Pharmacokinetics of Ketanserin in Man

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Summary. Kinetic data for the new antihypertensive agent ketanserin were determined in six healthy subjects after single oral (40 mg) or intravenous (0.15 mg/kg) doses. Plasma protein binding was 94.0 ± 1.8% (mean ± SD). Cumulative urinary excretion of unchanged drug was less than 4% within 48 h following the single dose. The maximal plasma level (c_{max}) of 193 ± 98.2 µg/l occurred within 0.5 to 4.0 h after oral intake. The ketanserin plasma level declined biexponentially after oral administration, and triexponentially over the 36 h following intravenous injection. The terminal elimination half-life (t_{1/2}) averaged 12.4 ± 2.9 h and 12.8 ± 4.8 h following oral and intravenous application, respectively. Total plasma clearance was 410 ± 62.0 (i.v.) and 829 ± 228 ml/min (p.o.) and the intravenous blood clearance averaged 602 ± 91 ml/min, which indicates partly flowdependent hepatic elimination. A substantial first-pass effect led to a bioavailability of about 50% (range: 27–69%). Hepatic clearance of ketanserin followed the non-restrictive pattern. No change in blood pressure or heart rate was observed following ketanserin administration to normal volunteers.

Key words: ketanserin, pharmacokinetics; protein binding, excretion, oral dosing, i.v. injection, first-pass effect, antihypertensive drug, serotonin antagonist

Recently considerable interest has been focused on the antihypertensive action of the 5-hydroxytryptamine Type 2 (5-HT_{2}) receptor antagonist ketanserin [1–3]; (Fig. 1). In addition to its 5-HT_{2} receptor antagonism [4], ketanserin has been observed to have alpha-adrenoceptor antagonistic properties [5], which could be responsible, at least in part, for its antihypertensive effect [6, 7].

The limited pharmacokinetic data available for humans [8] made it important to undertake further investigation of the kinetic behaviour of ketanserin.

Materials and Methods

Four male and two female, healthy, normal subjects, within 20% of ideal body weight, and aged 29 to 39 years, participated in the study. All but one were non-smokers. Written informed consent was given by all volunteers before entering the study, which had the approval of the Ethics Committee of the Robert-Bosch-Hospital.

Following an overnight fast, each subject received a single oral dose of ketanserin 40 mg (two tablets containing ketanserin tartrate each equivalent to ketanserin 20 mg) and ketanserin 0.15 mg/kg body weight as an intravenous injection over 3 min. For the first 4 h post-dosing the volunteers remained su-

[Fig. 1. Structure of ketanserin]
pine. The two parts of the cross-over study were separated by a drug-free interval of at least 10 days. Venous blood samples (10 ml) were taken from the arm contralateral to the intravenous injection site at zero time (blank), at 10, 20, 30, 45 min and 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 30 and 36 h after the injection, and 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 24, 30 and 36 h after the oral dose respectively.

The plasma protein binding of ketanserin was determined by ultrafiltration (Amicon micropartition system, MPS-1; ultrafiltration membrane type YMB, Danvers, Mass., USA). The ultrafiltration cell (capacity 1.2 ml) was filled with a fresh pre-study plasma sample from each subject containing a final concentration of ketanserin 50 ng/ml and about 8000 cpm $^3$H-ketanserin, and was centrifuged for 1 h (1350 g) at 37 °C. The solutions on either side of the membrane were then assayed for drug concentration using a standard liquid scintillation technique.

The blood/plasma concentration ratio was directly determined from the 1 h blood samples. Ketanserin concentrations in whole blood and centrifuged plasma samples were measured according to the previously published method [9].

Two complete 24-h urine specimens were collected from the subjects after intravenous ketanserin administration, to cover the 0–24 and 24–48 h periods post-dosing, and were analyzed for unchanged ketanserin. Blood pressure and heart rate in all subjects were recorded in parallel with the blood sampling.

Terminal elimination half-life times ($t_{1/2}$) after intravenous and oral administration of ketanserin were calculated by linear regression analysis of the terminal slope of a semilogarithmic plot. The steady state volume of distribution ($V_{dss}$) was calculated model-independently from the formula

$$V_{dss} = \frac{\text{dose} \times (\text{AUMC}_{0-\infty})}{(\text{AUC}_{0-\infty})^2}$$

assuming complete absorption after oral intake ($\text{AUC} = \text{area under the plasma concentration-time curve}$; $\text{AUMC} = \text{area under the first moment curve}$ [10]. Total body clearance (CI) was calculated from the ratio dose/AUC. AUC and kinetic data were generated from the curve fitting program "DRUGFUN", which is available through the PROPHET computer system [11]. CI was calculated for total and free plasma ketanserin:

$$\text{Cl}_{\text{free drug}} = \frac{\text{Cl}_{\text{total drug}}}{\text{fraction of free drug}}.$$  

Blood clearance was derived from plasma CI divided by the blood/plasma ratio. Bioavailability ($F$) of the oral preparation in each subject was assessed by comparing the AUC ($t = 0$ to infinity, extrapolated) after intravenous and oral administration of ketanserin.

Hepatic liver extraction ratio $E$ was calculated from to the equation

$$E = \frac{\text{Cl}_{\text{blood}}}{Q}$$

where $Q$ is hepatic blood flow, assuming 1500 ml/min for normal volunteers. In addition to calculation of the bioavailability $F$ by the AUC method, it was estimated by the expression $F = 1 - E$. All data are reported as mean ± SD.

Results

After a single intravenous dose plasma ketanserin levels declined triexponentially over the monitored period of 36 h. The curve was mainly bieponential