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Reduced Bioavailability and Effect of Furosemide Given with Food

B. Beermann and C. Midskov

Department of Medicine, St Eriks Hospital, Stockholm, Sweden and Biological Department, Dumex Ltd, Copenhagen, Denmark

Summary. 10 healthy volunteers were given 40 mg furosemide p.o. with and without breakfast. The meal reduced the peak level of furosemide and decreased its bioavailability by approximately 30%. A heavy meal given to 5 of the subjects had no further effect. The reduced bioavailability caused a reduction in the diuretic effect.

Key words: furosemide; meal effect, bioavailability

The short and intense diuresis after conventional oral furosemide tablets is a problem for many patients. It can be avoided by administration of a sustained release preparation of furosemide. It has been shown that despite the lower bioavailability of furosemide from such preparations than from conventional tablets, the diuretic and saluretic effects did not differ (Beermann 1982). The probable explanation of that was avoidance of a rebound phenomenon after the high plasma and urinary levels of furosemide produced by giving conventional tablets.

Kelly et al. (1974) and Hammarlund et al. (1982) found no change in the bioavailability of furosemide when given with food, although the initial high plasma peak of the diuretic was eliminated, and instead a smooth plasma curve was seen. Thus, if those results were confirmed, giving furosemide with food might be a simpler way than using a sustained release preparation to avoid the brief, intense diuresis that follows oral furosemide.

The aim of the present experiment was to determine whether the bioavailability and effect of furosemide was changed when given with food.

Material and Methods

The study was approved by the local Ethics Committee. Ten healthy women [5] and men participated in the study. They were between 20 and 40 years old, and were healthy according to history, clinical examination and clinical chemistry tests.

Experimental Procedure

Each subject participated in two experiments at least one week apart. They were given 40 mg furosemide at 8.00 a.m., after fasting overnight, with or without a standardized breakfast (100 ml milk, ½ Suiss roll with cheese and butter and 1 egg) in a randomized order. A standardized lunch (Findus Dinner, meatballs) was served at 12.00 and dinner (Findus Dinner, chicken) at 6.00 p.m. Tap water (150 ml) was given each hour during the first 10 hours except when breakfast was given. Over the remaining 24 h of the day 1000 ml water was given. Smoking was not allowed during the experiments. In addition, five of the subjects participated in a third experiment in which the breakfast was replaced by a heavy meal (1 avocado with sour cream, fish with wine sauce and mashed potatoes, and fruit salad with whipped cream). Venous blood samples were taken via an indwelling cannula at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and

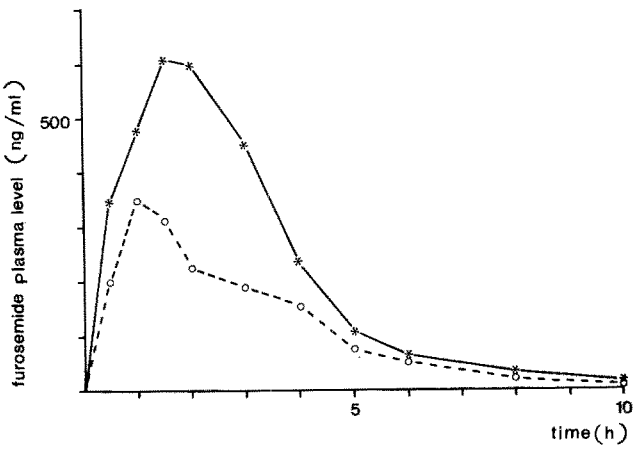

Fig. 1. Plasma levels of furosemide after 40 mg orally with (- - -) and without (-) breakfast

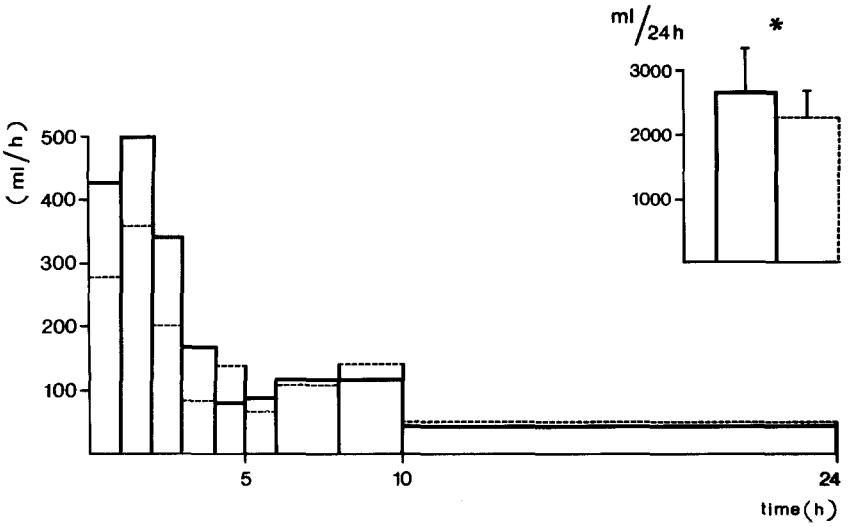

Fig. 2. Diuresis after 40 mg furosemide orally with (- - -) and without (-) breakfast, (*) $p < 0.05$

10 h. Urine was collected over 0-1, 1-2, 2-3, 3-4, 5-6, 6-8, 8-10, 10-24 and 24-48 h. All specimens were frozen at −20 °C until analysed.

Methods

Levels of furosemide in plasma and urine were determined according to Lindström and Molander (1974) with a minor modification. Areas under plasma concentration time-curves (AUC) were calculated according to the trapezoidal method and extrapolated to infinity.

Relative bioavailability (F_{rel}) of furosemide given pre- and postprandially was calculated as

$$F_{rel\ plasma} = \frac{AUC_{0-\infty\ postprandial}}{AUC_{0-\infty\ preprandial}}$$

and

$$F_{rel\ urine} = \frac{\text{Urinary recovery of postprandial furosemide}}{\text{Urinary recovery of preprandial furosemide}}$$

Statistical comparisons were made with Student's *t*-test for paired data.

Results

Maximal concentrations (C_{max}) of furosemide were reached on average 1.4 h (T_{max}) after pre- and postprandial intake of the drug (NS). The peak levels averaged 933 ± 272 and 423 ± 153 ng/ml (mean ± SD), respectively ($p < 0.001$; Fig. 1). The $AUC_{0-\infty\ h}$ was greater after preprandial than after postprandial (breakfast) administration: mean 2174 ± 668 and 1219 ± 403 ng/ml · h, respectively ($p < 0.01$).

The urinary recovery of unchanged furosemide during 48 h after preprandial administration averaged 11.4 ± 2.5 mg and after postprandial administration 8.4 ± 1.4 mg ($p < 0.01$).

$F_{rel\ plasma}$ and $F_{rel\ urine}$ averaged 0.63 and 0.78 respectively ($p < 0.01$).

Maximal plasma levels (356 ± 62 ng/ml), AUC (1169 ± 313 ng/ml · h) and urinary excretion of furosemide (8.8 ± 1.8 mg) after administration of the drug with a heavy meal were almost identical to those after furosemide given with breakfast, although T_{max} was somewhat later (2.2 h).

The time pattern of diuresis (Fig. 2), i.e. an intense diuresis lasting 3 h, was similar after pre- and postprandial administration of furosemide.

The cumulative diuresis over 10 h averaged 2072 ± 347 ml and 1640 ± 347 ml ($p < 0.05$), respectively, when the diuretic was given without and with food.

The corresponding mean diuresis during 24 h was 2668 ± 691 ml and 2270 ± 397 ml ($p < 0.05$).

Discussion

In the present study food reduced the C_{max} of furosemide but had no influence on T_{max}. In keeping with this, administration of frusemide with food reduced the initial diuresis, but, as expected, did not induce a prolonged diuresis.

The intake of breakfast reduced the bioavailability of furosemide by approximately 30%, as judged by urine and plasma data. An almost identical reduction was seen when the drug was given with a heavy meal, which tended to prolong T_{max}. This indicates that the reduced bioavailability was not caused by prolongation of the gastric emptying time.

The present results contrast with those of Kelly et al. (1974). However, they used a furosemide assay

only sensitive to an 0.5 μg/ml change in serum and of even lower precision for urinary determinations. The low sensitivity can completely explain the difference between the two studies.

The statistically significant reduction in the bioavailability of furosemide when given with food in this study strengthens the findings of Hammarlund et al. (1984). They found 16% lower postprandial AUC, although the difference did not achieve significance. On the other hand, the 37% fall in the urinary recovery was significant. Taking that information together with the present finding of a postprandial reduction in AUC, urinary furosemide recovery and diuresis, it seems likely that the lack of a significant diffence in the pre- and postprandial AUCs in the study of Hammarlund et al. (1984) is a Type 2 error.

The difference in mean diuresis over the 24 h after pre- and postprandial furosemide, 2668 and 2270 ml, respectively, may appear clinically unimportant although statistically significant. However, the mean diuresis in 10 healthy subjects given placebo under identical circumstances averaged 2080 ml (unpublished results). Thus, the increase in diuresis after preprandial furosemide was about 600 ml and that after postprandial furosemide was only 200 ml, which is a fall of approximately two thirds.

In conclusion, furosemide given with food did not behave as a sustained release preparation, and instead a decreased diuretic effect was seen. Thus, furosemide should not be given with food.

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Dr. B. Beermann
Department of Medicine
St. Eriks Hospital
S-112 82 Stockholm, Sweden