Toxic and Vascular Nephropathy Associated with Orotic Acid Administration in Laboratory Cats

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Dear Sir,

Orotic aciduria with subsequent orotate crystalluria occasionally has resulted in ureteral or urethral obstruction in humans with hereditary orotic aciduria or other disorders of pyrimidine metabolism. Oral administration of orotic acid (OA) can result in urolithiasis in mice [1]. We serendipitously noted renal and urinary tract complications in a group of cats with experimentally induced orotic aciduria.

Our research group has been studying the idiopathic hepatic lipidosis syndrome in cats, which is the most common hepatic disease seen by veterinarians in feline practice. One theory on the pathogenesis of this disease is that cats may develop arginine deficiency, which could result in impaired urea synthesis and alterations in nitrogen metabolism. When urea cycle function is impaired, nitrogen is shunted into the pyrimidine pathway, increasing endogenous concentrations of orotic acid, a pyrimidine precursor. OA is known to induce hepatic lipidosis in rats. In humans, hereditary orotic aciduria may occur with defects in pyrimidine synthesis, leading to marked crystalluria with sedimentation of urine, occasionally resulting in ureteral or urethral obstruction. Feeding OA to mice induces urolithiasis.

As part of this ongoing study 20 cats were treated with 0.3-0.6 g OA/kg metabolic body weight (MBW) for 29 days [Dimski DS, et al., unpublished data]. The OA was given either in a liquid suspension (13 cats) or a capsule (7 cats). Serum urea, creatinine, and urine orotate: creatinine ratios (OACR) were evaluated weekly throughout this period.

The 7 cats treated with 0.6 g/kg MBW OA in a capsule developed depression, dehydration, and anorexia within 1 week after OA

administration was begun. Laboratory evaluation identified azotemia and increased urinary OACR. One cat died on day 28 of the study. The remaining 6 cats were euthanized on day 29. Necropsy examination revealed wedge-shaped, depressed areas of the renal cortex, which corresponded to interstitial fibrosis and inflammation (fig. 1).

Histopathologic changes seen in the kidneys included toxic tubular-nephrosis and vasculitis with thrombosis (fig. 2). The tubular changes consisted of epithelial necrosis, degeneration with

dilatation, and regeneration. Partially mineralized crystals, some of which were birefringent, were present in affected tubules in varying numbers, especially promi-

Fig. 1. Left kidney of cat 18. Wedge-shaped areas of renal cortex corresponding to areas of fibrosis and inflammation can be seen (arrowheads). A single orotate urolith can be seen in the renal pelvis (arrow).

nent at the corticomedullary junction (fig. 3). In affected areas, interstitial lymphocytic infiltration was prominent, and tended to be perivascular in distribution. In some affected kidneys, tubules in the renal pelvis were dilated and filled with mucopurulent exudate. These tubules were lined by multilayered hyperplastic urothelium which was often infiltrated with neutrophils (fig. 4).

The vascular changes varied from perivascular lymphocytic-eosinophilic inflammatory infiltrate to severe vasculitis with occluding thrombosis. The changes were limited to large subcapsular veins in which severe vascular wall inflammation was present, and vessel lumens were totally occluded by fibrin-

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Fig. 2. Left kidney of cat 19, original magnification x 55. Thrombosed subcapsular vein. The vascular wall is severely infiltrated by lymphocytes (arrow) and the lumen is occluded by a fibrin-platelet thrombus (asterisk).

Fig. 3. Right kidney of cat 20, original magnification x 55. Degenerate tubules at corticomedullary junction. There are dilated tubules (arrows) with attenuated epithelial cells and formations of orotate crystals (asterisks) within tubular lumens. Focal lymphocytic infiltrate is present in the interstitium.

Fig. 4. Left kidney of cat 18, original magnification x 136. Collecting tubules in pelvis. There is marked hyperplasia of urothelium (arrow) and dilation of tubule with luminal mucus and neutrophils (asterisk).

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platelet thrombi with many sequestered leukocytes, mainly neutrophils. Deeper veins, to the level of the corticomedullary junction, had milder lymphocytic infiltration and peri-vascular lymphocytic cuffing, with occasional eosinophils. Glomeruli were not involved and arterial lesions were rarely seen and were always very mild. Minimal fibrosis and lymphocytic infiltration were present around less severely involved veins in these areas.

The cause of renal failure in these cats cannot be specifically determined from this study. However, it is possible that a dose-related toxicity of OA was the cause. Although this group of cats was given a similar dose of OA as other cats in the study, the administration of OA in a capsule form was associated with less excess salivation and vomiting when compared to administration of OA in a suspension. Therefore, it is conceivable that cats receiving OA capsules absorbed a higher dose and excreted a higher concentration of OA, resulting in urolith formation and renal failure. Cats receiving OA in a capsule form had increased OACR compared to cats receiving an OA suspension, implying an increased dosage. Orotate urolithiasis has been reported in mice fed OA and was related to a higher percentage of urinary excretion of OA (27%), as compared to rats receiving a similar dose (7%) [1]. Although increased excretion of OA could cause toxic tubular changes and urolithiasis, the cause of renal vascular changes in these cats is unknown. To our knowledge, vascular changes of this type have not been reported in conjunction with OA toxicity.

Further research needs to be directed toward the mechanism of OA-induced renal failure.

Characterization of OA-associated renal disease in cats may allow this species to serve as a model for study of tubular and vascular renal disease in humans. Additionally, cats may serve as models of OA crystalluria/urolithiasis for hereditary orotic aciduria and ornithine transcarbamylase deficiency in humans.

References

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