# MEDICATION FOR EXERCISE-INDUCED PULMONARY HAEMORRHAGE AND ITS EFFECTS ON OTHER MEDICATIONS

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## SUMMARY

Exercise-induced pulmonary haemorrhage (EIPH) expressed as the bleeding from the nostrils of horses during racing, has been a well-known problem in racehorses. Previous treatments, including oxalic and malonic acids, vitamin K and conjugated oestrogens, were used based on the theory that EIPH was caused by clotting defects or pulmonary hypertension. The efficacy of these treatments has not been proven to date.

The current treatment of choice is the administration of a diuretic, principally furosemide, given pre-race. There are recent scientific data supporting the widely held belief that furosemide can return a EIPH horse to its optimal performance level. Furosemide appears to act by clearing pulmonary oedema, but the exact mechanism of furosemide EIPH prophylaxis is currently under debate.

The diuretic effect of furosemide has the potential to interfere with the detection of illegal drugs in racehorses. Furosemide does not effect the detection of any drug in blood samples. However, certain water soluble drugs and drug metabolites can be diluted in urine for up to two hours or so after a dose of furosemide. "Four-hour" racing rules and detention barn systems have been used to counter this problem in jurisdictions allowing the use of pre-race furosemide. Recently developed sensitive immunoassay detection methods may allow a quantitative testing system to replace previous methods in the regulation of EIPH medication.

## INTRODUCTION

Approaches to the treatment of exercise-induced pulmonary hemorrhage (EIPH) epistaxis or "bleeding" have tended to be empirical and the results obtained evaluated in terms of clinical impressions. Historically, the approaches taken have been based on the hypotheses that the horses involved have been suffering from defects in either their clotting mechanisms or that they have been suffering from pulmonary hypertension. Treatments have been based on these approaches despite the fact that there is no evidence for either reduced clotting or pulmonary hypertension as being an important factor in the development of EIPH. More recently, furosemide has become the treatment of choice in the treament of epistaxis, and is the recommended treatment of the American Association of Equine Practitioners. Whilst evidence for the efficacy of furosemide in the treatment of bleeders was at first based on clincal impressions, there is now some scientific evidence to support the use of furosemide in the prophylaxis of EIPH (Pascoe 1985).

## EARLY EIPH TREATMENTS

### OXALIC AND MALONIC ACIDS

One of the earliest treatments for EIPH was the administration of small amounts of oxalic and malonic acids. The rationale for this approach was that EIPH was due to a clotting defect. On this basis, administration of an appropriate amount of either of these agents would chelate a small but sufficient amount of calcium to improve the clotting process and thereby reduce the incidence of EIPH. This approach is now regarded as obsolete (Clarke 1986).

### VITAMIN K

Another interpretation of the clotting defect hypothesis holds that this defect can be remedied by administration of appropriate amounts of vitamin K. However, since classic EIPH can occur without any clearcut evidence of a clotting defect, therapy with vitamin K would not appear to provide a rational or effective basis for treatment of this condition (Clarke 1986).

### CONJUGATED OESTROGENS

Conjugated oestrogens have been reported to reduce capillary bleeding and to accelerate blood clotting in laboratory animals. Similarly, women on oral contraceptives have been reported to have a higher incidence of blood clotting and embolic disorders than women not taking these drugs. While the scientific basis for the use of conjugated oestrogens in EIPH is not clear, it appears likely that these observations form the basis for their use in the prophylaxis of EIPH (Tobin and Combie 1980).

No scientific evidence is available concerning the efficacy of conjugated oestrogens in the treatment of EIPH. In the human female the increase in the incidence of clotting disorders of patients on these drugs is small and difficult to demonstrate. Beyond this, there are a number of problems with the approach of using a conjugated molecule. This is because conjugated molecules are generally much less active pharmacologically than their parent molecules, so the administration of conjugated oestrogens for treatment of EIPH appears likely to be a less efficacious way of administering these drugs.

### OTHER MEASURES

Other approaches to the problem of EIPH include bleeding of the horse and the withholding of water for several hours before the race. The rationale for these approaches appears to be the same as the use of diuretics, ie. that the reduction in fluid volume will lead to a reduction in blood pressure in the pulmonary system. No good scientific evidence in support of either of these manoeuvres is available.

## FUROSEMIDE TREATMENT

### EFFICACY OF FUROSEMIDE IN THE TREATMENT OF EIPH

For about the last fifteen years the treatment of choice for EIPH in racing horses has been furosemide (Lasix®, American Hoechst, Somerville, NJ). The drug is given prophylactically at about four hours before the race to horses that are thought to be predisposed to bleeding. The recommended dose is about 250 mg/horse IV, and the drug should not be administered closer to race time than about four hours. At this dose

furosemide produces a prompt diuretic effect when given intravenously, which is largely over within one hour of administration of the drug (Tobin 1978).

There is recent work (Pascoe *et al* 1985) to support suggestions that furosemide reduces the incidence of EIPH. The effect is small but statistically significant. Horsemen and equine practitioners hold that furosemide pre-treatment helps horses with their "wind" or with their breathing.

## EFFECTS OF FUROSEMIDE ON PERFORMANCE

Early work on the effects of furosemide on the performance of racing horses asked the question whether or not pre-treatment with furosemide could affect the performance of horses. In general, the answer to this question is that, in horses that have not been shown to be bleeders, there was no evidence that the drug improved the racing performance of horses. More recently, however, a study of Soma *et al* (1985) has shown that if one takes horses whose performance has deteriorated for three successive races, then examines these horses endoscopically for evidence of EIPH, and if you elect to treat the bleeders with furosemide, you can return these treated horses to their baseline or starting performance, ie. their best performance before the deterioration began. While there are a number of problems in the design and interpretation of this study, it is a very provocative study since it suggests that, while furosemide may not improve the performance of a racing horse, it may be able, under some circumstances, to restore performance that has declined due to EIPH or other furosemide treatable problems.

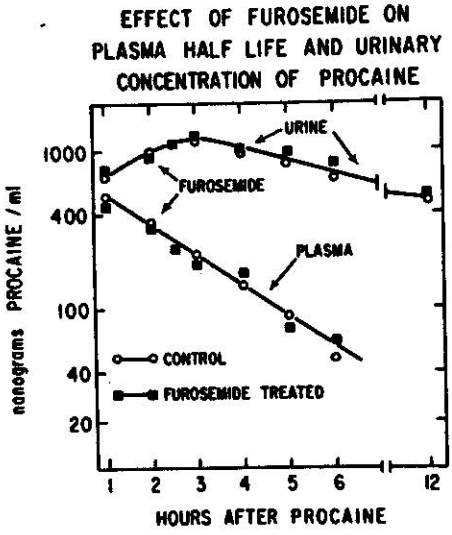


**Figure 1:**

Lack of effect of furosemide on plasma and urinary levels of procaine. The open circles (○) show plasma and urinary concentrations of procaine after 10 mg/kg of procaine was given by IM injection. The solid squares (■) show plasma and urinary levels when the same dose of procaine was followed by 1 mg/kg of furosemide IV. The data show that the administration of furosemide had no significant effect on plasma or urinary levels of procaine. Reproduced with permission from *J. Equine Med. Surg.*

## PULMONARY EFFECTS OF FUROSEMIDE

Given the effects of furosemide on the pulmonary system, and its possible effects on performance, the question then arises of how furosemide produces its pulmonary effects since the drug is primarily a diuretic. It turns out, however, that furosemide has clearcut actions on the pulmonary system in most species. In human beings, in laboratory animals, and presumably in the horse, furosemide acts to rapidly clear pulmonary oedema. However, the mechanism by which furosemide produces this effect is not clear (Tobin and Combie 1980). Furosemide acts to decrease transvascular hydraulic pressure and increase protein osmotic pressure which results in decreased lymph and lymph protein flows in the lungs. Additionally, it also causes renal and extra-renal release of prostaglandins which are thought to affect the pulmonary vasculature and airways. Volume shifts and fluid losses (but more likely volume shifts) may be important in its actions against pulmonary oedema, but the effects of furosemide on pulmonary oedema occur very rapidly and in the absence of significant urine formation. The actions of furosemide on pulmonary oedema are thought to involve the release of prostaglandins by the kidney, which affect pulmonary fluid volumes and airway diameter, and thus affect the degree of EIPH observed. Finally, a matter of interest primarily to American practitioners is that furosemide is approved by the Federal Drug Administration for the treatment of pulmonary oedema in horses.

## ACTIONS BY FUROSEMIDE ON DRUG DETECTION

### DRUG DETECTION IN BLOOD

The principal problem with the approval of furosemide for use in racing horses is the ability of furosemide to interfere with the detection of some drugs in the urine of racing horses (Tobin 1981). While the actions of furosemide on drug detection were poorly understood for some time, the actions of furosemide on drug detection are now well described and allow a number of clearcut statements about the actions and effects of furosemide on drug detection in racing horses.

Furosemide does not affect the detection in blood of any drug studied to date. The reason for this lack of effect on the detection of drugs in blood relates to the relative volumes of the diuretic effect of furosemide and the fluid volume of a horse. While the diuretic effect of furosemide appears substantial, it only amounts to about one to two percent of the total fluid in a horse. For this reason one should not expect treatment with furosemide to reduce the amount of a given drug in a horse by more than approximately one to two percent. Since these very small changes are well within the error level of most analytical methods, it is very unlikely that administration of a single dose of furosemide at the levels used in racing horses will lead to a significant reduction in the plasma levels of the drug in question. In general, this conclusion has been borne out by the small number of studies in this area (Gabel *et al* 1977).

### DRUG DETECTION IN URINE

Furosemide treatment does not appear to substantially affect the detection in urine of basic lipid soluble drugs such a methylphenidate, amphetamine, or procaine (Tobin *et al* 1978). When we administered furosemide to horses and looked for an effect on the detection of these drugs in urine, there was relatively little effect of furosemide treatment on the urinary levels of these drugs (Figure 1). It appears that these drugs are sufficiently lipid soluble, that they readily equilibrate with the increased urinary volume caused by furosemide, and the concentration of drug in the urine is not reduced. The primary determinant in this case appears to be the ease with which the drug can equilibrate across

the renal tubule, and, if the drug is sufficiently lipid soluble this apparently occurs readily. However, the actual amount of drug eliminated in the urine is increased by the same amount as the increased volume of urine.

If the drug in question is not particularly lipid soluble, treatment with furosemide will dilute out urinary levels of water soluble drugs or drug metabolites (Combie *et al* 1981). Examples of such drugs are phenylbutazone, pentazocine, apomorphine, acepromazine, and fentanyl (Figure 2).

In the case of these water soluble drugs and drug metabolites the dilution is essentially proportional to the diuretic effect. Because furosemide is an acidic drug, one might expect a small effect of furosemide in reducing the elimination of acidic drugs due to competition for the organic anion active transport system. Such an effect, if it exists, is apparently small and is overwhelmed by the diuretic effect of furosemide.

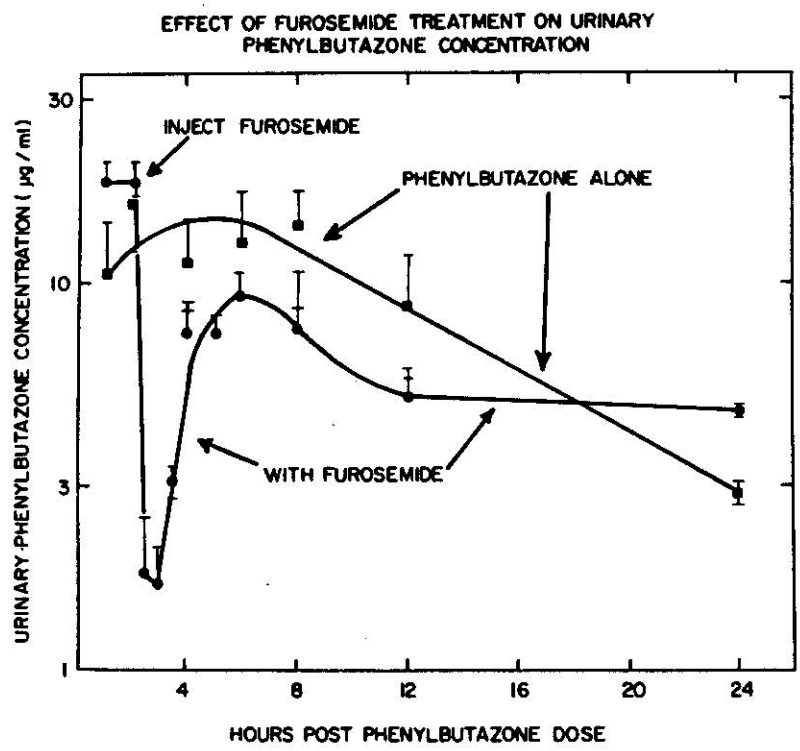


**Figure 2:**

Diluting effect of an antiepistaxis dose of furosemide on urinary phenylbutazone. Four horses were dosed with 2 gm/1000 lb. of phenylbutazone IV at indicated zero time and then with either saline or 0.33 mg/kg (3.5 ml) of furosemide at two hours. The solid circles (●-●) show the urinary concentrations of phenylbutazone in the horses receiving saline, while the solid squares (■-■) show urinary levels of phenylbutazone in the horses treated with furosemide. Reproduced with permission from Charles C. Thomas, Publisher.

## FORENSIC SIGNIFICANCE OF THE DILUTION PROBLEM

The forensic significance of this dilution problem is that illegal medications can be much more difficult to detect in the urine of horses shortly after a dose of furosemide. For example, the diluting effect on fentanyl after a dose of 0.5 mg/kg of furosemide peaks at about a twenty-fold dilution within thirty minutes after drug administration (Figure 3). However, the concentrations of fentanyl in the urine have returned to normal within about two hours of drug administration (Combie *et al* 1981). These observations and other work have lead to the rule that furosemide should be given to racing horses within four hours before post-time to prevent the dilution effect of furosemide on the post-race detection of this drug. Because of the complexity of the furosemide rule, it is often enforced by use of a detention barn in which the horses are sequestered and supervised for four hours prior to the race (Woods *et al* 1988).

It is important that the rules with regard to furosemide be strictly enforced. This is because the unregulated use of furosemide can facilitate illegal medication. Recent unpublished work from our laboratories has shown that, for at least the first ninety minutes after administration of furosemide, a recent administration of buprenorphine cannot be detected. This is despite the fact that our buprenorphine enzyme-linked immunosorbent

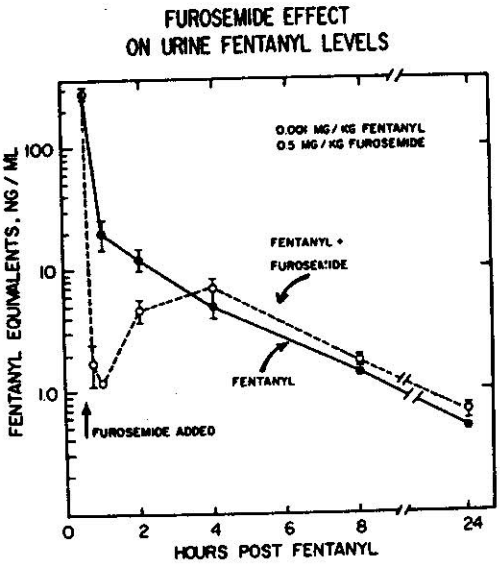


**Figure 3:**

Urinary levels of fentanyl after 0.5 mg/kg furosemide. The solid circles (●-●) show urinary concentrations of fentanyl as fentanyl equivalents (radioimmunoassay) after administration of 0.5 mg of fentanyl to three horses. The open circles (○-○) show urinary levels of fentanyl equivalents when 0.5 mg/kg of furosemide was administered at thirty-one minutes after the fentanyl. The data show that this dose of furosemide reduced the urinary concentrations of fentanyl about fifteenfold and that the effect lasted for about two and one-half hours. Reproduced with permission from Charles C. Thomas, Publisher.

assay (ELISA) is the most sensitive test available for this drug. Since detention barns are only as good as the quality of supervision that a horse receives, the possibility of illegal administration of a second dose of furosemide always exists. Based on recent work from our groups, we have therefore developed a quantitative method for furosemide to monitor compliance with furosemide regulations which we believe to be superior to and more economical than the detention barn system (Woods *et al* 1988).

## FUROSEMIDE QUANTITATION

Detention barns are an administrative problem for racetracks. They are cumbersome to manage, expensive to use, disliked by horsemen, and unless meticulously supervised, of doubtful efficacy. While the appropriate dose of furosemide is given under supervision shortly after the horse enters the barn, it is quite possible for a horse to receive a second dose of furosemide at any time prior to post. This second dose obviates the function of the test barn, which is to ensure that such second doses of furosemide are not used to "cover up" administration of illegal drug.

We have investigated the use of quantitative testing to substitute for the furosemide detention barn. We have raised an antibody to furosemide and developed a rapid and sensitive particle concentration fluorescence immunoassay (PCFIA) test for furosemide (Figure 4). Using this test we can rapidly and sensitively determine the plasma levels of furosemide in a sample (Woods *et al* 1988). Based on previous work we can then determine whether or not this level of furosemide is in excess of the regulatory level of furosemide permitted by the

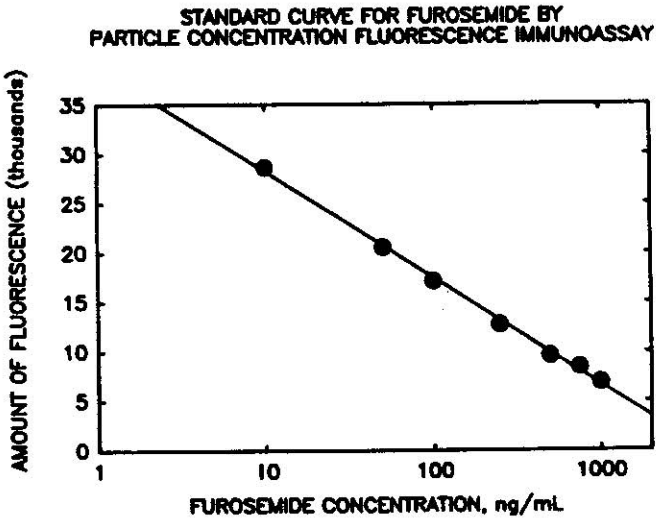


**Figure 4:**

The standard curve for the inhibition of furosemide-fluorophore fluorescence (PCFIA) by the addition of the indicated concentrations of furosemide was constructed. Furosemide (10-1000 ng/ml) was added to normal race track serums which were diluted 1:10 for assay. No extractions were conducted. Reproduced with permission from *Res. Comm. Chem. Path. Pharmacol.*

racing rule (Chay *et al* 1983). For example, one racing commission has chosen to set this level at 50 ng/ml of furosemide, since the probability of a horse dosed with the specified amount of furosemide exceeding this level is less than one in one million.

In the event that a horse exceeds this regulatory level in the immunoassay screen, the remainder of the plasma sample will be subjected to high performance liquid chromatography (HPLC) or gas chromatography-mass spectrometry (GC/MS) to definitively establish the level of furosemide in the sample. The final quantitative analysis will then be reported to the Commission for regulatory purposes.

Because of the characteristic plasma kinetics of furosemide (Chay *et al* 1983) this regulatory method will be highly effective and should detect administration of a second dose of furosemide close to post-time. This is in contrast with the detention barn and honour systems, which leave possibility of such second doses open.

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