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DRUG INTERACTIONS IN THE HORSE: EFFECT OF FUROSEMIDE

ON PLASMA AND URINARY LEVELS OF PHENYLBUTAZONE

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ABSTRACT

Horses pretreated with 6.6 mg/kg of phenylbutazone were injected with 1 mg/kg of furosemide intravenously. Furosemide had no clinically significant effect on either plasma levels or plasma half-life of phenylbutazone. Furosemide reduced urinary levels of phenylbutazone 18-fold to concentrations which may result in inconsistent drug detection in routine screening tests. The results show that it is not possible to monitor compliance with phenylbutazone medication rules by means of urinalysis alone if the use of furosemide is permitted. Furosemide treatment, however, does not interfere with monitoring by plasma level determinations.

INTRODUCTION

Spontaneous epistaxis (nosebleed) occurs in a small number of racing horses. It is a serious problem in racing in that a horse's running is immediately affected and thus, endangers other horses and riders. Affected animals are known popularly as "bleeders" (Cook, 1974).

Clinical experience suggests that epistaxis in racehorses can be prevented by pretreatment with the diuretic drug furosemide. The mechanism by which furosemide produces its effects is unknown. However, to reduce the incidence of nosebleed, many racing authorities permit pretreatment of horses with furosemide shortly prior to racing.

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Phenylbutazone was the commercially available injectable form from W. A. Butler & Company, Columbus, Ohio. Furosemide was the injectable form and was a kind gift of Hoechst-Roussel Pharmaceuticals, Inc., Somerville, New Jersey. All experimental points are the means of five or more experimental determinations and all lines were fitted by eye.

### RESULTS

Figure 1 shows the effects of furosemide on urine volume and urine specific gravity in phenylbutazone-treated horses. These animals were

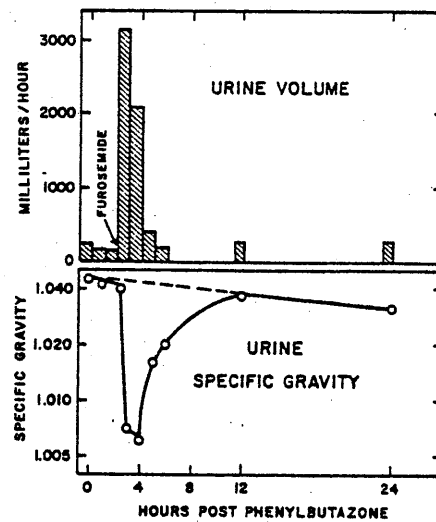


Fig. 1. Urine volume and specific gravity after furosemide.

At 2.5 hours after administration of phenylbutazone, horses were challenged with 1 mg/kg of furosemide. Panel A shows the diuretic response to furosemide in ml/hour of urine formed. Panel B shows the specific gravity of the formed urine.

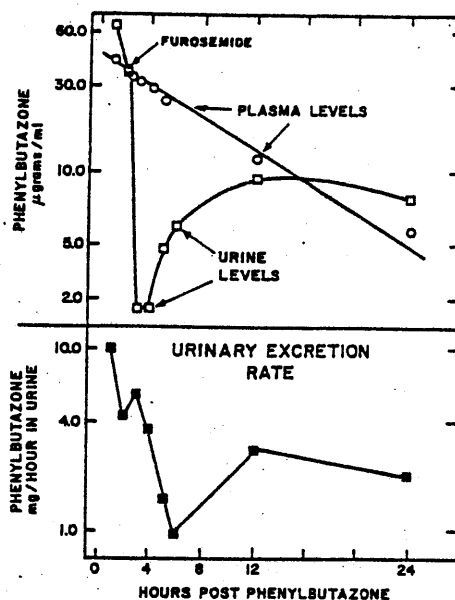


Fig. 2 Plasma and urinary levels and excretion rates of phenylbutazone following furosemide.

The open circles (O - O) show plasma levels of phenylbutazone before and after treatment with furosemide. The open squares (□ - □) show urinary levels of phenylbutazone. The solid squares (■ - ■) show the urinary excretion rates for phenylbutazone before and after furosemide.

experiments a similar dose of furosemide subcutaneously reduced urinary levels of the drug to about  $0.58 \pm .48 \mu\text{g/ml}$ . These levels are close to the detection limit of the flame ionization method and are marginal for detection by routine U.V. screening. By 12 hours post-dosing, however, urinary levels of the drug had recovered to  $9.41 \pm 3.7 \mu\text{g}$  in the experiments reported here.

The lower panel of Fig. 2 suggests that, as well as reducing the concentration of phenylbutazone in the urine, furosemide may also reduce the rate of elimination of phenylbutazone. Thus, immediately after the administration of furosemide the rate of urinary excretion of phenylbutazone is close to

from its binding sites in plasma and, thereby, increase free plasma and urinary levels of the drug. However, *in vitro* experiments showed no mutual displacement of either of these drugs by the other at pharmacological concentrations. In agreement with these observations, the results reported here show no evidence that furosemide acts to increase the rate of elimination of phenylbutazone.

Another possible point of interaction for furosemide and phenylbutazone is at the level of the organic acid secretory system. Furosemide is secreted into the renal tubule by this system (Hirsch *et al.*, 1970), and inhibition of this system by various organic acids (Shelp and Rieselbach, 1970) results in higher plasma levels of furosemide and a reduction in the diuretic response to this drug (Hook and Williamson, 1967). Thus, phenylbutazone and furosemide, both organic acids, could theoretically interfere with each other's renal transport and, thus, urinary levels. Figure 2, showing a low point in the urinary excretion rate of phenylbutazone after the administration of furosemide, suggests that such an effect may be occurring, but in this experiment at least the effect is small.

The principal effect of furosemide on urinary levels of phenylbutazone, thus, appears to be a diluting effect, and in this experiment the increase in urinary volume was sufficient to account for the decline in urinary levels of phenylbutazone. Because of this close correspondence between increased urine volume and drug dilution, it appears that there is little tendency for phenylbutazone to move into the increased volume of urine and re-equilibrate with the increased urine volume. This is presumably dependent on both the extensive protein binding of this drug (95%) and the fact that the bulk (99.7%) of the small amount of phenylbutazone which is free

REFERENCES

- Cook, W. R. (1974). Epistaxis in the racehorse. *Equine Vet. J.* 6, 45-58.
- Hirsch, G. H., Pakuts, A. P., and Bayne, A. J. (1975). Furosemide accumulation by renal tissue. *Biochem. Pharmacol.* 24, 1943-1946.
- Hook, J. B. and Williamson, H. E. (1965). Influence of probenecid and alterations in acid base balance on the saluretic activity of furosemide. *J. Pharmacol. Exp. Therap.* 149, 404-408.
- Koch-Weser, J. and Sellers, E. M. (1976). Binding of drugs to serum albumin. *N. Eng. J. Med.* 294, 526-531.
- Shelp, W. D. and Rieselbach, R. E. (1971). The effect of furosemide on residual nephrons of the chronically diseased kidney in man. *Nephron* 8, 427-439.
- Tobin, T., Blake, J. W., and Valentine, R. (1976). Drug interactions in the horse. I. Effects of chloramphenicol quinidine and oxyphenbutazone on phenylbutazone metabolism. *Am.J. Vet. Res.*, in press, 1976.

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