Comparison of chlortenoxicam and indomethacin on frusemide-induced diuresis

A. Hitoglou-Makedou, M. Lawson, P. Turner and H.P. Ferber¹

Department of Clinical Pharmacology, St. Bartholomew's Hospital, London EC1A 7BE, UK and ¹Chemie-Linz AG, Linz, Austria

Summary: A single oral dose of chlortenoxicam 4 mg, a new non-steroidal anti-inflammatory drug, significantly antagonized the diuretic and natriuretic actions of frusemide when compared with placebo in normal human volunteers. Indomethacin 50 mg significantly reduced the natriuretic, but not diuretic action of frusemide.

Introduction

The diuretic and natriuretic actions of frusemide and other loop and thiazide diuretics are antagonized by concurrent treatment with most, if not all, non-steroidal anti-inflammatory drugs.^{1–4} Chlortenoxicam is a new non-steroidal anti-inflammatory drug of the oxicam group,⁵ and because it may be given to patients requiring treatment with frusemide it is important to know if it influences frusemide-induced diuresis and natriuresis.

Methods

Twelve healthy volunteers of either sex (6 females) aged 22–45 years were studied. The study was double-blind, randomized and placebo controlled, using a three-way cross-over comparison of chlortenoxicam, indomethacin as a positive control and placebo.

The study was approved by the local ethics committee, every subject gave written consent to participate, and all completed the study.

Volunteers avoided alcoholic and caffeine-containing drinks for 24 hours before and during each study day, moderated their intake of foods high in sodium and potassium for 3 days prior to each study day, and avoided medication containing aspirin for one week before each study day. Smoking was prohibited on the study days. The following oral treatments were given at 08.00 h after an overnight fast and a light breakfast on three separate occasions at least one week apart: chlortenoxicam 4 mg, indomethacin 50 mg and matched placebo. 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.

An independent running quality sample was analysed every 7 test samples. Coefficients of variation were 0.1 for both sodium and potassium estimations.

The urine volume and total excretion per hour of sodium and potassium were analysed using multiple linear regression analysis with treatments, time of measurements and subjects included as independent variables, using the dummy variable technique. Chlortenoxicam and indomethacin were compared with the placebo.

Results

Mean values for urinary volume, sodium and potassium excretion associated with the three treatments are shown in Figure 1 and the results of the statistical analysis in Table I. Chlortenoxicam significantly reduced the frusemide-induced diuresis over 6 hours, and both chlortenoxicam and indomethacin reduced the increase in sodium excretion when compared with

Correspondence: Professor P. Turner, M.D., B.Sc., F.R.C.P.
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placebo. Neither drug significantly influenced potassium excretion.

Figure 1 Cumulative urinary volume (ml), sodium and potassium excretion (mmol) per hour over 6 h following administration of placebo (●—●), chlortenoxicam (○—○) 4 mg and indomethacin (□—□) 50 mg followed by frusemide 20 mg. Each point represents the mean ($\pm$ s.e.m.) of 12 subjects.

Discussion

Non-steroidal anti-inflammatory drugs (NSAID) influence renal function in at least two ways. Firstly,

Table I Results of the multiple regression statistical analysis of the effect of chlortenoxicam and indomethacin on urine volume, Na⁺ and K⁺, compared with placebo

Treatment (independent variable)	Regression coefficient	F ratio (1, 197)	P value
Urine volume			
chlortenoxicam	− 42.71	4.20	< 0.05
indomethacin	− 22.03	1.12	N.S.
Na excretion			
chlortenoxicam	− 4.261	5.29	< 0.025
indomethacin	− 3.620	3.84	< 0.05
K excretion			
chlortenoxicam	− 0.599	0.92	N.S.
indomethacin	− 0.408	0.42	N.S.

N.S. = not significant.

some are known to be nephrotoxic and the early evaluation of new members of this group of drugs should include an assessment of their effects on renal function. Piroxicam, a compound related to chlortenoxicam, has been shown to cause nephrotoxicity in dogs, mice and rats, and there have been reports in man.^{6,7} A recent study of chlortenoxicam in healthy male volunteers showed no evidence of nephrotoxicity in doses up to 6 mg twice daily for two weeks.⁸ A second way in which most, if not all, these drugs influence renal function is by antagonizing the diuretic and natriuretic effects of loop and thiazide diuretics. The mechanism of this interaction is uncertain, but may involve inhibition of renal prostaglandin biosynthesis.⁴ Chlortenoxicam appears, from the results of this study, to share with most, if not all, other NSAID the property of antagonizing the diuretic and natriuretic action of frusemide. This potential interaction should be borne in mind when patients receiving frusemide or other loop or thiazide diuretics are considered for treatment with chlortenoxicam.

Only a modest dose of indomethacin was used as a positive control in this study, and it would be unwise to draw any conclusion on the relative effects of indomethacin and chlortenoxicam from the results.

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