A comparison of isoxicam pharmacokinetics in young and elderly subjects

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1 The pharmacokinetics of isoxicam have been compared in 57 volunteers with an average age of 31.3 years and 48 elderly subjects with an average age of 71.9 years.

2 Isoxicam was given in a single daily dose of 200 mg for up to 22 days. Similar plasma concentrations were obtained in the two age groups, average maximum concentrations being 39.7 mg l^{-1} in those under 65 and 38.1 mg l^{-1} in the elderly. There were no significant differences in the half-life which averaged 30.4 and 32.1 h respectively.

3 Approximately 9% of all those studied had half-life values in excess of 50 h. The results are consistent with the possibility of genetic polymorphism of isoxicam hydroxylation.

4 It is concluded that isoxicam is suitable for use in once daily dosage and that there are no clinically significant differences in its pharmacokinetics between young and elderly subjects.

Keywords isoxicam young elderly pharmacokinetics

Introduction

It is well established that the elderly receive a disproportionate number of drugs (Dunnell & Cartwright, 1972; Stolley *et al.*, 1972; Balter *et al.*, 1974; Law & Chalmers, 1976; Skegg *et al.*, 1977). Also elderly patients are more likely to develop an adverse effect from drug treatment (Hurwitz, 1969; Castleden & George, 1984). A number of explanations exist for these differences in response to drug therapy which include altered drug pharmacokinetics.

Non-steroidal anti-inflammatory analgesics are among the agents which are most widely prescribed for elderly patients. Previous studies have shown that the half-life of some of these, e.g. phenylbutazone, is prolonged in elderly

patients (O'Malley *et al.*, 1971). More recently, benoxaprofen was withdrawn because of fatalities in the elderly (Goudie *et al.*, 1982; Taggart & Alderdice, 1982) and there is evidence to suggest that these were a consequence of altered pharmacokinetics of the drug in this age group (Hamdy *et al.*, 1982).

Isoxicam (4-hydroxy-2-methyl-N-(5-methyl-3-isoxazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide) is a new drug with potent anti-inflammatory properties and a long half-life (Downie *et al.*, 1984).

The present study was undertaken to define the steady-state and elimination pharmacokinetics of isoxicam in order to establish whether

there are differences in these between young and elderly subjects.

Methods

The study was multicentre: the participating patients and volunteers were studied in Dublin, Glasgow and Birmingham. All isoxicam analyses and calculations were carried out in Southampton. The patients and volunteers gave informed consent to the study which had received approval from the local ethics committees.

Subjects in the younger age group were in normal health. Those in the elderly group were either in normal health with respect to their age or had an arthritic condition which required the use of a non-steroidal anti-inflammatory drug. All underwent a detailed physical examination and baseline assessment of haematological and biochemical parameters. Those showing clinically significant deviations from normal were excluded from the study, as were others with any history of drug hypersensitivity (or other allergic disease).

Treatment

All patients and volunteers took two 100 mg capsules of isoxicam once daily after breakfast. The original protocol allowed for continued treatment for 21 days but in one centre this was extended to 22 days in order to avoid sampling at the weekend.

Blood sampling

Blood samples (10 ml) for plasma drug assays, were taken from an antecubital vein immediately prior to dosing on days 1 (blank), 3, 8, 10, 15, 19, 20 and 21. Further samples were taken once daily (at the same time as the last dose of isoxicam on day 21) on days 22, 23, 24, 25, 26, 27, and 28 or 30 to allow calculation of the elimination half-life of isoxicam. After withdrawal, blood was centrifuged and the plasma separated and stored at -20°C .

Assay conditions

Assays were performed in duplicate on 200 μl samples of plasma to which 10 μg of piroxicam in 10 μl of dioxan were added as an internal standard. The mixture was acidified with 2 ml citric acid (0.1 M) and after mixing the drug was extracted with 4 ml chlorobutane: 1,2-dichloroethane (4:1) by shaking mechanically for 5 min. After centrifugation, the top layer was removed and

evaporated to dryness at 70°C under oxygen-free nitrogen. The residue was redissolved in dioxan (400 μl) before injecting onto the h.p.l.c. apparatus.

Samples (9 or 18 μl) were injected using a Waters WISP autoinjector and the compounds were detected by their u.v. absorption at 320 nm at 0.05 or 0.1 A full scale using a Waters Model 481 variable wavelength detector. Isoxicam (retention time 4.3 min) was separated from piroxicam (retention time 2.7 min) using a Hypersil 3 μm ODS column (15 cm $\times$ 4.6 mm) and a mobile phase composed of 50% 0.01 M ammonium phosphate buffer (pH 2.5) and 50% acetonitrile at a flow of 1.5 ml min^{-1} produced by a Waters M6000A pump. The compounds were quantified by measurement of the peak height ratio of isoxicam to piroxicam and comparison with standards (50 $\mu\text{g ml}^{-1}$) prepared in control plasma. One standard was assayed for every four/five samples and six/eight standards analysed per batch. The standards routinely showed coefficients of variation of less than 5% and the assay was linear over the range 0.250 $\mu\text{g ml}^{-1}$: the limit of detection for routine samples was approximately 0.5 $\mu\text{g ml}^{-1}$. Samples for which the duplicate values differed by more than 5% were re-analysed and the mean of three or four values used.

Pharmacokinetic analysis

The areas under the plasma concentration-time curves were calculated by the trapezoidal rule with extrapolation to infinity. These values were corrected (when necessary) to 21 days dosing. The terminal elimination half-life was calculated by least squares regression analysis.

Statistical analyses

Comparisons between mean values of data for old and young individuals were undertaken using the Mann-Whitney U test. Correlations between the pharmacokinetic parameters obtained and age were undertaken by least squares regression analysis. Finally, in addition to a frequency distribution analysis of the plasma half-life data, a probit analysis was undertaken.

Results

Details of the 105 subjects who entered the study are given in Table 1. Of the 105 subjects who entered, satisfactory plasma concentration-time data were obtained to allow the calculation of the half-life in 104 subjects. One elderly subject

Table 1 Demographic details of subjects studied

	Young (18–64 years)	Elderly (65 years and over)
Men	26	21
Women	31	27
Mean age (years) $\pm$ s.e. mean	31.3 $\pm$ 1.44	71.9 $\pm$ 0.82
Mean weight (kg) $\pm$ s.e. mean	65.8 $\pm$ 1.35	69.8 $\pm$ 1.6
Smokers	16	5
Non-smokers	41	39
Unknown	0	4
Duration of therapy		
> 21 days	0	10
21 days	53	23
10–20 days	3	12
< 10 days	1	3

was excluded from all analyses because of variable plasma concentrations consistent with poor compliance, multiple drug therapy (likely to alter the pharmacokinetics of isoxicam) and the lack of correlation between his plasma concentrations with time after the drug had supposedly been withdrawn.

A typical series of results for one individual are shown in Figure 1. A steady-state (the average of the previous two plasma concentrations was greater than 90% of that after the last dose) was obtained by day 19. As in this subject, following withdrawal of isoxicam there was an excellent log-linear decline in plasma concentration with time.

From these data, four parameters were obtained: the maximum concentration attained ($C_{\max}$), the time of maximum concentration ($t_{\max}$), area under the concentration-time curve ($AUC_{0-\infty}$) (corrected for 21 days dosing), and half-life. The overall results from the three centres are shown in Table 2 and for half-life in Figure 2. It is apparent that there were no systematic differences in the pharmacokinetics of isoxicam in young and elderly subjects. Furthermore, no correlation was found between either the maximum (steady-state) concentration or the plasma AUC of isoxicam and age.

Nevertheless, a further examination of the half-life results indicated that nine of the subjects studied had half-life values in excess of 50 h (Figure 2). A frequency distribution analysis of these values is shown in Figure 3, from which it is clear that the data were bimodally distributed. Further evidence for this possibility comes from the probit analysis shown in Figure 4. There were highly significant correlations found between both peak plasma concentration and AUC of isoxicam and its half-life ($r = 0.75$, $P < 0.001$ and $r = 0.77$, $P < 0.001$ respectively).

Unwanted effects

The study had to be terminated prematurely in four elderly subjects. In three the cause was the development of peripheral oedema and in the fourth, indigestion occurred. Two of the three

Figure 1 Concentration-time curve for isoxicam in a single subject dosed for 21 days. After cessation of therapy there was a log-linear decline in the plasma concentration with time and a half-life of 1.1 days.

Table 2 Summary of pharmacokinetic parameters obtained for isoxicam in young and elderly subjects. Values are mean $\pm$ s.e. mean.

Age group	n	Half-life (h)	$t_{\max}$ (days)	$C_{\max}$ (mg l ⁻¹)	AUC (mg l ⁻¹ day)
Less than 65 years	57	30.4 $\pm$ 1.1	17.6 $\pm$ 0.6 ¹	39.7 $\pm$ 1.7 ¹	663.3 $\pm$ 29.1 ³
65 years and over	47	32.1 $\pm$ 1.8	17.0 $\pm$ 0.7 ²	38.1 $\pm$ 2.4 ²	727.7 $\pm$ 51.4 ⁴

1 – Based on data for 54 individuals

2 – Based on data for 41 individuals

3 – Based on data for 57 individuals

4 – Based on data for 47 individuals

elderly patients with oedema gave a previous medical history of heart failure.

Discussion

Analgesic drugs are very frequently used in elderly patients (Castleden & George, 1984). For some, e.g. phenylbutazone, there is evidence of an age-related increase in serious adverse effects (Inman, 1977) and a prolongation of the half-life has been demonstrated (O'Malley *et al.*, 1971). More recently, fatal jaundice associated with the use of benoxaprofen in elderly patients (Goudie *et al.*, 1982; Taggart & Alderdice, 1982) led to its withdrawal from the market.

The results of the current study are reassuring in that there is no systematic difference in the pharmacokinetics of isoxicam between young and elderly patients treated with the same daily dose of 200 mg. Thus, similar plasma concentrations were obtained during regular dosing and the half-life showed no alteration in the elderly. However, despite the normal pharmacokinetics, in the current study three elderly patients had to be withdrawn as a consequence of oedema. This problem has been seen previously with potent anti-inflammatory analgesics such as phenylbutazone, indomethacin and piroxicam. The most likely explanation is that non-steroidal anti-inflammatory drugs inhibit the intrarenal synthesis of prostaglandins (Lifschitz, 1983).

Figure 2 Plasma half-lives for isoxicam against age in 104 subjects studied.

Figure 3 Frequency distribution analysis of the half life data shown in Figure 2. The data are apparently bimodally distributed.

Despite the absence of a systematic difference in the pharmacokinetics of isoxicam between the young and elderly subjects studied, about 9% of the total population showed a half-life value in excess of 50 h. The frequency distribution analysis for half-life shown in Figure 3 is consistent with the existence of genetic polymorphism and this suggestion is reinforced by the probit analysis given in Figure 4.

The metabolic fate of isoxicam has been studied in man and a number of animal species using ^{14}C -labelled material (Borondy & Michniewicz, 1984). The most important metabolic pathways are shown in Figure 5. Hydroxylation takes place mainly on the methyl group of the isoxazole ring.

It is not, as yet, clear whether the polymorphism displayed by isoxicam is genetically based and if so, whether it is concordant with debrisoquine, as has been shown for metoprolol and various other drugs (see Rawlins, 1985), or discordant, as has been shown for other commonly used drugs including nifedipine (Kleinbloesem, 1984). Further studies are in progress which are designed to elucidate the basis of the polymorphism and the locus of the possible 'deficient hydroxylator' status of isoxicam.

Figure 4 Probit analysis of the half-life data for isoxicam in a total of 104 subjects.

Figure 5 Diagram to show the metabolic fate of isoxicam in man.

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