FUROSEMIDE : AN UNLIKELY CANDIDATE FOR LONG TERM ADVERSE RESPONSES.

BY

Thomas Tobin, Kimberly Brewer and Colleagues.

The Maxwell H. Gluck Equine Research Center
University of Kentucky

for the

2013 Winter Meeting of the National HBPA
Tampa Bay Downs

10:00AM, Saturday, February 23nd, 2013

5 PM draft, February 22nd, 2013

FUROSEMIDE LONG TERM TOXICITY FROM FUROSEMIDE: A VERY UNLIKELY CANDIDATE

Furosemide is a very unlikely candidate for long term toxic effects because:

1/ Furosemide is administered as single IV dose [not daily or two or three times daily, as it may be in human medicine].

2/ A single IV dose is very rapidly cleared by the horse, plasma half-life is 38 minutes.

3/ It is cleared by being pumped unchanged at high concentrations into the urine, where it produces its diuretic response.

4/ Furosemide is therefore rapidly, efficiently and essentially completely eliminated by the horse.

5/ Water and ionic losses are very short lived, there being no reason to believe that they are not rapidly replaced.

6/ In racing, Furosemide simply provides a brief transient protective effect against the pulmonary damage inescapably associated with racing.

6/ No reason whatsoever to suspect any long term cumulative adverse effects from pre-race administration of furosemide.

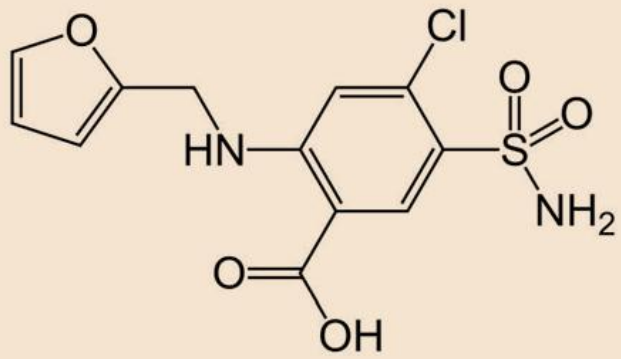
FUROSEMIDE LONG TERM TOXICITY FROM FUROSEMIDE: A VERY UNLIKELY CANDIDATE

BASED ON ITS PHARMACOLOGY, THERE IS NO REASON WHATSOEVER TO SUSPECT ANY LONG TERM CUMULATIVE ADVERSE EFFECTS ASSOCIATED WITH PRE-RACE ADMINIS-TRATION OF FUROSEMIDE.

Lasix/ Salix: FUROSEMIDE 4-chloro-2-(furan-2-ylmethylamino)- 5-sulfamoylbenzoic acid

Formula $C_{12}H_{11}ClN_2O_5S$

Mol. mass 330.745 g/mol



1/ A loop diuretic, acts by inhibiting the kidney Na-K-Cl co-transporter, where it reabsorbs sodium, potassium and chloride.

2/ Blocks reabsorbtion of these ions→diuresis.

PHARMACOKINETICS OF FUROSEMIDE

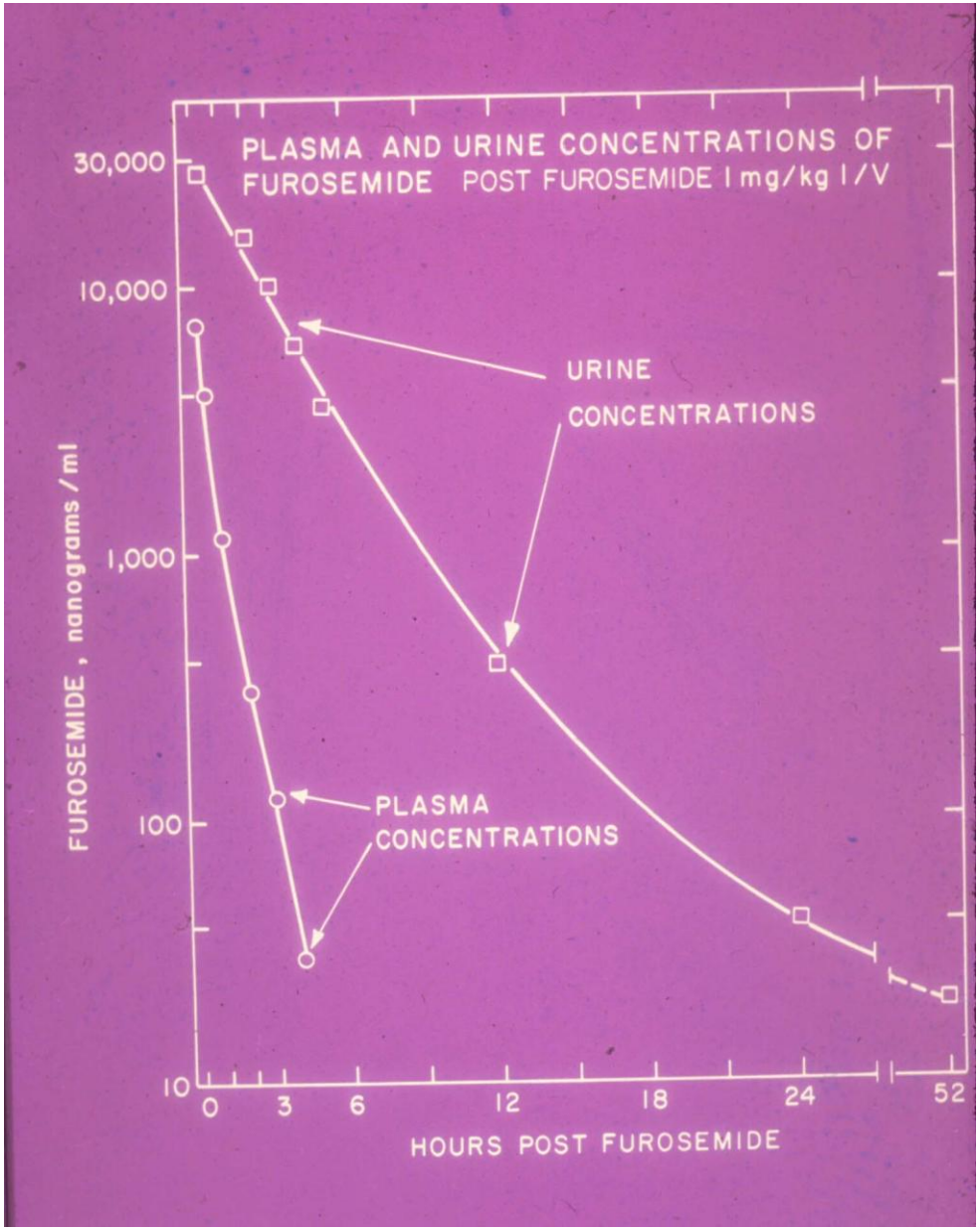
1/ 500 mg, rapid I/V injection.

2/ <u>ORGANIC ACID</u>, rapidly <u>PUMPED</u> from plasma to urine.

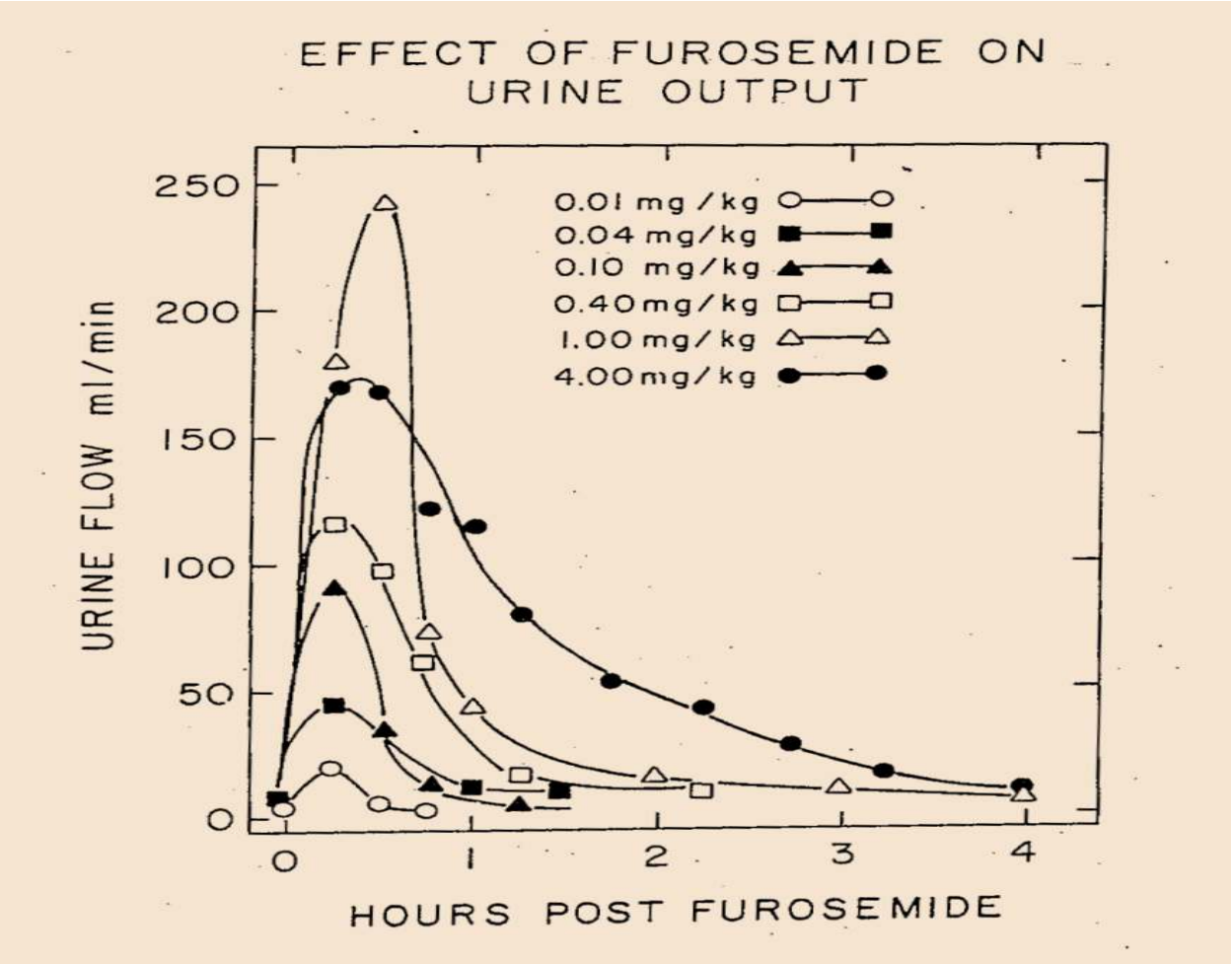
3/ Plasma concentrations drop with a t1/2 of about 38 minutes.

4/ Urine concentrations very much higher and longer lasting.

5/ <u>DIURESIS RELATIVELY SHORT LIVED</u>

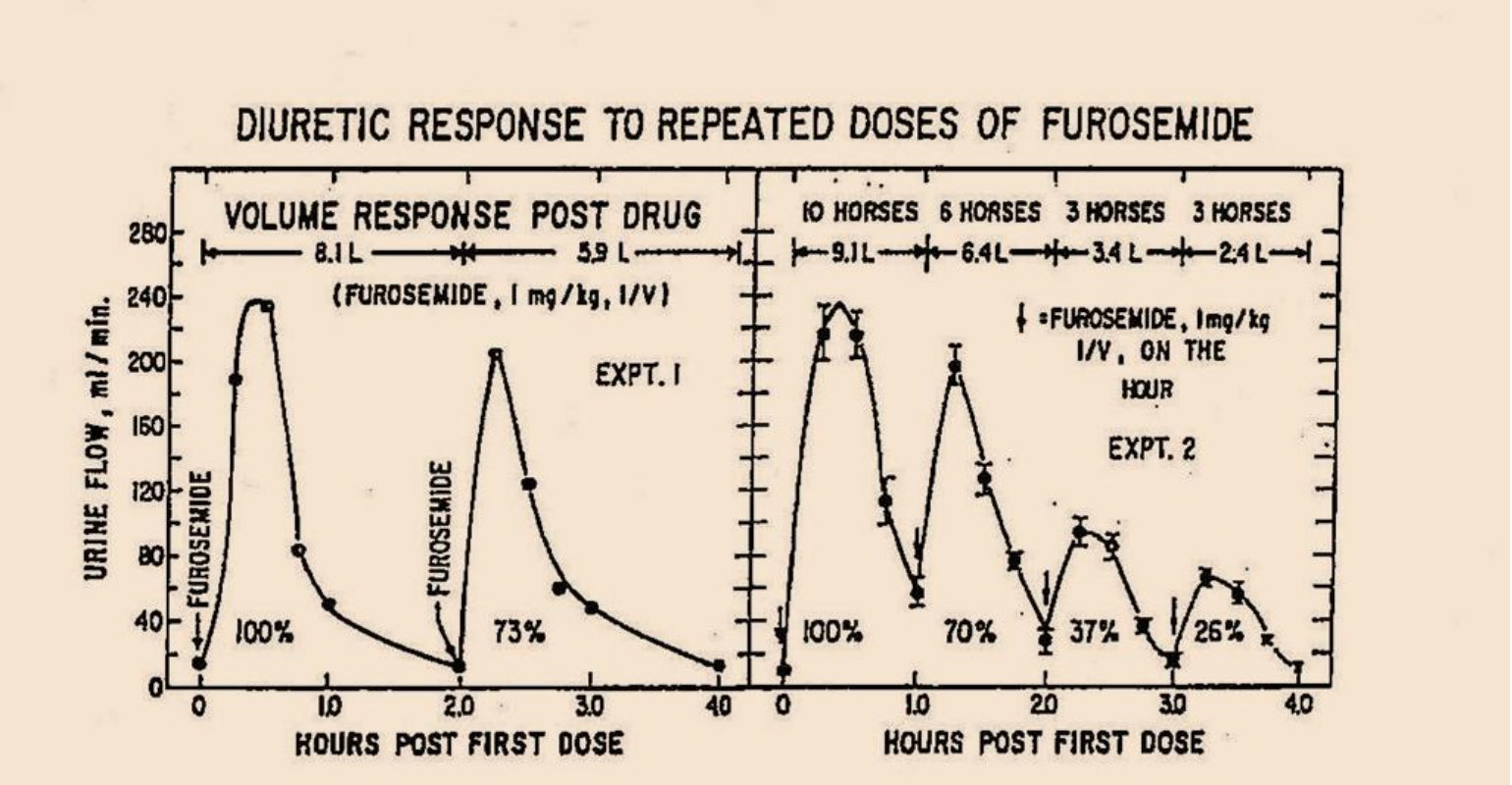


BRIEF DURATION OF ACTION OF FUROSEMIDE FOLLOWING I/V ADMINISTRATION



FUROSEMIDE WAS ADMINISTERED BY RAPID I/V INJECTION AT THE INDICATED DOSES AND THE URINE FLOW IN ML/MINUTE PLOTTED AGAINST TIME.

DIURETIC ACTION OF FUROSEMIDE FOLLOWING REPEATED I/V ADMINISTRATION



FUROSEMIDE WAS ADMINISTERED BY RAPID I/V INJECTION AT THE INDICATED DOSES AND URINE FLOW IN ML/MIN. PLOTTED AGAINST TIME

FUROSEMIDE

- Pharmacology
  - Dose dependent diuretic effect in horses
  - Decreases re-absorption of electrolytes and water
  - Produces mild metabolic alkalosis
  - Greater diuretic effect after IM administration
- Pharmacokinetics
  - Rapidly cleared by renal mechanisms
  - Extensively protein bound at physiological concentrations
  - Small volume of distribution
  - **NOT METABOLIZED**
  - **EXCRETED RAPIDLY IN URINE**

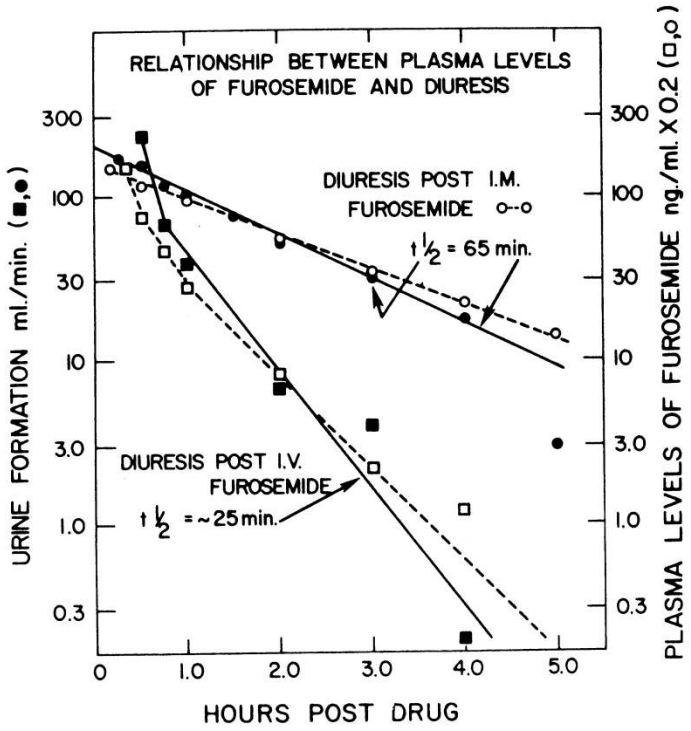
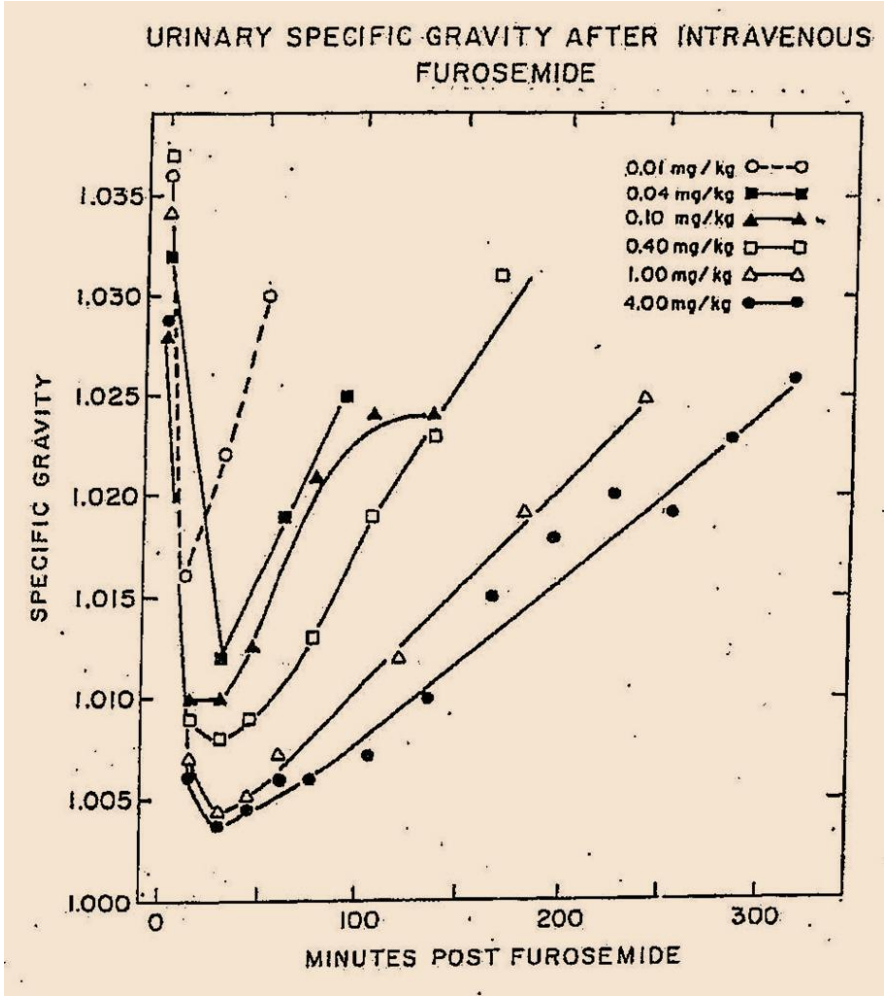


Fig 8—Relationship between plasma levels of furosemide and diuresis. The solid symbols and lines show rates of urine formation in ml/minute after IV injection (solid squares, ■-■, replotted from Fig 1) and after IM injection (solid circles, ●-●, replotted from Fig 6) of 1 mg/kg furosemide. Control rates of urine formation were subtracted from all values so the points represent diuresis due to furosemide only. The open squares (□-□) and circles (○-○) show plasma levels of drug after similar doses of furosemide, replotted from Roberts *et al.*[14] Plasma levels of furosemide were superimposed on urinary flow rates by multiplying all plasma levels by 0.2. The approximate half-lives for the diuretic effect after each route of administration compare with kinetically determined plasma half-lives for furosemide of about 30 and 86 minutes, respectively (Roberts *et al.*[14]).

I/V ADMINISTRATION OF FUROSEMIDE AND URINARY SPECIFIC GRAVITY



FUROSEMIDE WAS ADMINISTERED BY RAPID I/V INJECTION AT THE INDICATED DOSES AND URINE SPECIFIC GRAVITY PLOTTED AGAINST TIME.

FUROSEMIDE LONG TERM TOXICITY FROM FUROSEMIDE: A VERY UNLIKELY CANDIDATE

Furosemide is an extremely unlikely candidate for long term toxic effects because:

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2/ A single IV dose is very rapidly cleared by the horse, plasma half-life is 38 minutes.

3/ Pumped at high concentrations unchanged into the urine, where it produces its diuretic response.

4/ Furosemide is rapidly, efficiently and completely eliminated by the horse.

5/ Diuretic and ionic loss effects are very short lived, and no reason to believe that they are not rapidly replaced.

6/ As used in racing the effect of Furosemide is simply a brief protective effect against the pulmonary damage associated with racing.

6/ No reason whatsoever to suspect any long term cumulative adverse effects from pre-race administration of furosemide.

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ACKNOWLEDGMENTS:

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CLENBUTEROL : AN UNLIKELY CANDIDATE FOR LONG TERM ADVERSE RESPONSES.

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