RACE DAY MEDICATION AND DRUG TESTING

Richard Sams, PhD
Director
HFL Sport Science, Inc.
Lexington, Kentucky
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.\textsuperscript{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.\textsuperscript{14}).
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
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. 1. Mean (± 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, tripelennamine 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 of 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 poi
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, tripelennamine 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, tripelennamine 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, ketoprofen, 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
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
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](image)
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