Effect of food on the absorption of frusemide and bumetanide in man

J. L. MCCRINDLE, T. C. LI KAM WA, W. BARRON & L. F. PRESCOTT
Clinical Pharmacology Unit, The Royal Infirmary, Edinburgh, UK

1 The influence of food on the absorption of frusemide and bumetanide was compared in two separate randomized crossover studies.

2 On three separate occasions frusemide 40 mg was administered to eight healthy male volunteers intravenously, orally in the fasting state and orally after a standard breakfast. Blood and urine were collected at intervals over 8 h and urine alone for a further 16 h. The study was then repeated in nine healthy volunteers using intravenous and oral bumetanide 2 mg.

3 Breakfast significantly reduced the peak plasma concentration of frusemide from $2.35\pm0.49$ to $0.51\pm0.19$ mg l$^{-1}$ (95% confidence intervals (95% CI)=1.39 to 2.28 mg l$^{-1}$) and delayed the time to peak concentration from $0.69\pm0.21$ to $1.91\pm0.93$ h (95% CI=0.41 to 2.03 h). The oral bioavailability of frusemide was significantly reduced by approximately 30% (75.6±10.6 to 43.2±16.8%; 95% CI=13.5 to 51.4%).

4 With bumetanide, the meal also significantly reduced the peak concentration from $0.097\pm0.015$ to $0.036\pm0.012$ mg l$^{-1}$ (95% CI=0.048 to 0.073 mg l$^{-1}$) and delayed the time to peak from $0.53\pm0.08$ to $1.36\pm0.72$ h (95% CI=0.23 to 1.44 h). However, food had no statistically significant effect on the bioavailability and urinary recovery of bumetanide.

5 In this study, the absorption of bumetanide was affected less than frusemide by food.

Keywords frusemide bumetanide food absorption

Introduction

Frusemide and bumetanide are loop diuretics commonly used in the treatment of oedematous states associated with cardiac, renal and hepatic disease [1, 2]. Frusemide is absorbed incompletely from the gastrointestinal tract and there is considerable intra- and inter-individual variability in its bioavailability [3, 4]. In healthy volunteers, food had variable effects on its absorption. Kelly et al. [5] and Hammarlund et al. [6] found that food had no statistically significant influence on the extent of absorption of frusemide although Hammarlund et al. [5] reported that it delayed absorption. In contrast, Beermann & Midskov [7] observed a 30% reduction in the bioavailability of frusemide given as a tablet with food.

Bumetanide is 40–60 times more potent as a diuretic than frusemide on a weight basis and it has a greater oral bioavailability (approximately 80% vs 40%) [8–10]. However it is not known whether the absorption of bumetanide is affected by food. It was reported in an abstract that food delayed the response to oral bumetanide in healthy volunteers but no pharmacokinetic data were presented [11]. The present studies were therefore conducted to obtain additional information on the effects of food on frusemide and bumetanide absorption in man.

Methods

Subjects

Eight healthy male volunteers, aged 21 to 38 years (28±5 (s.d.) years) and weighing 51 to 82 kg (70±10 kg), participated in the first, randomized, crossover study with frusemide. In the second study with bumetanide, nine healthy male volunteers (aged 27±5 years and weighing 67±7 kg) took part. Three of these subjects...
had previously participated in the frusemide study. All the volunteers were healthy according to medical history, clinical examination, haematological and biochemical tests. They gave written informed consent and the study was approved by the Lothian Healthy Volunteer Research Ethics Subcommittee. The volunteers avoided taking any other medication for 1 week prior to and throughout the studies. They abstained from alcohol for 24 h and refrained from food and caffeine containing drinks from 22.00 h the evening before each study day.

Protocol

In the first study with frusemide, each volunteer attended at 08.00 h following an overnight fast on three separate occasions, at least 1 week apart. Intravenous cannulae were inserted into each forearm, one for drug administration and fluid replacement, and the other for collection of blood samples. After emptying their bladders, the volunteers received either:

1 Intravenous frusemide 40 mg infused at constant rate over 5 min
2 Oral frusemide solution 40 mg
3 Oral frusemide solution 40 mg immediately after breakfast.

The frusemide was given as 10 mg ml$^{-1}$ Lasix® for injection. Oral frusemide was taken in 100 ml of orange squash (Kia-Ora), washed down with a further 100 ml of water. When taken with food, the drug was ingested immediately after a standard breakfast consisting of orange juice (200 ml), scrambled eggs, cornflakes with milk and two slices of toast with butter and jam. The volunteers remained supine throughout each study (except when passing urine) and they had nothing to eat or drink until 5 h after dosing, when a light lunch was provided. To replace fluid losses, 500 ml of 0.9% sodium chloride solution was given intravenously over the first hour and subsequently, hourly urine volumes were replaced by the same volume of intravenous 5% dextrose.

Venous blood was collected into lithium heparin tubes before, and at 3, 5, 10, 15, 30, 45, 60, 90, 120 min, and hourly for the next 6 h after the intravenous dose. Following oral doses samples were taken at 0, 10, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180 min, and hourly for the next 5 h. The plasma was separated and stored at $-20^\circ$ C. Urine was collected at 1, 2, 3, 4, 5, 6 and 8 h after dosing and from 8–24 h. Urine volumes were recorded and aliquots stored at $-20^\circ$ C.

In the second study, bumetanide 2 mg solution was administrered as 0.5 mg ml$^{-1}$ Bumires® injection intravenously and orally with and without breakfast exactly as described for frusemide. A similar schedule was used for blood and urine sampling.

Analytical methods

Frusemide in plasma was measured by h.p.l.c. according to Russel et al. [12]. The h.p.l.c. system consisted of a Waters 510 HPLC pump and a Waters 710B WISP (Division of Millipore, Milford, MA, U.S.A.). Separation was carried out using a Radial Compression reverse phase column (Waters Novapak C$_18$ ODS, 4 μm). Frusemide and the internal standard, desmethylnaproxen, were measured using a luminescence spectrophotometer (Perkin Elmer Ltd, Beaconsfield, Bucks, U.K.) with excitation and emission wavelengths of 275 and 400 nm, respectively. The sensitivity of the assay was 50 μg l$^{-1}$. Bumetanide in plasma was analysed using h.p.l.c. with fluorescence detection as described by Wells et al. [13]. A Waters 5 μm ‘Resolve’ C$_18$ column was used. Pirtenanide was used as the internal standard and the excitation and emission wavelengths were set at 228 and 418 nm, respectively. The limit of detection of the assay was 2.5 μg l$^{-1}$. For both frusemide and bumetanide, urine samples containing the internal standards were injected directly onto the h.p.l.c. column. Frusemide and bumetanide concentrations were determined by comparing peak area ratios of drug to internal standard with a standard calibration curve.

Pharmacokinetic analysis

Noncompartmental analysis was used following oral administration with food because the data could not be fitted to a conventional model. The area under the plasma concentration versus time curve up to 8 h (AUC(0,8 h) was calculated by the trapezoidal rule and the area beyond the last measured concentration to infinity was estimated as the concentration divided by the intravenous elimination rate constant. It was assumed that the disposition of the drugs would be similar after intravenous and oral administration. The bioavailabilities of oral frusemide and bumetanide were calculated as the ratios of the respective AUCs after oral and intravenous administration.

Statistical analysis

All values are expressed as means±s.d. Statistical differences between doses were determined using analysis of variance and $P$ values of <0.05 were considered significant.

Results

Frusemide

Mean plasma concentrations for oral frusemide given with and without food are shown in Figure 1. The presence of food dramatically changed the shape of the curve. The mean peak plasma concentration ($C_{\text{max}}$) was reduced from 2.35±0.49 to 0.51±0.19 mg l$^{-1}$ (95% CI for mean difference=1.39 to 2.28 mg l$^{-1}$; $P<0.001$) and the time to peak concentration ($t_{\text{max}}$) was significantly delayed (0.69±0.21 to 1.91±0.93 h; 95% CI=0.41 to 2.03 h; $P<0.01$). The mean AUC was 3.54±0.82 mg h l$^{-1}$ when frusemide was administered
administration of doses of 40 mg and 2 mg respectively.

Values are mean ± s.d.

**Compared with fasting:** *P<0.05, **P<0.01, ***P<0.001.

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British Journal of Clinical Pharmacology 42, 743–746
given with and without food. However, the study by Kelly et al. [5] was terminated 4 h after frusemide administration and Hammarlund et al. [6] did find a significant fall in the urinary recovery of frusemide when it was taken with food. Beermann & Midskov [7] found that a breakfast similar to that used in the present study decreased the bioavailability of a frusemide tablet by 30%. Since we gave frusemide in solution the reduction in the bioavailability is unlikely to be related to problems with the dissolution of frusemide in the presence of food. Many other investigators have reported a reduced rate of absorption of a variety of drugs when taken with food, and this has usually been attributed to delayed gastric emptying [14–17]. However, in such circumstances the total amount absorbed was not usually reduced, and the explanation for the reduced bioavailability of frusemide taken with food is unclear.

Comparison of the results of our two studies indicates that food had a lesser effect on the absorption of bumetanide than frusemide. Although \( C_{\text{max}} \) was reduced and \( t_{\text{max}} \) increased by food, the bioavailability and 24-h urinary recovery of bumetanide were not significantly reduced.

The natriuretic and diuretic response to frusemide and bumetanide is determined by the amount of drug reaching the renal tubule and on the time course of drug delivery to its active site, the ascending loop of Henle [2, 8, 18, 19]. The present studies were not designed to study these pharmacodynamic effects which would ideally require experiments under balanced conditions where compliance with sodium and fluid intake could be assured. However it might be predicted from the kinetic data that food would have a lesser effect on the action of bumetanide than frusemide.

The clinical relevance of our findings needs further investigation since these diuretics are often taken at from enteric coated dosage forms. Many investigators have reported a reduced rate of drug delivery to its active site, the ascending loop of Henle [2, 8, 18, 19]. The present studies were not designed to study these pharmacodynamic effects which would ideally require experiments under balanced conditions where compliance with sodium and fluid intake could be assured. However it might be predicted from the kinetic data that food would have a lesser effect on the action of bumetanide than frusemide.

We thank Leo Laboratories Limited for the gift of bumetanide for use as a reference analytical standard.

References


(Received 30 May 1996, accepted 23 July 1996)