

RACE DAY MEDICATION AND DRUG TESTING

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Race Day Medications

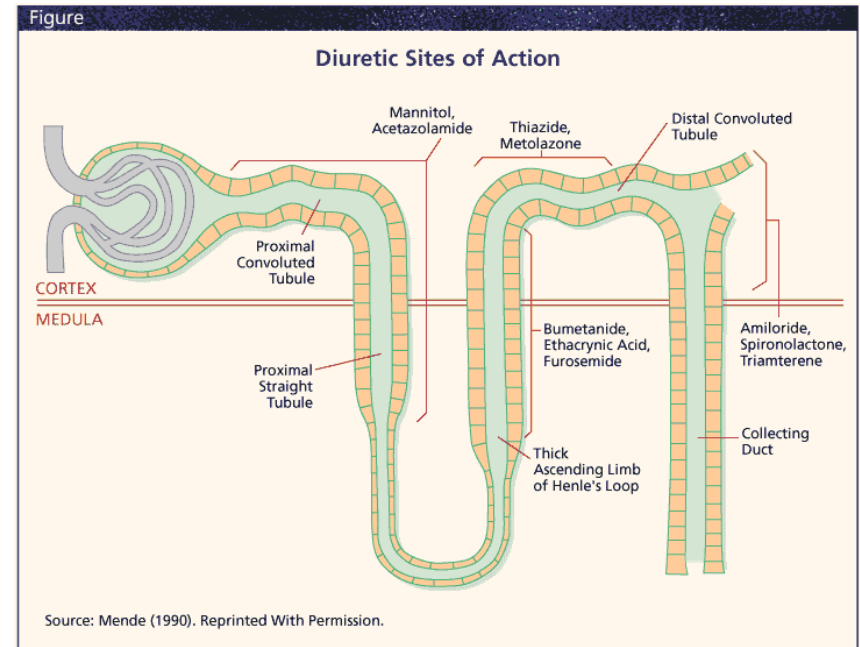
- High Ceiling Loop Diuretics
 - Furosemide
 - Bumetanide
 - Ethacrynic Acid
 - Torsemide
- Fibrinolysis Inhibitors
 - Aminocaproic Acid
 - Tranexamic Acid
- Antihemorrhagic Agents
 - Carbazochrome
 - Etamsylate
- Others

LOOP DIURETICS

Furosemide and related diuretics

Loop Diuretics

- The functional unit of the kidneys is the glomerulus
- Water and electrolytes are normally reabsorbed from the glomerulus
- Waste products are eliminated
- Loop diuretics competitively inhibit Na-K-Cl transporter in the Loop of Henle
- Inhibition of chloride reabsorption decreases driving force for water reabsorption
- More than 98% of the water entering the glomerulus is normally reabsorbed

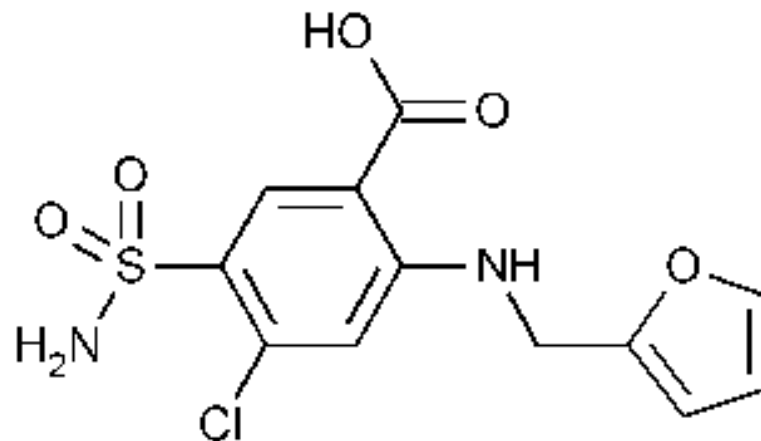


Loop Diuretics

Furosemide

- High ceiling loop diuretic
- Marketed as Lasix™ and Salix™
- Available as oral and parenteral products
- First use in horses reported from late 1960s
- Readily detected in blood and urine by contemporary methods of analysis

Chemical Structure



Furosemide

- Synthesized in early 1960s
- Results of clinical trials reported in 1963
- Approved in human medicine for treatment of hypertension from Hoechst (now Sanofi Aventis) in July 1966
- Injectable veterinary product from Hoechst introduced in 1967
- Intervet purchased furosemide from Hoechst and renamed it Salix™



Furosemide

- Lasix™ Injectable available from Hoechst as approved veterinary product in 1967
- First injectable diuretic approved for use in horses
- Indications: For the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency, and acute non-inflammatory tissue edema (US FDA).
- Pioneering work on diuretic efficacy in horses by Dr. Marvin Beeman of Littleton, Colorado



Furosemide

- Administered to horses to prevent EIPH by late 1960s
- Earliest use of furosemide in bleeders attributed to Dr. Alex Harthill
- Lasix™ use permitted under “permissive medication” programs by mid-1970s
- Use listed in racing programs
- Dose, route, and time of administration were not regulated or standardized
- Urine samples submitted from treated horses were often dilute
- Concerns were raised about effect of furosemide induced diuresis on drug detection
- Veterinary advisory committee to NASRC recommended that NASRC prohibit furosemide in racing
- NASRC voted to prohibit furosemide in racing in 1983
- Several racing commissions followed NASRC recommendation
- Various groups of trainers threatened to boycott racing

Furosemide

- The AHC (Tom Aronson and Rich Rolapps) took the lead in addressing the furosemide impasse
- They asked the AAEP for a recommended dose, route, and time of administration
- AAEP specified:
 - IV route only
 - 250 mg total dose
 - 4 hours before racing
- Fixing the dose led to studies to determine whether samples collected 5-6 hours after dosing were dilute
- George Maylin and I conducted studies on effects of this dose regimen on detection of drugs and metabolites in urine by TLC methods
- Results indicated no significant effects on detection of ten drugs
- Dose, route, and time were fixed based on these studies
- Various commissions approved furosemide use with dosing restrictions
- All racing commission had approved Lasix use by 1996

Furosemide

- Pharmacology
 - Dose dependent diuretic effect in horses
 - Decreases reabsorption 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

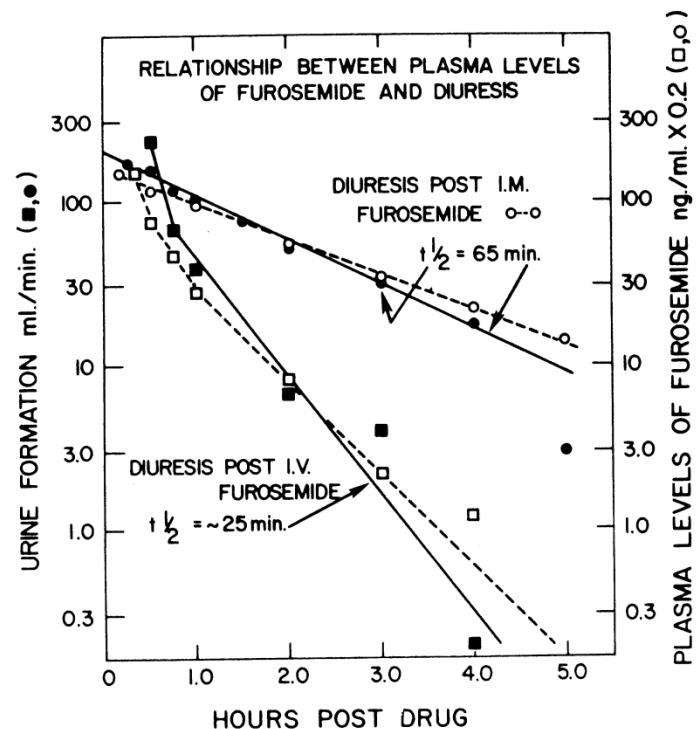


Fig 8—Relationship between plasma levels of furosemide and diuresis. The solid symbols and lines show rates of urine formation in ml/minute after IV injection (solid squares, ■-■, replotted from Fig 1) and after IM injection (solid circles, ●-●, replotted from Fig 6) of 1 mg/kg furosemide. Control rates 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).

Furosemide

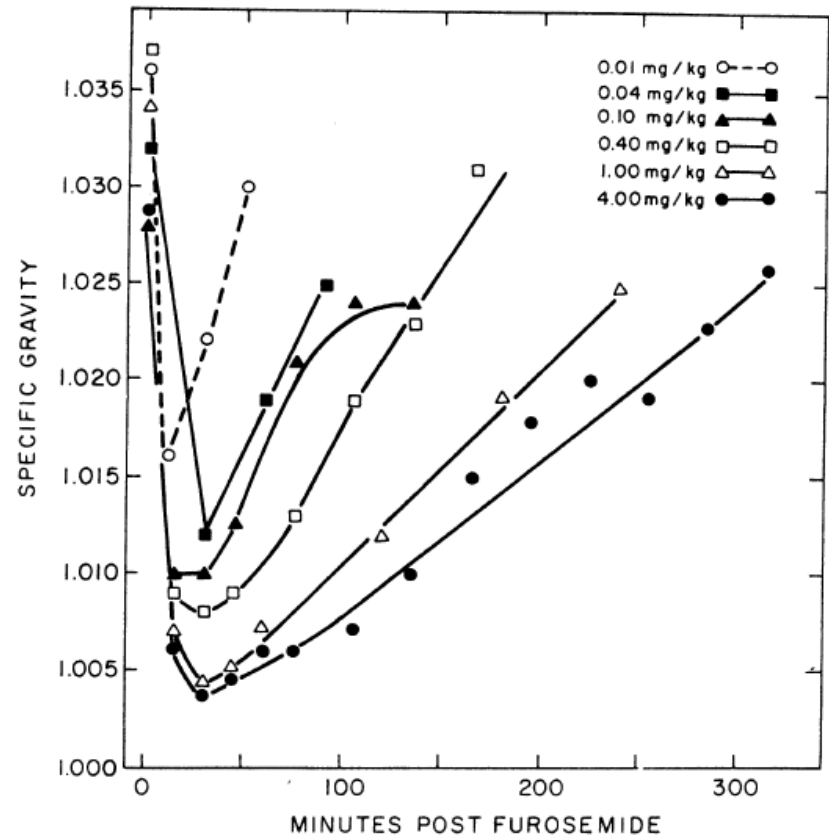
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URINARY SPECIFIC GRAVITY AFTER INTRAVENOUS FUROSEMIDE



Furosemide

- Pharmacology
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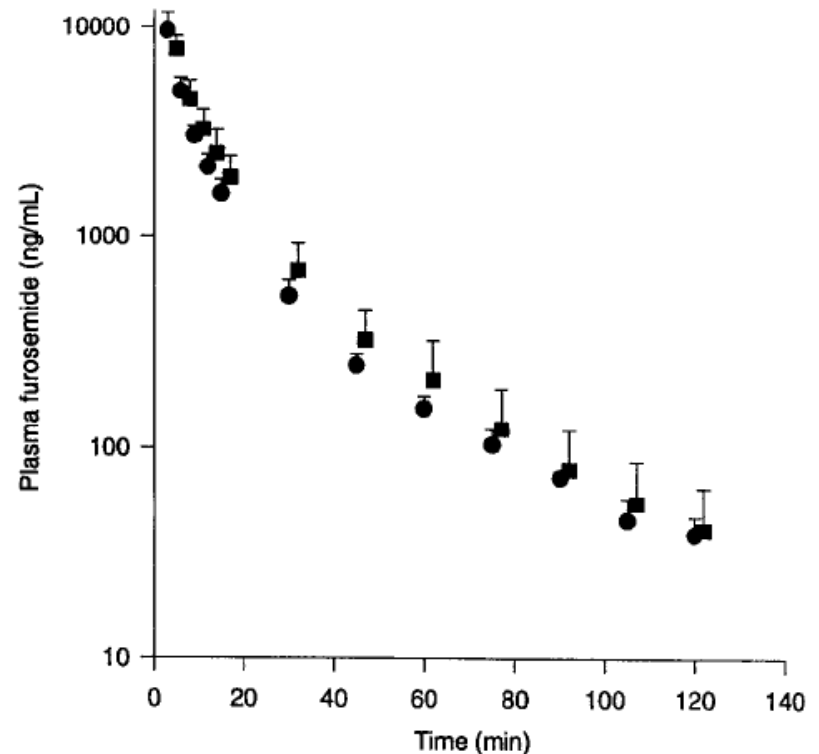


Fig. 1. Mean (\pm SD) plasma concentration (ng/mL) of furosemide after i.v. administration of furosemide at 1.0 mg/kg to six horses while non-exercised (●) or immediately before 60 min of submaximal treadmill exercise (■).

Furosemide

- Effects of diuresis on detection of other drugs
 - Diuresis decreases urine concentration of polar drugs and metabolites up to 50x at peak diuresis – excretion rates are not appreciably affected
 - Pentazocine, morphine, lidocaine metabolites, mepivacaine metabolites, butorphanol, etorphine, nalbuphine, pyrilamine metabolites, glycopyrrolate, tripeleennamine metabolites, etc.
 - Diuresis alters the urine concentrations of lipid soluble drugs and metabolites several fold – excretion rates are increased during peak diuresis
 - Caffeine, theophylline, phenylbutazone, flunixin, naproxen, ketoprofen, etc.

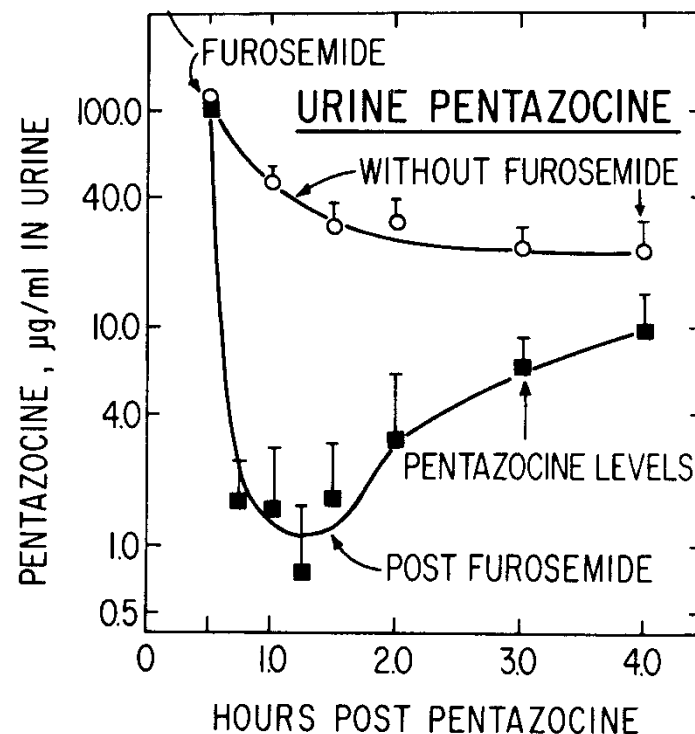
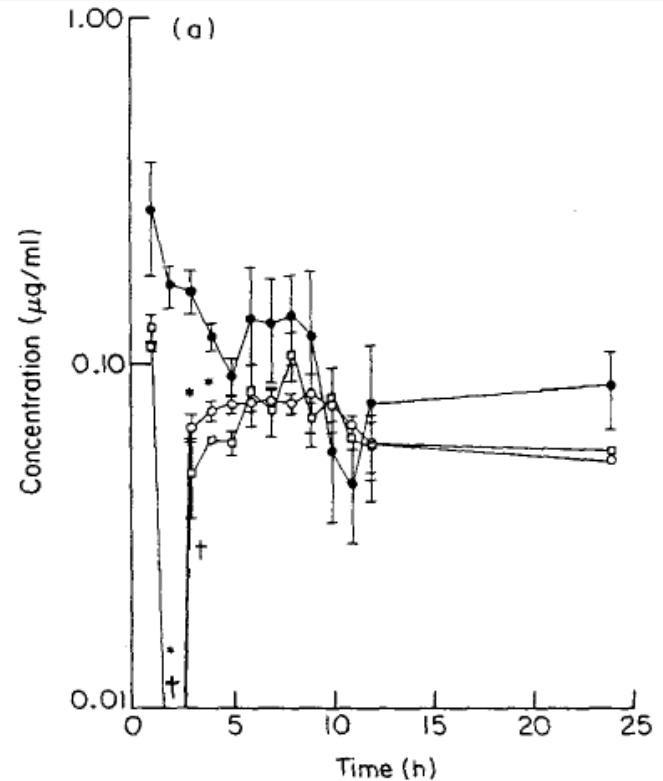


Fig 10—Effect of furosemide on urinary concentrations of a glucuronide metabolite of pentazocine. Horses were injected IV with 0.33 mg/kg pentazocine at indicated zero time. The open circles (○) show urinary concentrations of a glucuronide metabolite pentazocine in control horses. The solid squares (■) show urinary concentrations of this metabolite in horses treated with 1 mg/kg of furosemide IV 30 minutes postpentazocine. All data points

Furosemide

- Effects of diuresis on detection of other drugs
 - Diuresis decreases urine concentration of polar drugs and metabolites up to 50x at peak diuresis – excretion rates are not appreciably affected
 - Pentazocine, acepromazine metabolites, morphine, lidocaine metabolites, mepivacaine metabolites, butorphanol, etorphine, nalbuphine, pyrilamine metabolites, glycopyrrolate, tripeleennamine metabolites, etc.
 - Diuresis alters the urine concentrations of lipid soluble drugs and metabolites several fold – excretion rates are increased during peak diuresis
 - Caffeine, theophylline, phenylbutazone, flunixin, naproxen, ketoprofen, etc.



Effect of furosemide on detection Of acepromazine metabolites.

Furosemide

- Effects of diuresis on detection of other drugs
 - Diuresis decreases urine concentration of polar drugs and metabolites up to 50x at peak diuresis – excretion rates are not appreciably affected
 - Pentazocine, morphine, lidocaine metabolites, mepivacaine metabolites, butorphanol, etorphine, nalbuphine, pyrilamine metabolites, glycopyrrolate, tripeleennamine metabolites, etc.
- Diuresis may alter the urine concentrations of lipid soluble drugs and metabolites several fold – excretion rates are increased during peak diuresis
 - Procaine, methylphenidate, caffeine, theophylline, phenylbutazone, flunixin, naproxen, ketorofen, etc.

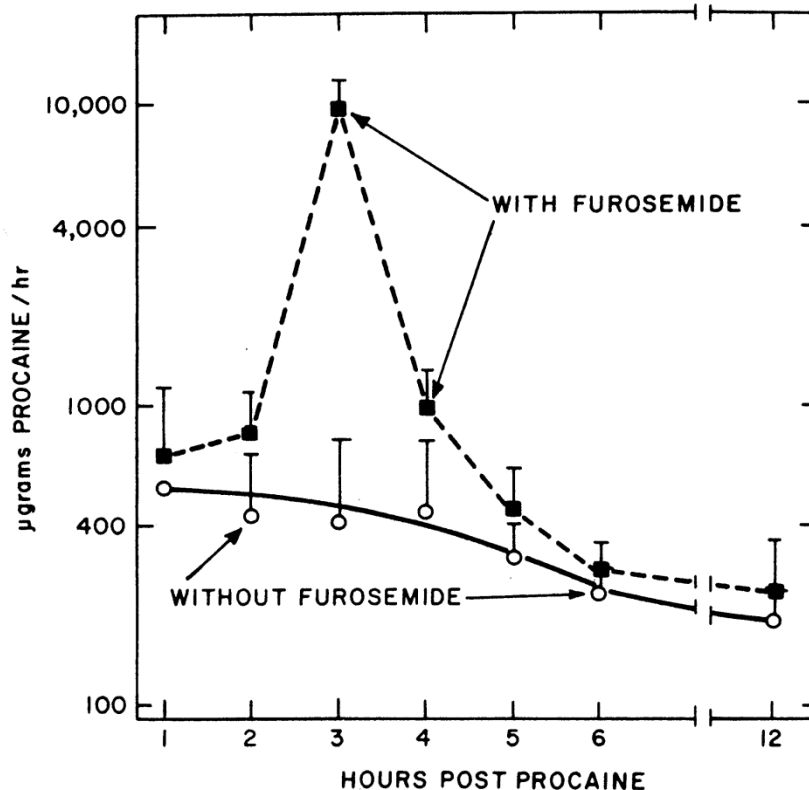
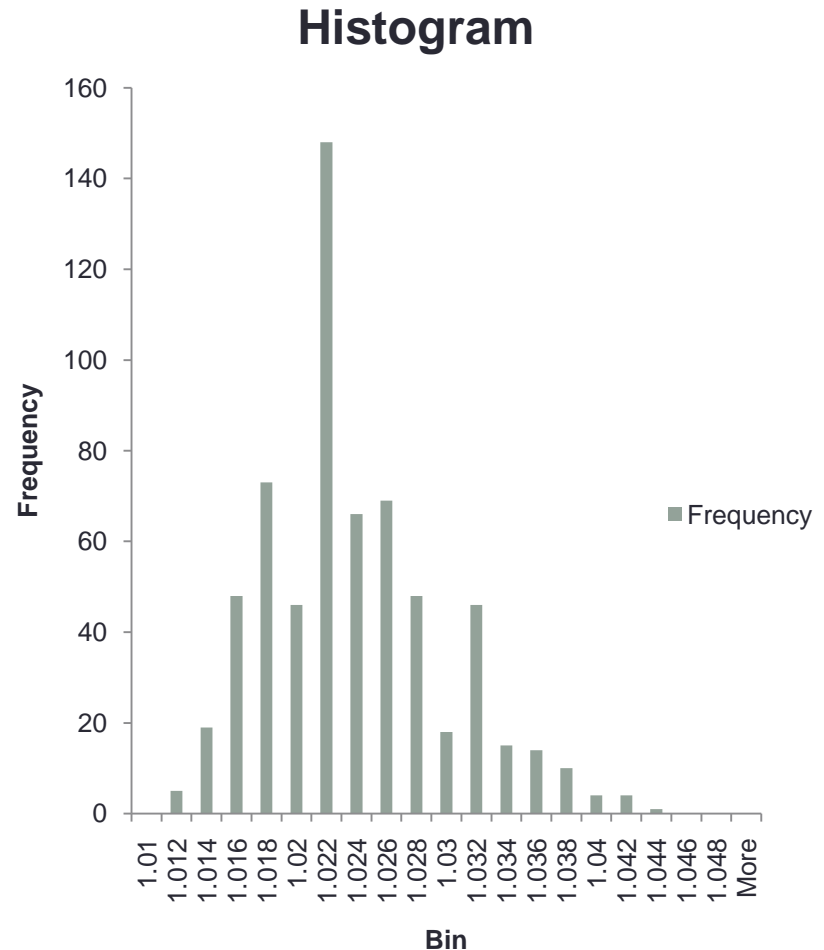


Fig 6—Effect of furosemide on urinary excretion of procaine. The open circles (○ - ○) show urinary elimination of procaine after 10 mg/kg of procaine HCl IM, the solid squares (■ - ■) show elimination of procaine after 1 mg/kg furosemide IV at 2 hours. All experimental points are the means of determinations of 4 different horses ± standard error of the mean.

Furosemide

- Dose Limitations
 - IV route only
 - Dose from 100-500 mg
 - Four hours or more before post-time
 - Dose administered by regulatory vet
- Regulatory controls
 - Specific gravity < 1.010 and
 - Plasma or serum concentration over 100 ng/mL
- Evidence for Compliance
 - Urine specific gravity
 - 635 consecutive urine samples from Thoroughbred horses racing on furosemide
 - Furosemide confirmed
 - Mode: specific gravity = 1.022
 - Fives values less than 1.012
 - All values greater than 1.010
 - Serum furosemide concentration

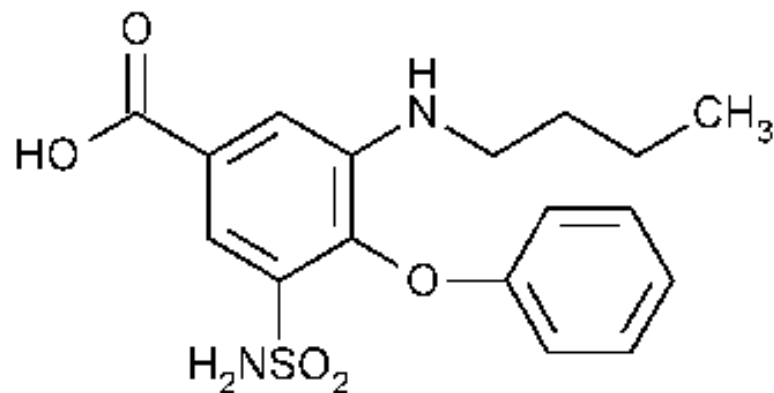


Loop Diuretics

Bumetanide

- High ceiling loop diuretic
- Marketed as Bumex™
- Available as oral and parenteral products
- Detected and reported from horse urine in 1990s where furosemide was not permitted
- Readily detected by contemporary methods of analysis

Chemical Structure



Loop Diuretics

Bumetanide

- Rapidly cleared by renal excretion
- Half-life shorter than that of furosemide
- More potent than furosemide
- Maximum diuretic effect is equal to that of furosemide

Pharmacokinetics

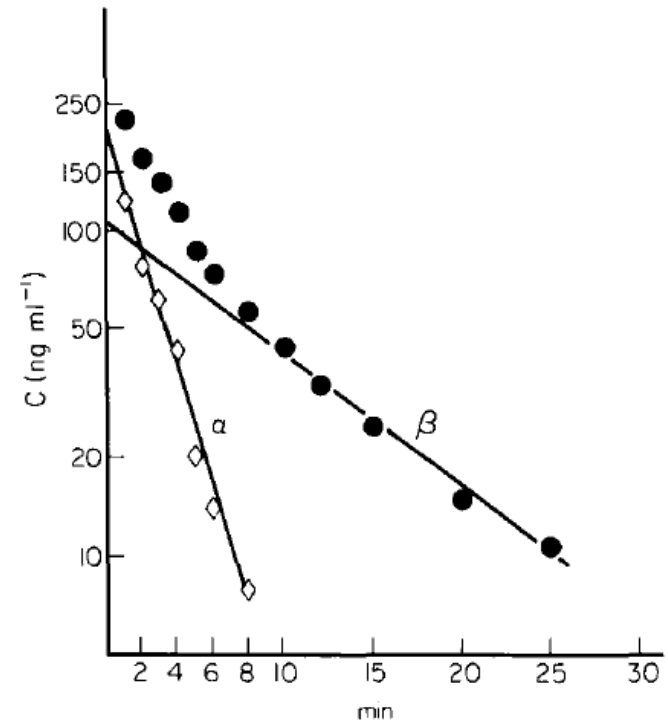


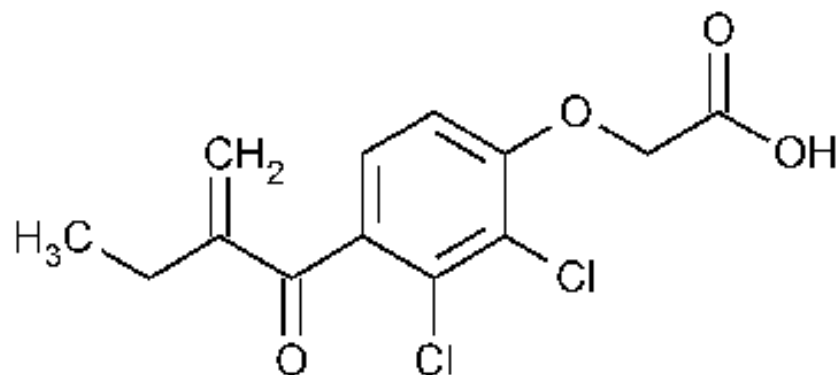
FIG. 1. Mean plasma levels of bumetanide after i.v. injection of 15 µg/kg to five horses.

Loop Diuretics

Ethacrynic Acid

- High ceiling loop diuretic
- Marketed as Edecrin™
- Available as oral and parenteral products – generics available
- Detected and reported from horse urine in 1980s where furosemide was not permitted
- Readily detected by contemporary methods of analysis

Chemical Structure

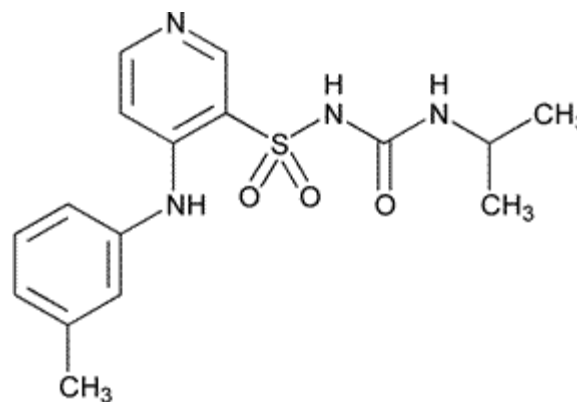


Loop Diuretics

Torsemide

- High ceiling loop diuretic
- Marketed as Demadex™
- Available as oral and parenteral products – generics available
- Detected and reported from horse urine in 2000s
- Readily detected by contemporary methods of analysis

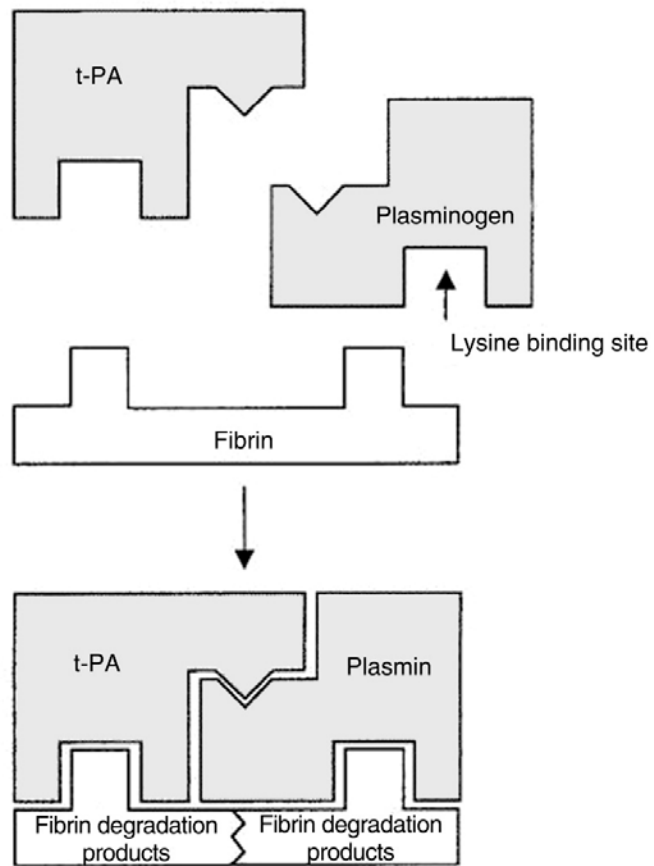
Chemical Structure



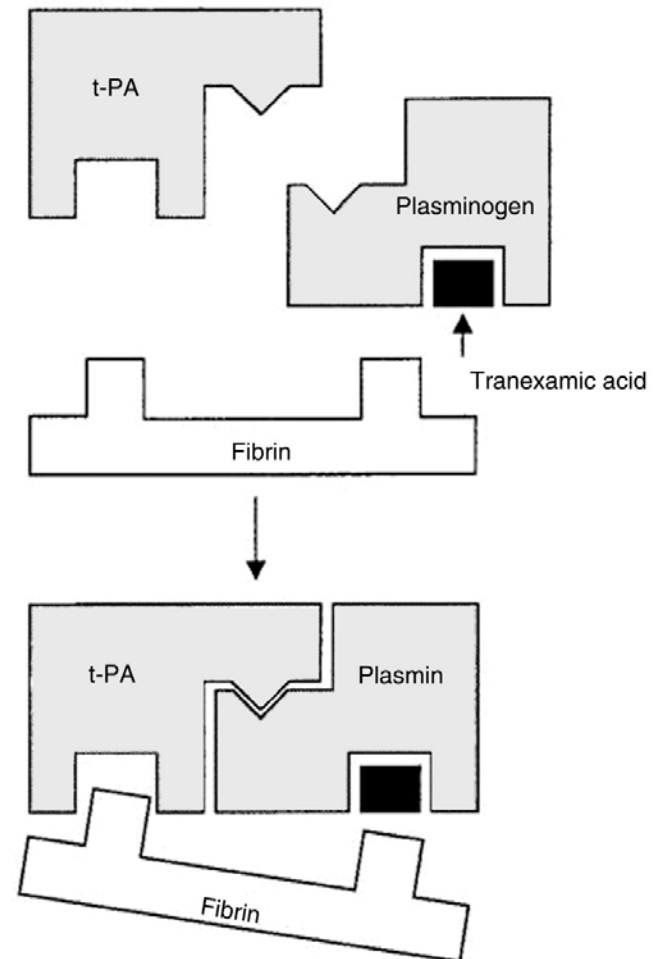
FIBRINOLYSIS INHIBITORS

Drugs that inhibit clot dissolution

Fibrinolysis Inhibitors



A



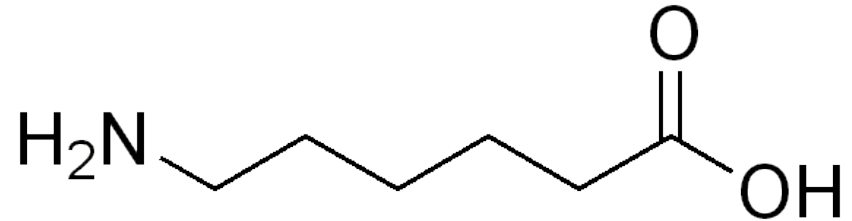
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Fibrinolysis Inhibitors

Aminocaproic Acid

- Chemically similar to lysine
- Marketed as Amicar™
- Inhibits fibrinolysis
- Used in human medicine to treat excessive post-operative bleeding (e.g., coronary artery bypass surgery)
- Not approved for use in horses
- Classified as “adjunct bleeder” medication
- Readily detected by contemporary methods of analysis

Chemical Structure

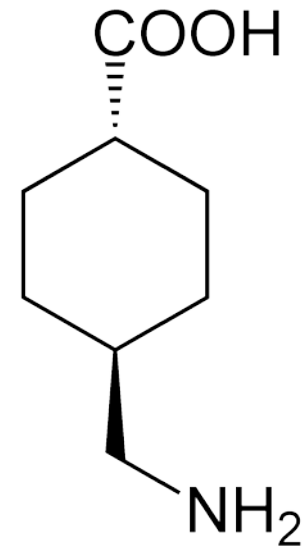


Fibrinolysis Inhibitors

Tranexamic Acid

- Chemically similar to lysine
- Marketed as Cyklokapron™
- Inhibits fibrinolysis
- Used in human medicine to treat excessive post-operative bleeding (e.g., coronary artery bypass surgery)
- Not approved for use in horses
- Classified as “adjunct bleeder” medication
- Readily detected by contemporary methods of analysis

Chemical Structure



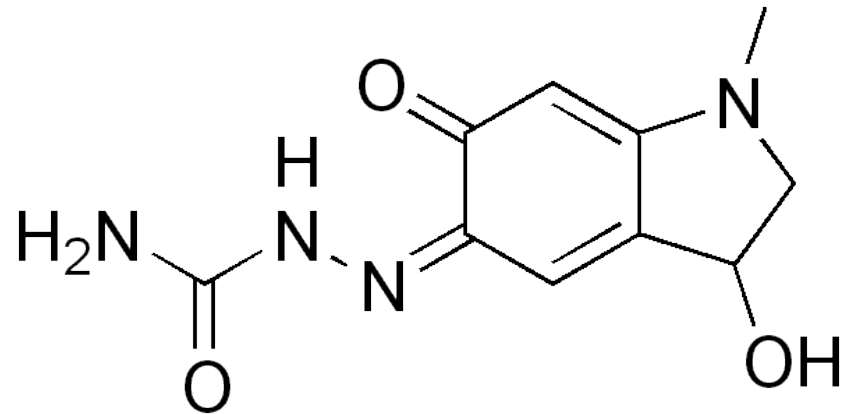
ANTIHEMORRHAGIC AGENTS

Antihemorrhagic Agents

Carbazochrome

- Oxidation product of epinephrine
- Component of Kentucky Red
- Promotes platelet aggregation and adhesion
- Not approved for use in the horse
- Readily detected using contemporary methods of analysis
- Identified as “adjunct bleeder” medication

Chemical Structure

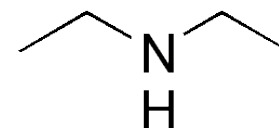
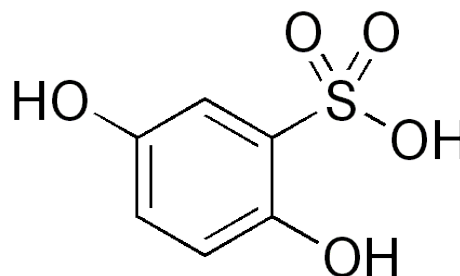


Antihemorrhagic Agents

Etamsylate

- Promotes platelet aggregation and adhesion
- Not approved for use in the horse – not approved for use in US
- Readily detected using contemporary methods of analysis
- Not identified as “adjunct bleeder” medication

Chemical Structure



OTHER SUBSTANCES

Conjugated estrogens and other substances

Other Substances

- Conjugated estrogens
 - Endogenous substances without thresholds
- Ergot alkaloids
 - Ergotamine
 - Vasoconstrictor
 - Readily detected

CONCLUSIONS

Conclusions

- Furosemide is widely used in race horses under controlled conditions
- Uncontrolled use of furosemide results in profound effects on drug concentrations in urine but negligible effects on drug concentrations in blood
- Effects on drug detection are largely eliminated when furosemide dosing is tightly controlled
- Samples are checked for adherence to furosemide dosing restrictions – evidence for compliance is good
- Adjunct medications are readily detected and do not interfere with test procedures
- Other race day medications are readily detected