Sorbinil pharmacokinetics in male and female elderly volunteers

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Sorbinil pharmacokinetics were studied, following a single oral dose, in eight male and eight female healthy, elderly volunteers. Elimination half-life tended to be longer in males than in females. There was no sex difference in AUC or renal clearance. The long elimination half-life of sorbinil in the elderly suggests that accumulation is likely to occur with chronic dosing.

Keywords sorbinil pharmacokinetics age

Introduction

The concentration of sorbitol increases in nerves from diabetic patients (Ward et al., 1972) and it has been suggested that this contributes to the development of peripheral neuropathy. Sorbinil is an aldose reductase inhibitor which is under evaluation as a treatment for some of the complications of diabetes mellitus. Aldose reductase inhibitors reduce the conversion of glucose to sorbitol.

The elimination of sorbinil is thought to be mainly by biotransformation in the liver and two metabolites—2-hydroxy-sorbinil and IHFH [2,4-imidazolidinedione, 5-(2-hydroxyethyl)-5-(5-fluoro-2-hydroxyphenyl)]—can be assayed in urine. One fifth of a dose is recovered as unchanged drug in the urine within 48 h and the predicted total recovery is approximately 33% (Foulds et al., 1981). In young healthy volunteers the elimination half-life after a single oral dose is about 40 h (Foulds et al., 1981). The aim of this study was to investigate the pharmacokinetics of sorbinil in elderly male and female healthy volunteers since diabetes mellitus often affects elderly patients.

Methods

Eight male (age 70–85; mean 75.6 years) and eight female (age 66–82; mean 72.3 years) elderly ambulant, out-patient volunteers in good general health were selected for study. All had normal renal (serum creatinine < 120 μmol l⁻¹) and hepatic function (serum bilirubin < 25 μmol l⁻¹; aspartate aminotransferase < 30 u l⁻¹ and γ-glutamyl transpeptidase < 35 u l⁻¹) and blood glucose concentrations. Fourteen subjects were taking no regular medication, one was taking aspirin 300 mg day⁻¹ for a previous transient ischaemic attack and one praxilene intermittently for mild peripheral vascular disease. Ethical approval was granted by the Grampian Health Board/Aberdeen University Joint Ethical Committee and written informed consent was obtained from all subjects.

All subjects were studied 1 h after a light breakfast (tea or coffee and toast). Each subject received 250 mg sorbinil orally with 100 ml of water. No other drugs were taken on the study day. Blood samples (5 ml) were withdrawn into lithium-heparin tubes prior to dosing and at 0.5, 1.5, 4, 6, 9, 24, 48, 72, 96 and 168 h post-dosing. Plasma was removed and stored at −20°C until analysis. Patients were allowed home after 4–6 h with further sampling carried out in their own homes. Urine was collected prior to dosing and 24 h collections were made from 0–24, 24–48 and 48–72 h post-dosing. After measurement of urine volume a 20 ml aliquot of each collection was stored at −20°C until analysis.

Plasma sorbinil concentrations were measured by high performance liquid-chromatography (Foulds et al., 1981). The lower limit of sensitivity was 100 ng ml⁻¹ and coefficient of variation was 6.5%. Urine sorbinil and metabolite concentrations were measured by a modified h.p.l.c.
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method. (Pfizer, U.S.A.—personal communication). This method involved extraction into ethyl acetate after adjustment to pH 8 and chromatographic separation using acetonitrile/0.01 M KH₂PO₄, pH 6 as mobile phase and partisil 5 ODS G8 as stationary phase.

Pharmacokinetic parameters were calculated as follows: AUC by the trapezoidal rule to the last data point and extrapolated to infinity by the addition of C(last)/k; elimination half-life by linear regression using the post-absorption and distribution phase of the concentration-time curve (usually 9–168 h); apparent volume of distribution (V/F) was calculated from the equation:

\[ V = \frac{Dose}{F} \times AUC \]

and renal clearance from the equation:

\[ CLR = \frac{fe(0.72) \times D}{AUC(0.72) \times body \ weight} \]

where \( fe(0.72) \) is the fraction of the dose \( (D) \) excreted as sorbinil in urine in the first 72 h post-dosing.

Statistical analysis was by the Mann-Whitney U test.

Pulse and blood pressure were recorded over the first 24 h. Electrocardiograms were carried out before dosing and 24 h post-dosing. Biochemical and haematological screens were performed before dosing and 24 h post-dosing.

Results

The plasma drug concentration-time curves in male and female subjects (mean values ± s.e. mean) are shown in Figure 1. Pharmacokinetic parameters are listed in Table 1. There was no significant difference at the 5% level between

![Figure 1](Plasma sorbinil concentration-time curves in male (●) and female (○) healthy elderly volunteers (mean ± s.e. mean).)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient details and pharmacokinetic parameters (mean ± s.e. mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td><strong>Male</strong></td>
</tr>
<tr>
<td><strong>Serum creatinine (μmol l⁻¹)</strong></td>
<td>Pre-dose</td>
</tr>
<tr>
<td>122</td>
<td>102</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
</tr>
<tr>
<td>73.3</td>
<td>73.6</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td></td>
</tr>
<tr>
<td>70.4</td>
<td>70.4</td>
</tr>
<tr>
<td><strong>CLR</strong></td>
<td>Mean</td>
</tr>
<tr>
<td>3.43 ± 0.34</td>
<td>3.43 ± 0.34</td>
</tr>
</tbody>
</table>
males and females in $C_{\text{max}}$, $t_{\text{max}}$, AUC or renal clearance. Elimination half-life was longer in males than in females but the difference was not statistically significant at the 5% level using a Mann-Whitney U test ($0.05 < P < 0.10$). $V/F$ was found to be greater in males ($0.71 \pm 0.11$ l kg$^{-1}$) than in females ($0.62 \pm 0.07$ l kg$^{-1}$) ($0.05 < P < 0.1$). For comparison with the study in young male volunteers (Foulds et al., 1981) elimination half-life was also calculated over the period 6–48 h in our elderly male subjects when a mean value of 53 h was found (39 h in young subjects). The recovery of unchanged sorbinil in 0–72 h urine was 26 ± 7% in both male and female subjects. IHFH accounted for 7% of the dose and 2-hydroxysorbinil less than 1%. Serum creatinine concentration in males was found to be higher 24 h post dosing with sorbinil ($P < 0.05$). There was no change in serum urea in the same samples. In females there was no significant rise in serum creatinine concentration. There were no changes noted in pulse, blood pressure, ECG or haematological or other biochemical indices.

**Discussion**

There was no statistically significant difference between males and females at the 5% level (Mann-Whitney U test) in any of the kinetic parameters measured. However, the difference in elimination half-life almost reached significance with males tending to have higher values. The tendency to longer half-life values in males may be due to a larger volume of distribution in males rather than a change in total or renal clearance. Males have a greater muscle:fat ratio than females which suggests the possibility that sorbinil may bind to muscle protein and not be concentrated in fat stores. However, it is not known whether or not this occurs in man.

The rise in serum creatinine concentration noted in our elderly male volunteers was not observed with long term treatment in younger diabetic men (Pfizer, personal communication). In 45 males (age < 65 years) with diabetes mellitus mean serum creatinine (μmol l$^{-1}$) values of 91 ± 3 at day 0, 89 ± 2 at day 14 and 87 ± 3 at day 28 were found while on treatment with 250 mg of sorbinil daily. The increase in serum creatinine in our study may have occurred by chance. The possibility that long term sorbinil treatment could have a similar effect is under surveillance in current studies which include diabetic patients up to 70 years old on entry.

The elimination half-life values for elderly subjects (67.7 ± 4.4 h) in the present study were longer than those reported for young male volunteers (Foulds et al., 1981). This could reflect delayed elimination in the elderly but an alternative explanation is that the period of sampling was different in the two studies. Sampling stopped at 48 h in the young group. Examination of the concentration-time curves in the elderly males reveals a slower rate of elimination for the terminal part of the curve after 72 h.

The longer elimination half life of sorbinil in the elderly compared with young volunteers indicates a longer time to reach steady state and a greater degree of accumulation during chronic treatment. The clinical significance of greater accumulation in the elderly is being monitored as part of current studies of the safety and efficacy of long term sorbinil treatment in diabetic patients.

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Plasma sorbinil concentrations were measured at the Robens Institute, University of Surrey.

Urinary sorbinil was measured at Ronfield Pfizer Groton (Central Research).

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**References**


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