Placental transfer of carbamazepine in the rat

Drug placental transfer in recent years, has been a cause for concern because of the possible toxic effects on the foetus and newborn (Mirkin, 1973; Symposium on Drugs and the Unborn Child, 1973). While with anticonvulsant drugs like diphenylhydantoin, phenobarbitone and diazepam the placental transfer has been extensively studied and documented both in experimental animals and man (Mirkin, 1971; Waddell & Mirkin, 1972; Idänpään-Heikkilä, Jouppila & others, 1971; Desmond, Schwanecke & others, 1972; Waddell, 1972; Sereni, Morselli & Pardi, 1973; Mandelli, Morselli & others, 1975), no data are currently available on carbamazepine (CBZ) placental transfer. The use of this drug to treat both trigeminal neuralgia and epilepsy has increased in recent years and there is the possibility that pregnant women may receive it. We report some preliminary observations on pregnant CD rats (Charles River, Italy) (3 weeks gestation) which show a rapid placental transfer of the drug.

Carbamazepine was administered intraperitoneally to 28 pregnant rats at the end of the third week of gestation and to 28 non-pregnant rats (average weight 350 $\pm$ 15 and 300 $\pm$ 10 g respectively) at a dose of 70 mg kg^{-1}. The animals were killed 30 min, 1, 2, 3, 4, 6 and 8 h after the drug and plasma and brains from mothers as well as the head and bodies of 8 foetuses per mother were collected and stored at $-20°$ until analysis. Carbamazepine concentrations in the plasma and tissues were determined according to the g.l.c. procedure of Morselli, Biandrate & others (1973).

The pharmacokinetic analysis of the plasma concentrations was performed by applying the one compartment model with absorptive phase for CBZ administered intraperitoneally. A Hewlett Packardcalculator model 9810 A was used with the proper program for obtaining a primary estimate of the pharmacokinetic parameters.

Subsequently the primary estimates were included as input for iterative non linear, least square fitting by using a non linear program BMOX to obtain the best estimates with s.d. for Kas, Vd (1 kg^{-1}) and total body clearance (ml min^{-1} kg^{-1}). Data for plasma concentrations were weighted using the reciprocal of variance of each point. The computer output represented the best estimate of the kinetic parameters with their standard deviation. Statistical analysis of kinetic parameters was according to Boxenbaum, Riegelman & Elashoff (1974).

Table 1 gives the concentrations of carbamazepine found in the mothers and foetuses and in non-pregnant animals. It can be seen that as early as 30 min after drug administration plasma concentrations observed in foetal heads and foetal bodies (20·4 s.d. 2·4 and 21·5 s.d. 3·2 μg ml^{-1} respectively) are similar in value to the concentration in the mothers (18·1 s.d. 2·6 μg ml^{-1}) and that a relative parallelism in concentrations between maternal plasma and foetal tissues exists for the whole observation period.

Table 1. *Carbamazepine plasma ($\mu g\ ml^{-1}$) and tissues ($\mu g\ g^{-1}$) concentrations after a single administration of 70 mg kg^{-1}, i.p.*

Experimental group	Tissue	Time after administration (min)						
		30	60	120	180	240	360	480
Control rats	Plasma	29·5 s.d. 0·6	29·0 s.d. 0·8	26·8 s.d. 2·8	24·5 s.d. 0·8	23·6 s.d. 0·7	15·2 s.d. 0·6	10·7 s.d. 0·9
	Brain	38·2 s.d. 2·8	39·5 s.d. 2·5	35·3 s.d. 2·3	35·4 s.d. 0·5	34·3 s.d. 0·7	24·3 s.d. 1·2	12·9 s.d. 1·5
Pregnant rats	Plasma	18·1 s.d. 2·6	23·5 s.d. 1·2	26·8 s.d. 0·4	27·5 s.d. 2·7	22·0 s.d. 2·5	18·4 s.d. 0·8	16·2 s.d. 0·8
	Brain	28·8 s.d. 6·0	36·4 s.d. 1·5	42·7 s.d. 2·1	38·3 s.d. 1·9	30·3 s.d. 2·8	27·9 s.d. 6·4	25·3 s.d. 4·5
Foetuses	Head	20·4 s.d. 2·4	24·0 s.d. 0·5	31·2 s.d. 2·6	24·8 s.d. 1·7	21·3 s.d. 2·0	17·6 s.d. 3·6	15·6 s.d. 2·5
	Body	21·5 s.d. 3·2	24·5 s.d. 1·2	30·2 s.d. 0·8	23·7 s.d. 1·1	19·0 s.d. 0·5	15·4 s.d. 2·0	13·6 s.d. 3·1

Each point is the mean of 4 animals.

Table 2. *Kinetic parameters (with s.d.) of carbamazepine in pregnant and non pregnant rats.*

	Pregnant	Non-pregnant	*P*
Kas (min^{-1})	0·034 s.d. 0·009	0·087 s.d. 0·017	<0·02
Vd $(1\ kg)^{-1}$	1·759 s.d. 0·178	1·523 s.d. 0·099	>0·05
TBC ($ml\ min^{-1}\ kg^{-1}$)	3·08 s.d. 0·42	5·34 s.d. 0·36	<0·01

Kas = first order rate constant of absorption from the peritoneum.
Vd = apparent relative volume of distribution.
TBC = relative total body clearance.

In pregnant animals plasma and tissue peak concentrations are achieved within 120–180 min, while in controls peaks are attained within 30–60 min. The ratio between tissue and plasma is practically the same in the two groups.

The kinetic parameters for CBZ in pregnant and control rats are reported in Table 2. In pregnant rats absorption and disposition rates of carbamazepine were slower in comparison to non-pregnant rats. The apparent volume of distribution (Vd) even if higher in pregnant rats was not statistically different from controls. On the contrary, the total body clearance which expresses the efficiency of carbamazepine removal was much lower for pregnant than for non-pregnant rats ($P < 0{\cdot}01$). This is in good agreement with previous reports indicating a slower drug disposition during pregnancy (Wulf, 1973).

The reported data indicate that in pregnant animals carbamazepine quickly crosses the placenta and that an equilibrium between maternal plasma and foetal tissues is achieved in a relatively short time. The fact that the apparent disappearance rate from the foetuses does seem to parallel that of mother-plasma is suggestive of no selective accumulation in foetal tissues.

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