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Equine Communications

A digest of clinical notes and letters.

Letters may include preliminary communications discussing recent developments, first observations of a new disease, a new pathological finding, or any other brief article or case history of outstanding importance or general interest.

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Pharmacology Review: A Review of Recent Research on Furosemide in the Horse

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Furosemide* is a member of the "high ceiling" group of diuretics and is a safe and very effective diuretic in the horse.[4] Outside of the usual medical indications for diuretics, furosemide is also useful in racehorses because it is believed to be effective in the control of epistaxis (nosebleed). Epistaxis, however, only occurs in about 2% of horses, while up to 80% of the horses running in some meets may be on furosemide.[2] This article will review recently acquired knowledge concerning furosemide in the horse and may suggest some reasons for the widespread use of furosemide in racing horses.

Furosemide was introduced into the equine medical literature by Dr. Marvin Beeman and his colleagues in Colorado.[9] It is useful in edema from all causes. It is particularly useful in cases of pulmonary edema because it acts to rapidly remove this fluid, even before it begins to move fluid out through the kidneys.[1] Its ability to increase the volume of urine may also be used to dilute out substances in urine and prevent renal damage. Thus, when a horse "ties up," the released myoglobin may deposit in and damage the kidneys. In situations such as this, the increased urine volume due to furosemide greatly reduces the possibility of renal damage.[4]

The diuretic action of furosemide is due to its inhibition of active reabsorption of chloride in the renal tubules. Sodium and water reabsorption normally follow chloride reabsorption, so administration of furosemide leads to greatly increased losses of sodium, chloride, and water.[3]

In a 1,000-pound horse, 4 ml of furosemide (50 mg/ml) produces about 4 liters of urine in about 40 minutes. This is the dose recommended for use in epistaxis (nosebleed) in the horse. A 10-ml dose, which is a common clinical dose, produces about 9 liters of urine, mostly within 1 hour. Forty milliliters of furosemide will produce about 21 liters of urine within about 2 hours, and this is close to the maximum response in a normal horse.[6]

The diuretic action of furosemide is therefore relatively short lived, especially after small intravenous (IV) doses. This short lived action of furosemide is not due to any inability of the horse to respond, as a second dose of furosemide will usually produce a very good response. Rather, the action of furosemide in the horse is brief because furosemide is rapidly pumped out of the blood into the renal tubules.[6] This pumping accounts for the short plasma half-life ($T_{\frac{1}{2}}$ = about 35 minutes) of the drug, its very rapid onset of action in the kidneys, and the fact that up to 60% of the drug is found unchanged in the urine. This is a very high proportion of a drug to be excreted unchanged in the horse.[6]

Because furosemide is secreted directly into the urine, it is found there in very high concentrations. A good analyst can easily detect furosemide in equine urine for 12 hours after a 10-ml dose, and the drug can be detected for up to 52 hours. Because the pharmacological actions of furosemide are largely over within 2 hours after an intravenous dose, there appears to be no need for detection of the drug for more than 12 hours after its administration. Racing chemists should bear this in mind when setting the level of sensitivity of their test systems.[6]

If furosemide is given intramuscularly (IM), its plasma half-life is greatly increased ($T_{\frac{1}{2}}$ = 86 minutes), and the diuretic response also lasts longer. After IM injection of 1 mg/kg of furosemide, about a 50% greater urinary response is observed than after its in-

* All the work reported here refers to injectable Lasix®, 50 mg/ml from National Laboratories Corp. subsidiary of American Hoechst Corp., Somerville, NJ.

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travenous injection. Onset of the diuretic effect is, however, almost as fast as after IV injection, so IM injection would appear to be the route of choice if a prolonged or greater diuretic effect is required.[6]

Like the diuretic effects of furosemide, the cardiovascular effects of furosemide are also transient. After intravenous injection, furosemide reduces pressure in the pulmonary circulation within minutes. This effect occurs independently of the diuretic effect and may be the basis of the action of furosemide against epistaxis. In the systemic circulation, furosemide produces a decrease in cardiac output with a small increase in heart rate. Furosemide does not alter blood pressure in the systemic circulation. After 1 mg/kg (about 10 ml) intravenously, these effects are usually over within 2 hours.[5]

After intravenous injection, 10 ml furosemide increases total plasma solids about 10%, hematocrit by about 5%, and rapidly reduces plasma K^+ levels. These effects peak between 10 and 30 minutes after administration of the drug and decline back to control levels by 2 hours postdosing.[5,6]

In studies in a number of laboratories, furosemide was found not to reduce the plasma levels of any drugs tested to date.[4] Furosemide does not, therefore, act to "flush" drugs out of the blood or plasma of horses and should not interfere with blood testing for drugs.[7] Similarly, it did not significantly affect the urinary concentrations of a number of drugs tested, such as procaine or methylphenidate, and a closely related drug did not affect amphetamine.[4] These drugs are all basic, relatively lipid soluble drugs, and it appears likely that furosemide has little or no effect on urinary concentrations of this group of drugs.[7]

On the other hand, furosemide treatment caused up to 50-fold reductions in the urinary concentrations of both phenylbutazone and the major metabolite of pentazocine, which is a water soluble pentazocine glucuronide conjugate. In the case of phenylbutazone, this reduction in concentration was sufficient to render the drug difficult to detect in our routine screening tests on racetrack samples at the University of Kentucky. Since both furosemide and phenylbutazone are permitted medications in Kentucky, we now routinely take both blood and urine samples for testing. In our opinion, blood samples are necessary to accurately test for medication with phenylbutazone if the use of furosemide is also permitted.[7]

Some racing jurisdictions, such as Illinois or California, have rules which set upper limits on the concentration of phenylbutazone permitted in horse urine on race day. These rules make little sense if furosemide is also a permitted medication. This is because simple administration of furosemide either IV or IM as close to race time as possible will easily reduce the concentration of phenylbutazone in the postrace urine to below the critical level.[7]

By and large, however, the actions of furosemide on phenylbutazone concentrations in urine are not a serious problem for the racing chemist, in contrast with the likely actions of furosemide on some other groups of drugs. The 50-fold dilution of the major water soluble metabolite of pentazocine also probably occurs with all other drugs detected as water soluble metabolites, such as apomorphine, morphine, and related narcotics and the phenothiazine tranquilizers. Since these drugs are effective at very low plasma concentrations and are difficult or impossible to find in equine plasma, their dilution by furosemide in equine urine is a serious problem for the analyst. The potential for furosemide to interfere with detection of these drugs in urine is probably the most serious problem associated with the approval of furosemide for use in racing horses.[7]

The performance effects of furosemide have been studied in some detail at both the University of Kentucky and the Ohio State University.[8] As pointed out earlier, furosemide has a very rapid action against pulmonary edema and is thought by track veterinarians to greatly assist the breathing of horses with respiratory problems, such as follicular pharyngitis. However, double blind trials on healthy Standardbred horses at both the University of Kentucky and the Ohio State University showed no statistically significant effects of furosemide on the performance of Standardbred horses.[4,8]

Because the numbers of horses involved in these trials were small and the horses were all clinically normal, we elected to perform a further study on the effects of furosemide on racing performance under track conditions. To this end, the Kentucky Harness Commission made available to us the "Lasix list" for the Louisville Downs Summer 1977 Harness Racing Meet. At this meet, furosemide was the only permitted medication, and its use was monitored by urinalysis. Horses could elect to go on furosemide at any time throughout the meet, but once on furosemide had to stay on furosemide. From the "Lasix list," 58 horses were selected, and for these horses 160 times prefurosemide and 232 times postfurosemide were obtained. It turned out that the horses were actually 0.14 seconds slower on furosemide than before they went

on furosemide, though this difference was not statistically significant. The only conclusion from this experiment seems to be that the horsemen at Louisville Downs or their veterinary advisors were, on the whole, not able to improve the performance of their horses with furosemide.[8]

Furosemide appears to be a very safe drug in the horse. The usual dose administered in the treatment of epistaxis is a relatively small dose, and when administered IV, its action is brief. Given access to water and salt, any drug-induced losses of fluid or ions should be rapidly replenished. In another series of experiments 10-ml (1 mg/kg) doses of furosemide were given daily to horses for 4 consecutive days, and a series of hematological parameters followed. No cumulative changes in any of these parameters over the 4-day test period were observed. However, if these same 4 doses were given at hourly intervals, a 40% drop in serum K^+ was observed. Thus, the only likely acute toxicity with furosemide would appear to be the possibility of inducing hypokalemia with rapidy (hourly) repeated doses.[8]

In conclusion, furosemide is a very effective, safe, and rapidly acting diuretic in the horse. It clearly acts to dilute out and interfere with testing for certain drugs in equine urine. It does not appear to affect the performance of Standardbred horses. Clinical experience suggests that furosemide is effective in the treatment of epistaxis, and it may be useful in horses with respiratory problems, but no hard evidence to support these clinical impressions is currently available.

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Piperazine Toxicity in Horses

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Clinical signs of horses involved in an epidemic of iatrogenic piperazine citrate poisoning are described. The disease was reproduced by similarly overdosing an experimental horse. No treatment was necessary for a complete recovery.

Introduction

Toxic reactions subsequent to oral administration of piperazine compounds for the treatment of helminth infestations of man and domestic animals are uncommon. Vomiting, urticaria, blurred vision, weakness, nystagmus, and convulsions may occur with normal or excessive dosing in humans.[1,2,10,12] Occasional emesis, diarrhea, and transient neurotoxic symptoms are seen with excessive dosing in small animals.[4,5,10,19,20] Mild gastrointestinal signs are reported after administering high doses to calves.[13] Therapeutic activity is attributed to the neuromuscular blocking activity of these compounds in the parasite, which allows normal intestinal peristalsis of the host to expel the intact parasite from the gut. The effects of the drug on neuromuscular activity within the host are minimal.[10,16]

Reports of toxicity in horses are rare. Toxic signs were not produced in foals treated with 6 times the normal dosage levels of piperazine adipate.[17] However, in a more recent study, involving trials with both levamisole and piperazine, neurotoxic signs were produced in a horse dosed with piperazine monohydrochloride at 6 times the normal dosage levels.[7] This paper reports the clinical signs associated with an outbreak of iatrogenic piperazine citrate poisoning on a Standardbred stud and the experimental reproduction of the disease.

Case History

A group of 10 weanling Standardbred colts were running in a 50-acre paddock grassed with improved pasture. All had suffered a mild upper respiratory tract infection during the 3 weeks prior to anthelmintic treatment. There was no other history of illness in any of the horses. During a 2-day period, every horse on the property had been treated via nasogastric intubation with piperazine citrate and thiabendazole pow-