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The conduct of equine anesthesia is a multi-faceted process dependent upon a thorough understanding of the pharmacology (effect), pharmacokinetics (disposition) and pharmacodynamics (dose-effect relationship) of drugs used to produce calming (anxiolysis), sedation, analgesia, muscle relaxation, and ultimately unconsciousness. All drugs approved for use in horses are considered to be safe and effective emphasizing the importance of patient characteristics (physical status, behavior, size, weight, breed), the type of procedure being performed (standing, recumbent) and the duration of “standing chemical restraint” or anesthesia required. No single drug has emerged as the “ideal” anesthetic for all horses or all circumstances requiring anesthesia. “Ideal” anesthesia (sedation, analgesia, muscle relaxation, unconsciousness) in horses is most commonly achieved by administering multiple drugs in combination or sequence in order to produce the desired effect for the circumstances presented. The advantages of this “multimodal” approach include but are not limited to an increase in the potential for additive or synergistic beneficial anesthetic effects an increase in the scope of anesthetic activity (ex. analgesia and muscle relaxation) and the potential to reduce the dose of each drug administered thereby potentially reducing the probability for side effect or an adverse event. The disadvantages include the potential for adverse drug interactions resulting in a greater potential for side effect (ex. bradycardia, ileus, ataxia), adverse events (ex. hypotension, respiratory depression) and prolonged recovery from drug effects. It is, therefore, prudent for the equine veterinary surgeon to become knowledgeable and proficient in administering a select group of drugs that provide all of the aforementioned anesthetic qualities if the “best” outcome is to be achieved. A multitude of chemical compounds representing derivatives of the same chemical or different chemicals comprise the various drug families used to produce anesthesia in horses. In general these drug families include anxiolytics and sedatives (phenothiazines, butyrophenones, alpha-2 agonists), analgesics (opioids, alpha-2 agonists), muscle relaxants (guaifenesin, benzodiazepines) and drugs that are typically employed to produce “general” anesthesia (dissociatives, hypnotics, inhalant anesthetics).¹⁻³ Butyrophenones (azaperone) are no longer in common use in horses due to their unpredictability and potential to produce abnormal behavioral responses in some horses and will not be discussed.⁴ Neuromuscular blocking drugs (NMBDs) produce skeletal muscle paralysis and are frequently administered in human anesthesia and occasionally during equine anesthesia (ophthalmologic surgery), to provide added muscle relaxation. Atracurium is the most popular NMBD used in equine anesthesia due to its rapid onset, minimal cardiovascular effects and predictable duration of action.⁵⁻⁸ Clinically effective doses of all NMBDs, however, paralyze the diaphragm producing apnea thereby mandating the use of manual or mechanical artificial ventilation in order to prevent hypoxia. Furthermore, NMBDs do not produce sedation, unconsciousness or analgesia and require special monitoring equipment and techniques in order to determine the magnitude and duration of their effect.¹ NMBDs will not be discussed.
The drugs that are most commonly used to produce anesthesia in horses include the phenothiazine acepromazine, the opioids morphine, butorphanol and buprenorphine, the alpha-2 agonists xylazine, detomidine, medetomidine and romifidine, the muscle relaxants guaifenesin, diazepam, midazolam and zolazepam (muscle relaxant component of Telazol®), dissociative anethetics, ketamine and tiletamine (dissociative anesthetic component of Telazol®), the hypnotic thiopental (propofol is similar but not currently recommended for use in horses), and the inhalant anesthetics (halothane [not available in the US] isoflurane, sevoflurane and desflurane). The drug combination zolazepam-tiletamine (Telazol®) produces pharmacologic effects similar if not identical to that of diazepam-ketamine drug combinations although somewhat more pronounced and prolonged. Telazol® is not as popular as diazepam-ketamine drug combination in horses due to a more prolonged and less acceptable quality of recovery and will not be discussed. Desflurane has unique physical chemical properties making it highly controllable. Cardiorespiratory effects are similar to isoflurane and sevoflurane but it is unfamiliar to most equine veterinarians and will not be discussed. What then is the pharmacology and what are the advantages and disadvantages of this select group of drugs and how are they best used in combination to produce anesthesia in the horse? Emphasis will be placed upon drug effects that are most pertinent to the production of anesthesia and include actions upon the central nervous system, respiration, the heart and circulation and other organ systems (ex. gut, kidney) when appropriate.

Acepromazine produces its central nervous system effects by antagonizing the effects of the neurotransmitter dopamine in the basal ganglia and limbic (emotion, behavior) portions of the brain and by depressing nervous system activity in the reticular formation and spinal cord resulting in dose dependent anxiolysis, calming and varying degrees of muscle relaxation. Larger doses (> 0.1 mg/kg, IV) produce prolonged calming effects, stupor and marked ataxia in some horses. In addition to calming and muscle relaxation acepromazine reduces stress (antiadrenergic, antisypathetic, antihistaminic) and possesses antiarrhythmic and antishock effects. Acepromazine is not an analgesic and does not produce analgesia when administered alone but does potentiate the analgesic effects of drugs that are analgesic (ex. opioids, alpha-2 agonists). The two greatest concerns associated with acepromazine administration are its potential to decrease arterial blood pressure (ABP) and priapism in yearling colts and flaccid paralysis of the penis in breeding stallions. Decrease in ABP is due to a decrease in sympathetic tone, decrease in venous return of blood to the heart and the blockade of alpha adrenergic receptors in the peripheral circulation. Large decreases in arterial blood pressure leading to hypotension and occasionally collapse (“fainting”) are most likely to occur following the intravenous administration of acepromazine to excited, stressed (blood loss) or frightened (sympathetically dependent) horses. Intramuscular administration and fluid loading prior to acepromazine administration reduce the potential for hypotension. Acepromazine induced hypotension is heralded by profound ataxia, sweating, tachycardia and tachypnea in conscious horses and by lower than acceptable arterial blood pressure (mean ABP< 60 mmHg) in anesthetized horses. Hypotension is almost always successfully treated by the administration of fluids (crystalloids, colloids) administered to effect. The production of priapism or flaccid paralysis of the penis in male horses, although rare, is unpredictable and can be disastrous leading to amputation of the penis. No universally effective therapy has been identified for the treatment of priapism although the administration of anticholinergics (benztropine), opioid antagonists (naloxone) could nursing care and time generally result in resolution. Acepromazine is compatible with all other anesthetic drugs has the potential to reduce the amount of injectable or inhalant anesthetic required to produce anesthesia. Opioids produce their pharmacologic effects by activating a variety of distinct central and peripheral opioid receptors resulting in analgesia and, in horses, minimal cardiovascular
and respiratory effects, temporary decreases in gastrointestinal activity and behavioral changes. Larger doses of almost all opioids are known to produce excitement, agitation, stereotypic behavior and increased locomotor activity which can be prevented by the prior administration of acepromazine or, when necessary, the opioid antagonists naloxone. Larger or repeated doses of opioids can produce ileus predisposing to impaction colic, urine retention, pica(?), and esophageal obstruction (“choke”). Opioids are best administered at the low end of their dose range in combination with calming drugs (acepromazine) or sedatives (alpha-2 agonists) in order to enhance analgesic activity and minimize behaviorally related side effects. Butorphanol is the least potent analgesic of the commonly used opioids and the least likely to produce gastrointestinal or behavioral side effects although marked ataxia can occur in some horses. Regardless, butorphanol is a good analgesic for the treatment of visceral pain and produces good to excellent analgesic effects when administered in combination with alpha-2 agonists (xylazine, detomidine, medetomidine, romifidine) to injured horses or as preanesthetic medication prior to surgery. Opioids are compatible with all other anesthetic drugs and based upon their analgesic effects have the potential to reduce the amount of injectable or inhalant anesthetic required to produce anesthesia although this effect is controversial in horses. The adverse effects of opioids can be anticipated by the administration of opioid antagonists (naloxone, naltrexone). The alpha-2 agonists xylazine, detomidine, medetomidine and romifidine are differentiated by their selective ability to activate alpha-1 and more importantly alpha-2 adrenergic receptors in the central nervous system and throughout the body. This activity is responsible for their different potencies in producing anxiolysis, sedation, analgesia and muscle relaxation. Alpha-2 agonists also decrease central nervous system sympathetic output which contributes significantly to their sedative and cardiovascular effects. The intensity of sedation is dose dependent but most dosage sched-
and colic in some horses that can be treated by administering an alpha-2 antagonist (tolazoline, atipamazole). Alpha-2 agonists induce urination in most horses due to effects on renal tubular function and suppression of insulin release by the pancreas resulting in transient increases in blood glucose values (osmotic diuresis). Some horses will develop an allergic response to the intramuscular administration of xylazine which is responsive to treatment with antihistamines. Alpha-2 agonists are compatible with other drugs used to produce anesthesia in horses and based upon the sedative and analgesic effects have the potential to reduce the amount of injectable or inhalant anesthetic required to produce anesthesia. Alpha-2 agonists can be antagonized by the administration of alpha-2 antagonists (yohimbine, tolazoline, atipamazole). The benzodiazepines diazepam, midazolam and others in this family produce their effects by promoting binding of the inhibitory neurotransmitter gamma-aminobutyric acid to GABA type A (GABA<sub>A</sub>) receptors. Increases in GABA<sub>A</sub> receptor binding facilitates chloride channel activity and hyperpolarization of nerve cell membranes resulting in centrally mediated behavioral changes, muscle relaxation and anticonvulsant effects. Both diazepam and midazolam produce minimal cardiopulmonary or adverse side effects when administered at clinically recommended doses although some conscious horses may become anxious, ataxic and recumbent when larger doses (> 0.1 mg/kg) are administered. Guaifenesin produces muscle relaxation, recumbency and depression of consciousness by blocking nerve impulse transmission at interneuronal neurons in the spinal cord, brainstem and subcortical areas of the brain. Lower dosages of guaifenesin (25-50 mg/kg, IV) do not produce “anesthesia” and should not be considered as adequate analgesia for surgical procedures. Minimal cardiorespiratory effects are produced at clinically relevant doses (15-50 mg/kg) administered relatively rapidly IV although decreases in arterial blood pressure, hypotension, respiratory depression and apneustic patterns of breathing can occur when excessive dosages (<100 mg/kg) are administered. Some horses may develop an allergic response during guaifenesin administration exemplified by hives on the shoulders and croup and responsive to treatment with antihistamines. Diazepam, midazolam and guaifenesin are not analgesics and do not appreciably enhance the analgesic activity of drugs that are analgesics (opioids, alpha-2 agonists). They are compatible with all other anesthetic drugs and based upon the inhibitory CNS effects have the potential to reduce the amount of injectable or inhalant anesthetic required to produce anesthesia. The benzodiazepines diazepam and midazolam can produce marked ataxia in conscious horses which can be antagonized, if necessary, by the benzodiazepine receptor antagonist flumazenil. Thiopental and ketamine are the only two injectable anesthetics are currently approved or popular for producing short term intravenous anesthesia, total intravenous anesthesia (TIVA) or for induction to general anesthesia using an inhalant anesthetic. Thiopental and other hypnotics like it (propofol, etomidate) act predominantly at GABA<sub>A</sub> receptors in the CNS to produce sedation, unconsciousness and muscle relaxation. Although variable in their potency and hypnotic activity they produce dose dependent CNS cardiorespiratory and other organ system depression. Thiopental is an excellent hypnotic producing unconsciousness and centrally mediated muscle relaxation within seconds (approx. 10-15 s) of IV administration. Thiopental is not a particularly effective analgesic when administered at subanesthetic doses or only decreases the horses response to noxious (ex. surgical) stimulation when a level of unconsciousness is attained that prevents conscious perception. Clinically relevant doses (3-5 mg/kg) of thiopental produce marked respiratory depression and apnea resulting in hypoxemia (low PaO2), hypercarbia (high PaCO<sub>2</sub>) and respiratory acidosis. Bolus dosages of thiopental generally produce a transient increase in heart rate (sinus tachycardia) and transient increases in arterial blood pressure associated with the loss of consciousness in otherwise normal healthy horses but may produce decreases in heart rate hypotension in...
heavily sedated or sick horses. Thiopental produces vasodilation, impairs cardiac contractile activity and decreases venous return which collectively decrease cardiac output and arterial blood pressure. Thiopental is also capable of inducing cardiac, particularly ventricular, arrhythmias and may sensitize the myocardium to the arrhythmogenic effects of catecholamines. Finally thiopental is solubilized in relatively strong alkaline solutions leading to severe inflammation and necrosis of tissues if inadvertently administered outside of the vein. Thiopental should no longer be administered by itself in bolus doses to induce or produce general anesthesia. Neither should it be depended upon as the only or principal drug used to maintain anesthesia. Thiopental can be used in combination with sedatives (alpha-2 agonists) muscle relaxants (guaifenesin) and analgesics (opioids, alpha-2 agonists) to produce relatively short term (< 1 hr) anesthesia in horses. Considerable caution and close monitoring should be employed when administering thiopental to anemic, hypoproteineemic and acidotic horses since adverse drug effects will be magnified and the duration of drug activity will be prolonged.

The precise mechanism by which dissociative anesthetic drugs (ketamine, tiletamine, phencyclidine) produce their anesthetic effects remains unknown although they depress and disorganize electrical activity in the brain, hyperpolarize some CNS neurons and produce variable n-methyl-d-aspartate receptor (NMDA) blockade. The latter of these effects, NMDAR blockade, is believed to be responsible for ketamines analgesic effects although its activity and efficacy in this regard has not been conclusively demonstrated. It is more likely that the surgically relevant analgesic activity produced by ketamine is a result of a loss or alteration of consciousness or additive or synergistic drug effects when administered with other known analgesic drugs (ex. opioids, alpha-2 agonists). Regardless of mechanism ketamine produces relatively rapid (30-60 s) unconsciousness following IV administration which is associated with excessive muscle rigidity, catatonia and seizures in some horses making its use as the sole source of anesthesia unacceptable in horses. Ketamine should therefore be administered in conjunction with potent sedatives (ex. xylazine, detomidine, medetomidine, romifidine) or benzodiazepines (diazepam, midazolam). When used at clinically recommended dosages ketamine is the safest injectable anesthetic drug available and can be administered either as a bolus for by infusion for longer procedures. Ketamine does not produce significant cardiovascular depressant effects and may increase heart rate, cardiac output and arterial blood pressure in minimally sedated horses. Clinically relevant doses of ketamine reduce inhalant anesthetic requirement, do not produce cardiac arrhythmias in horses and have not been demonstrated to sensitize the myocardium to the arrhythmogenic effects of catecholamines. Respiratory depression although minimal at recommended doses does occur following the IV administration of ketamine but may not be represented by a decrease in respiratory rate but rather a decrease in tidal volume and an apneustic (breath holding) pattern of breathing resulting in hypercapnea and respiratory acidosis. All other organ systems are relatively unaffected by the pharmacologic effects of ketamine other than how they relate to changes in cardiorespiratory status.

Although the precise mechanism for the loss of consciousness and the production of amnesia, analgesia and muscle relaxation remain debatable and the subject of ongoing investigation it is clear from both experimental and clinical experience that horses like humans and other animals lose consciousness before motor control. Inhalant anesthetic concentrations that are in current clinical use and are required to prevent gross purposeful movement exceed the concentrations that provide optimal cardiorespiratory status. All inhalant anesthetics produce dose dependent depression of the CNS. Their administration requires a working familiarity with anesthetic delivery equipment including vaporizers, pressurized gases (oxygen), anesthetic circuits, anesthetic waste scavenging systems and assisted or controlled breathing strategies (ideally mechatri-
cal ventilators). Isoflurane and sevoflurane produce analgesia and decreases in respiratory rate and tidal volume resulting in increases in PaCO₂ and respiratory acidosis which frequently requires the initiation of assisted breathing techniques or the use of a mechanical ventilator. The administration of inhalant anesthetics to horses has been demonstrated to provide safe, effective, stable and highly controllable anesthesia for periods up to and exceeding 12 hours without producing significant drug accumulation and post anesthetic adverse effects. Inhalant anesthesia, however, in conjunction with the patients size, positioning and the duration of surgery may predispose some horses to ventilation perfusion mismatching and increased venous admixture resulting in unacceptably low PaO₂ regardless of the administration of 100% oxygen. Isoflurane and sevoflurane produce similar hemodynamic effects, are more controllable and are considerably safer (lower morbidity) then their predecessor, halothane, regarding the maintenance of tissue perfusion, muscle blood flow and oxygen delivery. In addition isoflurane and sevoflurane are not inherently arrhythmogenic and do not sensitize the heart to catecholamines. Both are potent vasodilators, which in conjunction with dose dependent decreases in cardiac contractile force and venous return can lead to marked, and in some instances, dangerous decreases in cardiac output and arterial blood pressure. Equally as important is the clinical observation that general anesthetic concentrations of inhalant anesthetics in horses markedly suppress homeostatic responses which in conjunction with the aforementioned cardiovascular effects depresses the anesthetized horses ability to respond surgical events (ex. blood loss, hypotension) by readjusting heart and cardiovascular function unless the anesthetic concentration is reduced. Since this requires decreases in the depth of anesthesia and the potential for the horse to awaken, veterinary surgeons need to be familiar with the administration of drugs that providing an appropriate level of unconsciousness and support the cardiovascular system (ex. dopamine, dobutamine). Alternati-vely equine surgeons need to become familiar with the pharmacology and administration of analgesic anesthetic adjuncts in order to reduce the amount of inhaled anesthetic needed to prevent movement to noxious (ex. surgical) stimulation. Several examples of safe and effective AAA that reduce the amount of inhalant anesthetic required to prevent a physical response to noxious stimuli include lidocaine or lidocaine administered in conjunction with alpha-2 agonists and opioids. Inhalant anesthesia and the choice of anesthetic drugs used to produce equine anesthesia is associated with a stress response and that the degree of stress produced in horses can be reduced by administering injectable (TIVA) compared to inhalant anesthetics. Inhalant anesthesia should be accompanied by the administration of select anesthetic adjuncts that help to maintain blood glucose and support hemodynamics (arterial blood pressure, cardiac output). The importance of these findings is highlighted by published reports that document the high rates of morbidity (5%) and mortality (1%) in otherwise normal healthy horses compared to other species (dogs approx. 0.01%; humans < 0.001%). Safe and effective short term (1-2 hr or less) general anesthesia can be produced in horses under “field” conditions by administering an alpha-2 agonist, waiting for the desired effect (sedation, ambivalence, reluctance to move). Pre-anesthetic medication should be administered with a nonsteriodal anti-inflammatory drug in order to accentuate analgesia and “preempt” surgical pain. Induction to anesthesia can be safely accomplished by the IV administration of a benzodiazipine (diazepam or midazolam) and ketamine. The duration of anesthesia can be extended by administering drug combinations that include an alpha-2 agonist, ketamine and guaifenesin (“triple drip”). Additional calming (acepromazine) or sedatives (alpha-2 agonist) may be administered before inducing anesthesia in order to insuare a quiet controlled induction to anesthesia. The intramuscular administration of acepromazine 30-60 minutes before administering an alpha-2 agonist minimizes the potential for acepromazine induced hypotension, improves sedative and analgesic effects. Pre-anesthetic medication should be administered with a nonsteriodal anti-inflammatory drug in order to accentuate analgesia and “preempt” surgical pain. Induction to anesthesia can be safely accomplished by the IV administration of a benzodiazipine (diazepam or midazolam) and ketamine. The duration of anesthesia can be extended by administering drug combinations that include an alpha-2 agonist, ketamine and guaifenesin (“triple drip”). Additional calming (acepromazine) or sedatives (alpha-2 agonist) may be administered before inducing anesthesia in order to insuare a quiet controlled induction to anesthesia. 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response to alpha-2 agonists or opioids (butorphanol), if administered, and may improve muscle blood flow during anesthesia providing arterial blood pressure is maintained. The arterial pulse pressure or ideally arterial blood pressure should be monitored if acepromazine is administered as preanesthetic medication. More involved or prolonged surgical procedures are best completed by administering isoflurane or sevoflurane anesthesia following the same general approach (alpha-2 agonist, diazepam-ketamine, inhalant anesthetic). The equine veterinary surgeon that uses inhalant anaesthetics should become thoroughly familiar with analgesic protocols, mechanical ventilation and a select group of anesthetic techniques and drugs that support the cardiovascular system.

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