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The effect of varying extents of Fluosol-DA or normal saline haemodilution on the dose dependent kinetics of phenytoin in the rat

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Abstract—Phenytoin kinetics were determined in rats in which the blood was moderately haemodiluted with 20 or 40 mL kg^{-1} of Fluosol-DA or normal saline. Rats received one of three intravenous phenytoin doses (10, 40, 50 mg kg^{-1}) 0·5, 24, 48, or 72 h after haemodilution and were compared with non-exchanged controls. Haemodilution with either 20 or 40 mL kg^{-1} of Fluosol or saline had no influence on the dose-dependent kinetics of phenytoin. Haemodilution with 40 mL kg^{-1} of Fluosol decreased the half-life of phenytoin's major metabolite, HPPH, after a 50 mg kg^{-1} dose. Neither Fluosol nor saline haemodilution affected the normal delay in biliary cycling of HPPH.

Perfluorochemical (PFC) emulsions are being evaluated as blood substitutes because of their ability to dissolve oxygen. After administration, PFC particles are captured by the reticuloendothelial system (RES) and distributed primarily to the liver and spleen, and secondarily to the kidneys, bone marrow, and lungs (Lowe & Bollands 1985). The maximum PFC hepatic content occurs at two days after the administration of moderate doses (Lutz & Metzenauer 1980). Not unexpectedly, PFC administration or haemodilution has been found to alter the disposition of several drugs.

In a previous report (Shrewsbury et al 1987), haemodilution with 40 mL kg^{-1} of Fluosol-DA (Fluosol) reduced phenytoin clearance (Cl) and apparent volume of distribution (V_d) at 24 h in a 72 h study. Saline (0·9% NaCl) haemodilution, included to show the effect of haemodilution alone, reduced phenytoin Cl and V_d at 24, 48, and 72 h. As phenytoin is metabolized by phenobarbitone-induced cytochrome P-450 isoenzymes (Roy & Snodgrass 1988), these findings appeared to be inconsistent with the report that perfluorodecalin, a constituent of Fluosol, induced the same cytochrome P-450 isoenzymes (Grishanova et al 1988).

The present investigation examined the influence of the extent of Fluosol and saline haemodilution on the dose-dependent kinetics of phenytoin. Phenytoin displays a pronounced dose-dependent elimination in both rats and man with linear kinetics seen at 10 mg kg^{-1} doses and non-linear kinetics observed at 40 mg kg^{-1} doses or higher (Perucca et al 1978). Saline haemodilution was again included to show the influence of haemodilution alone.

Materials and methods

The materials used, source of animals, haemodilution protocol, and analytical and statistical procedures have been reported (Shrewsbury et al 1987). Phenytoin kinetics were examined in unexchanged (CONT) rats and rats haemodiluted with 20 mL kg^{-1} or 40 mL kg^{-1} of Fluosol or saline. Haemodiluted animals received phenytoin doses of 10, 40, or 50 mg kg^{-1}, 0·5, 24, 48 or 72 h, respectively, after being exchanged (codes = 0·5HF, 24HF, 48HF, 72HF for the Fluosol groups; 0·5HS, 24HS, 48HS, 72HS for the saline groups). CONT animals received the phenytoin dose 24 h after the cannulation surgery.

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Results

Phenytoin dose dependency in rats is due to product inhibition by the major metabolite (±)-5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) (Vicuna et al 1980). With product inhibition, first order drug disposition will be seen at each dosage, but the half-life ($t_{\frac{1}{2}}$) will increase (Perrier et al 1973). Phenytoin disposition was found to be first order at all three dose levels, and the $t_{\frac{1}{2}}$ increased in all groups regardless of the extent of haemodilution or time after haemodilution (Tables 1, 2). Phenytoin clearance (Cl) would also be expected to decrease as the dosage was increased, and this was seen in all groups regardless of the extent of haemodilution or time after haemodilution. Phenytoin Cl values were significantly different in only four groups and V_d was significantly increased in only three groups. The only significant finding from the HPPH data was that haemodilution with 40 mL kg^{-1} of Fluosol doubled the HPPH overall elimination rate constant (K_{el}) and decreased the HPPH $t_{\frac{1}{2}}$ by one-half in all groups after the 50 mg kg^{-1} phenytoin dose (data not shown). Saline haemodilution did not appear to have any influence on HPPH disposition.

Discussion

The phenytoin data suggest that Fluosol or saline haemodilution did not impair or influence the dose-dependent metabolism of phenytoin. The findings were unexpected since perfluorodecalin induces the phenobarbitone inducible cytochrome P-450 isoenzymes (Grishanova et al 1988), and these same isoenzymes mediate phenytoin metabolism (Roy & Snodgrass 1988). Bachmann et al (1988) have suggested that phenytoin Cl is not an effective discriminator between factors that induce or inhibit mixed function oxidase activity. It is also of interest that phenytoin Cl was not altered after 70% blood replacement with Fluosol-43 (Matsumoto-Kikuchi et al 1983), but was significantly reduced after 90% blood replacement (Matsumoto et al 1983). These reports suggest that the Fluosol dosage used in this investigation may not have been high enough to effectively change phenytoin Cl.

The observed increased HPPH K_{el} and decreased HPPH $t_{\frac{1}{2}}$ after a 50 mg kg^{-1} dose might suggest that HPPH elimination was enhanced after haemodilution with 40 mL kg^{-1} of Fluosol. HPPH is almost quantitatively glucuronidated after its formation (Asconape & Penry 1982); thus, Fluosol haemodilution may influence non-microsomal glucuronidation.

Approximately 30% of the animals studied displayed a second HPPH plasma concentration peak. In animals dosed with 10 mg kg^{-1}, this second peak occurred between 180 and 240 min. 15% of the animals dosed with 40 or 50 mg kg^{-1} displayed the second plasma peak between 480 and 600 min. Glazko et al (1969) showed that biliary cycling of HPPH was delayed, either because

Table 1. Averaged disposition parameters of phenytoin at three doses after haemodilution with 20 mL kg^{-1}.

	Treatment groups								
	CONT	0·5 HF	24 HF	48 HF	72 HF	0·5 HS	24 HS	48 HS	72 HS
Parameters									
$t_{\frac{1}{2}}$ (min)									
10 mg kg^{-1}	22·8†	25·2	19·8	19·2	17·2	15·6	18·6	18·9	24·4
	16·1	10·4	7·8	4·2	8·2	4·7	11·1	6·5	6·4
40 mg kg^{-1}	45·1	48·5	64·2	66·1	77·0	51·3	43·9	55·3	70·2
	14·0	7·3	30·5	12·6	28·5	13·7	18·0	24·7	22·6
50 mg kg^{-1}	67·9	86·2	58·4	83·1	64·7	82·5	79·3	88·8*	131·3*
	4·4	25·1	21·0	21·6	21·4	21·3	19·8	22·1	22·9
V_d (mL kg^{-1})									
10 mg kg^{-1}	938	1432*	944	884	1260	1106	672	844	921
	191	225	197	282	1010	450	438	223	227
40 mg kg^{-1}	899	1233	1250	2171*	1459	920	1046	1332	1155
	499	510	646	725	493	308	621	537	481
50 mg kg^{-1}	1548	1714	1124	1531	1250	1462	1275	1168	1323
	640	527	412	228	377	276	517	185	245
Cl (mL min^{-1} kg^{-1})									
10 mg kg^{-1}	36·9	43·9	36·7	32·6	48·0	48·0	42·3	32·1	27·2
	15·2	14·6	14·5	12·1	16·3	9·8	24·2	8·7	9·1
40 mg kg^{-1}	13·2	17·4	13·3	22·4*	14·3	12·3	16·1	17·9	13·1
	3·9	5·4	3·6	4·4	4·9	1·1	6·0	7·6	9·6
50 mg kg^{-1}	15·8	14·5	13·5	13·2	13·7	12·8	10·8	9·5	7·0*
	6·4	4·4	2·1	2·1	2·6	3·5	2·2	2·7	0·5

*Significantly different from CONT ($P \leq 0{\cdot}05$).
†Mean (s.d.)

Table 2. Averaged disposition parameters of phenytoin at three doses after haemodilution with 40 mL kg^{-1}.

	Treatment groups								
	CONT	0·5 HF	24 HF	48 HF	72 HF	0·5 HS	24 HS	48 HS	72 HS
Parameters									
$t_{\frac{1}{2}}$ (min)									
10 mg kg^{-1}	28·1†	22·1	25·1	29·0	21·7	34·9	23·3	23·8	29·9
	6·4	11·3	16·2	30·4	10·7	25·6	16·5	9·5	14·8
40 mg kg^{-1}	53·8	60·2	55·6	58·0	48·0	155·3*	69·2	60·3	66·1
	11·5	21·1	26·6	19·4	18·9	43·3	30·7	36·5	22·8
50 mg kg^{-1}	77·7	78·0	144·8	75·1	59·6	85·4	67·0	83·2	121·0
	37·7	25·4	65·5	62·5	30·3	8·9	34·8	32·3	50·6
V_d (mL kg^{-1})									
10 mg kg^{-1}	1209	1574	827	880	1012	1576	636	629	871
	999	379	798	168	232	769	397	250	434
40 mg kg^{-1}	1182	1079	1291	1324	1523	2453*	1123	826	1842
	203	176	659	109	402	263	650	157	1039
50 mg kg^{-1}	1223	959	2537	896	1458	1423	809	1254	1170
	617	250	486	583	675	473	310	495	191
Cl (mL min^{-1} kg^{-1})									
10 mg kg^{-1}	28·1	53·8*	21·3	32·8	36·5	36·0	21·1	18·9	21·6
	20·8	14·8	6·3	15·5	12·1	13·9	11·2	6·2	11·8
40 mg kg^{-1}	15·4	13·2	16·4	17·0	24·8	11·8	14·3	11·0*	19·0
	1·4	3·9	4·5	4·9	9·4	3·9	6·2	3·2	8·2
50 mg kg^{-1}	11·8	9·3	13·2	10·0	19·4	11·4	8·8	11·9	7·9
	4·2	3·2	3·5	3·7	8·5	3·4	1·6	5·7	3·8

*Significantly different from CONT ($P \leq 0{\cdot}05$).
†Mean (s.d.).

of a slow conversion of phenytoin to HPPH or a slow glucuronidation of HPPH to HPPH glucuronide. They also showed that the maximum HPPH urinary excretion rate occurred 6 to 8 h after phenytoin dosing in humans. Low phenytoin doses (10 mg kg^{-1}) in monkeys showed a maximum HPPH excretion rate from 2 to 4 h, and high doses (50 mg kg^{-1}) had the maximum excretion rate occuring between 2 and 8 h (Glazko et al 1977). Haemodilution with either Fluosol or saline apparently did not prevent this characteristic delay in biliary cycling regardless of haemodiluent used, the extent of haemodilution, the time after haemodilution, or the phenytoin dosage.

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