Comparison of flupirtine and indomethacin on frusemide-induced diuresis

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Summary: A single oral dose of flupirtine maleate, a novel analgesic agent, did not antagonize significantly the diuretic action of frusemide when compared with indomethacin and placebo in normal human volunteers.

Introduction

The diuretic and natriuretic actions of frusemide are antagonized by concurrent treatment with aspirin^{1,2} and indomethacin.³ Flupirtine is a new non-narcotic analgesic which is thought to act centrally rather than peripherally,⁴ and because it may be given to patients requiring treatment with frusemide it is important to know if it influences frusemide-induced diuresis.

Methods

The study was double-blind, randomized and placebo controlled, using a three-way cross-over comparison of three treatments in 12 healthy volunteers (5 male), aged 19–38 years, weight 41–82 kg. Written consent was given and the protocol was approved by the local ethics committee.

Volunteers were instructed that no alcoholic drinks should be taken for 24 hours before, and during each study day. No beverages containing caffeine were taken from the evening before until the end of each study day, and smoking was prohibited on the study days. Medication containing aspirin was avoided for one week before each study day.

The following oral treatments were given at 08.00 h after a light breakfast on three separate occasions at least one week apart; flupirtine maleate 200 mg, indomethacin 50 mg, and placebo. A double-dummy technique was used to conceal the identity of the treatments. One hour after each treatment, frusemide 20 mg orally was given. All treatments were taken with 100 ml water. Following administration of frusemide,

100 ml water was given hourly for 6 hours.

Volunteers emptied their bladders before receiving the test treatments and hourly total urine collections were made up to 6 h after the dose of frusemide. Urine volumes were recorded and 10 ml aliquots stored at –20°C until analysis.

Urinary sodium and potassium concentrations were analysed by automated flame photometry (IL 943, Instrument Laboratory (UK) Ltd). The instrument was calibrated using a standard containing 100 mmol/l of both sodium and potassium. The calibration was checked and the instrument recalibrated automatically every 16 samples. Coefficients of variation were 1.2% and 0.9% for sodium and potassium respectively.

An independent running quality sample was arranged every 7 test samples. Coefficients of variation were 6.2% and 5.7% for the sodium and potassium running quality controls respectively.

Results

Statistical comparisons were made between all treatments using two-way analysis of variance (ANOVA). If this proved significant ($P < 0.05$), then pairwise comparisons were made using Duncan's multiple comparison test.⁵ Owing to missing samples there were no sodium or potassium results for four time points. The mean values for the appropriate treatments and times were substituted for these data before statistical analysis. The results of the statistical analysis are shown in Table I.

Mean values for urinary volume, sodium and potassium excretion associated with the three treatments are shown in Figure 1.

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Figure 1 Urinary volume (ml), sodium and potassium excretion (mmol) following administration of indomethacin (—○—), flupirtine (—●—) and placebo (—▲—) followed by frusemide.

Urine volume and sodium excretion There was a significant treatment effect ($P < 0.01$), indomethacin producing significant reductions ($P < 0.05$) in volume and sodium excretion compared with both placebo and flupirtine. There was no significant difference between placebo and flupirtine.

Urinary potassium excretion There was a significant treatment effect ($P < 0.05$), indomethacin producing a significant reduction ($P < 0.05$) compared with flupirtine but not with placebo. There was no significant difference between placebo and flupirtine.

Time course of diuresis The study was not designed to investigate in detail the time course of the frusemide-induced diuresis. Figure 1 shows, however, that the increased urine volume and excretion of sodium and potassium induced by frusemide appears to persist longer after pretreatment with flupirtine.

Discussion

These results confirm the observations of Kramer *et al.*³ that indomethacin antagonizes the natriuretic and diuretic actions of frusemide, and demonstrate for the first time that the novel centrally acting analgesic drug flupirtine does not show this antagonism in a single therapeutic oral dose of 200 mg. The mechanism of the antagonistic effect of indomethacin is still uncertain, but is thought by some investigators to involve inhibition of intrarenal prostaglandin biosynthesis.⁶ It has also been suggested that competition for a common secretory mechanism in the organic acid transport system of the proximal tubule may be involved.⁷

Whatever the mechanisms responsible, inhibition of the diuretic actions of frusemide by non-steroidal anti-inflammatory drugs such as aspirin and indomethacin may have important implications in patient care, and the absence of such an effect by a useful analgesic drug is a potentially valuable property. Single doses of flupirtine appear not to influence frusemide diuresis significantly, and confirmation that this applies in long term use is being sought and awaited with interest.

Figure 1 demonstrates that in this study a single therapeutic dose of flupirtine delayed the diuresis induced by frusemide but did not impair the overall response to frusemide. This effect might have been due to pharmacokinetic interaction between flupirtine and frusemide such as delayed absorption of frusemide due to delayed gastric emptying and/or reduced gut motility produced by flupirtine. A further possibility is a pharmacodynamic interaction in which flupirtine delayed the renal tubular action of frusemide by about 2 hours. Finally, inhibition of prostaglandin synthesis cannot be excluded but is unlikely since the lack of effect on total urine volume and electrolyte excretion contrasted markedly with indomethacin. In order to determine whether kinetic or dynamic interactions account for these findings, measurements of frusemide plasma concentrations would be necessary.

Table I Results of statistical analysis of comparisons made between placebo, flupirtine and indomethacin in their influence on frusemide induced diuresis

	Placebo	Flupirtine	Indomethacin
Volume			
Placebo	x	NS	$P < 0.05$
Flupirtine		x	$P < 0.05$
Indomethacin			x
Sodium excretion			
Placebo	x	NS	$P < 0.05$
Flupirtine		x	$P < 0.05$
Indomethacin			x
Potassium excretion			
Placebo	x	NS	NS
Flupirtine		x	$P < 0.05$
Indomethacin			x

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