Evaluation of the Effects of Flunixin Meglumine, Ketoprofen and Phenylbutazone Administration on the Brain, Renal and Hepatic Functions in Iranian Cross-Breed Goats

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Abstract: Flunixin meglumine, ketoprofen and phenylbutazone were classified with the group of compounds commonly referred to as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). The purpose of this study was to evaluate the brain, renal and hepatic effects of 3 NSAIDs (flunixin meglumine, ketoprofen and phenylbutazone) when administered IV to clinically normal Iranian cross-breed goats. The experiments were conducted on twenty clinically normal adult male goats. Goats were randomly assigned to 4 groups: saline (n = 5), flunixin meglumine (n = 5) ketoprofen (n = 5) and phenylbutazone (n = 5). Drug administration was initiated at 8 AM on day 1 and continued every 12 h for 12 days. Flunixin meglumine, ketoprofen and phenylbutazone were administered at the dose rate of 2.2, 2.2 and 4.4 mg kg⁻¹, respectively. Daily blood and urine samples were collected from all goats for hematology, enzyme activities and urinalysis. Immediately after euthanasia, complete necropsy was performed on all goats and gross lesions were recorded. Clinically, mild anorexia and diarrhea were observed during the study only in phenylbutazone treated group. Mean total and differential of leukocytes, RBC and PCV did not changed significantly. Serum biochemical analysis indicated a significant treatment effect on urea nitrogen, creatinine and enzyme activities. Treatment effect was not significantly evident in results of urinalysis. Macroscopic and microscopic findings: Considering brain, renal and hepatic lesions, the toxic potential of the NSAIDs, when use of these compounds is contemplated in clinical cases, the risk of adverse effects and the comparative toxic potential should be considered, along with the efficacy of the compound for the condition being treated.

Key words: Phenylbutazone, flunixin meglumine, ketoprofen, goat, adverse effects

INTRODUCTION

Flunixin meglumine, ketoprofen and phenylbutazone are classified with the group of compounds commonly referred to as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). The major categories of NSAIDs include salicylates (aspirin), propionic acids (ibuprofen, fenoprofen, ketoprofen and naproxen), pyrazolones (phenylbutazone), anthranilic acids (melofenamic acid) and aminonicotinic acids (flunixin meglumine). The NSAIDs are a diverse group compounds that are antipyretic, anti-inflammatory and analgesic agents. They share a basic mechanism of inhibiting cyclooxygenase, resulting in decreased production of prostaglandin (Insel, 1990). Flunixin meglumine was introduced into veterinary medicine in the late 1970s. It has been used effectively in the treatment of musculoskeletal disease and colic in horse (Houdeshell and Herrissey, 1977). Flunixin meglumine also is reported to reduce the adverse effects of endotoxin (Dunkle et al., 1985; Moore et al., 1986). Toxic effects of flunixin meglumine in foals include gastrointestinal tract ulceration and diarrhea (Traub et al., 1988). Ketoprofen is relatively new in veterinary medicine. It was approved for use in 1990 and is recommended for alleviation of inflammation and pain associated with musculoskeletal disorders. Phenylbutazone was introduced to veterinary medicine in the 1950s and soon became the non-steroidal anti-inflammatory drug of choice in equine medicine (Tobin and Chay, 1986). Phenylbutazone is indicated for treatment of various musculoskeletal disorders. It also is reported to decrease the adverse effects, but not to increase the survival rate when administered after endotoxin (Burrows, 1981). In 1979, substantial adverse
effects of phenylbutazone were reported in ponies (Snow et al., 1979). Numerous investigators have confirmed the potential of phenylbutazone to cause adverse reactions in ponies, foals and adult horses (Mesczer et al., 1990). NSAIDs are just only studied for determination of its pharmacokinetic and pharmacodynamic properties in ruminants, anyway. So, I would prefer to create a new hypothesis focusing on the side effects and the mechanism with which it inflict these side effects (Welsh et al., 1993; Konigson et al., 2003). The toxic changes caused by NSAIDs were not documented in goats. The purpose of this study was to evaluate the brain, renal and hepatic effects of flunixin meglumine, ketoprofen and phenylbutazone when administered IV to clinically normal Iranian cross-breed goats.

MATERIALS AND METHODS

The study was conducted from 2008 to 2009. The experiments were conducted on twenty clinically normal adult female Iranian cross-breed goats. Goats were examined physically to determine that they were in good health prior to entry into the study. The diet given to study goats was similar to control group and contained mixed-grain ration 0.45/50 kg of body weight and free grass hay. All animals were allowed for 1 week to adapt to the diet and environment before starting the study. During the first 2 days of the acclimation period, all goats were dewormed with albendazole blouze (Divern, Damloran CO, Iran) at dose rate of 7.5 mg kg⁻¹.

Experimental design: Goats were randomly assigned to 4 groups: saline (n = 5), flunixin meglumine (n = 5) ketoprofen (n = 5) and phenylbutazone (n = 5). Individuals performing the physical examinations, necropsy and laboratory analyses did not administer the drugs and did not know the drug assigned to each goat or group.

Experimental procedure: Drug administration was initiated at 8 AM on day 1 and continued every 12 h for 12 days. Flunixin meglumine, ketoprofen and phenylbutazone were administered IV via an indwelling jugular vein catheter at dose rate of 2.2, 2.2 and 4.4 mg kg⁻¹, respectively. After each injection, IV catheters were flushed with heparinized physiologic saline solution. The volume of normal saline administered in group 1, was equal to the volume of drugs in the treatment groups.

Daily physical examinations were performed completely on all goats. Appetite was assessed at the time of physical examination. In addition to daily physical examinations, all goats were checked every 12 h for signs of adverse reaction to treatment. Daily blood samples were collected from all goats for CBC, PCV (by an automatic cell counter, model Sysmex KX-21, Japan), serum biochemical analysis (total protein, albumin, urea nitrogen and creatinine (by auto analyzer, RA 1000, Technicon, America), aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase activities by using biochemical procedure (Tietz et al., 1994) and fecal samples were submitted for occult blood determination. Urine was collected from the goats by catheterization for urinalysis. Urine samples were examined for the presence of proteins, glucose, ketones, blood, bilirubin, urobilinogen, nitrate, WBC, RBC, epithelial cells, bacteria, crystals and casts. Color, appearance, specific gravity and pH were also assessed. Urinalysis was done using urine indicator paper (Arak Chemical CO, Iran, IROST). On day 13 all goats were euthanatized. Immediately after euthanasia, complete necropsy was performed on all goats and gross lesions were recorded. Tissue samples were fixed in 10% neutral buffer formalin and sent for pathology. Tissue slides stained with hematoxylin and eosin and examined under light microscope.

Statistical analysis: Data were expressed as Mean±SE. One-way ANOVAs was used (SPSS/PC software) to compare them between different groups. The differences were considered significant at values of p<0.05 (Petrie and Waton, 2006).

RESULTS

Clinically no apparent abnormalities observed on physical examinations. None of the normal saline, flunixin meglumine and ketoprofen treated goats developed anorexia during the study. In phenylbutazone treated group, mild anorexia was observed during the study. Mild watery diarrhea developed in 1 goat in the phenylbutazone group. Mean total and differential of leukocytes, RBC and PCV did not change significantly (p>0.05) in comparison with normal limits for all groups (Table 1). Serum biochemical analysis indicated a
significant treatment effect (p<0.05) on urea nitrogen, creatinine, AST, GGT and ALP activities (Table 1). Treatment effect was not significantly (p<0.05) evident in the results of unanalysis. Macroscopic findings included congestion in brain, kidney and liver. Microscopic findings in treatment groups included ischemic cell changes in the brain (Fig. 1), interstitial nephritis with glomerular hypercellularity (Fig. 2), hydropic degeneration of hepatocytes (Fig. 3), infiltration of mononuclear cell to portal space, hyperplasia of bile ducts.

**DISCUSSION**

None of the normal saline, flunixin meglumine and ketoprofen treated goats developed anorexia during the study. In phenylbutazone treated group, mild anorexia was observed during the study. MacAllister et al. (1993) reported that six horses (6/16) were mildly anorectic during their study. The anorexia was the clinical sign of NSAIDs toxicosis. The presence of appetite in flunixin meglumine and ketoprofen treated groups may be due to mild to moderate lesions in comparison with phenylbutazone treated group.

Mild watery diarrhea developed in 1 goat in the phenylbutazone group. The cause of diarrhea was not determined. Diarrhea was reported to be manifestations of NSAIDs toxicosis (MacAllister et al., 1993). Serum albumin and total protein concentrations in this study were not significantly changed which was not consistent with findings from other studies (MacAllister et al., 1993). Gastroenteropathy was the cause of protein loss in these studies. In present study gastroenteropathy did not occur. Renal and hepatic disease developed in the all drug treated groups, although a treatment effect was not found for urinalysis. The association between NSAIDs and liver disease is poorly documented. Reports of hepatic injury range from insignificant and transient liver enzyme elevation to severe and fulminating hepatitis (Manoulakos and Carson, 1996). Long-term exposure to the anti-inflammatory agent induced kidney tumors in rats and liver tumors in mice (Kan et al., 1995). Renal crescent necrosis has been reported as a manifestation of nephropathy caused by NSAIDs in human beings (Clive and Stoff, 1984; Carnichael and Shankel, 1985) and in horses (Gunson, 1983; Read, 1983). Renal disease is attributed to impaired blood supply, particularly in the medulla of the kidney (Clive and Stoff, 1984). Renal prostaglandins exert little or no important control over basal renal blood flow and glomerular filtration rate in healthy animals or human beings (Gunson, 1983; Clive and Stoff, 1984). In response to renal hypoperfusion, however the kidneys increase local production of prostaglandins, which act as autoregulators to increase renal perfusion. Inhibition of prostaglandin synthesis by NSAIDs results in decreased ability of the kidneys to autoregulate blood flow (Gunson,
1983; Clive and Stoff, 1984). Increasing of activities of the AST, GGT and ALP in this study may be due to hepatic and renal lesions respectively. Increasing of urea nitrogen and creatinine confirmed renal injury in present study.

Increasing of glutamate dehydrogenase activity following administration of a new dosage schedule of a phenylbutazone paste was reported (Lees and Higgins, 1987). Results of PCV and number of RBCs in the present study indicated no abnormality. Anemia following administration of a new dosage schedule of a phenylbutazone paste was reported (Lees and Higgins, 1987). A significant inhibition of the growth in length and width of the bone was observed by NSAIDs (Mizuno et al., 1990). Using of long duration of NSAIDs in goats is associated with severe brain, renal and hepatic lesions and must be used with cautious.

REFERENCES


