frohner E. Morphinum hydrochloricum. Salzsures morphium. In: *Lehrbuch der arzneiverordnungslehre fur tierarzte*. Stuttgart (Germany): Verlag von Ferdin & Enke; 1921. p. 62–70.
7. Amadon RS, Craigie AH. The actions of morphine on the horse. Preliminary studies: diacetylmorphine (heroin), dihydrodesoxymorphine-D (desomorphine) and dihydroheterocodeine. *J Am Vet Med Assoc* 1937;91:674–8.
8. Carregaro AB, Luna SP, Mataqueiro MI, et al. Effects of buprenorphine on nociception and spontaneous locomotor activity in horses. *Am J Vet Res* 2007;68:246–50.
9. Clarke KW, Paton BS. Combined use of detomidine with opiates in the horse. *Equine Vet J* 1988;20:331–4.
10. Combie J, Dougherty J, Nugent E, et al. The pharmacology of narcotic analgesics in the horse. IV. Dose and time response relationships for behavioral responses to morphine, meperidine, pentazocine, anileridine, methadone, and hydromorphone. *J Equine Med Surg* 1979;3:377–85.

11. Combie J, Shultz T, Nugent EC, et al. Pharmacology of narcotic analgesics in the horse: selective blockade of narcotic-induced locomotor activity. *Am J Vet Res* 1981;42:716–21.
12. Bennet RC, Steffey EP. Use of opioids for pain and anesthetic management in horses. *Vet Clin North Am Equine Pract* 2002;18(1):47–60.
13. Tobin T, Combie J, Miller JR, et al. The pharmacology of narcotic analgesics in the horse. II. Studies on the detection, pharmacokinetics, urinary clearance times and behavioral effects of pentozocine and fentanyl in the horse. *Ir Vet J* 1979;33:169–76.
14. Kamerling SG, DeQuick DJ, Weckman TJ, et al. Dose-related effects of ethylketazocine on nociception, behaviour and autonomic responses in the horse. *J Pharm Pharmacol* 1985;38:40–5.
15. Nolan AM, Besley W, Reid J, et al. The effects of butorphanol on locomotor activity in ponies: a preliminary study. *J Vet Pharmacol Ther* 1994;17:323–6.
16. Mama KR, Pascoe PJ, Steffey EP. Evaluation of the interaction of mu and kappa opioid agonists on locomotor behavior in the horse. *Can J Vet Res* 1992;57:106–9.
17. Bogan JA, Mackenzie G, Snow DH. An evaluation of tranquilizers for use with etorphine as neuroleptanalgesic agents in the horse. *Vet Rec* 1978;103:471–2.
18. Pascoe PJ, Taylor PM. Effects of dopamine antagonists on alfentanil-induced locomotor activity in horses. *Vet Anaesth Analg* 2003;30:165–71.
19. Nolan AM, Chambers JP, Hale GJ. The cardiorespiratory effects of morphine and butorphanol in horses anaesthetized under clinical conditions. *J Vet Anaesth* 1991;18:19–24.
20. Muir WW, Skarda RT, Sheehan WC. Hemodynamic and respiratory effects of xylazine-morphine sulfate in horses. *Am J Vet Res* 1979;40:1417–20.
21. Kalpravidh M, Lumb WV, Wright M, et al. Effects of butorphanol, flunixin, levorphanol, morphine, and xylazine in ponies. *Am J Vet Res* 1984;45:217–23.
22. Pascoe PJ, Black WD, Claxton JM, et al. The pharmacokinetics and locomotor activity of alfentanil in the horse. *J Vet Pharmacol Ther* 1991;14:317–25.
23. Sellon DC, Monroe VL, Roberts MC, et al. Pharmacokinetics and adverse effects of butorphanol administered by single intravenous injection or continuous intravenous infusion in horses. *Am J Vet Res* 2001;62:183–9.
24. Hall LW, Clarke KW. *Trim CM veterinary anaesthesia*. 10th edition. London: WB Saunders; 2001. p. 255.
25. Kohn CW, Muir WW. Selected aspects of the clinical pharmacology of visceral analgesics and gut motility modifying drugs in the horse. *J Vet Intern Med* 1988;2:85–91.
26. Szoke MO, Blais D, Cuvellez SG, et al. Effects of buprenorphine on cardiovascular and pulmonary function in clinically normal horses and horses with chronic obstructive pulmonary disease. *Am J Vet Res* 1998;59:1287–91.
27. Carregaro AB, Neto FJ, Beier SL, et al. Cardiopulmonary effects of buprenorphine in horses. *Am J Vet Res* 2006;67:1675–80.
28. Pippi NL, Lumb WV. Objective tests of analgesic drugs in ponies. *Am J Vet Res* 1979;40:1082–6.
29. Brunson DB, Majors LJ. Comparative analgesia of xylazine, xylazine/morphine, xylazine/butorphanol, and xylazine/nalbuphine in the horse, using dental dolorimetry. *Am J Vet Res* 1987;48:1087–92.
30. Kamerling S, Weckman T, Donahoe J, et al. Dose related effects of the kappa agonist U-50,488H on behaviour, nociception and autonomic response in the horse. *Equine Vet J* 1988;20:114–8.

31. Kalpravidh M, Lumb WV, Wright M, et al. Analgesic effects of butorphanol in horses: dose-response studies. *Am J Vet Res* 1984;45:211–7.
32. Stucki F, Armbruster S, Moens Y, et al. Comparative studies on analgesia provoked by butorphanol or L-polamidone in detomidine sedated horses. *Proceedings of the Association of Veterinary Anaesthesia & European Society of Laboratory Animal Veterinarians, Newcastle (UK), 1999.*
33. Schatzman U, Armbruster S, Stucki F, et al. Analgesic effect of butorphanol and levomethadone in detomidine sedated horses. *J Vet Med A Physiol Pathol Clin Med* 2001;48:337–42.
34. Le Bars D, Gozariu M, Cadden SW. Animal models of nociception. *Pharmacol Rev* 2001;53:597–652.
35. Spadavecchia C, Spadavecchia L, Andersen OK, et al. Quantitative assessment of nociception in horses by use of the nociceptive withdrawal reflex evoked by transcutaneous electrical stimulation. *Am J Vet Res* 2002;63:1551–6.
36. Spadavecchia C, Arendt-Nielsen L, Andersen OK, et al. Comparison of nociceptive withdrawal reflexes and recruitment curves between the forelimbs and hind limbs in conscious horses. *Am J Vet Res* 2003;64:700–7.
37. Muir WW. Drugs used to produce standing chemical restraint in horses. *Vet Clin North Am Large Anim Pract* 1981;3(1):17–44.
38. Stout RC, Priest GT. Clinical experience using butorphanol tartrate for relief of abdominal pain in the horse. In: Moore JN, White NA, Becht JL, editors, *Equine colic research. Proceedings of the second symposium at the University of Georgia, vol. 2. Lawrenceville (NJ): Veterinary Learning Systems; 1986.* p. 68–70.
39. Walker AF. Sublingual administration of buprenorphine for long-term analgesia in the horse. *Vet Rec* 2007;160:808–9.
40. Clarke KW, England GC, Goossens L. Sedative and cardiovascular effects of romifidine alone and in combination with butorphanol in the horse. *J Vet Anaesth* 1991;18:25–9.
41. Dyson DH, Pascoe PJ, Viel L, et al. Comparison of detomidine hydrochloride, xylazine, and xylazine plus morphine in horses: a double blind study. *J Equine Vet Sci* 1987;7:211–6.
42. Lowe JE. Xylazine, pentazocine, meperidine and dipyrone for relief of balloon induced equine colic: a double blind comparative evaluation. *J Equine Med Surg* 1978;2:286–91.
43. Jochle W, Moore JN, Brown J, et al. Comparison of detomidine, butorphanol, flunixin meglumine and xylazine in clinical cases of equine colic. *Equine Vet J Suppl* 1989;7:111–6.
44. Love EJ, Taylor PM, Clark C, et al. Analgesic effect of butorphanol in ponies following castration. *Equine Vet J* 2009;41:552–6.
45. Sanz MG, Sellon DC, Cary JA, et al. Analgesic effects of butorphanol tartrate and phenylbutazone administered alone and in combination in young horses undergoing routine castration. *J Am Vet Med Assoc* 2009;235:1194–203.
46. Corletto F, Raisis AA, Brearley JC. Comparison of morphine and butorphanol as pre-anaesthetic agents in combination with romifidine for field castration in ponies. *Vet Anaesth Analg* 2005;32:16–22.
47. Doherty TJ, Geiser DR, Rohrbach BW. Effect of acepromazine and butorphanol on halothane minimum alveolar concentration in ponies. *Equine Vet J* 1997;29:374–6.
48. Steffey EP, Eisele JH, Baggot JD. Interactions of morphine and isoflurane in horses. *Am J Vet Res* 2003;64:166–75.

49. Pascoe PJ, Steffey EP, Black WD, et al. Evaluation of the effect of alfentanil on the minimum alveolar concentration on halothane in horses. *Am J Vet Res* 1993;54:1327–32.
50. Matthews NS, Lindsay SL. Effect of low dose butorphanol on halothane minimum alveolar concentration in ponies. *Equine Vet J* 1990;22:325–7.
51. Caure S, Cousty M, Tricaud C. Effects of adding butorphanol to a balanced anaesthesia protocol during arthroscopic surgery in horses. *Vet Rec* 2010;166:324–8.
52. Hofmeister EH, Mackey EB, Trim CM. Effect of butorphanol administration on cardiovascular parameters in isoflurane-anesthetized horses – a retrospective clinical evaluation. *Vet Anaesth Analg* 2008;35:38–44.
53. Doherty TJ, Goiser DR, Rohrbach BW. Effects of high-volume epidural morphine, butorphanol and ketamine on halothane MAC in the horse. *J Vet Anaesth* 1995;22:37.
54. Rampil IJ, Laster MJ. No correlation between quantitative electroencephalographic measurements and movement response to noxious stimuli during isoflurane anesthesia in rats. *Anesthesiology* 1992;77:920–5.
55. Hall LW, Clarke KW. *Veterinary anaesthesia*. 8th edition. London: Bailliere Tindall; 1983. p. 242.
56. Mircica C, Clutton RE, Blissitt KJ. Problems associated with perioperative morphine in horses: a retrospective case analysis. *Vet Anaesth Analg* 2003;30:147–55.
57. McBride SD, Long L. Management of horses showing stereotypic behaviour, owner perception and the implications for welfare. *Vet Rec* 2001;148:799–802.
58. Clark L, Clutton RE, Blissitt KJ, et al. Effects of peri-operative morphine administration on recovery from halothane anaesthesia in horses. *Vet Anaesth Analg* 2008;35:22–9.
59. Love EJ, Lane JG, Murison PJ. Morphine administration in horses anaesthetized for upper respiratory tract surgery. *Vet Anaesth Analg* 2006;33:179–88.
60. Taylor PM. Effect of postoperative pethidine on the anaesthetic recovery period in the horse. *Equine Vet J* 1986;18:70–2.
61. Johnson CB, Taylor PM, Young SS, et al. Postoperative analgesia using phenylbutazone, flunixin or carprofen in horses. *Vet Rec* 1993;133:336–8.
62. Lal H. Narcotic dependence, narcotic action and dopamine receptors. *Life Sci* 1978;17:483–96.
63. Raekallio M, Taylor PM, Bennett RC. Post operative analgesia after arthroscopy in horses abstract. *Proceedings, 5th International Congress of Veterinary Anesthesia*. Guelph (Canada); 1994. p. 145.
64. Roger T, Bardon T, Ruckebusch Y. Colonic motor responses in the pony: relevance of colonic stimulation by opiate antagonists. *Am J Vet Res* 1985;46:31–6.
65. Davies JV, Getting EL. Effect of spasmolytic analgesic drugs on the motility patterns of the equine small intestine. *Res Vet Sci* 1983;34:334–9.
66. Sojka JE, Adams SB, Lamar CH, et al. Effect of butorphanol, pentazocine, meperidine, or metoclopramide on intestinal motility in female ponies. *Am J Vet Res* 1988;49:527–9.
67. Boscan P, Van Hoogmoed LM, Farver TB, et al. Evaluation of the effects of the opioid agonist morphine on gastrointestinal tract function in horses. *Am J Vet Res* 2006;67:992–7.
68. Kamerling SG, Hamra JG, Bagwell CA. Naloxone-induced abdominal distress in the horse. *Equine Vet J* 1990;22:241–3.
69. Tinkler MK, White NA, Lessard P, et al. Prospective study of equine colic incidence and mortality. *Equine Vet J* 1997;29:448–53.

70. Tinkler MK, White NA, Lessard P, et al. Prospective study of equine colic risk factors. *Equine Vet J* 1997;29:454–8.
71. Cohen ND, Gibbs PG, Woods AM. Dietary and other management factors associated with colic in horses. *J Am Vet Med Assoc* 1999;215:53–60.
72. Hillyer MH, Taylor FG, Proudman CJ, et al. A case control study of simple colonic obstruction and distension colic in the horse. *Equine Vet J* 2002;34:455–63.
73. Senior JM, Pinchbeck GL, Dugdale AH, et al. Retrospective study of the risk factors and prevalence of colic in horses after orthopaedic surgery. *Vet Rec* 2004;155:321–5.
74. Jones RS, Edwards GB, Brearley JC. Commentary on prolonged starvation as a factor associated with post operative colic. *Equine Vet Educ* 1991;3:16–8.
75. Steinbrook RA. Epidural anesthesia and gastrointestinal motility. *Anesth Analg* 1998;86:837–44.
76. Little D, Redding WR, Blikslager AT. Risk factors for reduced fecal output in horses: 37 cases (1997–1998). *J Am Vet Med Assoc* 2001;218:414–20.
77. Roger T, Ruckebusch Y. Colonic α_2 -adrenoreceptor-mediated responses in the pony. *J Vet Pharmacol Ther* 1987;10:310–8.
78. Merritt AM, Burrow JA, Harless CS. Effect of xylazine, detomidine, and a combination of xylazine and butorphanol on equine duodenal motility. *Am J Vet Res* 1998;59:619–23.
79. Van Hoogmoed L, Rakestraw PC, Snyder JR, et al. In vitro effects of nonsteroidal anti-inflammatory agents and prostaglandins I₂, E₂, and F₂-alpha on contractility of taenia of the large colon of horses. *Am J Vet Res* 1999;60:1004–9.
80. Lester GD, Bolton JR, Cullen LK, et al. Effects of general anesthesia on myoelectric activity of the intestine in horses. *Am J Vet Res* 1992;53:1553–7.
81. Andersen MS, Clark L, Dyson SJ, et al. Risk factors for colic in horses after general anaesthesia for MRI or nonabdominal surgery: absence of evidence of effect from perianaesthetic morphine. *Equine Vet J* 2006;38:368–74.
82. Senior JM, Pinchbeck GL, Allister R, et al. Reported morbidities following 861 anaesthetics given at four equine hospitals. *Vet Rec* 2007;160:407–8.
83. Johnston GM, Taylor PM, Holmes MA, et al. Confidential enquiry of perioperative equine fatalities (CEPEF-1): preliminary results. *Equine Vet J* 1995;27:193–200.
84. Milks HJ. Practical veterinary pharmacology, materia medica and therapeutics. 5th edition. Chicago: Eger Inc; 1946. p. 158–84.
85. Phaneuf LP, Grivel ML, Ruckebusch Y. Electromyography during normal gastro-intestinal activity, painful or non-painful colic and morphine analgesia, in the horse. *Can J Comp Med* 1972;36:138–44.
86. Clutton RE. Unexpected responses following intravenous pethidine injection in two horses. *Equine Vet J* 1987;19:72–3.
87. Muir WW, Skarda RT, Sheehan WC. Cardiopulmonary effects of narcotic agonists and a partial agonist in horses. *Am J Vet Res* 1978;29:1632–5.
88. Robertson JT, Muir WW, Sams R. Cardiopulmonary effects of butorphanol tartrate in horses. *Am J Vet Res* 1981;42:41–4.
89. Clark L, Clutton RE, Blissitt KJ, et al. Effects of peri-operative morphine administration during halothane anaesthesia in horses. *Vet Anaesth Analg* 2005;32:10–5.
90. Van Dijk P, Nyks SK. Changes in heart rate, mean arterial pressure, blood biochemistry, plasma glucose, plasma lactate and some plasma enzymes during sufentanil halothane anaesthesia in horses. *J Vet Anaesth* 1998;25:13–8.
91. Kaartinen MJ, Pang DS, Cuvelliez SG. Post-anesthetic pulmonary edema in two horses. *Vet Anaesth Analg* 2010;37:136–43.

92. Senior M. Post-anaesthetic pulmonary oedema in horses: a review. *Vet Anaesth Analg* 2005;32:193–200.
93. Muir WW. Standing chemical restraint in horses. In: Muir WW, Hubbell JA, editors. *Equine anesthesia. Monitoring and emergency therapy*. St Louis (MO): Mosby-Year Book; 1991. p. 247–80.
94. Sellon DC, Roberts MC, Blikslager AT, et al. Effects of continuous rate intravenous infusion of butorphanol on physiologic and outcome variables in horses after celiotomy. *J Vet Intern Med* 2004;18:555–63.
95. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995; 332:1685–90.
96. Sheehy JG, Hellyer PW, Sammonds GE, et al. Evaluation of opioid receptors in synovial membranes of horses. *Am J Vet Res* 2001;62:1408–12.
97. Manning M, Wilson D, Hendrickson D et al. The effects of intrarticular administration of morphine and buprenorphine on the middle carpal joints of ponies abstract. *Proceedings, 5th International Congress of Veterinary Anesthesia. Guelph (Canada); 1994. p. 155.*
98. Raekallio M, Taylor PM, Johnson CB, et al. The disposition and local effects of intra-articular morphine in normal ponies. *J Vet Anaesth* 1996;23:23–6.
99. Lindegaard C, Thomsen MH, Larsen S, et al. Analgesic efficacy of intra-articular morphine in experimentally induced radiocarpal synovitis in horses. *Vet Anaesth Analg* 2010;37:171–85.
100. Santos LC, de Moraes AN, Saito ME. Effects of intraarticular ropivacaine and morphine on lipopolysaccharide-induced synovitis in horses. *Vet Anaesth Analg* 2009;36:280–6.
101. Mills PC, Cross SE. Regional differences in transdermal penetration of fentanyl through equine skin. *Res Vet Sci* 2007;82:252–6.
102. Matthews NS, Peck KE, Mealey KL. Transdermal fentanyl: absorption and plasma levels in horses abstract. *Proceedings, 6th International Congress of Veterinary Anaesthesiology. Thessaloniki (Greece); 1997. p. 116.*
103. Orsini JA, Moate PJ, Kuersten K, et al. Pharmacokinetics of fentanyl delivered transdermally in healthy adult horses – variability among horses and its clinical implications. *J Vet Pharmacol Ther* 2006;29:539–46.
104. Thomasy SM, Slovis N, Maxwell LK, et al. Transdermal fentanyl combined with nonsteroidal anti-inflammatory drugs for analgesia in horses. *J Vet Intern Med* 2008;18:550–4.
105. Wegner K, Franklin RP, Long MT, et al. How to use fentanyl transdermal patches for analgesia in horses. *Proceedings of the American Association of Equine Practitioner* 2002;48:291–4.
106. Dhanjal JK, Wilson DV, Robinson E, et al. Intravenous tramadol: effects, nociceptive properties and pharmacokinetics in horses. *Vet Anaesth Analg* 2009; 36:581–90.