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THE EFFECT OF DIURETICS ON THE FAECAL EXCRETION OF WATER AND ELECTROLYTES IN HORSES

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1 The effect on plasma, urinary and faecal electrolytes of frusemide and hydrochlorthiazide was measured in ponies, mean weight 180 kg.

2 The rapid loss in urine of large quantities of sodium had only a small effect on plasma sodium concentration.

3 Faecal sodium excretion was increased substantially after the administration of frusemide.

4 Frusemide increased faecal potassium during the 48 h following administration and faecal water in the 24/48 h period. It also produced a hypopotassaemia.

5 Hydrochlorthiazide increased faecal chloride during the 24 h after administration.

6 Frusemide increased the intestinal transit time of both liquid (polyethylene glycol) and particulate (Cr_2O_3) markers.

Introduction

It was found that the concentration of sodium in the plasma of stabled ponies showed wide fluctuations even in individual animals, and partial sodium depletion did not appear to affect the concentration of this ion in plasma (Alexander, 1974). Usually about three weeks were required to produce sodium depletion by salivary drainage as indicated by the typical change in the sodium/potassium ratio in saliva (Alexander, 1966). Although sodium depletion stimulates aldosterone secretion and thus increases retention of this ion, recent work (Carey, Smith & Ortt, 1976) has shown that, in rabbits, sodium excretion may be controlled through the gastrointestinal tract independent of aldosterone. The purpose of the present experiments was to ascertain whether a more rapid removal of sodium from the pony would change the plasma sodium concentration and, in view of the work of Carey *et al.* (1976) to study the effect on faecal excretion of sodium of the rapid removal of this electrolyte. The rapid excretion of sodium was produced by intravenous injection of frusemide or hydrochlorthiazide.

Methods

Four male, shetland-type ponies, weight 180 kg ± 8.4 (mean ± s.d.) were used in these experiments. The ponies were trained to stand in metabolism stalls which allowed the collection of urine and faeces (Warwick, 1966). They were fed hay (2.5 kg/day) without concentrates excepting when markers were given. The markers used were chromium oxide (10 g) and polyethylene glycol (200 g) which were thoroughly mixed in about 500 g of bran and oats and fed to the ponies. Frusemide and hydrochlorthiazide were given by injection into the jugular vein. Blood for analysis was taken from the jugular vein into airtight syringes containing either heparin (for blood gas analysis) or ammonium oxalate (for plasma electrolytes). The sample for sodium and potassium determinations was centrifuged and the plasma separated as soon as possible and always within 30 min of bleeding. The sample for pH and blood gas analysis was introduced into a Corning pH/Blood Gas Analyser 165 immediately after withdrawal from the vein. The pH and P_{CO_2} were determined directly by means of appropriate electrodes, and bicarbonate was calculated automatically from these values. Chloride concentration was measured with an Eel Chloride meter and sodium and potassium by means of a Corning Eel Flame Photometer. Urine was collected over 1 or 2 h periods for the first 6 h and thereafter over 24 h periods for 4 days. Complete faecal collections were made every 24 h for 4 days. The faeces were weighed and thoroughly mixed. A sample of faecal liquor was squeezed from an aliquot for the determination of sodium, potassium and chloride. A

500 g sample of mixed faeces was placed in a vacuum oven and dried to constant weight at below 100°C to ascertain the amount of water excreted in the faeces. The faeces for marker estimations were mixed with twice their weight of water and stirred intermittently for 5 hours. In later experiments mixing time was reduced to 5 min by using a Waring Blender of 5 litre capacity. A sample of the liquor was removed and filtered through No. 42 filter paper. The polyethylene glycol concentration in this filtrate was measured by the method of Hyden (1956) as modified by Smith (1962). Recoveries of polyethylene glycol added to faeces were 96.4 ± 3.2% (mean ± s.e.) for four experiments. The concentration of chromic oxide in dry faeces was determined by the method of Christian & Coup (1954). Recoveries of chromic oxide added to faeces gave values of 101 ± 3.4% (mean ± s.e.) for six experiments. The determinations of sodium and potassium concentration in various fluids were controlled by interposing standard solutions between every three or four samples and the blood gas analyser was standardized before each analysis. The results were analysed using Student's t test and the values for plasma sodium concentrations by paired comparisons to obtain additional sensitivity (Sokal & Rohlf, 1973).

The markers were fed together mixed with the bran and oats. Faeces were collected each 24 h period after feeding for three successive days and the amount of each marker excreted per 24 h was determined. Each of the four ponies was fed the markers as a single dose on at least one occasion without and similarly with the administration of frusemide (3.3 mg/kg). The drug was injected as soon as the meal containing the markers had been consumed.

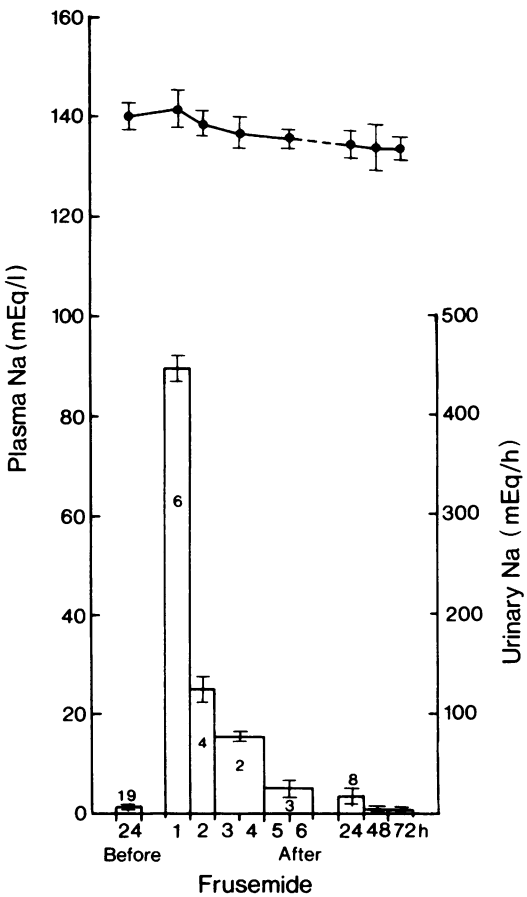

Figure 1 Effect of frusemide (3.3 mg/kg) on the sodium concentration in plasma and sodium excretion in urine of ponies. The plasma values at 6, 24 and 72 h after treatment differ from the control ($P < 0.1$). Plasma values (●) are shown as mean of eight observations. Vertical lines show s.e. means. Urinary values are shown as mean; number of observations indicated on columns. Vertical lines show s.e. means.

Results

The effect of frusemide on the concentration of sodium in plasma and the rate of sodium excretion in urine is shown in Figure 1. Although there appears to be a slight fall in the mean plasma value 6 h after

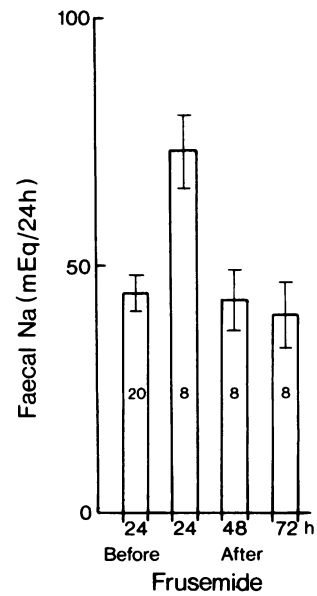

Figure 2 Faecal sodium excretion per 24 h following frusemide (3.3 mg/kg). Mean values are shown; vertical lines indicate s.e. means. Excretion increased during the 24 h following injection ($P < 0.01$). Figures in columns represent number of observations.

giving the drug the mean decrease at the 6th, 24th and 72nd hour was significant only at the $P < 0.1$ level. Frusemide treatment (3.3 mg/kg) produced a marked hypopotassaemia ($P < 0.02$) within 4–6 h of the drug being injected; the other constituents measured were unaffected, namely chloride, pH, PCO_2 and bicarbonate.

Hydrochlorthiazide (3.3 mg/kg) did not produce a significant change in the plasma sodium, potassium, chloride, bicarbonate, PCO_2 or pH. The diuretic action was less marked than that of frusemide and slower in onset. The sodium excreted in the urine during the 24 h following hydrochlorthiazide was only 1/20th and the urine volume 2/5ths of that produced in the same period by a similar dose of frusemide.

Frusemide produced a marked increase in the faecal excretion of sodium, potassium and water. This is shown in Figures 2, 3 and 4. Although hydrochlorthiazide had a similar effect on faecal sodium when given in the same dose (mg/kg) as frusemide it was significant only at the $P < 0.1$ level. However, this dose of hydrochlorthiazide increased the faecal chloride excretion ($P < 0.01$) whereas the faecal chloride excretion after a similar dose of frusemide was not significantly changed (Figure 5).

The transit time through the alimentary tract of both a particulate (chromic oxide) and a liquid (polyethylene glycol) marker was increased following the administration of frusemide (Figure 6). Frusemide (3.3 mg/kg) increased faecal weight ($P < 0.05$) and water ($P < 0.01$) in the second 24 h period after administration whereas hydrochlorthiazide (3.3 mg/kg) increased faecal weight ($P < 0.01$) only in the first 24 h following the injection.

Discussion

Although the rapid removal of a substantial amount of sodium in the urine after frusemide administration appeared to reduce the plasma sodium concentration, the reduction was significant only at the $P < 0.1$ level. This was due probably to the wide fluctuations of the

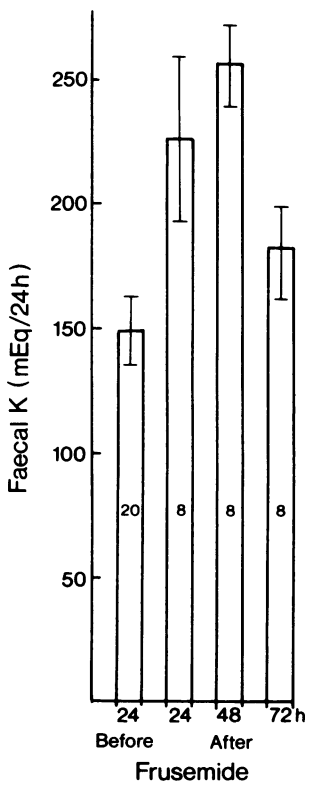

Figure 3 Faecal potassium excretion increased during the 24 h ($P < 0.05$) and 24/48 h ($P < 0.01$) following frusemide (3.3 mg/kg) injections. Mean values are shown; vertical lines indicate s.e. means. Numbers in columns represent number of observations.

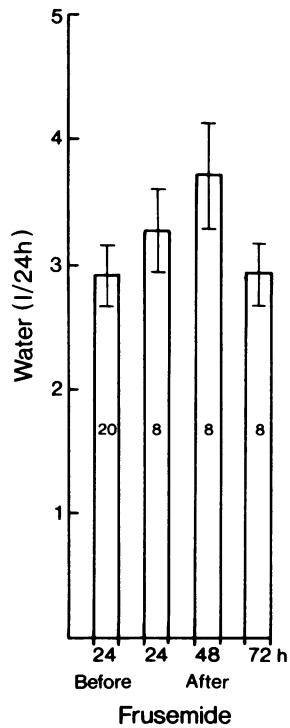

Figure 4 Increased faecal water excretion ($P < 0.01$) produced by frusemide in the 24/48 h period after injection (3.3 mg/kg). Mean values are shown; vertical lines indicate s.e. means. Figures in columns indicate number of observations.

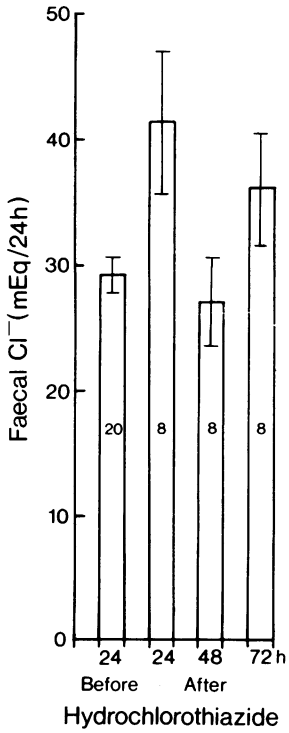

Figure 5 Increase in faecal chloride excretion ($P < 0.01$) in the 24 h following hydrochlorthiazide administration (3.3 mg/kg). Mean values are shown; vertical lines indicate s.e. means. Numbers in columns indicate number of observations.

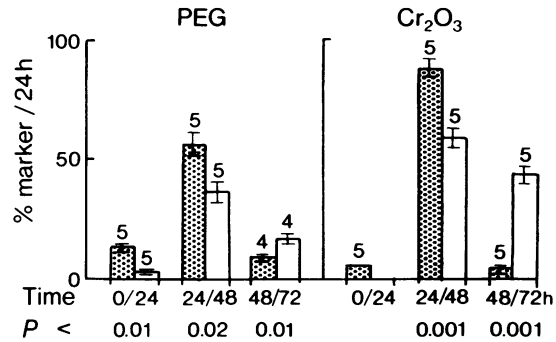

Figure 6 Excretion of liquid (polyethylene glycol, PEG) and solid (Cr_2O_3) markers in faeces. Mean values are shown; vertical lines indicate s.e. means. Numbers on the columns show the number of observations. Stippled columns—no treatment; open columns—frusemide 3.3 mg/kg.

pre-treatment plasma sodium concentration noted earlier (Alexander, 1974) and which has so far defied explanation.

The possibility was considered of the sodium in the liquid contents of the capacious gut providing a reservoir from which the pony could rapidly replenish a deficit in the extracellular sodium. However, the urinary excretion of about 2000 mEq of sodium within 24 h of frusemide injection was accompanied by a significant ($P < 0.01$) increase in faecal sodium. Had the sodium in the intestinal liquor been used to compensate for the sodium lost in the urine the faecal sodium would surely have fallen.

Sodium depletion in ponies reduced faecal sodium excretion to about 1/12 of that in replete animals (Alexander, 1966). It was assumed that, as in other species, this increased sodium retention was mediated through the increased secretion of aldosterone. Consequently the urinary sodium loss produced by the diuretics by stimulating aldosterone secretion would, to some extent, have decreased faecal sodium excretion. Despite this the diuretics produced an overall increase in faecal sodium excretion.

Hydrochlorthiazide differed from frusemide in the greater faecal chloride excretion produced so that when the same dose of each drug was given, on a body weight basis, frusemide did not produce a significant change in faecal chloride whereas hydrochlorthiazide caused an increased ($P < 0.01$) faecal excretion of this electrolyte.

In view of the relationship between rate of flow and concentration of salivary sodium (Burgen & Emmelin, 1961) it seemed important to determine whether the increased faecal sodium excretion produced by diuretics reflected a decrease in transit time and a consequent reduction in time for absorption. Since frusemide was the more potent drug, in respect of faecal sodium excretion, studies were limited to this agent.

Argenzio, Lowe, Pickard & Stevens (1974) found differences in transit time through the ponies' gut of various particulate and liquid (polyethylene glycol) non-absorbable markers; therefore in the present experiments transit time was determined using both a liquid (polyethylene glycol) and particulate (Cr_2O_3) marker. Frusemide slowed the transit of both markers hence the increased sodium excretion could not be due to the diuretic hastening the transit of intestinal contents through the gut.

It has been shown that the diuretics ethacrynic acid and chlorothiazide inhibited sodium and water transport in isolated sacs of hamster ileum (Binder, Katz, Spencer & Spiro, 1966). More recently Humphreys (1976) found the absorption of sodium chloride from the perfused rat ileum to be inhibited by frusemide. The increased faecal excretion of sodium produced by frusemide and hydrochlorthiazide as described in the present experiments could be due to these drugs impeding the absorption of sodium from the horses' gut. Since the main site of sodium

absorption from the gut appears to be the large intestine (Alexander, 1962) this could also be the site of action of the two diuretics. The results of these experiments could be interpreted as supporting evidence of functional similarities between the kidneys and gut which has been accumulating for some time (Binder *et al.*, 1966).

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