Pharmacokinetics of intravenous and oral pindolol in hypertensive patients with chronic renal failure

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Summary

1. The pharmacokinetics of intravenous and oral pindolol were determined in 24 hypertensive patients with normal or impaired renal function.

2. In patients with normal renal function, the total clearance of the drug was the sum of both the renal and non-renal clearances in equal parts. The non-renal clearance was found to equal the hepatic clearance directly measured from the hepatic extraction ratio and hepatic blood flow.

3. Compared with patients with normal renal function, patients with chronic renal failure exhibited (i) unchanged transfer rate constants and distribution volumes, (ii) decreased total body clearance with decreased renal clearance and unchanged non-renal clearance.

4. Analysis of data obtained after oral administration of the drug by the Loo-Riegelman method showed that the pindolol absorption kinetic was non-linear. Compared with patients with normal renal function, patients with chronic renal failure exhibited (i) a significantly decreased fraction of dose effectively absorbed, (ii) an increased initial rate of absorption. The initial rate of absorption was inversely correlated with creatinine clearance.

5. The study provided evidence that in patients with renal insufficiency, (i) no increase in the metabolism of the drug accompanied the decrease in renal function, and (ii) decreased bio-availability was associated with a reduced fraction of the dose effectively absorbed and an increased rate of absorption.

Key words: \(\beta\)-adrenoreceptor-blocking agents, chronic renal failure, hypertension, pharmacokinetics.

Introduction

In patients with chronic renal failure, most kinetic studies of \(\beta\)-adrenoreceptor-blocking agents have been performed to evaluate the roles of decreased renal clearance and/or altered protein binding (see review in Fabre & Balant, 1976). Little information exists about liver metabolism and absorption kinetics in these patients.

In the present study, the pharmacokinetics of pindolol were determined in hypertensive patients with chronic renal failure and compared with those of hypertensive patients with normal renal function. Hepatic clearance was measured by the direct determination of hepatic extraction ratio. Absorption kinetics included the estimation of both the fraction of the dose absorbed and the rate of absorption, according to the Loo–Riegelman (1968) method.

Materials and Methods

Twenty-four untreated hypertensive patients were studied. Their mean age was 47 years (range: 23–63 years). Three days before starting the study, the patients were admitted to hospital and given a standardized sodium diet (110 mmol/day). In all patients, diastolic blood pressure was constantly above 90 mmHg on day 3 of admission. No subject had cardiac or neurological involvement or anuria. All had normal plasma transaminase, bilirubin and alkaline phosphatase concentrations and sulphobromophthalein clearances. Consent for investigation was obtained from all patients after a detailed description of the procedure.

The pharmacokinetics of intravenously and orally administered drug were measured in 9 patients with chronic renal failure (mean creatinine clearance: 20 ml/min; range: 7–38 ml/min) and
compared with those of 9 patients with normal renal function (creatinine clearance >69 ml/min). On day 3 of admission to hospital, a bolus dose of 0.04 mg/kg of pindolol was administered intravenously through a catheter inserted into an antecubital vein. Blood samples were taken before and 5, 10, 15, 30, 45, 60, 90, 120 and 180 min after injection of the drug. In the same subjects, on day 5 of admission, a single dose of 10 mg of pindolol was administered orally. Blood samples were taken, using an indwelling catheter, before and 45 min, 1, 1-5, 2, 3, 4, 6 and 8 h after administration. Total volumes of urine were collected following both intravenous and oral administration. Calculations for data analysis have been described elsewhere (Chau, Weiss, Safar, Lavène, Georges & Milliez, 1977).

Hepatic clearance was measured in 6 patients with renovascular hypertensive, for whom it was clinically necessary to determine plasma renin activity in both renal veins. A catheter was introduced via the right femoral vein by the Seldinger technique under fluoroscopic control into the right hepatic vein, as previously described (Safar, Weiss, Fontaliran, Simon & Pauleau, 1978). The procedure began with the estimation of liver flow, using the Indocyanine Green technique (Caesar, Sheldon, Chiandrini, Guevara & Sherlock, 1961). The Indocyanine Green infusion was continued throughout the procedure to determine hepatic blood flow before and during pindolol administration. Pindolol was given intravenously as a rapid injection of 0.04 mg/kg followed by a continuous infusion at a rate of 0.015 mg h\(^{-1}\) kg\(^{-1}\) in order to achieve a plasma concentration plateau of 20 ng/ml (Lavène, Weiss, Safar, Loria, Aboras, Georges & Milliez, 1976). Blood samples were taken from the hepatic and peripheral veins before and 45 min, 1, 1.25 and 1.5 h after starting the infusion. The hepatic clearance of pindolol was the product of hepatic blood flow and the hepatic extraction of the drug (Weiss, Safar, Lehner, Simon & Milliez, 1978).

Pindolol concentration in plasma and urine was assayed fluorometrically using the method of Pacha (1969). The lower levels of sensitivity were about 5 ng/ml and 10 ng/ml respectively. The recovery was about 89% in plasma and 80% in urine. The ratio of the amounts of the drug in erythrocytes and in total blood was 0.42 ± 0.01. The average percentage of pindolol bound to plasma proteins was 50-6 ± 2.5 both in patients with normal renal function and in patients with chronic renal failure.

Results

Kinetics following intravenous administration

The data obtained after intravenous administration of the drug were found to fit the sum of 2 exponentials of time. The initial \( \alpha \) phase was the same in patients with and without impaired renal function. The terminal \( \beta \) phase was lower (0.15 ± 0.01 vs 0.35 ± 0.04 h\(^{-1}\); \( P < 0.001 \)) in patients with chronic renal failure. Transfer rate constants were the same in the 2 groups whereas the elimination rate constant was reduced in renal insufficiency (0.37 ± 0.08 vs 0.84 ± 0.14 h\(^{-1}\); \( P < 0.01 \)). Distribution volumes were somewhat higher in patients with impaired renal function. Table 1 indicates that: (i) in patients with normal renal function, total clearance was the sum of both the renal and non-renal clearances, in equal parts, and (ii) in patients with renal insufficiency, total and renal clearance were reduced (\( P < 0.001 \)) whereas non-renal clearance was unchanged. The renal drug clearance correlated directly with creatinine clearance (\( r = 0.89; P < 0.01 \)).

Hepatic clearance

Pindolol induced an insignificant decrease in hepatic blood flow (1075 ± 90 vs 1527 ± 258 ml/min). The hepatic extraction ratio of pindolol was 23 ± 4%. Hepatic clearance was 263 ± 57 ml/min.

Kinetics and bio-availability following oral administration

Both the fraction of the dose effectively absorbed and the rate of absorption of pindolol were determined (Chau et al., 1977) by the Loo–Riegelman (1968) method. Analysis of the curves demonstrated that the absorption kinetics were not first

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<tr>
<th>TABLE 1. Pindolol clearances in nine hypertensive patients with chronic renal failure and nine hypertensive patients with normal renal function</th>
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<td>Patients with Patients with</td>
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<td>normal renal function chronic renal failure</td>
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<tr>
<td>(ml/min)</td>
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<tr>
<td>Total clearance</td>
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<tr>
<td>538 ± 51</td>
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<td>Renal clearance</td>
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<td>272 ± 40</td>
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<td>Non-renal clearance</td>
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<td>266 ± 29</td>
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Mean results ± 1 SEM are shown. *** \( P < 0.001 \).
order. In patients with normal renal function, a fast absorption phase from 0 to about 4 h was followed by a slower absorption phase from 4 to 8 h. The mean fraction absorbed was 87 ± 7%. In patients with chronic renal failure, the initial absorption was more rapid. The fraction of the dose absorbed reached a maximum value of 52 ± 8% ($P < 0.01$ vs controls) at about 4 h. At 3 h, nearly all of this fraction had already been absorbed. In the overall population studied, creatinine clearance did not correlate with the fraction of dose absorbed but only with the initial absorption rate ($r = -0.94; P < 0.001$) (Chau et al., 1977).

Discussion

The data on hypertensive patients with normal renal function are similar to those reported by Gugler, Herold & Dengler (1974) in normotensive patients and constitute a reference for comparison with patients with impaired renal function. The total clearance was the sum of both the renal and non-renal clearances in equal parts. From the direct evaluation of the hepatic extraction of pindolol, non-renal clearance was found to equal hepatic clearance. Thus, the total clearance of pindolol was the sum of both the renal (elimination) and hepatic (metabolism) clearances in equal parts.

In chronic renal failure, $\alpha$ phase, distribution volume, transfer rate constants and non-renal (hepatic) clearance were unchanged. In contrast, $\beta$ phase and total body clearance of the drug were reduced and bio-availability impaired. Since the decrease in total clearance was due only to a decrease in renal clearance, the results contrast with the previous observations of Ohnhaus, Nuesch, Meier & Kalberer (1974) and exclude increased metabolism of pindolol in patients with renal insufficiency (Ofé & Levy, 1975). Since protein binding of these patients was within the normal range, the described impaired bio-availability suggests some abnormality in gastro-intestinal absorption.

The fact that bio-availability was impaired in patients with chronic renal failure, compared with those with normal renal function was proven by the following observations: (i) the total fraction of the dose absorbed was reduced, (ii) this fraction was absorbed nearly completely much earlier (3 to 4 h instead of 6 to 8 h), and (iii) the initial rate of absorption was increased. Moreover, only the latter measurement (and not the fraction of dose absorbed) correlated with creatinine clearance. The results suggest the existence of some subtle disorder of gastro-intestinal absorption in patients with chronic renal failure.

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References


