Evaluation of the use of atropine sulfate, a combination of butylscopolammonium bromide and metamizole sodium, and flunixin meglumine to ameliorate clinical adverse effects of imidocarb dipropionate in horses

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Objective—To evaluate the ability of atropine sulfate, butylscopolammonium bromide combined with metamizole sodium, and flunixin meglumine to ameliorate the clinical adverse effects of imidocarb dipropionate in horses.

Animals—28 horses with piroplasmosis.

Procedures—28 horses were randomly assigned to 4 equal groups according to the pretreatment administered. Fifteen minutes before administration of 2.4 mg of imidocarb dipropionate/kg IM, horses in the first group were pretreated with 0.02 mg of atropine sulfate/kg IV, the second group with a combination of 0.2 mg of butylscopolammonium bromide/kg IV and 25 mg of metamizole sodium/kg IV, the third group with 1.1 mg of flunixin meglumine/kg IV, and the fourth (control) group with 1 mL of saline (0.9% NaCl) solution/50 kg IV. Physical examination, including evaluation of rectal temperature, heart and respiratory rates, capillary refill time, mucous membrane color, hydration status, abdominal sounds, signs of abdominal pain, salivation, diarrhea, and number of defecations, was performed.

Results—Imidocarb dipropionate use in the control group was associated with serious adverse effects including signs of abdominal pain (4/7 horses) and diarrhea (2/7). Horses pretreated with atropine had no diarrhea, but 6 had signs of abdominal pain. Only 1 horse that received butylscopolammonium-metamizole pretreatment had signs of abdominal pain and 3 had diarrhea, which was numerically but not significantly different than the control group. Of horses pretreated with flunixin, 3 had signs of abdominal pain and 3 had diarrhea.

Conclusions and Clinical Relevance—A combination of butylscopolammonium bromide and metamizole sodium may be useful to ameliorate the adverse effects of imidocarb dipropionate in horses, although group size was small and significant differences from the control group were not found. (Am J Vet Res 2013;74:1404–1408)
Imidocarb dipropionate is a derived form of carbanilide that has been used for more than 20 years for the treatment of certain protozoal diseases, including piroplasmosis in horses as well as cattle, sheep, and dogs. It is a bacillosidic drug; the drug combines with the parasite’s nucleic acids, causing partial uncoiling and denaturation of the DNA double helix.10,20 Imidocarb dipropionate also prevents inositol from entry into the affected erythrocytes, which leads to parasite starvation.21 However, imidocarb dipropionate inhibits acetylcholinesterase and this increases endogenous acetylcholine concentration and stimulates both muscarinic and nicotinic cholinergic receptors.21

When the therapeutic dose (2.4 mg/kg) is administered, imidocarb dipropionate is rapidly absorbed. Maximum plasma concentration is reached at 1.16 hours. Plasma concentrations rapidly decrease because of wide redistribution of the drug.23–26 Unfortunately, imidocarb dipropionate has serious adverse effects that appear after treatment with the therapeutic dose (2.4 mg/kg).22–24 including salivation, diarrhea, and signs of abdominal pain, which progress in some cases to death.8,27 These effects are related to the anticholinesterase activity of imidocarb. Overstimulation of muscarinic receptors can lead to salivation, lacrimation, signs of abdominal pain, vomiting, diarrhea, increased frequency of defecation and urination, dyspnea caused by increased bronchial secretions and bronchospasm, bradycardia, and miosis. Activation of nicotinic receptors results in muscle tremors, muscular weakness, and paralysis. If the CNS is stimulated, affected animals have restlessness, signs of anxiety, hyperactivity, seizures, and signs of profound depression.22,23 Administration of atropine sulfate is recommended by small and large animal veterinarians to offset the adverse effects of imidocarb dipropionate, and this recommendation is based on anecdotal reports and not related to experimental work or controlled case studies. A crossover study in 8 horses was done to evaluate the ability of atropine sulfate or glycopyrrolate to ameliorate the adverse effects of imidocarb dipropionate, and it was concluded that only glycopyrrolate was effective.28 Atropine sulfate ameliorated the clinical gastrointestinal tract effects; unfortunately, it significantly inhibited gastric motility, small intestinal motility, or both.28 However, glycopyrrolate availability has regional variations whereas atropine sulfate is generally readily available in private practices and has several other uses in equine medicine.29

Butylscopolammonium bromide is an anticholinergic and antispasmodic drug used to manage abdominal pain (colic).30 Commercially, it is combined with an analgesic, metamizole sodium. Flunixin meglumine is the most clinically accepted NSAID used to treat acute abdominal disease in horses.31 Butylscopolammonium bromide and flunixin meglumine are readily available to general practitioners.

The objective of the study reported here was to determine the ability of atropine sulfate, butylscopolammonium bromide plus metamizole sodium, or flunixin meglumine to ameliorate the clinical adverse effects of imidocarb dipropionate use in horses. The hypothesis was that flunixin meglumine or butylscopolammonium bromide plus metamizole sodium can be used to help reduce the adverse effects associated with use of imidocarb dipropionate.

Materials and Methods

Study animals and design—Twenty-eight horses affected clinically with piroplasmosis were enrolled in the study. These horses were allocated randomly into 4 groups of 7 horses each. Horses were client-owned, and the owners gave consent for use of the horses in the study. The study was approved by Jordan University of Science and Technology Animal Care and Use Committee.

Fifteen minutes before administration of 2.4 mg of imidocarb dipropionate/kg IM as a treatment for equine piroplasmosis, horses in the first group were pretreated with 0.02 mg of atropine sulfate/kg IV, the second group with a combination of 0.2 mg of butylscopolammonium bromide/kg IV and 25 mg/kg of metamizole sodium/kg IV, the third group with 1.1 mg of flunixin meglumine/kg IV, and the fourth group with 1 mL of saline (0.9% NaCl) solution/50 kg IV. Horses in the fourth group were assigned as controls, and they also were administered 2.4 mg of imidocarb dipropionate/kg for treatment of piroplasmosis, without any pretreatment.

Data collection—A data collection form was completed for each horse and included the breed, age, sex, and body weight as well as the owner’s name and stable or farm location. Physical examination findings (rectal temperature, heart rate, respiratory rate, capillary refill time, mucous membrane color, hydration status evaluated by skin tenting and scored as present or absent, muscle tremor, and abdominal sounds [borborygmi] at the 4 quadrants of the abdomen) and other findings, including presence of signs of abdominal pain, diarrhea, hypersalivation, and number of defecations, were recorded for each horse at the time of initial evaluation and throughout the study. Signs of abdominal pain, diarrhea, and hypersalivation were scored as present or absent. Abdominal sounds auscultated at the 4 quadrants were classified as absent, decreased, normal, or increased (converted to scores 0, 1, 2, and 3, respectively). The score for each horse included the sum of the readings of the 4 quadrants. Physical examination and other observational findings were recorded by a veterinarian unaware of group assignments at (hours:minutes): 0:00, 0:45, 1:45, 2:45, 3:45, 4:45, 5:15, 24:00, and 48:00 hours. The different pretreatments were given at 0:00, just after the initial physical examination, and imidocarb dipropionate was given at 0:15.

Venous blood samples were collected from a jugular vein of each horse at 0:00 and 24:00 and stored in a refrigerator until they were transported to the laboratory (within 24 hours after collection). Blood in tubes containing EDTA was used for CBC analysis and fibrinogen concentration determination. Serum was obtained from blood in tubes that did not contain anticoagulant and was used for biochemical analyses performed with an automated analyzer.

Statistical analysis—Data analysis was performed with a computer software program.3 Cases with a miss-
The abdominal pain signs varied in severity from mild (stretching and restlessness) to moderate (frequent attempts to urinate and frequent pawing). In the atropine group, 6 of 7 horses had abdominal pain signs ranging from mild to severe for 15 minutes to > 3 hours. In the butylscopolammonium-metamizole group, 1 of 7 horses had abdominal pain signs, which began 1.3 hours after treatment with imidocarb and rapidly progressed to rolling and sweating. Signs resolved over the following 30 minutes with walking. In the flunixin meglumine group, 3 of 7 horses had abdominal pain signs (2 mild and 1 severe). These values were significantly (P = 0.01) different between the atropine and butylscopolammonium-metamizole groups. Of the horses that had signs of abdominal pain, 3 horses in the atropine group and 1 horse in the flunixin meglumine group required a dose of flunixin meglumine as a treatment.

With the exception of the atropine group (no horses with diarrhea), 3 of 7 horses in each group had diarrhea. This finding in the atropine group was significantly different from the other groups.

There were no significant differences among groups in values for CBCs, serum alanine transferase or γ-glutamyltransferase activities or fibrinogen, total protein, creatinine, BUN, and total bilirubin concentrations. Serum ALP activity decreased significantly (P = 0.018) after administration of atropine sulfate, and aspartate aminotransferase activity increased significantly after administration of butylscopolammonium-metamizole (P = 0.018). Creatine kinase activity and direct bilirubin concentration increased significantly after administration of flunixin meglumine (P = 0.028 and 0.034, respectively).

**Discussion**

We hypothesized that either butylscopolammonium-metamizole or flunixin meglumine could ameliorate the adverse effects of imidocarb dipropionate. Results of this study indicated that signs of abdominal pain but not diarrhea may be ameliorated by administration of butylscopolammonium-metamizole. Flunixin meglumine did not alter either signs of abdominal pain or diarrhea. Atropine sulfate may have worsened signs of abdominal pain, potentially because of its effects on gastrointestinal tract motility. Imidocarb dipropionate was administered to 7 horses in the control group, of which 4 developed signs of abdominal pain and 3 had diarrhea. These adverse signs were probably caused by cholinesterase inhibition and were consistent with muscarinic stimulation. The abdominal pain signs varied in severity from mild (stretching and restlessness) to moderate (frequent attempts to urinate and frequent pawing). The signs of abdominal pain seen after imidocarb dipropionate administration were presumed to originate from strong intestinal smooth muscle contractions with intestinal spasms.

Administering atropine sulfate with imidocarb dipropionate did not decrease the prevalence of signs of abdominal pain, and more horses had signs of abdominal pain in the atropine group than in the control group. These findings were consistent with a previous study of the use of atropine with imidocarb dipropionate. In that study, borborygmi were significantly reduced, suggesting that ileus and potentially gas accumulation may have been the cause of the signs of abdominal pain. Furthermore, none of the horses in the atropine group had diarrhea, whereas diarrhea occurred in the rest of the experimental groups. This was likely caused by the known direct effect of atropine sulfate on gastrointestinal tract motility rather than antagonism of the effects of imidocarb. On the basis of the findings of this study, atropine sulfate should not be used to ameliorate the adverse effects of imidocarb dipropionate.
Numerically, the combination of butylscopolammonium bromide and metamizole sodium decreased the adverse effects of imidocarb dipropionate; borborygm was not reduced, and signs of abdominal pain were seen in only 1 of 7 horses after butylscopolamine-metamizole administration. Butylscopolammonium bromide is known to block muscarinic receptors of the gastrointestinal tract and therefore relieve intestinal spasms. However, butylscopolammonium-metamizole did not alter the frequency of diarrhea, compared with that observed in the control group.

The results did not support our hypothesis that flunixin could be used to ameliorate the adverse effects of imidocarb, because it did not prevent signs of abdominal pain or diarrhea. This lack of a significant difference from the control group may have been related to the low power of the study caused by the small group size. Flunixin may still be useful for the treatment of abdominal pain signs and did not worsen the clinical signs.

One of the shortcomings of this study was low statistical power. To obtain a power > 0.5, 50 horses/group were needed; this would be difficult to achieve in a clinical trial in our region. Additionally, 4 horses (3 in the atropine group and 1 in the flunixin meglumine group) were treated with flunixin meglumine for signs of abdominal pain, which may have affected results in those groups. However, the atropine-treated horses still had significantly worse results than controls despite the extra anti-inflammatory medication. The cause of the changes in certain serum biochemical values was unknown. In large animals, ALP is not organ specific, and decreased serum ALP activity is usually an irrelevant finding. Aspartate aminotransferase is found in high concentration in various tissues including muscles, kidneys, and liver. Creatine kinase is a useful indicator of muscle damage. Further tests to identify the causes of the changes in these variables were not performed.

In the present study, atropine sulfate failed to ameliorate the adverse effects of imidocarb dipropionate in horses, and, on the contrary, its use appeared to increase the prevalence of these effects. Although a significant difference in the proportion of horses with signs of abdominal pain was not found between the control and butylscopolammonium-metamizole groups, the number of horses in the butylscopolammonium-metamizole group with signs of abdominal pain (1/7) was substantially lower than the number in the control group (4/7). Because of the low number of horses in the study, the power to detect statistical differences between groups was low, and we believe that with a larger number of horses, a significant difference may have been detected. We speculate, therefore, that pretreatment with butylscopolammonium-metamizole may be clinically useful in horses being treated with imidocarb dipropionate. However, additional study is necessary.

a. SPSS 17.0 software for Windows, SPSS Inc, Chicago, Ill.

References