Chlortenoxicam pharmacokinetics in young and elderly human volunteers

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Summary: The pharmacokinetics of chlortenoxicam, a new non-steroidal anti-inflammatory drug, have been compared in young and elderly healthy human volunteers. Chlortenoxicam was found to have a relatively short mean elimination half-life of about 4 hours, with considerable inter-subject variability, but there was no significant difference between young and elderly subjects. There was no evidence of accumulation with repeated administration. No unchanged chlortenoxicam was found in urine from any subject, suggesting that it undergoes extensive metabolism in man.

Introduction

Chlortenoxicam (Figure 1) is a non-steroidal anti-inflammatory drug belonging to the 'oxicam' chemical class. In animal models it has been shown to possess analgesic and anti-inflammatory activity, with a potency about ten times that of piroxicam or tenoxicam.¹

There is as yet only limited experience of chlortenoxicam in man. In a double-blind ascending single dose study in 24 healthy men, however, it was well tolerated in a dose range of 0.3-21.0 mg, and no clinical routine laboratory adverse effects were noted.²

Non-steroidal anti-inflammatory drugs are commonly used by elderly patients, who may have a reduced capacity to metabolise and excrete them.³ We have, therefore, carried out pharmacokinetic studies with single and repeated doses of chlortenoxicam in young and elderly human volunteers.

Figure 1 Structural formula of chlortenoxicam.

Study 1. Young subjects

Methods

Four groups of six healthy male volunteers were studied, aged 19-29 years and weighing 63-95 kg. The study was approved by the local ethics committee, every subject gave written consent to participate, and all but one completed the study.

The first group of six volunteers (Group A) received oral chlortenoxicam 2 mg in tablet form once daily for 14 days at 09.00 h. Subjects presented themselves after an overnight fast, and blood samples were obtained before and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h after dosing on days 1, 7 and 14, and before the dose on days 8, 9, 10, 12, 13 and 14. Total urine collections were made from 12 h before and from 0-6, 6-12 and 12-24 h after the dose on days 1, 7 and 14. Screening laboratory tests (haematology, biochemistry and urinalysis) were performed before the study, after 7 and 14 days of treatment, and 2 days after completing the study.

Groups B, C and D each comprised six volunteers who received oral chlortenoxicam 2 mg twice daily, 4 mg twice daily and 6 mg twice daily respectively for 14 days, undergoing the same schedule. Doses were taken at 09.00 and 21.00 h, except on days 1, 7 and 14 when only the 09.00 h doses were given.

Plasma and urine concentrations of chlortenoxicam were assayed by a reverse phase HPLC

method with UV detection. Extraction was carried out with dichloromethane and isoxicam was used as an internal standard. Coefficients of variation for control samples of 150, 75 and 15 µg/l were 14%, 13% and 27% respectively. Pharmacokinetic analysis was performed by a standard computer programme.⁴

Results

Plasma concentrations of chlortenoxicam were low or below the lower limit of detection in Group B subjects. No assays were carried out, therefore, on samples for Group A subjects. Assays in Groups B–D showed that their pre-dose concentrations of chlortenoxicam indicated good compliance with treatment. Pharmacokinetic parameters are shown in Table I. There were no significant differences between days 1, 7 and 14 of dosing, and there was no evidence of drug accumulation except in subject 24 (see below). Mean peak concentrations (C_{max}) of chlortenoxicam generally increased with increasing doses. The mean elimination half life ($t_{1/2}$) was not dose dependent, being about 4 hours overall, with moderate inter-subject variability.

Subject 24 (Group D) had very high C_{max} values of 484 µg/l on day 7, associated with a long elimination half-life (43 h). His serum alanine transferase was mildly raised at entry to the study, and this enzyme and his aspartate transaminase showed increasing levels during the first 9 days of treatment but all other liver function tests remained normal. He was withdrawn from the study and the transaminase levels fell to pre-study values within 7 days of stopping treatment. The major routes of chlortenoxicam metabolism in man are not yet

known, but as he was subsequently found to be an extensive hydroxylator of debrisoquine it is unlikely that his slow elimination of chlortenoxicam was associated with defective hydroxylation.

Examples of urine samples from all subjects showed no detectable levels of unchanged drug. Metabolites were not sought.

One subject in Group B developed epigastric pain 1 hour after taking the drug on the ninth evening. It lasted about 15 minutes. Another subject in Group B suffered indigestion on several occasions about 20 minutes after taking chlortenoxicam from day 5 onwards. His symptoms were relieved by food. None of the other subjects experienced any adverse events, and laboratory tests showed no significant abnormalities except for subject 24 (see above).

Study 2. Elderly subjects

Methods

Twelve elderly volunteers (6 men) aged 66–79 years and weight 51–79 kg consented to take part in the study which had been approved by the local ethics committee. Nine were normal on clinical history, physical examination and 12 lead ECG recording. Two subjects had been diagnosed previously as having hypertension and were receiving atenolol 50 mg and 100 mg daily respectively. Another subject was receiving brompheniramine maleate tablets (Dimotane) 4 mg daily for chronic catarrh and cough. All subjects had normal results in haematological, biochemical and urinalysis screening tests before the study commenced.

Table I Pharmacokinetic parameters of chlortenoxicam in young volunteers in Groups B, C and D. ($n=6/\text{group}$)

	Day 1			Day 7			Day 14		
	B	C	D	B	C	D	B	C	D
t_{max} (h) median	2.5	3.0	6.0	2.5	2.5	2.5	3.0	3.0	3.0
Range	2.0–4.0	2.0–3.0	2.0–6.0	2.0–4.0	2.0–6.0	2.0–6.0	2.0–4.0	2.0–6.0	0.5–6.0
C_{max} (µg/l) mean	133	299	309	169	363	372	113	387	327
s.d.	56	63	92	85	160	40	59	78	154
Range	86–218	226–397	210–548	62–279	253–684	306–411	27–209	280–477	127–489
$t_{1/2}$ elim (h) mean	2.4	5.2	3.7	5.3	4.8	4.4	5.4	3.0	3.7
s.d.	1.3	3.5	2.2	3.3	1.5	1.5	4.4	0.7	1.2
Range	1.1–4.5	1.9–10.5	2.3–7.5	1.4–10.9	2.7–7.1	2.8–6.8	2.7–14.3	2.7–4.2	2.4–5.5
AUC _{0–∞} (µg/l) mean	546	1744	1595	780	2001	2080	487	1932	1978
s.d.	342	348	592	478	583	404	239	469	982
Range	269–1018	1317–2300	1006–2488	255–1406	1432–2977	1666–2625	167–894	1274–2490	982–2603

Note – Subject 24 (Group D) has been excluded from these data (see text).

Group B: chlortenoxicam 2 mg twice daily by mouth; Group C: chlortenoxicam 4 mg twice daily by mouth; Group D: chlortenoxicam 6 mg twice daily by mouth.

The subjects received oral chlortenoxicam 4 mg in tablet form at 09.00 h for 9 days. On days 1 and 9 blood samples were taken before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after dosing. Total urine collections were made from 0–12 h. On days 3, 7 and 8, blood samples were collected before dosing.

Results

All subjects completed the study, and pre-dose drug concentrations showed good compliance with treatment. Pharmacokinetic parameters (Table II) showed no significant differences between days 1 and 9 of dosing, and there was no evidence of drug accumulation. No unchanged drug was detected in any urine sample from any subject.

Four subjects experienced mild indigestion on one occasion each during the treatment period, and one noted moderate nocturia for 1 week after the last dose. Results of routine laboratory tests before and after treatment showed no significant abnormality in any subject.

Discussion

This study has demonstrated that chlortenoxicam has a relatively short mean elimination half-life in

Table II Pharmacokinetic parameters of chlortenoxicam in elderly volunteers receiving a daily morning oral dose of 4 mg ($n=12$)

	Day 1	Day 9
$t_{\max}(h)$ median	2.0	2.0
Range	1.5–4.0	2.0–4.0
$C_{\max}$ ($\mu\text{g/l}$) mean	353	276
s.d.	127	71
Range	199–589	169–369
$t_{1/2}$ elim (h) mean	2.5	2.5
s.d.	0.5	0.7
Range	1.8–3.5	1.5–4.0
$\text{AUC}_{0-\infty}$ ($\mu\text{g/l}$) mean	1552	1338
s.d.	386	470
Range	1055–2280	784–2474

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