Effects of frusemide on the urinary excretion of dopamine and 5-hydroxytryptamine in normal man

Clinical Pharmacology Unit, Department of Medicine, The Royal Infirmary, Edinburgh, UK

The effects of frusemide on the urinary excretion of dopamine and 5-hydroxytryptamine (5-HT) were investigated in eight healthy male subjects in a randomized, placebo-controlled, cross-over study. Frusemide produced the expected rise in urinary dopamine excretion but it did not affect 5-HT excretion when compared with placebo. The lack of an effect on 5-HT excretion in man contrasts with studies in the rat which have reported a marked increase in 5-HT excretion after administration of this loop diuretic.

Keywords: frusemide, dopamine, 5-hydroxytryptamine, kidney.

Introduction

Frusemide increases the urinary excretion of dopamine in man [1–5] and in the rat [6–8]. The renal responses following frusemide of natriuresis, kaliuresis and diuresis in the rat were reduced by the non-selective dopamine antagonist haloperidol and by the dopamine-1 receptor antagonist SCH 23390 indicating that dopamine may contribute to the sodium, potassium and water excretion produced by the loop diuretic [7]. Benserazide, an L-amino acid decarboxylase (LAAD) inhibitor, produced a marked inhibition of the rise in urine dopamine after frusemide together with at least a 60% reduction in the frusemide-induced diuresis, natriuresis and kaliuresis, again suggesting that these effects of frusemide may be partially mediated by dopamine [8]. However, in contradiction to these observations in the rat, Jeffrey et al. [3] had demonstrated in man that carbidopa, another LAAD inhibitor, lowered urinary dopamine to undetectable levels but had no effect on the natriuretic response to frusemide.

The above studies did not consider the possible effect of frusemide or LAAD inhibition on renal 5-hydroxytryptamine (5-HT) production which could exert a confounding influence on sodium excretion. 5-HT, like dopamine, may be synthesised within the kidney, and studies in the rat [9, 10] and man [11, 12] suggest that intrarenally generated 5-HT has an opposite effect to dopamine on urinary sodium excretion. In man, carbidopa reduced not only the urinary excretion of dopamine [3, 12], but also that of 5-HT, to undetectable levels [12]. In addition, frusemide has been shown to increase the urinary excretion of 5-HT and to simultaneously decrease the renal tissue content of 5-HT in the rat [13, 14]. The concentration of 5-HT in the urine at the time of maximal diuresis in rats treated with frusemide (1.32 mg kg⁻¹ intramuscularly) was almost 600-fold higher than in untreated animals. The elevation in urine 5-HT continued after the period of maximum diuresis and the cumulative 5-HT excretion over an 8 h period was 1000 times that in the control rats. There has been no report on the effect of frusemide on urinary 5-HT excretion in man.

The present study examined the effects of acute intravenous administration of frusemide on the urinary excretion of both dopamine and 5-HT in healthy human subjects.

Methods

Eight healthy male subjects, aged 20–41 years (mean 31.6 years), attended on two occasions, at least 1 week apart, in this randomized, placebo-controlled, cross-over study. They had been given general dietary advice to avoid excessive intake of salt over the 36 h prior to each study day. They refrained from alcohol for 24 h, abstained from caffeine-containing beverages from 18.00 h, and fasted from 22.00 h the evening before each of the study days. They reported to the clinical investigation unit at about 08.00 h, having drunk 200 ml of tap water 1 h previously. They emptied their bladder on arrival and drank a further 200 ml of water, followed by 200 ml of water every 0.5 h until the end of the study. After 1 h (time = 0 h), they emptied their bladder and received either 40 mg of frusemide (Lasix®, 10 mg ml⁻¹), made up to a total volume of 30 ml with 0.9% NaCl,
or placebo (30 ml of saline). These solutions were infused intravenously over 10 min. Urine was collected at hourly intervals over the next 6 h, and any urine passed before the end of an hour period was summated. The subjects remained semi-recumbent throughout the experiment except for rising to pass urine. The volume of each urine collection was measured and aliquots stored at −40°C for analysis of sodium, potassium, dopamine and 5-HT. Urine samples for dopamine and 5-HT were acidified (pH < 3.0) with 5 M HCl to prevent their oxidation. Sodium and potassium were measured by an ion-selective electrode analyser, and dopamine and 5-HT were determined by h.p.l.c. as described previously [11]. All results are expressed as mean ± s.d. The urinary dopamine and 5-HT data on the 2 experimental days were compared by repeated measures analysis of variance. The urinary excretion rates during the first hour and the cumulative data on the 2 days were compared by Student’s t-test for paired observations, and the 95% confidence intervals of the differences between the means (95% CIdiff) are quoted where appropriate. Effects were considered to be statistically significant when the P values were less than 0.05.

Results

Furosemide produced a natriuresis, kaliuresis and diuresis (Figure 1). The sodium excretion during the first hour after frusemide administration was 13 times that after placebo infusion. The potassium excretion during the same period was 2.7 times and the urine output 8.4 times the corresponding values after placebo infusion. The urinary excretion of sodium, potassium and water remained elevated during the second hour but after this time tended to be lower than following the placebo infusion.

Compared with placebo, furosemide produced a significant increase in urinary excretion of dopamine (P < 0.001) (Figure 2). The baseline dopamine excretion on the placebo day (1.3 ± 0.3 nmol min⁻¹) was not significantly different from that on the furosemide day (1.4 ± 0.3 nmol min⁻¹). Urinary dopamine excretion during the first hour after furosemide administration (1.8 ± 0.3 nmol min⁻¹) was, however, significantly higher than that observed after placebo (1.1 ± 0.4 nmol min⁻¹; 95% CIdiff 0.5 to 0.9 nmol min⁻¹; P < 0.001).

The 5-HT excretion values before infusion of placebo and furosemide were not significantly different at 0.4 ± 0.1 nmol min⁻¹ and 0.5 ± 0.1 nmol min⁻¹ (Figure 2). The urinary 5-HT excretion rate decreased during the first hour after placebo and then remained relatively constant. Similarly, there was an initial fall in 5-HT excretion rate after frusemide. There were no significant differences between the changes in 5-HT excretion from baseline on the 2 study days at corresponding time periods. The 6-h cumulative 5-HT excretion values after administration of placebo and furosemide were 112.5 ± 12.8 nmol and 126.2 ± 13.0 nmol respectively (95% CIdiff = −1.9 to 29.2 nmol).

Discussion

In the present study, furosemide produced the expected diuresis, natriuresis and kaliuresis [15]. It increased urinary dopamine excretion transiently in agreement with similar observations by other investigators [1–5]. Increased urinary excretion of dopamine has also been observed in man after administration of torasemide, another loop diuretic [4], and following hydrochlorothiazide and triamterene in the rat [6]. In contrast, spironolactone in man had no effect on dopamine excretion [2]. There was an initial lowering of urinary 5-HT excretion after both furosemide and placebo in the present study. The reason for this is unclear but it may be that the subjects had not yet achieved a steady state, and that a longer run-in phase before drug administration would have been more appropriate. There was no significant difference in the urinary 5-HT excretion between the two experimental days. The absence of a rise in 5-HT excretion in man following furosemide infusion in the present study contradicts studies in rats which demonstrated marked increases in the urinary excretion of the amine after administration of furosemide, hydrochlorothiazide and mersalyl [13, 14]. The disparity
in results may reflect either a species difference in 5-HT response to diuretics or the effects of a relatively higher dose of frusemide (in terms of body weight) in the rat. Both studies which reported an effect of diuretics on 5-HT excretion in the rat came from the same laboratory [13, 14], and it would be of interest to see if similar results are found by other investigators.

In conclusion, the present study demonstrated in man that frusemide increased urinary dopamine excretion, but only for a short period, and had no effect on 5-HT excretion. It is most unlikely, therefore, in man that either amine contributes materially to the increase in sodium output produced by frusemide, or alternatively acts in an opposite sense to limit the natriuresis.

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References


10. Itskovitz HD, Chen Y-H, Stier CT Jr. Reciprocal renal effects of dopamine and 5-hydroxytryptamine formed before and after administration of placebo (...) and frusemide (+). Placebo (P) or frusemide (F) was administered at time 0 h. Values shown are means ± s.d. (n = 8).