Ulcerative cystitis associated with phenylbutazone administration in two horses

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Case Description—A 15-year-old Quarter Horse gelding and a 26-year-old Thoroughbred gelding were evaluated because of hematuria of 4 to 6 days’ duration following prolonged oral administration of phenylbutazone.

Clinical Findings—The horses had received either treatment with phenylbutazone for 3 months or intermittent long-term phenylbutazone treatment prior to development of hematuria. Each horse was systemically stable but had orthopedic or neurologic problems. Clinico-pathologic findings included normochromic normocytic anemia in both horses and hypoalbuminemia and high BUN concentration in 1 horse. In both horses, urinalysis revealed proteinuria and RBCs, but no evidence of WBCs or bacteria. Ulceration and hemorrhage of the urinary bladder with no evidence of uroliths were observed via cystoscopy. Gastric ulceration along the margo plicatus was observed via gastroscopy.

Treatment and Outcome—For each horse, phenylbutazone treatment was discontinued and a synthetic prostanoid (misoprostol) was administered. The hematuria resolved, and results of a follow-up CBC, serum biochemical analysis, urinalysis, and cystoscopy 25 or 30 days after cessation of phenylbutazone treatment were unremarkable in both cases.

Clinical Relevance—Given the known adverse effects of NSAID treatment in several species, phenylbutazone and its metabolites were suspected to have caused ulceration of the urinary bladder, resulting in hematuria, in the 2 horses. A definitive cause of urinary bladder ulceration was not confirmed in these cases; however, resolution of ulceration after discontinuation of phenylbutazone treatment and administration of synthetic prostanoglandins and exclusion of other causes suggested an association between phenylbutazone administration and ulcerative cystitis in these horses. (J Am Vet Med Assoc 2011;239:499–503)

Abbreviations

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<td>PG</td>
<td>Prostaglandin</td>
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<td>USG</td>
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and butorphanol tartrate (0.01 mg/kg, IV) for urinary tract catheterization to obtain a sterile urine sample for urinalysis and aerobic bacterial culture and to empty the bladder prior to cystoscopic evaluation. The catheterization procedure was uneventful, and there was no macroscopic hematuria in the urine sample collected. Cystoscopically, the epithelium in the proximal portion of the urethra appeared reddish. The urinary bladder mucosa was hemorrhagic and ulcerated (Figure 1). The ureteral openings were also hemorrhagic. Grossly normal urine was observed flowing from both ureters. Collection of a bladder biopsy specimen for histologic and microbiological evaluation was suggested, but the owner declined. A urine sample was obtained for analysis during the catheterization procedure to drain the bladder prior to endoscopic evaluation. At that time, USG was 1.013, urine pH was 8.5, and proteinuria (1+) was detected; microscopically, 0 to 1 RBCs/hpf, rare WBCs, and no microorganisms were evident. Aerobic bacterial culture of the urine sample yielded no growth. On the basis of the history of long-term administration of phenylbutazone along with the examination and laboratory findings, a complete transabdominal ultrasonographic examination and gastroscopy were performed. The right dorsal colon wall appeared mildly thickened (5 mm) and irregular; in transabdominal ultrasonographic images, the wall had a hypoechoic appearance, compared with the remainder of the normal-appearing large colon wall in other areas of the abdomen. Gastroscopy revealed mild chronic and ongoing ulceration along the margo plicatus and diffuse hyperkeratosis of the gastric squamous epithelium.

A clinical diagnosis of gastric ulceration and ulcerative cystitis was made. The horse was discharged from the hospital, and the owner was instructed to administer trimethoprim sulfamethoxazole (30 mg/kg [13.6 mg/lb], PO, q 12 h for 2 weeks) to prevent development of infection of the urinary tract secondary to the bladder wall mucosal damage. All administration of phenylbutazone was to be discontinued, and use of this medication in the future was not recommended. Additionally, the horse was to receive omeprazole (4 mg/kg [1.8 mg/lb], PO, q 24 h for 2 weeks, followed by 2 mg/kg [0.9 mg/lb], PO, q 24 h for 2 weeks), misoprostol (a synthetic PGE1 analogue; 2 µg/kg, PO, q 12 h for 5 days), and phenazopyridine (4 mg/kg, PO, q 12 h for 5 days).

Twenty-five days following diagnosis of the ulcerative cystitis, the horse was returned for a follow-up examination. Physical examination findings were unremarkable. A blood sample was collected after the horse was sedated with xylazine hydrochloride (0.3 mg/kg [0.14 mg/lb], IV); serum biochemical variables were within reference ranges, but a CBC revealed normocytic normochromic anemia (Hct, 26%). The mild anemia was attributed to the administration of the sedative. Transabdominal ultrasonography revealed no abnormalities in the kidneys, urinary bladder, ureters, or right dorsal colon. Cystoscopically, the urethra and urinary bladder appeared normal with no remaining areas of reddening or irritation (Figure 1). A urine sample was obtained for analysis via urinary catheterization to drain the bladder prior to cystoscopy after the horse had been sedated. Results of the urinalysis were considered normal, and USG was 1.010. Gastroscopy revealed marked improvement of the gastric ulceration with resolving hyperkeratosis and 2 small ulcers along the margo plicatus. The horse was discharged from the hospital, and the owner was instructed to administer
Discussion

In the horses of this report, prolonged administration of phenylbutazone appeared to be associated with the development of hematuria secondary to ulceration and hemorrhage of the urinary bladder mucosa given that other causes were ruled out. In both cases, hematuria and ulceration of the urinary bladder resolved upon the discontinuation of phenylbutazone administration. Cystitis induced by NSAIDs in people and rats has been reported.4 According to a survey performed by urologists, this condition is poorly recognized and underreported because of the low level of awareness.9 The NSAIDs associated with hemorrhagic cystitis in people include tiaprofenic acid, indomethacin, diclofenac, ketoprofen, naproxen, acetyl salicylic acid, and piroxicam.4,6

The urinary bladder of mammals consists of 4 distinct layers: the serosa, muscularis, submucosa, and transitional cell epithelium.7 All layers except for the serosa have the capacity to synthesize prostanooids,7 and the synthesis of PGs such as PGE1, PGE2, PGF2, and thromboxane A2 have been detected in rats, rabbits, and humans.7–9 Urinary bladder distension, urine pH and osmolarity, and exposure to carcinogens are factors that influence the in vitro synthesis of prostanooids in rats.9,10 Roles of the urinary prostanooids include regulation of bladder smooth muscle activity and tone; local modulation of reflex micrituration; cytoprotection of the urothelium from irritation, ulceration, and bacterial adhesion through mucous secretion; and maintenance of the urothelial glycosaminoglycan barrier.9,12 However, not all prostanooids are cytoprotective—thromboxane A2 promotes ulcer formation in the gastric mucosa of dogs in vitro.9 The role of urinary PGs in tumor development is variable, ranging from cytoprotective effects to involvement in carcinogenesis.10

Decreased prostanooid synthesis as a result of NSAID administration may render the urinary bladder susceptible to ulceration, infection, and neoplasia.9,10 Removal of the mucosal glycosaminoglycan layers through the inhibition of PG synthesis allows the mucosal adherence of crystals (eg, calcium oxalate) and substances present in the urine, increased mucosal permeability,
Cystitis develops less commonly in horses, compared with other species, and is usually secondary to urine retention caused by physical, structural (urothelitis or acquired anomaly), or functional (bladder paralysis) obstruction; infection; neoplasia; and, less commonly, cantharidin toxicosis (a result of blister beetle ingestion).16–20 Primary cystitis is rare in horses.20 Common clinical signs in horses with cystitis include dysuria and pollakiuria,21 which were observed in the Quarter Horse of this report. The Thoroughbred with neurologic abnormalities did not have signs compatible with cauda equina dysfunction, such as decreased or absent tail, anal, rectal, and bladder tones; perceived perineal hyper- or hypoesthesia; and altered perineal reflex. Rectal palpation of the urinary bladder did not reveal abnormalities, and urination was observed to be normal in the Thoroughbred. Additionally, this horse did not have a history of urinary incontinence and did not have evidence of urine scaling of its pelvic limbs at evaluation. Hematuria is uncommon in horses, but it can be caused by urolithiasis, bacterial urinary tract infection, neoplasia, drug (NSAID)-induced nephrotoxicosis, idiopathic renal hematuria, verminous nephritis (infection with Halicarabulus gingivalis or Strongylus vulgaris), habronemiasis of the urethral process, vascular injury or anomaly (hematoma or aneurysm), exercise in association with urolithiasis, urethral rents, and cantharidin toxicosis; it may also be iatrogenic from catheterization.21–24 Blood from the reproductive tract could also be a cause of hematuria.21 Results of urinary tract endoscopy ruled out most of the possible causes of hematuria in the 2 horses of this report. First, there was no evidence of sabulous sediment accumulation, urolithiasis, or trauma to the urethra and ureters that would suggest the passage of uroliths in these horses. The urethral epithelium was reddened, likely as a result of catheterization because the reddening appeared acute and superficial. The ureteral openings were ulcerated symmetrically and to the same degree as the other ulcerated areas of the bladder, which was not likely consistent with passage of a urolith. Blood was observed to originate from the ulcerated bladder and not from the ureters. The bladder mucosa appeared ulcerated and hemorrhagic, but no tissue proliferation or masses suggestive of neoplasia were observed. Furthermore, follow-up cystoscopy revealed complete resolution of cystitis and bladder ulceration in both horses. Urethral rents and lesions of the urethral epithelium were also not observed. On the basis of ultrasonographic findings, 1 horse had a suspected hematoma in the renal pelvis; this may have been from renal medullary crest necrosis and bleeding, which are also associated with NSAID treatment. However, no seepage of blood from the ureter associated with that kidney was observed, although blood was observed originating from the ulcerated bladder mucosa. In both horses, microscopic examination of urine samples revealed rare WBCs and no microorganisms; and, results of an aerobic bacterial culture of urine were negative; thus, bacterial cystitis was considered much less likely. However, bacterial cystitis cannot be definitively ruled out. In California, cantharidin toxicosis in horses has only been reported when the animals were fed contaminated alfalfa hay transported from endemic areas.20 The horses of this report were fed locally grown and processed alfalfa hay. In addition, common clinical signs and clinicopathologic alterations of cantharidin toxicosis were not observed in these horses.

The reported adverse effects of NSAIDs in horses include oral, gastric, duodenal, and colonic ulceration; local or diffuse right dorsal colitis; acute necrotizing enterocolitis; renal medullary crest or papillary necrosis; and clinicopathologic alterations such as anemia, neutropenia, hypoproteinemia, hypoalbuminemia, hypocalcemia, high BUN concentration, and proteinuria.23–20 Higher than recommended doses or prolonged administration of NSAIDs and drug susceptibility of individuals can increase the likelihood of NSAID toxicosis.30,31 The Quarter Horse in this report was receiving intermittent long-term treatment with phenylbutazone (1.9 to 3.8 mg/kg [0.9 to 1.7 mg/lb], PO, q 24 h), and the Thoroughbred was being treated with phenylbutazone (5.2 mg/kg [2.4 mg/lb], PO, q 24 h) for an extended period (3 months). Both horses had gastric ulceration in the squamous epithelium close to the margo plicatus and clinicopathologic alterations similar to those reported for horses with NSAID toxicosis. The anemia in the horses of this report was believed to be attributable to blood loss from the gastrointestinal and urinary tracts. In the Thoroughbred, BUN concentration was high but serum creatinine concentration was within reference range, which was likely the result of gastrointestinal bleeding; similarly, hypoalbuminemia could have been the result of blood loss into the gastrointestinal tract. Proteinuria in both horses was thought to be attributable to the presence of blood in the urine.

On the basis of the history, physical examination findings, results of diagnostic testing, and resolution of the observed ulcerative cystitis with minimal medical intervention after discontinuation of phenylbutazone administration in these 2 cases, most other causes of cystitis and hematuria were ruled out and a high suspicion for NSAID-induced cystitis and ulceration remained. Phenylbutazone is mainly metabolized to oxypHENbutazone and γ-hydroxy-phenylbutazone and is excreted in urine at variable concentrations in horses.32,33 The bladder ulceration in the horses of this report could have been the result of the systemic and possible local effects of phenylbutazone and its metab-
olites. Oral or intravesical administration of synthetic PGs is effective for the treatment of interstitial cystitis and cyclophosphamide-induced cystitis in people.30,35 In horses, misoprostol has been shown to ameliorate the detrimental effects of flunixin meglumine on mucosal permeability in experimentally induced ischemic injury of the jejunum by providing an alternative source of reparative prostanoids.36 It is uncertain whether the use of misoprostol was absolutely necessary for the resolution of ulcerative cystitis in the horses of this report and whether discontinuation of phenylbutazone alone would have been sufficient to restore local production of PGs. Cause and effect was not confirmed in these cases, but the resolution of bladder ulceration upon the discontinuation of phenylbutazone and administration of supplemental synthetic PGs may suggest that the administration of phenylbutazone can induce ulceration and hemorrhage of the urinary bladder in horses, as has been observed in people and laboratory animals. Therefore, ulceration of the urinary bladder associated with the administration of phenylbutazone should also be considered as a possible cause of hematuria in horses.

References