

FUROSEMIDE (LASIX^R) IN THE HORSE: AN OVERVIEW PRESENTED TO THE
23rd ANNUAL CONVENTION OF THE AMERICAN ASSOCIATION OF EQUINE PRACTITIONERS.

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1. GENERAL

Furosemide is a sulfonamide derivative, a strongly acidic drug and a member of the "high ceiling" (very effective) group of diuretics. It is available as 50 mg/ml injectable Lasix^R or as 2 g. Bol-O-Tabs^R tablets.* All the work reported here refers to injectable Lasix^R, 50 mg/ml.

2. MODE OF ACTION

Furosemide acts to inhibit active chloride reabsorption in the ascending limb of the loop of Henle. Sodium and water normally follow chloride passively, so this blockade leads to chloruresis, naturesis, and diuresis.

3. DOSE RESPONSE

After intravenous injection, 0.4 mg/kg (about 4 ml) produces about four liters of urine in 2 hours, mostly within forty minutes. A dose of 1 mg/kg (about 10 ml) produces about 8.5 liters of urine, mostly within one hour. A dose of 4 mg/kg (about 40 ml) yields about 21 liters of urine in two hours. Ten mg/kg also yields about 21 liters, suggesting that this is the maximal response (SEE Fig 1).

4. TIME RESPONSE

At lower doses, the diuretic effect of Lasix^R is very short lived. This short duration of action is not due to any inability of the horse to respond because a second dose immediately produces a good response (SEE Fig 2). The reason that the action of Lasix^R is so short after an intravenous dose is that the drug is very rapidly eliminated from the blood stream of the horse.

5. KINETICS AND METABOLISM

After intravenous injection of 1 mg/kg Lasix^R, plasma levels of the drug drop very rapidly ($t_{1/2} = 35$ min). Plasma levels of the drug drop rapidly because Lasix^R is pumped out of plasma into the urine in the renal tubules. This pumping accounts for the fast onset of action of Lasix^R and results in at least 60% of the drug being excreted unchanged in the urine. This is a very high proportion of drug to be excreted unchanged in the horse (SEE Fig 3).

*National Laboratories Corp., Subsidiary of American Hoechst Corp., Somerville, NJ

LASIX, DOSE AND TIME RESPONSE

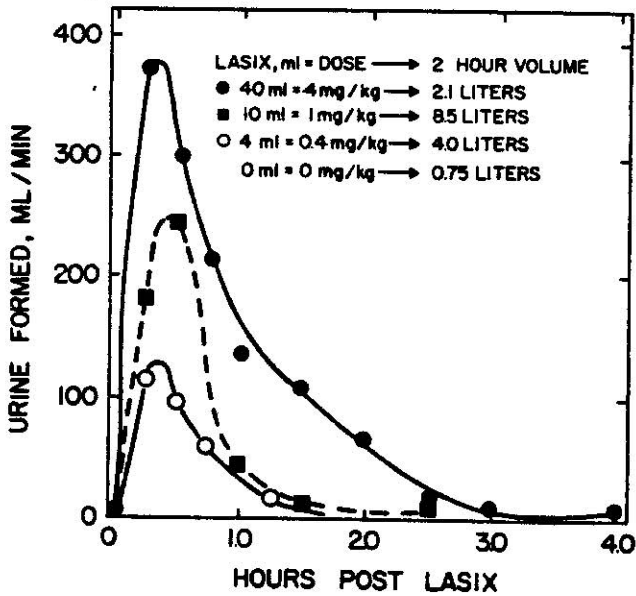


Fig. 1 The solid circles (●) show the diuretic response to 4 mg/kg (40 ml) of Lasix^R IV at zero time. The squares (■) and open circles (○) show the response to 1 mg/kg (10 ml) and 0.4 mg/kg (4 ml), respectively. All urine samples were obtained by bladder catheterization and the symbols represent the mean number of ml/minute excreted in the preceding time period. All points the means of at least four experimental determinations.



Fig. 2 Volume response of horses to repeated 1 mg/kg doses of furosemide IV. The percentage figures refer to each response as a percentage of the initial response.

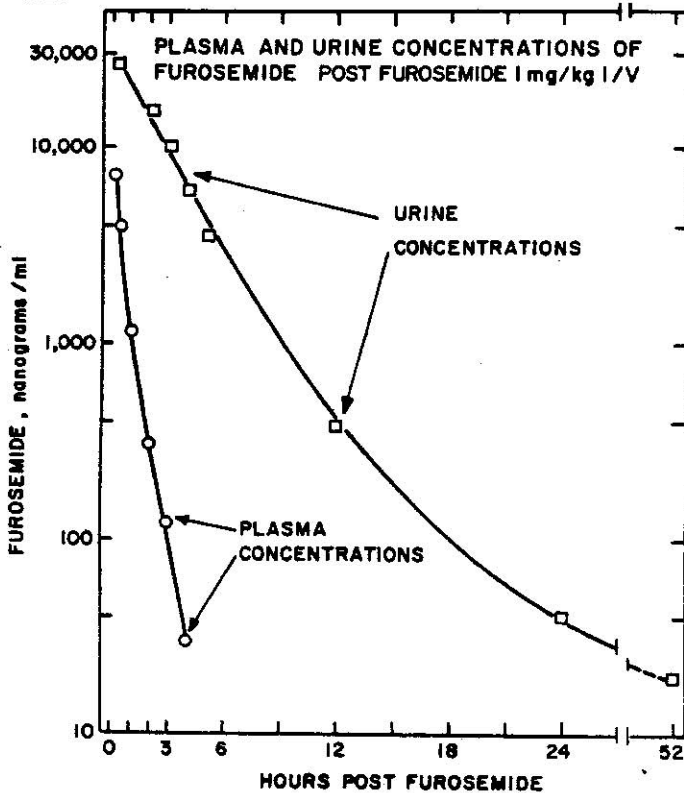
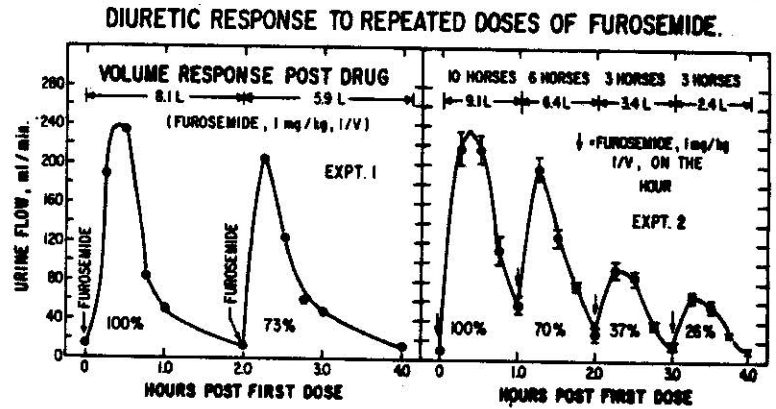


Fig. 3 The open circles (○) show plasma levels of furosemide after 1 mg/kg was administered IV. The open squares (□) show urinary levels after the same dose. Determinations in a single horse, typical of determinations on four horses. Note that urinary furosemide was detectable for up to 52 hours.

After 1 mg/kg, Lasix^R can be easily detected for up to 12 hours in equine urine, and it can be found for up to 50 hours.

One way to prolong the action of Lasix^R is to give it intramuscularly. Given intramuscularly, plasma levels fall more slowly ($t_{1/2} = 86$ min), the diuretic effect lasts longer, and up to 50% more fluid is excreted (Fig 4, Table I).

6. CARDIOVASCULAR EFFECTS

After intravenous Lasix^R (1 mg/kg) total plasma solids increase about 10%, hematocrit about 5%, and plasma K^+ drops sharply. Like the diuretic effect, these changes rapidly return to normal (Fig 5). Lasix^R also transiently decreases pressure in the pulmonary circulation, which effect may be related to its action against epistaxis.

7. EFFECTS ON OTHER DRUGS

Lasix^R did not reduce plasma levels of any drug tested to date. It had no forensically significant effects on urine concentrations of procaine or Ritalin^R (methylphenidate).

Lasix^R can reduce urinary concentrations of phenylbutazone or the principal glucuronide metabolite of pentazocine (Talwin^R) up to 50-fold. Lasix^R probably also reduces the urinary concentrations of glucuronide metabolites of apomorphine and the phenothiazine tranquilizers. These actions of Lasix^R (Figs 6 & 7) significantly interfere with routine urinary detection of drugs.

8. PERFORMANCE EFFECTS

Timed trials on Standardbred horses at the Ohio State University and the University of Kentucky have not shown any significant difference in the speed of Lasix^R-treated and control horses. An analysis of the pre- and post Lasix^R times of 58 horses running at the Louisville Downs meet this summer also showed no significant difference between the times of these horses before and after they went on Lasix^R (Lasix^R was the only permitted medication during this meet). (Table II)

9. TOXICITY

At the usual dosage, this drug appears very safe. Hypokalemia, after repeated doses of furosemide, appears to be the only likely acute problem.

10. CONCLUSIONS

- (a) Administered intravenously, Lasix^R is a short acting drug, the bulk of which is excreted unchanged in the urine.
- (b) Lasix^R transiently increases total plasma solids and hematocrit and decreases plasma K^+ and pulmonary blood pressure.
- (c) Intramuscular injection of Lasix^R prolongs plasma levels of the drug and its diuretic response.
- (d) Lasix^R can reduce urinary concentrations of phenylbutazone and the major metabolite of pentazocine up to 50-fold.
- (e) Lasix^R does not affect the times to pace one mile of Standardbred horses.

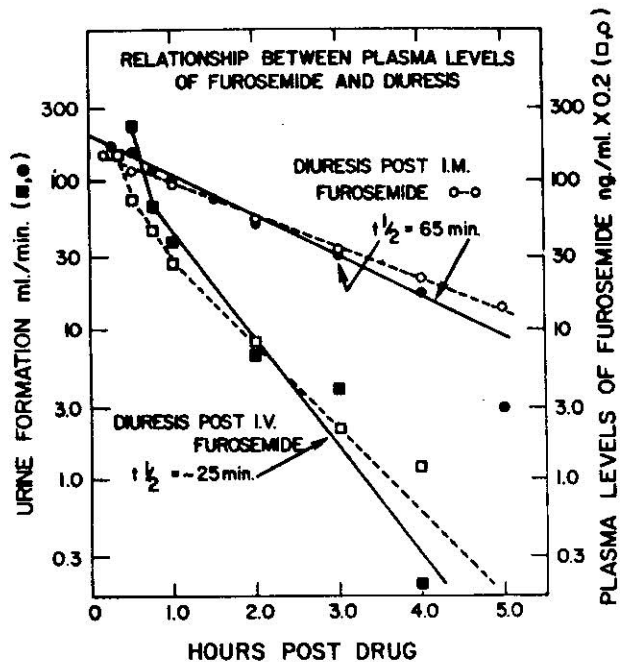


Fig. 4 The open symbols show plasma levels of Lasix^R after 1 mg/kg IV (open squares) or IM (open circles). The solid symbols show the diuretic effect associated with each route of administration. All apoints means of at least four determinations, with the vertical scale of the plasma levels adjusted to show the overlap.

Table I - Cumulative Water and Na⁺ Loss After 1 mg/kg Furosemide Intravenously and Intramuscularly (N = 4 horses).

Time after administration	1.0 mg/kg I.V.		1.0 mg/kg I.M.	
	Urine Vol. (L.)	Na ⁺ Excretion Meq./L.	Urine Vol. (L.)	Na ⁺ Excretion Meq./L.
1 hour	8.2*	732	8.4*	621
2 hours	9.0	744	12.6	887
4 hours	10.5	748	16.2	994

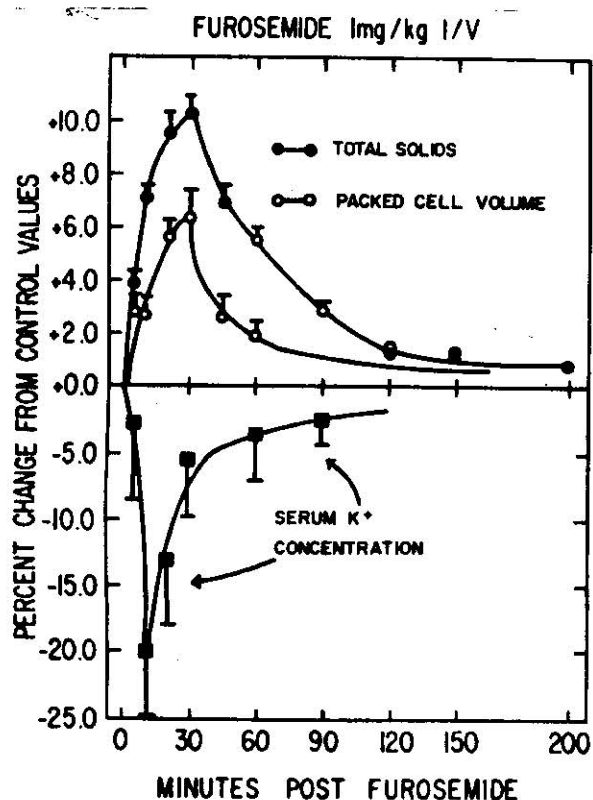


Fig. 5 The indicated symbols show the percent changes in total plasma solids, hematocrit and serum K⁺ levels after 1 mg/kg furosemide IV in six horses.

11. REFERENCES

1. Muir, W. W., Milne, D. W., Skarda, R. T.: Acute hemodynamic effects of furosemide administered intravenously in the horse. *Am. J. Vet. Res.*, 37, 1177, 1976.
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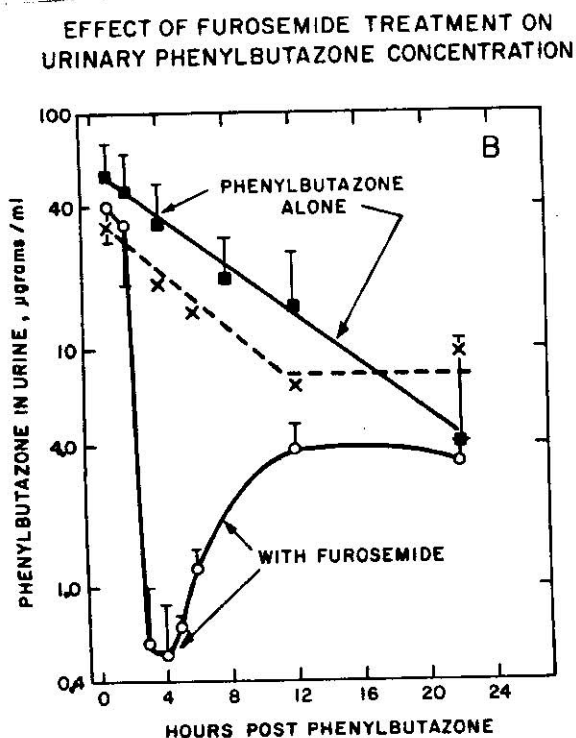


Fig. 6 Phenylbutazone at 3 gms/1000 lbs was administered to horses. The solid squares and crosses show PBZ in the urine of these animals. The open circles show urinary levels in horses so treated which were challenged with 1 mg/kg Lasix^R IV at 2.5 hours after the phenylbutazone. All points are means of experiments on at least four horses.

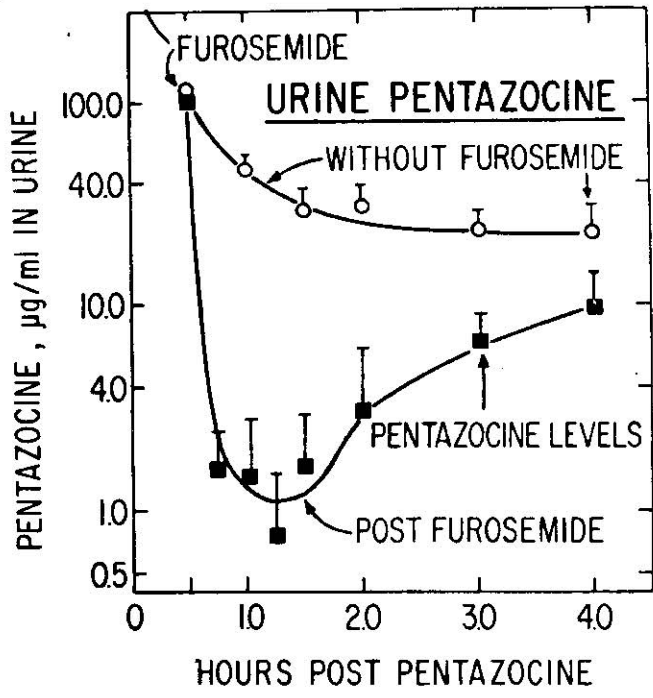


Fig. 7 ← Horses were treated with 150 mg of Pentazocine (Talwin^R) IV at zero time, followed by Lasix^R 1 mg/kg IV at 30 minutes. The open circles (○) show levels of the major glucuronide metabolite of pentazocine in control horses, the solid squares (■) levels in the urine of furosemide-treated horses.

Table II
Effect of Medication with Furosemide on the Performance of Horses Racing at Louisville Downs, Summer, 1976

	# of Horses	# of Trials	Mean Times	S.E.M.	
Pre-Furosemide	58	160	128.5925	0.2031	F = <0.00
With Furosemide	58	232	128.7366	0.1594	(F for significance should be >3.0)

At this meet furosemide was the only permitted medication and its use was checked by urinalysis. Horses could elect to go on furosemide at any time throughout the meet, but once on furosemide had to stay on it. Performance times for horses pre- and post-furosemide treatment were obtained from the meet programs and compared. Only times on good or fast tracks were taken. Of the 58 horses selected, 160 pre-furosemide times were available and 232 post-furosemide times. A randomized block design was used where each horse represented a block. After adjusting for blocks (i.e. differences between horses) there was no significant difference between treatments (i.e. times on and off furosemide).