THE PHARMACOLOGY AND THERAPEUTICS OF EXERCISE-INDUCED PULMONARY HEMORRHAGE (EIPH)

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Therapeutic approaches to exercise-induced pulmonary hemorrhage (EIPH) have either been empirical or based on the hypothesis that horses which bleed suffer from a clotting defect. This approach of trying to cure a "clotting defect" has been taken despite the fact that there is no evidence for a clotting defect in EIPH. More recently, however, furosemide has been suggested to be effective in the treatment of epistaxis. These suggestions, however, are based primarily on clinical observations and experience with furosemide and there is no direct experimental evidence to support this suggestion.[6]

Oxalic and Malonic Acids

One of the historic treatments for bleeders has been a mixture of oxalic and malonic acids. The rationale behind this approach has been that these agents act to produce a small decrease in plasma Ca^{++} level. This **small** reduction in plasma Ca^{++} is thought to **accelerate** the clotting process and thus reduce the incidence of bleeders. However, this proposed mechanism of action is regarded with skepticism by some authorities, and it has been suggested that the occasional reports of success with this method of treatment should be treated with caution.[6]

Vitamin K

Since a vitamin K deficiency or the presence of vitamin K antimetabolites (*e.g.* Warfarin) is associated with a reduced rate of blood clotting, it has been suggested that EIPH may respond to vitamin K therapy. For classic EIPH where there is no clotting defect, therapy with vitamin K appears unlikely to be successful.

Conjugated Estrogens

Another early treatment for epistaxis was conjugated estrogens. These substances have been reported to reduce capillary bleeding and to accelerate blood clotting in laboratory animals. Similarly, women on oral contraceptives containing estrogens have a slightly higher incidence of blood clotting and embolic disorders. These observations presumably form the basis for the use of conjugated estrogens in the prophylaxis of EIPH.

How efficacious conjugated estrogens are in the treatment of EIPH is

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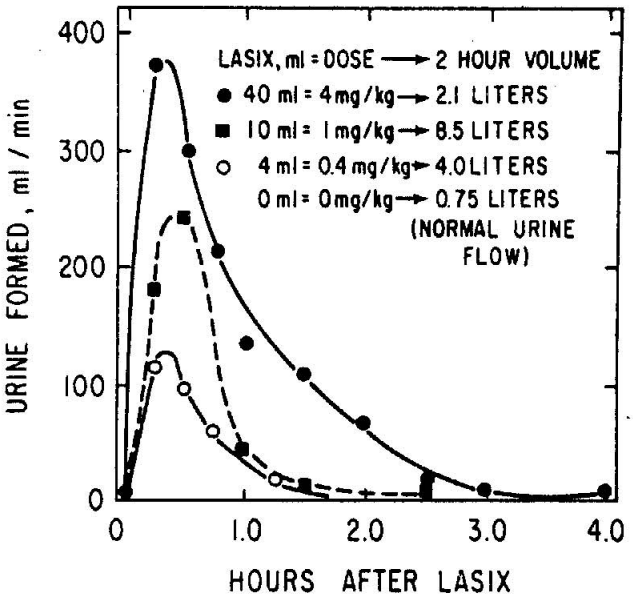

Fig. 1. The solid circles (•) show the diuretic response to 4 mg./kg. (40 ml.) of Lasix i.v. at zero time. The squares (■) and open circles (o) show the response to 1 mg./kg. (10 ml.) and 0.4 mg./kg. (4 ml.), respectively. All urine samples were obtained by bladder catheterization and the symbols represent the mean number of ml./minute excreted in the preceding time period. All points the means of at least four experimental determinations.

not clear. The increase in the incidence of clotting disorders in women is small and difficult to demonstrate. Further, as pointed out earlier, there is no reason to suspect that an increase in the coagulability of blood will significantly affect the incidence of EIPH. A further problem is that conjugated molecules are almost invariably less pharmacologically active than the parent drug, so administration of estrogens in their conjugated form seems to make even less sense.[1]

Other Measures

Other suggested maneuvers have included bleeding the horse and the withholding of water. Both of these methods appear to be based on the hypothesis that they will reduce blood volume in the horse and thus reduce the incidence of pulmonary hemorrhage. No good evidence to support the effectiveness of these maneuvers is available.

Furosemide

For about the last decade, the drug of choice in the treatment of EIPH has been furosemide. Furosemide is given in small doses* about one hour or more prior to race time to horses who it is thought may "bleed." In such

*About 3-4 ml. of Lasix (furosemide, 50 mg./ml.) is given intravenously about one hour before the effect is required.

small doses, furosemide produces a prompt diuretic effect which is largely over within one hour (Fig. 1). Some of the other effects of the drug may persist longer, but as a general rule it appears that the pharmacologic effects of furosemide are brief.[1]

Pulmonary Effects of Furosemide

Furosemide has clear-cut actions on the pulmonary system in most species. In human beings, laboratory animals and, presumably, in the horse, furosemide acts rapidly to reduce pulmonary edema. However, the mechanism of this action is not clear. Furosemide acts to decrease transvascular hydraulic pressure and increase protein osmotic pressure, which results in a decreased lymph and lymph protein flow in the lungs. 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 induced by furosemide may also be important in its action against pulmonary edema, but the effects of furosemide to reduce pulmonary edema may be seen prior to or in the absence of significant urine formation. Furosemide is approved by the FDA for the treatment of pulmonary edema in horses.

Actions in Racing Horses

Horsemen and equine practitioners hold that pre-treatment with furosemide reduces the incidence of EIPH in horses, and also helps horses in their "wind" or with their breathing.

While what is known about the pharmacology of furosemide is consistent with these effects, there is no direct experimental evidence to support either of these actions in racing horses.

Actions on Performance

To date, three independent studies have shown no evidence that furosemide can improve the performance of racing horses. Because furosemide does not stimulate the performance of horses, it cannot be used to run horses "hot and cold" (see Table I).

	# of Horses	# of Trials	Mean Times	S.E.M.	
Pre-Furosemide	58	160	128 5925	0.2031	F = $<$0.00
With Furosemide	58	232	128 7366	0.1594	(F for significance should be $>$3.0)

At this meet, furosemide was the only permitted medication and its use was checked by urinalysis. "Horses could elect" to go on furosemide at any time throughout the meet, but once on furosemide had to stay on it. Performance times for horses pre- and post-furosemide treatment were obtained from the meet programs and compared. Only times on good or fast tracks were taken. Of the 58 horses selected, 160 pre-furosemide times were available and 232 post-furosemide times. A randomized block design was used where each horse represented a block. After adjusting for blocks (*i.e.* differences between horses) there was no significant difference between treatments (*i.e.* times on and off furosemide).

Table I. Effect of medication with furosemide on the performance of horses racing at Louisville Downs, Summer, 1976.

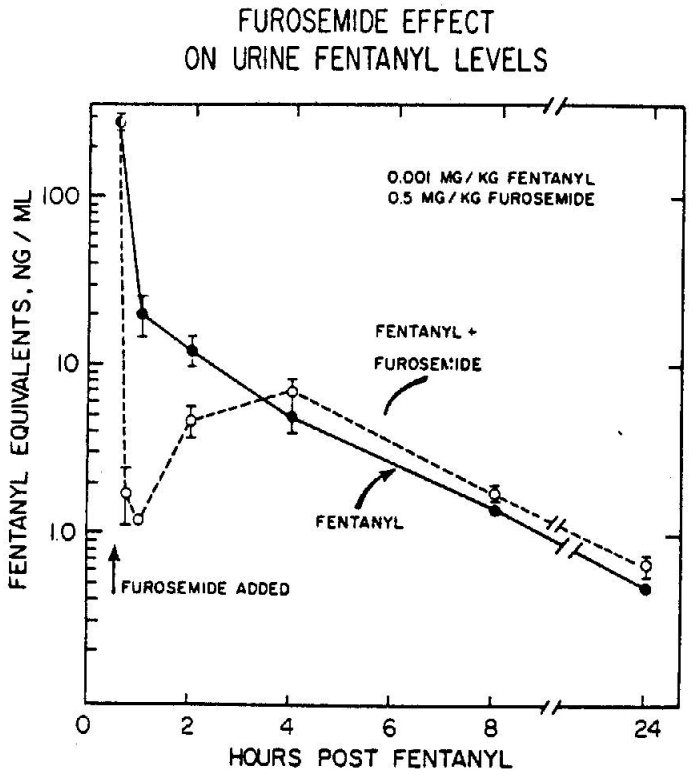

Fig. 2. Urinary levels of fentanyl after 0.5 mg./kg. furosemide.

The solid circles (●-●) show urinary concentrations of fentanyl as fentanyl equivalents after administration of 0.5 mg. of fentanyl to three horses. The open circles (o-o) show urinary levels of fentanyl equivalents when 0.5 mg./kg. of furosemide was administered at 31 minutes after the fentanyl. The data show that this dose of furosemide reduced the urinary concentrations of fentanyl about 15-fold, and that the effect lasted for about 2½ hours. (Reproduced with permission from "Drugs and the Performance Horse" by Thomas Tobin, Charles C. Thomas, Publishers, Springfield, Illinois, 1981.)

Actions on Drug Detection

(a) Furosemide has not significantly reduced the plasma levels of any drug studied to date. Further, since the volume of fluid removed from the horse in the treatment of epistaxis is small, pre-treatment with furosemide is unlikely to significantly affect plasma level monitoring of drugs.

Furosemide does not appear to affect the detection in urine of basic, lipid-soluble drugs such as methylphenidate, amphetamine or procaine.

(c) Furosemide will dilute the urinary levels of water-soluble drugs and drug metabolites. Examples of such drugs are phenylbutazone, pentazocine, apomorphine, acepromazine and fentanyl (Fig. 2 and 3).

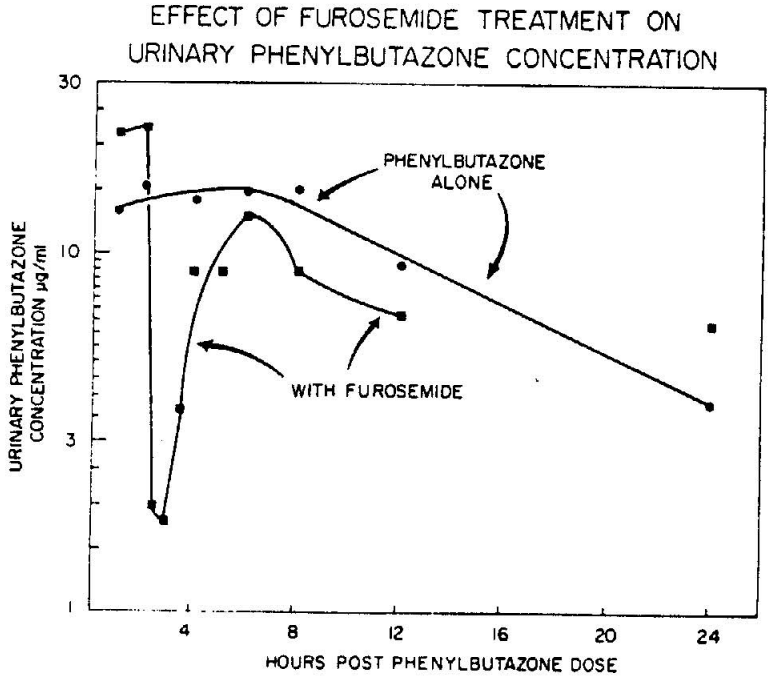

Fig. 3. Diluting effect of an anti-epistaxis dose of furosemide on urinary phenylbutazone.

Four horses were dosed with 2 Gm./1000 lb. of phenylbutazone i.v. 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 "Drugs and the Performance Horse" by Thomas Tobin, Charles C. Thomas, Publishers, Springfield, IL, 1981.)

(d) This dilution problem may be avoided by taking the post-race urine sample after the period of diuresis. This period may be as short as three hours after the 200 mg. dose used in the treatment of epistaxis, or longer if larger doses (1 Gm.) are used.

Efficacy of Furosemide Treatment

Recent studies by Pascoe and his co-workers suggest that furosemide is not likely to be more than about 50% effective in reducing the incidence of EIPH.

Clenbuterol

(1) Clenbuterol is a sympathomimetic β_2 agonist of high potency. Because β_2 adrenergic receptors are found in bronchi, the uterus and

skeletal muscle, its smooth muscle relaxing activities are restricted to these tissues. Clenbuterol is currently marketed for equine and human use in Europe.

(2) Clenbuterol is a very potent drug, 20 μg. i.v. in man being sufficient to prevent exercise-induced bronchoconstriction in human asthmatics. These doses produce few cardiovascular effects.

(3) Its dose in the horse is about 0.8 μg./kg., and its therapeutic effects appear to last for about six hours.

(4) As well as dilating bronchi, clenbuterol is thought to reduce the viscosity of bronchial secretions, thus aiding their clearance.

(5) If EIPH is indeed due to small airway obstruction, it seems reasonable that the incidence of this condition would be reduced by pre-treatment with drugs such as clenbuterol.

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