ELIMINATION OF GUANFACINE IN PATIENTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

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1 Total body clearance and renal clearance after single intravenous doses of guanfacine were 360 ± 262 (mean ± s.d.) and 233 ± 245 ml/min, respectively, in patients with normal renal function (glomerular filtration rate (GFR) > 90 ml/min), 308 ± 274 and 34 ± 22 ml/min, respectively, in patients with moderately impaired renal function (GFR 30–10 ml/min, and 257 ± 187 and 18 ± 15 ml/min, respectively, in preuremic patients (GFR < 10 ml/min).

2 The cumulative urinary excretion up to 48 h after a single intravenous injection of guanfacine was 57.0 ± 32.0% in patients with GFR > 90 ml/min, 14.0 ± 9.0% in patients with GFR 30–10 ml/min and 7.5 ± 2.4% in preuremic patients.

3 In normal as well as impaired renal function the elimination rate constant of guanfacine was 0.05 h⁻¹, which corresponds to an elimination half-life of 14 h, independent of renal function.

4 These results suggest that non-renal elimination of guanfacine plays an important role in patients with renal failure.

5 Intestinal absorption of guanfacine was calculated to be 59 ± 19% in patients with GFR > 90 ml/min, to 68 ± 16% in patients with GFR 30–10 ml/min, and to 73 ± 36% in preuremic patients.

Introduction

GUANFACINE (N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride) belongs to a new class of centrally acting antihypertensive drugs, the phenylacetyl-guanidines (Bream, Lauener, Picard, Scholtysik, & Waite, 1975; Scholtysik, Lauener, Eichenberger, Burki, Salzmann, Muller-Schweinitzer & Waite, 1975). Clinical studies with guanfacine have shown it to cause significant blood pressure reduction with relatively few side-effects (Esch, 1976; Jäättelä, 1976a; Jäättelä. 1976b; Kirch & Distler, 1978; Turner, 1974) The aim of the present study was to investigate the pharmacokinetic properties of the drug after single intravenous and chronic oral administration to patients with varying degrees of renal function.

Methods

Twenty hypertensive patients aged 21–64 yr (average age 46.7 ± 18.1 yr) were investigated and had given their informed consent to participate in the study. The glomerular filtration rate (GFR) of the patients ranged from 3.9–113 ml/min: group 1 = six patients with GFR > 90 ml/min; group 2 = six patients with GFR 30–10 ml/min; group 3 = six patients with GFR < 10 ml/minute.

Two uremic patients received guanfacine 3 mg intravenously before a single haemodialysis treatment. GFR was measured by creatinine clearance. If GFR was below 10 ml/min, a combined urea-creatinine clearance was also performed (Milutinovic, Cutter, Hoover, Hujesen & Scribner, 1975).

On the first day each patient received guanfacine 3 mg intravenously. Blood samples were drawn before injection and at appropriate intervals post-injection up to 48 hours. Urine was collected from 0–4, 4–8, 8–12, 12–24 and 24–48 hours. For the following 5 d guanfacine 1 mg was administered orally three times daily to patients. During this time blood samples were taken before and 3 h after the morning dose. On day 8 guanfacine 1 mg was given only in the morning. Blood samples and urine were collected before administration and at short intervals afterwards. The serum and urine samples were stored at 10°C until analyzed by a gas chromatographic method with mass spectrometric detection (Morin, & Laplanche, 1976). The pharmacokinetic results were calculated using a two-compartment open model (Gibaldi & Perrier, 1975).

Absorption and distribution of guanfacine

Absorption of guanfacine was calculated to be 59 ± 19% (mean ± s.d.) in patients with GFR > 90 ml/min, 68 ± 16% in patients with GFR between 30 and 10 ml/min, and 73 ± 36% in preuremic patients (Table 1).
The volume of distribution of guanfacine for the central compartment was $168 \pm 181$ l in patients with GFR > 90 ml/min, $264 \pm 239$ l in patients with GFR 30–10 ml/min, and $304 \pm 117$ l in patients with GFR < 10 ml/min. Corresponding values for the second compartment were $445 \pm 245$ l, $443 \pm 242$ l and $417 \pm 187$ l, respectively (Table 1).

**Elimination of guanfacine**

Elimination of guanfacine after intravenous administration from serum was biphasic (Figure 1). No significant differences in serum levels were observed in the different groups of patients with varying degrees of renal function. During chronic oral dosing serum levels were between 8.6 and 2.7 ng/ml in patients with normal renal function and between 10.5 and 2.8 ng/ml in end-stage renal failure. Total clearance, renal clearance and metabolic clearance were estimated after intravenous injection of guanfacine 3 mg. They were calculated to be $362 \pm 262$, $233 \pm 245$ and $127 \pm 112$ ml/min, respectively, in patients with normal renal function, $308 \pm 274$, $34 \pm 22$ and $278 \pm 265$ ml/min, respectively, in moderately impaired renal function, and $257 \pm 187$, $18 \pm 15$ and $237 \pm 171$ ml/min, respectively, in preuremic patients (Figure 2). The mean elimination rate constant calculated from urine and serum values was approximately 0.05 h⁻¹ in all groups of patients (Table 1), which corresponds to an elimination half-life of 14 hours. The cumulative urinary excretion up to 48 h after intravenous injection of unchanged guanfacine was averaged to $57.0 \pm 32.0\%$ in normal subjects, to $14.0 \pm 9.0\%$ in patients with GFR 30–10 ml/min, and to $75\%$ in preuremic patients.

![Figure 1](image1.png)

**Figure 1** Mean serum levels after single intravenous injection of guanfacine 3 mg in patients with normal renal function (▲) and in preuremic patients (○).

![Figure 2](image2.png)

**Figure 2** Mean total body clearance (open), renal clearance (hatched) and metabolic clearance (solid) of guanfacine (mean ± s.d.) in normal subjects (GFR > 90 ml/min), patients with moderately impaired renal function (GFR 10–30 ml/min), and preuremic patients (GFR < 10 ml/min).

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>GFR &gt; 90 ml/min</th>
<th>GFR 30–10 ml/min</th>
<th>GFR &lt; 10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_d$ (l)</td>
<td>$168 \pm 181$</td>
<td>$264 \pm 239$</td>
<td>$304 \pm 117$</td>
</tr>
<tr>
<td>$V_{dp}$ (l)</td>
<td>$445 \pm 245$</td>
<td>$443 \pm 242$</td>
<td>$417 \pm 187$</td>
</tr>
<tr>
<td>$K_g$ (h⁻¹) from serum values</td>
<td>$0.048 \pm 0.024$</td>
<td>$0.047 \pm 0.025$</td>
<td>$0.041 \pm 0.027$</td>
</tr>
<tr>
<td>$K_g$ (h⁻¹) from urine values</td>
<td>$0.048 \pm 0.012$</td>
<td>$0.064 \pm 0.026$</td>
<td>$0.045 \pm 0.013$</td>
</tr>
<tr>
<td>$C_{u(0-48)}$ (%) from acute intravenous study</td>
<td>$57 \pm 32$</td>
<td>$14 \pm 9$</td>
<td>$7.5 \pm 2.4$</td>
</tr>
<tr>
<td>$C_{u(0-48)}$ (%) from chronic oral study</td>
<td>$30 \pm 13$</td>
<td>$9 \pm 6$</td>
<td>$9 \pm 5$</td>
</tr>
<tr>
<td>Absorption (%)</td>
<td>$59 \pm 19$</td>
<td>$68 \pm 16$</td>
<td>$73 \pm 36$</td>
</tr>
</tbody>
</table>

$V_d$ Volume of distribution of the central compartment.

$V_{dp}$ Volume of distribution corresponding to the β phase.

$K_g$ Elimination rate constant of the β phase.

$C_{u(0-48)}$ Percentage of the initial dose eliminated in the urine from 0–48 h after administration.
Table 2  Serum values for chronic
Corresponding were 30.0
the
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References

ELIMINATION OF GUANFACINE IN RENAL FAILURE

Corresponding values for chronic oral administration were 30.0 ± 13.0%, 9.0 ± 6.0% and 9.0 ± 6.0%, respectively (Table 1).

Elimination of guanfacine during haemodialysis

Two patients received guanfacine 3 mg intravenously at the beginning of a 5 h haemodialysis period. Mean serum levels of guanfacine were 7.3 ± 2.5 ng/ml 15 min post-injection, and they had fallen to 4.3 ± 0.4 ng/ml at the end of haemodialysis treatment (Table 2). The elimination rate constant during haemodialysis was calculated to be 0.059 h⁻¹. Total body clearance was 460 ml/min, distribution volume of the central compartment was 410 l, of the second compartment 468 litres.

Discussion

In the present study cumulative urinary excretion and renal clearance of unchanged guanfacine were reduced in patients with renal failure compared with normal subjects. Total clearances, serum levels, elimination rate constant and elimination half-life of guanfacine did not differ significantly between patients with normal and impaired renal function.

Thus, increased non-renal elimination, especially metabolism by the liver, has to be assumed in renal impairment. If, as is the case with guanethidine (Rahn, 1973), there are increased concentrations of guanfacine metabolites in renal failure, which have no antihypertensive activity, it could be concluded that the dosage regimen of guanfacine in patients with renal dysfunction need not differ from that in normal subjects. This assumption, however, is in contrast to our clinical impression. In patients with impaired renal function an increased frequency of undesired effects like orthostatic hypotension and sedation was observed. Further studies about the effect and kinetics of guanfacine metabolites in renal failure are necessary.