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The pharmacokinetics of D-penicillamine in neonates

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The pharmacokinetics of D-penicillamine in premature babies was studied. The metabolism of the drug was characterized by a long half-life (115 min) with a low plasma clearance (2.84 ml/min/kg body weight) in contrast to adults. The mean volume of distribution (649/ml/kg body weight) was similar to that of adults.

Since 1973, D-penicillamine (D-pa) has been used in our department for the treatment of neonatal hyperbilirubinaemia and on the basis of more recent experimental and clinical observations, for the prevention of retrolental fibroplasia [2, 3]. It seems that the mechanism of action is based on the antioxidant activity of the drug [5]. Since oxygen-free radicals are generated continuously and the antioxidant defense mechanisms are inefficient in the early period of life, it seems advantageous to achieve high plasma levels of an exogenous antioxidant such as D-pa.

Throughout the several decades of the drug's use in adults kinetic studies in man have been lacking, primarily because a specific and sensitive assay was not available. Previously, the metabolism of radiolabelled D-pa has been studied in animals [8]. Unfortunately, in the interpretation of the results only few data were given about the pharmacologically active free D-pa. More recently the pharmacokinetics of D-pa was studied in adults using highly specific and sensitive assays [11, 12], but there are no data whatever concerning the pharmacokinetics of D-pa in neonates. Pongor et al [10] demonstrated the rapid clearance of D-pa from the plasma of two hyperbilirubinaemic patients by the TLC method. They measured the concentration of D-pa disulphide and the earliest time of measurement was 1 hour after the intravenous (i.v.) administration of the drug.

In the present study the concentration of pharmacologically active free D-pa was determined in preterm babies after a single i.v. dose of the drug.

Patients and Methods

The kinetics of D-pa was studied in 6 subjects with a gestational age of 29 to 32 weeks and a birth weight between 1200 g

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TABLE I

Clinical data of

	Gest. age (weeks)	Birth weight (g)	IRDS	pH	Htc	Hb (g/l)
1. V. I.	29	1250	—	7.38	0.62	194
2. D. P.	32	1450	I—II	7.28	0.56	156
3. N. A.	33	1900	II	7.36	0.45	160
4. K. G.	30	1300	I	7.40	0.50	148
5. M. A.	32	1600	I	7.40	0.45	143
6. H. Z.	34	1700	—	7.35	0.60	186

and 1900 g. The patients showed no evidence of serious disease. D-pa (Metalcaptase®, Knoll AG, Ludwigshafen) was applied i.v. in a single dose of 100 mg/kg body weight, and then serial blood samples were collected at 10, 15, 30, 60, 120, 240 min. Only two to three samples were obtained from the same patient. Clinical and laboratory data of the patients are shown in Table I. D-pa concentrations were corrected to an overall 0.5 haematocrit value. Plasma concentrations from different individuals belonging to the same point of time were averaged and an elimination curve was constructed (Fig.1). Plasma elimination half-lives ($Tl/2\beta$) for D-pa were determined by calculating the line of best fit from the linear regression of the logarithm of the plasma concentration vs time. The total area under each curve (AUC) was estimated by the trapezoidal rule [12]. This permitted calculation of the apparent plasma clearance (Cl) and of the volume of distribution (V_d) for D-pa. For determination of plasma D-pa concentration, Pal's method was adapted [7]. Blood was collected in EDTA containing tubes and centrifuged (3000 rpm for 15 min) as soon as possible. The plasma was separated and the plasma proteins were precipitated with two parts of ethanol containing 0.1 mol/l HCL. After centrifugation the supernatant was used for D-pa measurement. 0.1 ml was made up to 2.0 ml with distilled water. To each tube 0.5 ml of 0.2 mol/l KCN solution and 0.015 mol/l $FeCl_3$ solution was under mixing. After 5 minutes incubation in water bath at 65 °C the tubes were cooled and centrifuged. The blue supernatant was measured at 645 min in a photometer (Spectromom 195, MOM Budapest, Hungary). A standard solution of D-pa (100 μ/ml) was analysed parallel with the samples. The method was highly reproducible: the within run coefficient of variation was 0.5%, and the day to day coefficient of variation was 5.9%.

Results and Discussion

The elimination curve of D-pa after i.v. administration of a single dose of 100 mg/kg body weight was clearly biphasic (Fig. 1). During the distribution phase the free D-pa concentration in the plasma decreased quickly; after 30 minutes only a little amount of i.v. administered free D-pa could be measured.

The rapid distribution of D-pa in the extracellular space, oxidation to penicillamine disulphide and disulphide formation with cystein and other thiols, binding of free D-pa to proteins

study population

Blood glucose (mmol/l)	Sebi (μmol/l)	DPA μg/ml					
		10	15	30	60	120	240
		min. after injection					
2.5	162	317	—	—	—	61	31
3.1	156	—	248	—	112	—	—
5.8	150	232	—	115	—	63	—
3.6	178	—	282	—	97	—	34
3.1	153	329	—	146	—	—	—
2.6	147	—	296	—	124	—	47

were responsible for the phenomenon. The binding of D-pa to albumin was reversible and did not influence the albumin-bilirubin formation even at high concentration [1]. The rapid decrease of D-pa concentration in plasma is characterized by a large mean volume of distribution (649 ml/kg body weight).

The second phase of the elimination curve is influenced by the renal excretion of the drug [9]. The plasma elimination half-life was 115 min, slower than the 62 min reported for adults [12]. The plasma clearance was 2.84 ml/min/kg body weight. In comparison to that of adults (7.46 ml/min/kg body weight [12]), this value is quite low.

In our previous studies we found that D-pa has age related effects [4, 5, 6]. It seems that the pharmacokinetics of the drug in newborns differs from that in adults. Longer elimination and decreased plasma clearance of D-pa are characteristic of newborns.

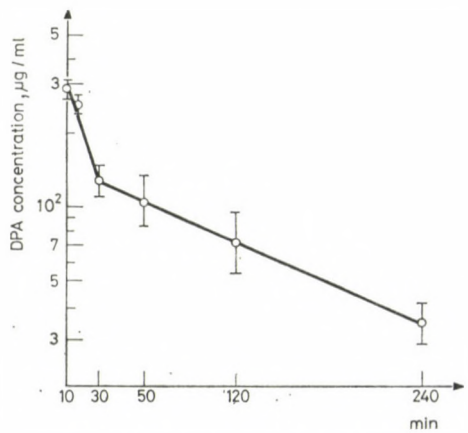

FIG. 1. Pharmacokinetics of D-penicillamine in preterm babies

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