Use of yohimbine to reverse prolonged effects of xylazine hydrochloride in a horse being treated with chloramphenicol

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- Chloramphenicol can prolong effects of drugs that are metabolized by cytochrome P-450 mixed-function oxidase enzymes.
- Concurrent use of xylazine hydrochloride and chloramphenicol can result in xylazine-induced prolonged sedation and gastrointestinal stasis. Antagonism of effects of xylazine with yohimbine can alleviate prolonged sedation and gastrointestinal stasis.

A 1-year-old 360-kg (792-lb) Standardbred stallion was admitted for evaluation of a laceration of the superficial flexor tendon in the left forelimb that had been incurred 2 weeks previously. On physical examination, the horse had a grade-4/5 lameness on the lacerated limb, but other abnormalities were not evident. Results of initial CBC and serum biochemical analyses were within reference ranges. Potassium penicillin G (20,000 U/kg [9,091 U/lb] of body weight, IV, q 6 h) and gentamicin sulfate (6 mg/kg [2.7 mg/lb], IV, q 24 h) were administered. The horse was sedated with xylazine hydrochloride (0.5 mg/kg [0.23 mg/lb], IV) and butorphanol tartrate (0.01 mg/kg [0.004 mg/lb], IV), and anesthesia was induced 45 minutes later with diazepam (0.1 mg/kg [0.04 mg/lb], IV) and ketamine hydrochloride (2.2 mg/kg [1 mg/lb], IV). Anesthesia was maintained with 2% halothane (vaporizer dial setting) in oxygen delivered by a large animal circle system. The wound was surgically debrided, and a drain was placed. Duration of surgery was 45 minutes, and the horse recovered without complications approximately 20 minutes after halothane administration was discontinued.

One week later, the horse was anesthetized for further wound debridement and removal of the drain. Results of a CBC were within the reference range, but serum biochemical analysis was not performed. The horse was sedated with xylazine (1 mg/kg [0.4 mg/lb], IV) to facilitate radiographic examination, and anesthesia was induced 45 minutes later with diazepam (0.1 mg/kg [0.04 mg/lb], IV) and ketamine (2.2 mg/kg [1 mg/lb], IV). Anesthesia was maintained with 2% halothane in oxygen delivered by a large animal circle system. Duration of surgery was 105 minutes, and the horse recovered without complications approximately 20 minutes after halothane administration was discontinued. Analysis of bacteriologic culture results indicated an extremely resistant bacterium that was susceptible only to chloramphenicol, and antibiotic treatment was changed to chloramphenicol (55 mg/kg [25 mg/lb], PO, q 6 h) immediately after surgery.

Five days later, the horse still had a grade-4/5 lameness and was anesthetized a third time for wound exploration. Results of a CBC were within the reference range, and serum biochemical analysis was not performed. The horse had become difficult to handle and was sedated with xylazine (0.75 mg/kg [0.34 mg/lb], IM), and anesthesia was induced 1 hour later, using xylazine (0.15 mg/kg [0.007 mg/lb], IV), followed 5 minutes later by infusion of guaifenesin (45 mg/kg [20 mg/lb], IV) and 2 g of thiopental sodium, IV, administered as a rapid bolus. Drugs for this anesthetic induction differed from drugs used in the first 2 anesthetic procedures because of the preference of the attending anesthesiologist. Anesthesia was maintained with 2% halothane in oxygen for the duration of the procedure (60 minutes), and the horse was not given additional injectable anesthetic agents. Heart and respiratory rates were within reference ranges throughout the procedure, and mean direct arterial pressure was between 70 and 80 mm of Hg. Analysis of a heparinized blood sample obtained 30 minutes after induction of anesthesia indicated respiratory acidosis (pH 7.223; P_{CO_2}, 74.2 mm of Hg; P_{O_2}, 159 mm of Hg), which was corrected by use of intermittent positive-pressure ventilation.

After surgery, the horse was taken to a padded recovery stall and was extubated 20 minutes later (140 minutes after initial administration of xylazine), but it did not attempt to stand. The horse's abdomen was moderately distended and became more distended during the next hour. One hour after being extubated (200 minutes after initial administration of xylazine), the horse stood, but appeared to be extremely weak and lethargic. Five minutes after standing, the horse had signs of abdominal pain. Transrectal palpation revealed an extremely distended large colon. Intestinal sounds were not detectable in any abdominal quadrants. Because of continuing abdominal distention and signs that the severity of pain was worsening, a trocar was inserted in the right paralumbar fossa. The horse appeared to be more comfortable after insertion of the trocar, but assumed sternal recumbency for 1 hour. At the end of that hour (260 minutes after initial administration of xylazine), the horse had abdominal distention, appeared to be extremely uncomfortable, and would stand, but was lethargic. The trocar was reinserted in the left paralumbar fossa, and the horse immediately appeared to be in less pain. Forty-five minutes later (305 minutes after initial administration of xylazine, 245 minutes after induction of anesthesia),

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the horse was still lethargic and, again, had abdominal distention and signs of pain. The horse still appeared to be sedated and was given yohimbine[a] (0.03 mg/kg [0.014 mg/lb], IV). Within 2 minutes, the horse became more alert. Within 5 minutes of yohimbine administration, the horse began to eat. Within 15 minutes, moderate flatulence developed, and intestinal sounds were auscultable in all 4 abdominal quadrants. The horse was returned to its stall 20 minutes after yohimbine administration (325 minutes after initial administration of xylazine). The remainder of recovery was uneventful.

Xylazine decreases motility in the small intestine,[1-3] cecum,[2,4,5] and large intestine[2,6-8] of horses and, therefore, might allow accumulation of intestinal gas. Decreased motility may result from direct xylazine-mediated inhibition of smooth muscle or from α_2-presynaptic stimulation and a subsequent decreased release of acetylcholine, a stimulator of gastrointestinal motility.[9] Yohimbine[8] and tolazoline hydrochloride,[6] which are α_2-antagonists, reverse the decrease in intestinal motility that follows administration of α_2-agonists. Motility generally is depressed for 20 to 30 minutes.[2,4,6] The continued sedation and impaired intestinal motility described here were believed to be the result of the effects of xylazine. Reversal of sedation and intestinal stasis by yohimbine supported this diagnosis. The exaggerated and prolonged duration (5 hours) of sedation and gastrointestinal stasis caused by xylazine in this horse was believed to be attributable to inhibition of hepatic metabolism of xylazine secondary to chloramphenicol administration.

Chloramphenicol inhibits oxidase activity of cytochrome P-450, a principal microsomal mixed-function oxidase enzyme located in hepatocytes that is responsible for catabolism of several endogenous hormones and biotransformation of numerous exogenous chemicals and drugs.[10] Thus, chloramphenicol treatment of short duration can produce marked prolongation of the effects of drugs that depend on cytochrome P-450 metabolism for culmination of therapeutic activity.[11,12] In horses, a single administration of chloramphenicol (25 to 50 mg/kg [11.4 to 22.7 mg/lb], IV) can prolong the plasma half-life of phenylbutazone, a drug that is metabolized primarily by cytochrome P-450 oxidase enzymes.[11,12] Chloramphenicol prolongs the duration of xylazine-ketamine anesthesia in rats,[13] but not in dogs.[14] Ketamine is metabolized by cytochrome P-450 enzymes[15] and could have been solely responsible for the increased duration of anesthesia described in these reports. However, this route of metabolism also is suggested for xylazine, because administration of xylazine is followed by rapid distribution and elimination, but without substantial amounts of unmetabolized drug detectable in the urine.[16] Xylazine metabolites recovered in urine of horses are almost exclusively products of oxidation.[b] Analysis of these combined data would suggest that chloramphenicol administration could prolong effects of xylazine in horses.

Thiopental sodium was not used in the first 2 uneventful anesthetic episodes. Concurrent use of chloramphenicol can prolong barbiturate-induced anesthesia.[11,17] A single administration of chloramphenicol (25 mg/kg [11.4 mg/lb], IV) in horses anesthetized with thiamylal sodium (6.6 mg/kg [3 mg/lb], IV) prolonged recumbency time (mean ± SD) from 21.8 ± 4.8 to 36.0 ± 8.3 minutes.[11] However, this was substantially less than the recumbency time for the horse described here, suggesting that thiopental sodium may have contributed to, but was not principally responsible for, the exaggerated and prolonged effects of anesthesia.

Guaifenesin, a centrally acting muscle relaxant, also is dependent on hepatic metabolism.[18] Similarly, general anesthesia induced by various techniques and maintained by inhalant anesthetic agents in oxygen can cause decreased gastrointestinal motility.[19] However, in the horse described here, reversal of sedation and gastrointestinal stasis by the α_2-antagonist yohimbine strongly suggested that these symptoms were mediated by the α_2-agonist xylazine, alone or in combination with thiopental sodium, and were not mediated by guaifenesin or halothane. This report serves to identify a possible complication resulting from drug interactions associated with routine administration of antibiotics and α_2-agonists.

[a]Yobine, Vet-A-Mix, Shenandoah, Iowa.

[b]Sams RA, The Ohio State Racing Laboratory, Columbus, Ohio: Personal Communication, 1996.

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From My Armchair: W. W. Armistead

Athletics versus academics

Playing big-time college football or basketball requires a tremendous amount of student athletes' time, undoubtedly interfering with academic study. On the other hand, many athletes could not have attended college at all but for their athletic scholarships. In any case, the veterinary colleges are not involved. Not since the 1940s have veterinary curriculums allowed enough free time for veterinary students to participate in intercollegiate sports. Even preveterinary students are rarely found on varsity teams.

There are those who believe that universities place too much emphasis on intercollegiate athletics. Especially resentful are some faculty scholars who complain that attention to big-time football or basketball comes at the expense of academic pursuits. The facts suggest otherwise.

To begin with, athletic programs at large universities usually are financially self-supporting. At major state universities, football revenues pay for entire intercollegiate athletic programs, including athletic facilities, and require no subsidy from state tax dollars. The most successful programs even produce profits that support academic scholarships. And by being successful in athletic competition, universities increase their visibility, attract students, and enlist political and financial support from alumni and other sports fans. Without successful athletic teams, there likely would have been less money for academic programs. The public should worry more about mediocre athletic programs that cannot survive without tax dollars appropriated for the support of classroom education.

Idealistic faculty members claim that too much emphasis on athletics distracts students from their studies and weakens the university's academic reputation. But "too much emphasis" actually translates to "to much success," usually the result of superior entrepreneurial talent in the athletic department, rather than conscious effort by the university administration to subjugate English or mathematics or chemistry.

One needs only to look at Stanford, Michigan, California, and Notre Dame to see that winning athletics and high scholarship can co-exist. I think it was Abraham Lincoln who said that the weak cannot be strengthened by weakening the strong. A university should not undertake any program in which it will not try to excel.

As to student distraction, on today's campuses there are many more dangerous distractions than athletic events.

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