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Pharmacokinetics and bioavailability of drotaverine in humans

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SUMMARY

The pharmacokinetics and bioavailability of drotaverine was studied in 10 healthy volunteers after administration of single 80 mg oral and intravenous doses of the HCl salt of the drug, in a crossover fashion. Plasma and urine samples were analyzed for the unchanged drug by HPLC. The pharmacokinetic parameters, such as elimination half-life, plasma clearance, renal clearance and apparent volume of distribution, were not influenced by the route of drug administration. The drug was mainly eliminated by non-renal routes since renal clearance accounted for only 0.31 ± 0.13% of the total plasma clearance. The absolute bioavailability was variable and ranged from 24.5–91% with a mean of 58.2 ± 18.2% (mean ± SD). It is suggested that the high variation in the bioavailability of drotaverine HCl after oral administration may result in significant interindividual differences in therapeutic response.

INTRODUCTION

Drotaverine, a benzylisoquinoline derivative, is chemically similar to papaverine and it is an effective spasmolytic drug (1). It has a more potent spasmolytic effect than papaverine and it is also used in the symptomatic treatment of various conditions, such as gastrointestinal diseases, biliary dyskinesia and vasomotor diseases associated with smooth muscle spasms (2).

It has been shown in animal experiments that metabolism in the liver plays a major role in the elimination of drotaverine (3,4) and considerable levels of the metabolites are excreted into bile (4,5). There are only a few reports on the disposition studies of drotaverine in humans. Total radioactivity measurements of blood following administration of labelled drotaverine have been used to study the concentration–time profiles of the drug in volunteers (6,7). The lack of specificity of this analytical method renders it inadequate for application in bioavailability and pharmacokinetic studies. It is, therefore, necessary to re-evaluate the disposition characteristics of drotaverine using a sensitive and specific method for the analysis of the drug.

With the development of liquid chromatographic techniques for the determination of drotaverine in blood (8,9), more specific methods are now available for plasma concentration studies in man. The present study aims at elucidating the bioavailability and additional pharmacokinetic parameters of drotaverine in healthy volunteers using a new HPLC method developed in our laboratory (10).

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MATERIALS AND METHODS

Subjects and drug administration

Ten healthy volunteers aged between 24–35 years consented to participate in the study. The study was approved by the local Ethics Committee. The volunteers were not allowed to take any other drug for at least 2 weeks before, and throughout the duration of the study. None of the volunteers was a smoker and alcohol consumption was disallowed during the study. After an overnight fast, each volunteer received a single 80 mg dose of drotaverine as the hydrochloride salt (2 tablets of No-Spa®, Chinoin, Hungary). A washout period of 1 week was allowed before the same volunteers received an intravenous administration, over a 5 min period, of the same dose of drotaverine hydrochloride injection (No-Spa®).

Sample collection and analysis

Venous blood samples (5 ml) were taken up into heparinized tubes by venepuncture of the antecubital vein at 0, 1, 2, 3, 6, 8, 24, 27 and 30 h following oral administration. The sampling schedule after intravenous administration was 0, 0.25, 0.5, 1, 3, 6, 8, 24 and 30 h. The blood samples were centrifuged immediately to obtain plasma. Blank urine and total urine voided between 0–6 h were also collected after administration of the drug through both routes. The volumes of urine were measured and an aliquot of 10 ml kept for analysis. The plasma and urine samples were either analyzed immediately or stored at –20°C until analysis. The drug was determined in the biological fluids by an HPLC method developed in our laboratory and reported earlier (10). This involved the separation of the unchanged drug from its metabolites and internal standard on a reversed-phase C_{18} 10 µm column (300 × 4.0 mm, i.d.) (Waters Associates, MA, USA). The mobile phase (pH 3.2) consisted of 0.02M NaH_2PO_4 : MeOH (30:70, v/v) containing 70 mM $HClO_4$ solution pumped through the column at 1.2 ml/min. The limit of detection was 6 ng/ml. The intra- and inter-day coefficients of variation (CV) in plasma were 8.3 and 7.1%, respectively, at 50 ng/ml. While the corresponding values at 500 ng/ml were 7.8 and 9.2%. The precision for the analysis of the drug in urine was less than 10% at 50 and 500 ng/ml.

Data analysis

The pharmacokinetic data were determined using compartment model independent formulae. The elimination half-life, $t_{1/2}$, of the drug was computed from linear regression analysis of the plasma drotaverine concentrations obtained at the terminal elimination phase following drug administration. In all cases, the concentration versus time correlation was more than 0.9. C_{max} is the maximum plasma concentration read from the plasma concentration-time curve and T_{max}, the time at which C_{max} occurs. The AUC_{0-30} was estimated using the trapezoidal method. The extrapolated AUC was determined from the ratio, C_t/β where β is the elimination rate constant and C_t is the last measured plasma concentration. The AUC_T is thus the sum of AUC_{0-30} and the extrapolated AUC. The absolute bioavailability was deduced from the equation (AUC_T after oral dosing)/(AUC_T after i.v. dosing) × 100%. The plasma clearance, Cl_p, was determined from the ratio, F × (Dose)/(AUC_T), where F is the absolute bioavailability after oral dosing expressed as a fraction. The apparent volume of distribution, V_d, was estimated from the ratio Cl_p/β. The renal clearance, Cl_r, was determined from the equation (Amount excreted unchanged)/AUC. The AUC used in this equation is that determined for the time period within the urine collection interval. Differences between pairs of data were evaluated using the Willcoxon test for paired observations.

RESULTS

The mean plasma concentration–time profiles after administration of single oral and intravenous doses of 80 mg drotaverine HCl to 10 volunteers are shown in Figure 1.

The individual absorption characteristics and pharmacokinetic parameters of drotaverine HCl in 10 volunteers are summarized in Tables I and II. After intravenous administration, the elimination half-life was 9.33 ± 1.02 h, (range 7.86–11.2 h). The plasma clearance was 243 ± 51 ml/min (range 184–381 ml/min) while the renal clearance was 0.73 ± 0.29 ml/min, (range 0.21–1.28 ml/min). The area under the plasma concentration-time curve (AUC) ranged from 3497–7247 ng/ml.h with a mean of 5688 æ 950 ng/ml.h, while the volume of distribution was 195 æ 48 l (Table I).

After oral administration, peak plasma concentrations were obtained after 1–3 h and varied between 136–409 ng/ml. The area under the plasma concentration-time curve (AUC) ranged from 1509–5005 ng/ml.h with a mean of 3251 ± 1010 ng/ml.h. The elimination half-life was 9.11 ± 1.29 h (range 7.0–11.95 h) while the renal clearance was 0.59 ± 0.18

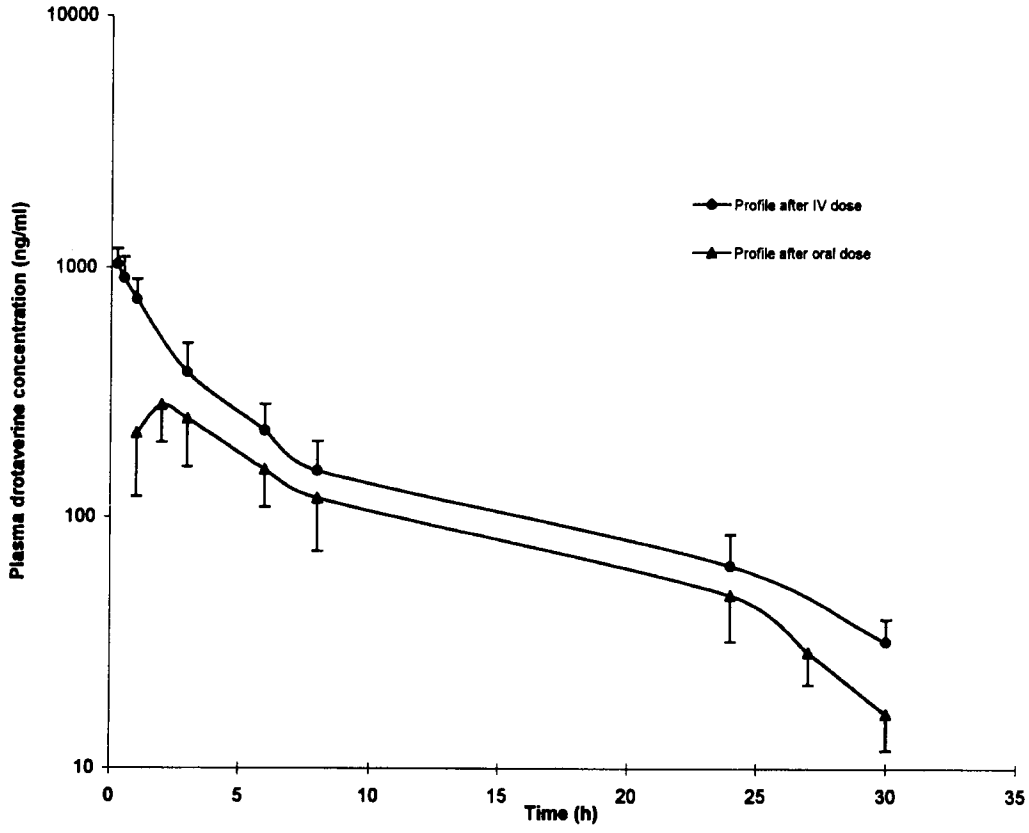

Fig. 1 : Mean plasma concentration–time profiles of drotaverine after single oral and intravenous administration of 80 mg doses of the drug to 10 volunteers in a crossover fashion. The bars represent SD values.

ml/min (range 0.43–0.90 ml/min). The absolute bioavailability was subject dependent and ranged between 24.5–91% with a mean of 58.2 ± 18.2% (Table II). Pharmacokinetic parameters such as $t_{1/2}$, Cl_p, Cl_r and V_d showed no significant differences in the two routes of administration.

Table I : Pharmacokinetic parameters of drotaverine HCl after an intravenous dose of 80 mg to 10 volunteers.

Volunteer	*Cl_p (ml/min)*	*Cl_r (ml/min)*	*$t_{1/2}$ (h)*	*V_d (l)*	*AUC_T (ng/ml.h)*
SHO	271	0.53	11.20	263	4923
IBU	228	0.84	10.60	210	5843
OSI	217	0.93	9.12	177	6152
OLU	240	–	8.66	180	5554
ADW	203	0.59	7.86	138	6572
ADY	221	0.21	10.34	198	6036
OMO	242	0.88	8.45	177	5508
OLW	184	0.58	9.42	134	7247
TOR	241	1.28	8.56	179	5543
OWO	381	0.75	9.00	296	3497
Mean	243	0.73	9.33	195	5686
± SD	± 51	± 0.29	± 1.02	± 48	± 950

Table II: Absorption characteristics and pharmacokinetic parameters of drotaverine HCl following oral administration of 80 mg single doses of the drug to 10 volunteers.

Volunteer	T_{max} *(h)*	C_{max} *(ng/ml)*	Cl_p *(ml/min)*	$t_{1/2}$ *(h)*	V_d *(l)*	AUC_T *(ng/ml.h)*	F *(%)*
SHO	2	235	271	11.95	281	2118	43.0
IBU	1	334	228	8.66	171	3362	57.5
OSI	2	136	216	10.70	188	1509	24.5
OLU	2	203	240	9.49	197	2509	45.2
ADW	1	395	209	7.0	127	4259	64.8
ADY	2	242	221	9.76	187	3182	52.7
OMO	2	409	242	9.25	194	5005	91.0
OLW	3	320	184	7.88	126	3787	52.3
TOR	2	398	240	8.89	185	4060	73.2
OWO	2	249	381	8.15	269	2712	77.8
Mean	1.9	292	243	9.11	193	3251	58.2
± SD	± 0.54	± 88	± 51	± 1.29	± 48	± 950	± 18.2

DISCUSSION

From the plasma drotaverine profiles shown in Figure 1, it is apparent that the drug is not completely bioavailable after oral administration. This fact is supported by the data on the absorption characteristics (Table II) which indicate that the bioavailability of drotaverine can be as low as 24.5% and is also highly variable. The mean bioavailability of 58.2% is consistent with the findings of Vargay et al. (11). Since drotaverine is chemically related to papaverine, it is not surprising that the low and variable bioavailability of drotaverine obtained in this study has also been observed for papaverine (12,13). The significant reduction in bioavailability after oral dosing may be attributed to an extensive first-pass effect, as was proposed for papaverine (14). However, inadequate drug absorption in the gastrointestinal tract resulting from incomplete in vivo release of the drug can also contribute to the low bioavailability.

It is pertinent to note that a bioavailability of 100% was reported for drotaverine following oral administration in human subjects (6,7). This apparent complete systemic availability may be connected with the non-specific analytical method, involving total radioactivity blood measurements, employed in the study. The lack of conformity of the result of the present study with that of Rutz-Coudray (6) underscores the importance of establishing the pharmacokinetics of drotaverine using specific assay techniques, which is in line with the objective of this study.

The disposition parameters, such as $t_{1/2}$, Cl_p, V_d and Cl_r, were indistinguishable when derived after oral and intravenous administration of the drug (Table II). Thus, it is evident that the route of administration has no significant effect on the disposition of drotaverine HCl. This corroborates the results of earlier studies which showed the elimination half-life and degree of metabolism of the drug to be independent of the route of administration (4,6). The Cl_r accounted for only 0.1–0.43% (0.31 ± 0.13%) of the total plasma clearance indicating that the drug is mainly eliminated through non-renal routes. This is in agreement with previous reports indicating that extensive hepatic metabolism plays a major role in the clearance of the drug from the body (3,4,7). Biliary excretion has no significant contribution to the elimination of the unchanged drug except when doses are much in excess of the therapeutic range (4).

In conclusion, a sensitive and specific analytical procedure has been employed to evaluate the disposition of drotaverine in human subjects. The results of this study demonstrate that the pharmacokinetics of drotaverine HCl is not influenced by the route of administration. It is suggested that the high variation in the bioavailability of the tablet formulation may result in significant interindividual differences in therapeutic response.

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