Pharmacokinetics of Sulpiride After Intravenous Administration in Patients with Impaired Renal Function

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Summary

Single intravenous doses of sulpiride 100mg were administered to 18 patients with renal function impairment, and 6 healthy volunteers. The plasma concentration-time profile is described by a 2-compartment open model.

The differences between the pharmacokinetic parameters of sulpiride for the 2 groups were statistically significant. Elimination half-life, mean residence time and area under the plasma concentration-time curve are significantly greater in renal failure; renal and total clearance, and the cumulative amount of unchanged sulpiride in urine, are significantly reduced but volume of distribution remains unchanged. Creatinine clearance was strongly correlated with renal clearance of sulpiride, elimination rate constant, area under the curve and cumulative amount excreted in urine.

For patients with impaired or physiologically reduced renal function receiving long term sulpiride treatment, a 35 to 70% reduction in dose, or extension of the dosage interval by a factor of 1.5 to 3, may be required.

Sulpiride [5-(aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl)-methyl]-2 methoxybenzamide], a disinhibitory psychotropic drug belonging to the O-anisamide or substituted benzamide class of antipsychotic agents, is rapidly becoming an important psychotherapeutic agent in many parts of the world. The drug, which exhibits neuroleptic and thymoleptic properties, is used in mental disorders as a behaviour regulator in the psychopathology of senesence, in depression and in schizophrenia, with a first dose of 200mg and a daily dose increment of 200mg to a maximum of 800mg (Alfredsson et al. 1984). It also finds use, at lower doses, in the treatment of gastrointestinal disorders such as gastric or duodenal ulcers, or irritable colon due to psychosomatic stress, and in the treatment of post-traumatic syndromes of head and neck followed by vertigo (Bressolle et al. 1984; Faure 1985).

For many years the efficacy of the antidepressive and disinhibiting effect of sulpiride has been the subject of controversy. Recently, several studies from different countries have demonstrated and confirmed the antidepressive action of the drug with mood inversion in hospitalised elderly subjects (Chassard et al. 1985; Delor et al. 1985; Jaques 1984; Lestynec 1983; Josserand 1978; Miyata 1975; Muller 1975; Waldmann 1976). 75% of patients over the age of 50 responded to sulpiride with release of inhibition and enhancement of alertness in the first few days of treatment.
Tolerance of sulpiride was always noted as excellent (Delor et al. 1985; Chassard et al. 1985), without production of tardive dyskinesia. In these studies the dosage varied between 50 and 150 mg/day, depending on the clinical state of the patient, occasionally rising as high as 200 and 300 mg/day (Muller 1975; Waldmann 1976) for periods of 30 to 90 days. Thus, it appears that dosage adjustment in elderly patients should be made on lines similar to that in the very young, based on current knowledge of the pharmacokinetics of sulpiride.

Studies published to date have failed to reveal evidence of sulpiride metabolites in human urine or faeces (Imondi et al. 1978; Sugnaux et al. 1978). In healthy subjects, the plasma concentration of unchanged drug versus time and urinary excretion rate versus time, following intravenous administration, were consistent with a 2-compartment open model. The apparent elimination half-life \((t_{1/2})\) was approximately 7 hours and the volume of distribution at steady-state \((V_{ss})\) was 1 L/kg. About 90% of the administered dose was recovered unchanged in urine; total and renal clearances were similar at 7.5 L/h (Bressolle et al. 1984; Faure 1985).

These facts indicate that sulpiride (which is not bound to plasma proteins) is predominantly excreted by the kidneys, mainly by glomerular filtration (GFR). Therefore, alterations in its pharmacokinetics and accumulation are likely to occur both in patients with renal disease and in the elderly (since GFR slowly decreases after age 40), and the dosage should be adjusted.

The aim of this study was to assess the pharmacokinetics of sulpiride in patients with impaired or reduced renal function, as pharmacokinetic data have not previously been reported for the drug in this situation. The intravenous route was used since on oral administration the bioavailability of sulpiride is about 35%, with very large interindividual variations, in both young volunteers and elderly patients.

It is hoped that the information given by this study will assist therapeutic drug monitoring and dosage regimen adjustments when sulpiride is used in patients with chronic renal failure, or physiologically reduced renal function in the case of geriatric patients.

Therapeutic drug monitoring is not mandatory but is suitable in clinical practice, since large interindividual variations have been shown (Alfredsson et al. 1984; Faure 1985).

Table I. Subject and patient demographic data (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>CLCR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 (3M, 3F)</td>
<td>30.20 ± 4.10</td>
<td>65.30 ± 8.75</td>
<td>175.00 ± 10.20</td>
<td>124.70 ± 23.90</td>
</tr>
<tr>
<td>2</td>
<td>6 (5M, 1F)</td>
<td>53.33 ± 13.87</td>
<td>68.43 ± 9.29</td>
<td>164.50 ± 5.75</td>
<td>49.75 ± 4.38</td>
</tr>
<tr>
<td>3</td>
<td>6 (4M, 2F)</td>
<td>64.33 ± 13.37</td>
<td>67.50 ± 15.56</td>
<td>164.30 ± 9.93</td>
<td>20.62 ± 7.25</td>
</tr>
<tr>
<td>4</td>
<td>6 (5M, 1F)</td>
<td>65.50 ± 5.96</td>
<td>63.22 ± 14.28</td>
<td>169.92 ± 5.26</td>
<td>6.78 ± 2.73</td>
</tr>
</tbody>
</table>

Abbreviations: \(CLCR\) = creatinine clearance; \(M\) = males; \(F\) = females.