Renal Papillary Necrosis in Horses after Phenylbutazone and Water Deprivation

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Abstract. Acute renal papillary necrosis occurred in five horses given normal therapeutic doses of phenylbutazone and deprived of water for 36 to 48 hours prior to euthanasia. Five horses given phenylbutazone alone and four horses subjected to water deprivation alone did not develop papillary necrosis. Urinalyses were normal prior to water deprivation, and also after water deprivation in the horses that did not receive phenylbutazone, but the water-deprived, phenylbutazone-treated horses had many red blood cells, transitional epithelial cells, and large numbers of oxalate crystals in their urine.

Ulceration of the alimentary tract was seen in more than 50% of these horses. Tongue ulceration was present in one of five horses given phenylbutazone and one of five horses which had phenylbutazone and water deprivation. Ulceration of the gastric mucosa was seen in two of the five phenylbutazone-treated horses, four of five horses with phenylbutazone treatment and water deprivation, and one of four horses with water deprivation alone. Severe colonic ulceration with perforation and peritonitis was present in one horse given phenylbutazone for three months. No other significant changes in the small or large intestine were seen in the other 13 horses.

It generally has been thought that phenylbutazone is not toxic to horses [10, 15], although deaths have resulted from its use in man [15]. Recently, however, severe adverse effects have been described in eight of ten ponies given normal therapeutic doses of phenylbutazone [20]. It was concluded that ponies were much more susceptible than horses to severe side effects during phenylbutazone treatment [3, 20]. Ulceration of the alimentary canal is a relatively common side effect of phenylbutazone therapy in equidae [5, 6, 10, 20, 21] and other species [15, 19], and recently gastrointestinal protein loss has been reported in both horses and ponies [21]. Although there is decreased urinary excretion of sodium and chloride [1], and raised blood urea nitrogen has been noted [20], no renal lesions have been described in any of these studies [1, 5, 6, 10, 20, 21]. Renal papillary necrosis has been seen, however, in a series of 16 horses in which therapy with antiprostaglandin drugs, mostly phenylbutazone, was an almost constant feature, as was dehydration or impaired water intake [8]. The present study was undertaken to determine
whether reduced water intake would precipitate renal papillary necrosis in horses which were given normal therapeutic doses of phenylbutazone; it did in all five horses treated this way, while none of the nine horses given either phenylbutazone or water deprivation had any indications of this lesion.

**Materials and Methods**

Fourteen horses weighing between 400 and 550 kg and one to 20 years of age were divided into three groups (table I). Group I (horses 1 to 5) had received 8.8 mg/kg/day phenylbutazone for four to 90 days (mean 42 days); group II (horses 6 to 10) had received 8.8 mg/kg/day phenylbutazone for four to 75 days (mean 27 days) and water was withheld for 36 to 48 hours prior to euthanasia. Group III, the control group (horses 11 to 14), received no phenylbutazone and water was withheld for 36 to 48 hours prior to euthanasia. The phenylbutazone was given orally, mixed with the feed twice daily at a dose of 4.4 mg/kg.

Horses 1 and 6 were given phenylbutazone for 30 days; sequential liver biopsies and Bromsulphalein (BSP) clearance tests were done every five days, starting at day 0, and both were always within normal limits. In groups II and III the hematocrit and serum total proteins were determined both before and after water deprivation and in each instance there was no significant change.

Serum creatinine was determined on horses 5, 7-10, and 12-14 and all were within the normal range. Red blood cell and white blood cell counts were also within the normal range. Two urinalyses were done on horses 7-9, 12, and 14, the first prior to water deprivation and the second just prior to euthanasia or at postmortem. The first urinalysis also was done on horse 10, but the urinary bladder was empty at postmortem.

Horses were killed with an overdose of intravenous barbiturate and postmortem examination was started immediately. Both kidneys were examined in detail and the papillae were scrutinized along their entire length. Slices of kidney that included capsule to papilla were taken from caudal and cranial poles and the central zone of both kidneys and put in 10% neutral buffered formalin within an hour of death. The oral cavity and gastrointestinal tract were examined in detail and multiple sections of stomach and small and large intestine were fixed in Bouin's solution. After embedding in paraffin, 5 \( \mu \)m sections were cut and stained with hematoxylin and eosin (HE).

**Results**

No adverse clinical signs related to the phenylbutazone therapy or the water deprivation were seen in any of the horses. Horses 1 and 6 each were given phenylbutazone for 30 days and sequential hematocrits were determined. Horse 1 had a precipitous fall in hematocrit from 38 to 24 on day 20. Thereafter red blood cell morphology showed a slight anisocytosis. Horse 1 had oral ulcers and severe gastric ulceration at necropsy, and it is probable that there was considerable blood loss from these ulcers which could have been responsible for the fall in hematocrit. Horse 6 had a constant hematocrit of 35 and no oral or gastric ulcers were present at postmortem examination.

Ulceration of the glandular gastric muscosa was seen in two of the five horses treated with phenylbutazone alone, four of the five horses treated with phenylbutazone and subjected to water deprivation, and in one of the four horses subjected to water deprivation alone (table I). Ulcers of the tongue and oral cavity were seen
Table I. Lesions in horses treated with phenylbutazone and/or water deprivation

<table>
<thead>
<tr>
<th>Group</th>
<th>Horse</th>
<th>Age (years)</th>
<th>Treatment</th>
<th>Ulcers</th>
<th>Papillary necrosis</th>
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<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>4</td>
<td>Phenylbutazone</td>
<td>Tongue &amp; stomach</td>
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<td>Phenylbutazone</td>
<td>Stomach</td>
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<td>II</td>
<td>6</td>
<td>12</td>
<td>Phenylbutazone &amp; water deprivation</td>
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<td>7</td>
<td>1½</td>
<td>Phenylbutazone &amp; water deprivation</td>
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<td>8</td>
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<td>Phenylbutazone &amp; water deprivation</td>
<td>Stomach</td>
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<td>9</td>
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<td>Phenylbutazone &amp; water deprivation</td>
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<td>14</td>
<td>7</td>
<td>Water deprivation</td>
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</table>

in horses 1 and 9. Horse 2 had received phenylbutazone for 90 days and there were two 20 mm diameter ulcers in the right ventral colon, one of which had perforated and was surrounded by a focus of fibrinous peritonitis to which several loops of small intestine were adhered. The mucosa and submucosa of the large colon and cecum in some horses contained sections of nematode parasites and foci of inflammation that were compatible with parasitic enteritis. No additional significant lesions were found either grossly or microscopically in the gastrointestinal tract.

Acute necrosis of the renal papilla was present in all horses in group II, but in no horses in groups I and III. This was visible grossly in horses 7 and 9 but only seen microscopically in horses 6, 8, and 10. The gross appearance was of yellow-green radial streaks occupying the papillae of both kidneys which were most prominent at three sites—the caudal and cranial poles and in the middle. There was a zone of intense hyperemia in the medulla surrounding these streaks (fig. 1). The inner half of the medulla was sometimes deep red and sometimes very pale in the horses of all three groups (fig. 2).

Microscopically there was sloughing of renal pelvic epithelium including the terminal lining of collecting ducts, with coagulative necrosis of the underlying papillary interstitium in horses 6 to 10 (figs. 3, 4). There was often mineralization of the necrotic debris that lay within the calyx (fig. 3). Necrotic papillary interstitium contained nuclear debris and fresh hemorrhage (fig. 4), but the sloughed pelvic epithelium often was intact as though it had simply fallen off because the underlying
interstitium became necrotic. There was dilation of collecting ducts and of cortical tubules in wedge-shaped segments of kidney tissue above each area of necrotic papilla.

Urinalyses (in which pH, specific gravity, color, the presence of glucose, ketones, occult blood, and bilirubin were noted and a microscopic examination was done on urine sediment) were within normal limits prior to water deprivation and also after water deprivation in horses 12 and 14. After water deprivation in horses 7, 8, and 9 there were red cells, transitional epithelium, and oxalate crystals found in the urine sediment.

**Discussion**

Our interest in the pathogenesis of equine renal papillary necrosis was stimulated through observations on a number of clinical cases which indicated that it might be a more common disease than generally is realized. In this study of 16 horses with renal papillary necrosis seen at necropsy, it appeared that this was an incidental
finding, but in two horses the necrosis was extensive and resulted in progressive, symptomatic renal disease [8]. There seemed to be an association between phenylbutazone therapy plus dehydration and papillary necrosis, but this was difficult to test in a retrospective study since these horses often had received several other drugs as well. We chose to examine the role of phenylbutazone plus water deprivation in the pathogenesis of renal papillary necrosis since water deprivation is associated with papillary necrosis in cattle and sheep after phenothiazine therapy [18]. Limited water deprivation also is known to enhance the development of renal papillary necrosis in rats [12] and man [13] undergoing analgesic therapy with aspirin and phenacetin. Other reports on the toxicity of phenylbutazone in equidae do not mention any renal changes.

Our results lead us to conclude that phenylbutazone alone, at a level of 8.8 mg/
kg/day for up to three months, does not appear to result in necrosis of the renal papilla; neither does limited water deprivation alone, however, a combination of phenylbutazone plus water deprivation results in mild to moderate bilateral renal papillary necrosis. In our water-deprived horses, there was no rise in the hematocrit, probably because in healthy animals there are compensatory shifts in extracellular fluid. Nevertheless, papillary necrosis occurred if there was concurrent phenylbutazone treatment. Presumably in conditions where the hematocrit does rise there could be more severe necrosis. We feel that, since phenylbutazone is such a widely used drug, care should be exercised to avoid or discontinue its use should dehydration occur if the horse should develop any condition likely to lead to dehydration.

There are several mechanisms by which renal papillary necrosis occurs in man and laboratory animals. One is lower urinary tract obstruction which leads to increased pressure in the renal pelvis [9]. Another is interference with blood flow in the vasa recta resulting in ischemia of the papilla [9]. Yet another is interference with urine flow in the papilla; this occurs with necrosis of the epithelium of the thin limbs of Henle in the bromoethylamine hydrobromide model of papillary necrosis [16]. In man, papillary necrosis is a well-known lesion of chronic analgesic abuse [9, 11], which may occur because metabolites of the analgesic drugs are concentrated in the papillary interstitium where they cause oxidative tissue damage [17]. The enzymes that normally protect against oxidative tissue damage are inhibited by these metabolites.

In man papillary necrosis is usually a chronic, slowly progressive disease whereas here we have described lesions developing within two days. This is, however, in accord with the findings of others [16] who found definite changes in the renal papillae of rats within 24 hours. Another difference between horses and man is in the distribution of the secondary cortical changes. In man papillary necrosis obliterates the long loops of Henle that arise from the juxtamedullary nephrons and these ultimately are destroyed. Thus, the cortical fibrosis that occurs is worse in the juxtamedullary or inner cortex. In the more chronic cases of equine renal papillary necrosis, the secondary cortical fibrosis extended the full depth of the cortex [8]. Even the early lesions seen here with little more than tubular dilation in the cortex had this change through the full-thickness of the cortex, suggesting that in the horse the nephrons that give rise to the long loops of Henle may not always be the juxtamedullary nephrons. In the horse the parts of the papilla which always become necrotic are the caudal and cranial poles and the middle. It is possible that the long loops of Henle are concentrated in these regions.

It has been postulated that prostaglandins are important for the maintenance of blood supply in the vasa recta under conditions of stress [14]. Thus drugs with antiprostaglandin activity, such as phenylbutazone, could be detrimental to blood flow in the vasa recta. The extreme hypertonicity of the papillary interstitium creates a rather precarious environment for cells in this area [7]. In addition, maintenance of blood flow in the vasa recta and urine flow in the thin loops of Henle are some of the factors responsible for maintaining appropriate conditions
in the renal papillary interstitium. We suggest that in phenylbutazone-treated horses reduced blood supply in the vasa recta leads to ischemia of the renal papilla. Reduced water intake leads to reduced urine output and probably reduced urine flow in the loops of Henle such that appropriate conditions can no longer be maintained in the papillary interstitium. These two events act synergistically resulting in necrosis of the papillary interstitium and loss of the overlying epithelium.

The potential for phenylbutazone to cause papillary necrosis is borne out in the mini-pig, where phenylbutazone and other nonsteroidal antiinflammatory compounds, given daily for two months, have caused papillary necrosis [2].

It is interesting that many of our phenylbutazone-treated horses also had oral and gastrointestinal ulceration. This has been described by others studying phenylbutazone toxicity in horses [21], ponies [20], and man [15]. The underlying reason for this is thought to be mucosal ischemia due to reduced blood supply brought about by the antiprostaglandin activity of phenylbutazone, since prostaglandins also are responsible for maintenance of normal mucosal blood flow [4]. Phenylbutazone is absorbed rapidly from the stomach and the sodium salt of phenylbutazone is non-ionized in the acid pH of stomach contents thereby enhancing its passage through the stomach wall. The higher incidence of gastric mucosal ulceration in the horses with water deprivation as well as phenylbutazone treatment, and the presence of gastric mucosal ulceration in one of the horses with water deprivation alone, is suggestive of a similar synergistic role for water deprivation in the pathogenesis of stomach ulceration.

Necrotizing phlebitis of the portal vein has been described in horses on long-term phenylbutazone therapy [6]. No lesions were found in the liver or in any hepatic vessels in the 14 horses in this study. Like others [5], we find it difficult to reconcile this study [6] with subsequent studies [1, 3, 5, 8, 10, 20, 21] in which portal phlebitis was not a feature. We have seen one horse with severe portal vein phlebitis in over a thousand equine necropsies. This was in a horse which has been on long-term phenylbutazone therapy, but it also had severe salmonellosis and Salmonella sp. was isolated from many body tissues including the portal vein.

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References


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