DELAYED ELIMINATION OF A PRAZOSIN METABOLITE COMPARED WITH KINETICS OF PRAZOSIN INJECTED INTRAVENOUSLY INTO RABBITS

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The hypotensive agent prazosin [1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine] (PZ) is excreted from man and animals chiefly in the form of metabolites [3, 8]. Among its biotransformation products in rats and dogs, 2-(1-piperazinyl)-4-amino-6,7-dimethoxy-quinazoline (MQ) has been identified [7]. Recently this metabolite was found in the serum and urine of patients receiving PZ [6], and unlike the unchanged PZ, during prolonged treatment marked accumulation of MQ was observed and its serum concentration in some cases was two or three times higher than the concentration of unchanged PZ. Since MQ, according to experimental data, possesses definite hypotensive activity, amounting to about 20% of the activity of PZ [2], it may make a distinct contribution to the therapeutic effect of PZ.

The marked cumulation of MQ may be due to its delayed elimination, and it was therefore decided to study the kinetics of MQ after intravenous injection into experimental animals, by comparison with the kinetics of PZ.

EXPERIMENTAL METHOD

Experiments were carried out on female Chinchilla rabbits weighing 2.5-3.3 kg. The animals were kept on a standard diet and were not fed on the day of the experiments. A solution of MQ or PZ in a mixture of propylene and water (2:8 by volume) was injected into the auricular vein in the course of about 20 sec in a dose of 0.5 mg/kg body weight. Blood (200 µl) was taken from the auricular vein at definite time intervals for 24 h. The serum was separated and kept at −18°C.

MQ was obtained from PZ by hydrolysis, as described previously [6]. All reagents used in the work were obtained from Merck (West Germany) and were "for analysis."

The serum levels of PZ and MQ were determined by high-performance liquid chromatography, using a fluorometric detector. The column (Partisil 10-SCX, 10 µ, 4.6 × 250 mm, from Whatman, England) was filled with a cation-exchange resin. The eluent consisted (by volume) of 14.7% acetonitrile, 0.3% diethylamine, 1% orthophosphoric acid, and 84% water, freed from ions and other impurities by means of the Milli RO/Milli Q system (Millipore, USA). The wavelength of excitation of the detector was 246 nm and emission was recorded through a 370 nm cutoff filter. To determine concentrations of MQ and PZ 3-5 µl of serum, after thawing, was introduced directly into the chromatography column. The method of absolute calibration was used for the calculations. Chromatograms of a control rabbit serum and of serum after intravenous injection of PZ and MQ are illustrated in Fig. 1.

The pharmacokinetic characteristics were: area under the concentration curve (AUC), the half-elimination time from the serum ($t_{1/2}$), the mean retention time (MRT), total clearance (CL), central and steady-state distribution volumes (V_0, V_{SS}), were calculated by model-independent methods [1], using the M-IND program, written by ourselves, for the HP-85 microcomputer (Hewlett-Packard).

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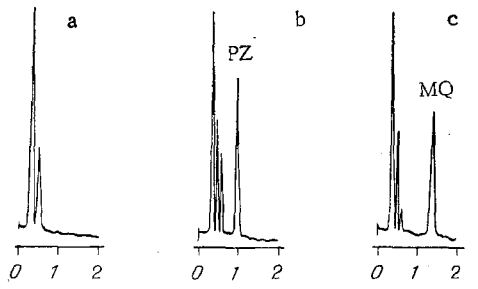

Fig. 1

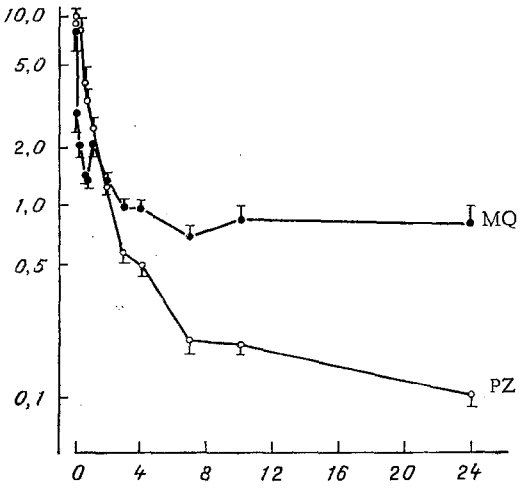

Fig. 2

Fig. 1. Chromatograms of rabbit serum. Horizontal axis — Time (in min). 1) Before; b) after injection of PZ; c) metabolite in a dose of 0.5 mg/kg. PZ) Peak of prazosin; MQ) peak of metabolite.

Fig. 2. Concentration profiles of PZ and MQ in rabbit blood serum. Abscissa, Time (in h); ordinate, concentration (in μM, logarithmic scale). Vertical lines denote standard deviations of average concentrations.

EXPERIMENTAL RESULTS

Averaged concentration profiles of PZ and MQ, obtained after intravenous injection into three rabbits, are shown in Fig. 2. Visual analysis shows that after injection of PZ there was a steady fall of its concentration, rapid at first, but later (starting from 4-6 h) slower, ending with a terminal logarithmically linear phase. The half-elimination time of PZ from the serum was calculated from the last three points. Meanwhile the MQ concentration, after a sharp decline during the first 45 min at 1.35 ± 0.15 μM, rose to 2.1 ± 0.2 μM in the first hour ($P < 0.05$). The MQ level then fell again, and starting from the fourth hour the concentration stabilized at the 0.9 μM level until the end of the experiment (24 h).

The results thus confirm the previous hypothesis regarding extremely slow elimination of MQ [6].

The fall of the serum MQ concentration in the terminal phase was too slow to allow calculation of the half-elimination time of MQ, and it was therefore impossible to assess its pharmacokinetic parameters. AUC was determined only between 0 and 24 h. The central distribution volume V_0 was estimated. These characteristics are shown in Table 1 with the pharmacolinetic characteristics of PZ.

The total clearance of MQ could be estimated as the ratio of the injected dose to the value of $AUC_{0-\infty}$, which is the sum of ACU_{0-24} and the unknown area under the part of the curve extrapolated to infinity, and determined by its slope in the terminal phase. Since the fall of the serum MQ concentration in this phase takes place extremely slowly, $AUC_{0-\infty}$ for MQ may be much greater than AUC_{0-24}. It is accordingly evident that the clearance of MQ was much less than the clearance of PZ, for AUC_{0-24} alone for MQ is greater than $AUC_{0-\infty}$ for Pz.

Values of the central distribution volume was lower for MQ than for PZ; in two cases, moreover, they were lower by almost an order of magnitude, evidence of its much weaker penetration into intensively perfused organs compared with PZ.

Enterohepatic recirculation which, as is well known, prolongs the half-elimination time of hepatotropic drugs [4], is one possible cause of the slow disappearance of MQ from the serum. MQ or (which is more probable) its conjugate is excreted into the intestine, where the conjugate is degraded and the MQ is reabsorbed into the blood stream. An argument in support of the existence of this process is the presence of a significant rise of the serum MQ concentration 1 h after injection. We know that secondary peaks of this kind are often observed when drugs that undergo enterohepatic recirculation are used.

TABLE 1. Pharmocokinetic Parameters of PZ and its Metabolite after Intravenous Injection (0.5 mg/kg)

Serial No.	PZ						MQ	
	$AUC_{0-\infty}$, μmoles/h	$t_{1/2}$, h	CL, liter/h/kg	V_{ss}, liter/kg	V_0, liter/kg	MRT, h	AUC_{0-24}, μmoles/h	V_0, liters/kg
1	12,1	9,6	0,11	0,72	0,16	6,5	22,5	0,015
2	11,1	8,9	0,12	1,15	0,14	9,6	18,1	0,1
3	9,5	9,5	0,14	0,97	0,16	6,9	27,6	0,02

Legend. $AUC_{0-\infty}$) Area under concentration curve of 0 to ∞; AUC_{0-24}) the same, between 0 and 24 h.

It is interesting to compare the data on the pharmacokinetics of PZ, when injected intravenously into rabbits, which we obtained for the first time with corresponding characteristics for man [5]. For instance, the mean values of CL and V_0 in man (0.14 liter/h/kg and 0.15 liter/kg, respectively) are close to their values for the rabbit (Table 1). Other modally independent parameters of the pharmacokinetics are not given in [5], but they can easily be calculated from the parameters of the two-compartment model used to describe the data. It was found that the mean values of MRT and V_{ss} (3.6 h and 0.52 liter/kg, respectively) differ a little from these parameters in rabbits, but are of the same order of magnitude. Rabbits thus constitute a good experimental model with which to study the pharmacokinetics of PZ.

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REGULATION OF ^{3}H-DOPAMINE RELEASE BY PRESYNAPTIC GABA AND GLUTAMATE HETERORECEPTORS IN RAT BRAIN NUCLEUS ACCUMBENS SYNAPTOSOMES*

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The possibility that GABA receptors are involved in the regulation of electrical and secretory activity of dopaminergic neurons in certain mammalian brain formations has been demonstrated previously [4]. The presence of a presynaptic receptor mechanism, sensitivity to GABA and controlling ^{3}H-dopamine (^{3}H-DA) release from nerve endings of the nucleus accumbens of the mesolimbic system of the rat brain was described by the writers previously [2]. Mean-

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