Pharmacokinetic observations of phenytoin disposition in the newborn and young infant

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SUMMARY The pharmacokinetic profile of phenytoin (DPH) was studied in 30 infants aged 2 days to 96 weeks. The plasma DPH half-life during the first week of life in term infants was prolonged and very variable (20.7 ± 11.6 h, mean $\pm$ SD). Thereafter the plasma half-life was much shorter (7.6 ± 3.5 h). In preterm infants the half-life was much longer (75.4 ± 64.5 h) and more variable. The mean apparent volume of distribution was similar in these groups of infants: preterm newborn 0.80 ± 0.22 l/kg, term infants during the first week of life 0.80 ± 0.26 l/kg, and term infants >2 weeks of age 0.73 ± 0.18 l/kg. Predictions of steady-state plasma DPH concentrations, based on these kinetic parameters, were confirmed. Very low 'trough' plasma DPH concentrations were observed after the 14th postnatal day in 19 infants receiving 8 mg/kg per 24 h orally. On the other hand, infants of less than one week of age receiving the same dose, especially if preterm, frequently showed drug accumulation to toxic plasma DPH concentrations. The impaired binding of DPH to newborn plasma protein was confirmed but 'normal adult values' were approached by the age of 3 months.

An intravenous loading dose of 8 mg/kg (sodium phenytoin) can be expected to generate a mean plasma DPH concentration of 10 mg/l ($40 \mu\text{mol/l}$) in the newborn. Loading doses of up to 12 mg/kg were given without untoward effects. During the first week or so of life plasma DPH half-life is so variable that no fixed dosage regimen can be derived from the available data. Beyond the second week of life, however, a dose of 8 mg/kg per 24 h is probably inadequate for most infants.

Convulsive disorders of diverse aetiology occur frequently in the neonatal period. Symptomatic treatment often involves termination of acute seizures with intravenous diazepam and subsequent maintenance therapy with phenobarbitone (Holden and Freeman, 1975), after excluding disorders requiring specific therapy, such as hypoglycaemia. The rate of elimination of phenobarbitone is slow especially in newborn infants in whom the mean plasma half-life is about 200 hours (Wallin *et al.*, 1974; Boréus *et al.*, 1975). Therefore, initiation of phenobarbitone maintenance therapy without a loading dose implies a substantial delay before achievement of steady-state plasma concentrations (Wallin *et al.*, 1974; Rosen and Pippenger, 1975). Nonetheless, the potential central nervous system depressant effects of such a loading dose of the

barbiturate have not been evaluated in the newborn, and may be detrimental in certain already depressed infants.

In this study a group of infants who had failed to respond to the usual therapy, which frequently included the use of phenobarbitone, were treated with phenytoin (DPH). This agent is of proven efficacy in the prevention of seizures both in children and adults (Buchthal *et al.*, 1960; Svensmark and Buchthal, 1964), and is devoid of significant depressant side effects (Toman, 1970). There is also evidence that DPH is useful in the treatment of acute repetitive seizures in adults when the maintenance dose is preceded by an appropriate intravenous loading dose (Wallis *et al.*, 1968). Reports of toxicity relating to phenytoin in the newborn (Yaffe and Juchau, 1974) are not well documented. Degeneration of Purkinje cells in the cerebellum has been reported in patients receiving phenytoin, but this appears to relate to

Received 18 June 1976

sustained toxic plasma concentrations and may therefore be avoidable and/or reversible (Valsamis and Mancall, 1973).

There are few published data regarding the developmental sequence of mixed-function oxidative metabolism of drugs in the neonate. Drugs eliminated via this pathway, such as theophylline, are now being used for extended periods in the newborn. This paper describes age-related changes in the disposition of DPH in newborn and young infants.

Patients and methods

Clinical. 30 infants were studied and clinical details are given in Table 1. 2 infants were born to epileptic mothers treated daily with DPH 300 mg plus phenobarbitone throughout pregnancy. Neither infant was breast fed. Signed, informed consent was obtained, and heparinized blood (about 100 μ l) was obtained from the infants by heel puncture every 12 hours for 3 days. All other infants were being treated with DPH for convulsive disorders.

Table 1 Clinical conditions related to phenytoin usage

Diagnosis	n	Patients*
<i>Newborn infants</i>		
Maternal epilepsy	2	A, B
Perinatal asphyxia alone	11	C, D, E, F, V, W, X, Y
Asphyxia, pulmonary haemorrhage	2	U
Seizures, aetiology uncertain	3	H, N
Prematurity, sepsis	4	M, O†, P, Z
Diaphragmatic hernia, hypoxia	1	—
Cerebral haemorrhage, birth trauma	1	G
<i>Others</i>		
Retarded, birth trauma	2	J, K
Hypoxia, electrolyte disturbance	2	I
Hydrocephalus	1	L
Nonketotic hyperglycinaemia	1	—

*Does not include 8 patients from groups II and III (Table 3).

†Patient O had histological evidence of severe liver disease at necropsy.

DPH therapy was started as an intravenous loading dose of 12 mg/kg phenytoin sodium (Epanutin, Parke Davis), given over 15–20 minutes by syringe infusion pump. 24 hours later oral maintenance therapy was started with phenytoin, about 8 mg/kg per 24 h, given in divided doses every 12 hours. Solid dose preparations of DPH do not permit the small changes in dosage needed in young infants. Dilantin Suspension (Parke-Davis) was therefore used and the usual precautions taken to minimize errors in dose (Capper and Smith, 1960). Patients E, F, M, O, P received the maintenance dose intravenously for 7–10 days. 'Trough' plasma DPH concentrations were measured daily immediately before

a dose was given throughout the study period. The plasma concentration of DPH was considered to be at steady-state, C_p^{ss} , only after at least 7 days of maintenance therapy. For the analysis of C_p^{ss} data (Table 3), infants were divided into 3 groups according to postnatal age. Group I had received DPH from the first or second day of life and the C_p^{ss} was measured on day 8. Group II infants were aged 14–25 days and group III infants 5–96 weeks when the C_p^{ss} was measured.

Plasma concentrations of DPH after the initial intravenous loading dose were studied in detail in 10 term and 4 preterm infants. Capillary blood samples were collected 30 minutes after the infusion and on several other occasions over the next 24 hours. $\log_{10}$ plasma concentration versus time curves conformed to one-compartment, first-order kinetic analysis. 2 infants with indwelling intravenous catheters had frequent early sampling after a 15-minute infusion which revealed a brief distribution phase which was 'completed' within 15–20 minutes. No evidence of saturation kinetics was observed within the plasma concentration and time constraints of the study (Fig. 1). Linear least-squares regression

Fig. 1 $\log_{10}$ plasma phenytoin (DPH) concentration-time curves in 3 patients. Conversion: Traditional units to SI—DPH: 1 mg/l $\approx$ 4 μ mol/l.

of the $\log_{10}$ plasma DPH concentration versus time curves was performed with the use of a PDP-8 computer. Time 0 refers to the onset of infusion. The apparent volume of distribution was calculated as dose/ C_p where dose equals mg/kg of administered phenytoin (92% of phenytoin sodium), and C_p equals the extrapolated zero time plasma DPH concentration.

Radioimmunoassay of DPH. Plasma DPH concentrations were determined by radioimmunoassay (RIA) described by Cook *et al.* (1973). ^3H -DPH (62 Ci/mmol) and sheep DPH antisera (batch no. DS131-5), were provided by the Chemistry and Life Sciences Division, Research Triangle Institute, North Carolina. In our laboratory precision was enhanced by performing the assay over the range 0.5–20 ng, instead of the reported 20–500 pg. Standard solutions of DPH, initially in ethanol, then diluted in buffer, were prepared. An antiserum dilution of 1:500 was used, and plasma samples were diluted 1:100 in sodium phosphate buffer, 0.1 mol/l, pH 6.7, before assay. A similar dilution of control human plasma (adult) was added to standards. A standard curve performed in the presence of neonatal plasma did not differ significantly. After an incubation period of 2.5 hours on ice, incubation volume 0.7 ml, separation of bound and free DPH was achieved with use of 0.5 ml dextran-coated charcoal, 0.5%. After centrifugation at 4°C, the supernatant was admixed with Bray's solution, and radioactivity was determined in a Beckman LS-150 scintillation counter with external quench correction. RIA data were analysed using a regression of logit B/B₀ versus log₁₀ standard concentration with a PDP-8 computer. Lederle quality control sera* were included in each assay at two dilutions corresponding to 5 and 20 ng DPH. 30 plasma samples containing DPH over the concentration range 0–35 mg/l (0–140 µmol/l) were analysed by RIA and by gas-liquid chromatography (Sherwin *et al.*, 1973) (Fig. 2).

Plasma protein binding of DPH. Plasma protein binding of DPH was measured using an ultra filtration technique (Amicon CF50 Cones, Boston, Mass.) after incubation of plasma samples, 2.0 ml, for one hour at 37°C under 5% carbon dioxide in air with ^{14}C -enriched DPH (New England Nuclear, Boston, Mass.) at a total DPH concentration of 15 mg/l (60 µmol/l). Plasma samples were obtained from

young adult volunteers, from cord blood collected after uneventful deliveries, and from infants and children who had venepuncture during the course of minor medical illnesses or elective minor surgery.

Results

Disposition of DPH after a single intravenous dose.

The plasma half-life and apparent volume of distribution of DPH determined after single intravenous doses in 16 patients aged 2 days to 96 weeks, given in Table 2 A, B, show an obvious relationship between postnatal age and plasma half-life of the drug. 7 term infants who initially received DPH between the ages of 17 days and 96 weeks showed a mean plasma half-life of 7.6 ± 3.5 h (mean $\pm$ SD) and a mean apparent volume of distribution of 0.73 ± 0.18 l/kg. The 6 infants studied within one week of birth

Table 2A Pharmacokinetic data in 12 term infants after single intravenous doses of Phenytoin*

Patient	Postnatal age	Volume of distribution (l/kg)	Plasma half-life (h)
A (TP)*	2 d	—	18.7
B (TP)*	2 d	—	22.3
C	2 d	0.71	41.9
D	3 d	0.47	16.6
E	4 d	1.00	6.8
F	4 d	1.02	17.7
Infants <1 week of age			
Mean		0.80	20.7
SD		0.26	11.6
C†	2.0 w	—	15.1
G	2.6 w	0.53	8.7
H	7 w	0.62	5.5
I	16 w	1.04	6.6
J	21 w	0.80	6.6
K	72 w	0.72	6.2
L	96 w	0.69	4.6
Infants >2 weeks of age			
Mean		0.73	7.6
SD		0.18	3.5

*2 infants received DPH transplacentally (TP).

†Plasma half-life in patient C was determined a second time after stopping DPH for 48 hours.

Table 2B Pharmacokinetic data in 4 preterm infants after single intravenous doses of phenytoin

Patient	Gestational age at birth (w)	Birthweight (g)	Postnatal age (d)	Volume distribution (l/kg)	Plasma half-life (h)
M	32	2120	2	0.57	19.6
N	36	2950	3	0.83	57.0
O	33	2040	4	—	160.0
O*	33	2040	10	—	125.0
P	26	760	18	1.00	15.6
Mean				0.80	75.4
SD				0.22	64.5

*Plasma half-life in patient O was determined a second time after stopping DPH.

Fig. 2 Comparison of DPH concentrations in 30 plasma samples measured independently by radioimmunoassay (RIA) and gas-liquid chromatography (GLC). The solid line was derived by linear least-squares regression analysis. The broken line is defined by the equation $Y=X$.

showed marked intersubject variability but a longer mean plasma half-life (20.7 ± 11.6) ($P < 0.01$, Mann-Whitney U test, performed because of unequal variances).

The apparent volume of distribution of DPH in the 4 infants for whom such calculations were possible was 0.80 ± 0.26 l/kg and did not differ from those derived for the older infants ($P > 0.1$, unpaired t-test). A group of 4 preterm infants (Table 2B) aged 2–18 days also showed prolonged and highly variable half-lives (75.4 ± 64.5 h). These 4 infants (and patient K) were the only patients in the entire study who did not receive phenobarbitone concurrently. The greatly prolonged half-life in patient O may also have related to severe liver disease in addition to prematurity. Since the study period in these infants with convulsive disorders was restricted to 24 hours, the numerical values assigned to the longer half-lives must be considered approximations.

Postnatal age and plasma concentrations of DPH during maintenance therapy. Assuming that these single dose pharmacokinetic results are applicable to repetitive dosing, certain consequences follow. (a) The prolonged but individually variable plasma DPH half-life early in the neonatal period predicts that after an appropriate loading dose a maintenance dose rate of 8 mg/kg per 24 h

would generate a transient rise in the plasma concentration of DPH in many individuals; (b) the consistently short plasma half-lives observed by the 2nd or 3rd postnatal week in term infants would predict much lower steady-state plasma concentrations of DPH by this age. The data presented in Fig. 3–5 conform to these predictions. Each of these 12 infants received an intravenous loading dose of DPH, followed by a maintenance dose of about 8 mg/kg per 24 h (mean 8.1 ± 0.1 SD).

Fig. 3 shows that 3 infants had substantial in-

Fig. 3 Plasma DPH concentrations measured before a dose in 3 patients receiving a maintenance DPH dose of about 8 mg/kg per 24 h given every 12 hours after an initial loading dose (see text). The first plasma concentration shown was measured just before the first maintenance dose. The broken lines (patient C) represent time periods during which plasma DPH half-life was measured.

creases in plasma DPH concentration during the early neonatal period; then on the same maintenance dose (per kg), plasma DPH concentrations decreased substantially with age to low steady-state values. A potentially toxic plasma DPH concentration of 28.6 mg/l ($114 \mu\text{mol/l}$) was observed in patient C on day 6. The rapidity of change in the elimination rate constant in this infant is shown by the DPH half-life measured separately on days 2 and 14, and calculated on day 25 from the steady-state plasma concentration; these half-lives were 41.9, 15.1, and 5.6 h, respectively. In one of these infants, patient V, seizures stopped shortly after the loading dose, but recurred on day 15 when the plasma DPH concentration had decreased to less than 3.0 mg/l. ($12 \mu\text{mol/l}$).

The 5 infants shown in Fig. 4 were treated with the

Fig. 4 Plasma DPH concentrations measured before a dose in 5 patients receiving a maintenance DPH dose of about 8 mg/kg per 24 h given every 12 hours after an initial loading dose (see text). The first plasma concentration shown was measured just before the first maintenance dose.

same dosage regimen but show a different pattern. E and Y had rapid decreases in plasma DPH concentration over the 24 hours after an intravenous loading dose to presumably subtherapeutic levels of <2 mg/l ($8 \mu\text{mol/l}$). The other patients (W, X, and F) behaved in an intermediate fashion. The 4 preterm infants (Fig. 5) showed patterns of drug accumulation which are also consistent with rapid maturation of oxidative drug metabolism occurring after the second week. 2 of these infants (M and O) attained potentially toxic plasma DPH concentrations in the second week of life. 2 older infants (P and Z), on the

Fig. 5 Plasma DPH concentrations measured before a dose in 4 premature infants. $\uparrow$ = Maintenance therapy started; $\downarrow$ = DPH stopped in patient O.

same dose, achieved much lower steady-state plasma DPH concentrations, <5 mg/l ($20 \mu\text{mol/l}$), not unlike term infants of similar postnatal age. However, the developmental pattern for DPH elimination in preterm infants has still to be defined.

Table 3 shows steady-state 'trough' plasma DPH concentrations in 27 infants grouped according to

Table 3 Steady-state plasma DPH concentrations 12 hours after a dose in 26 infants receiving a mean dose of 8.0 mg/kg per 24 h

Group	I	II	III
No.	8	10	9
Age*	8 d	14-25 d	5-96 w
Mean dose ($\pm$ SD) (mg/kg per 24 h)	8.1 $\pm$ 0.1	8.0 $\pm$ 0.8	8.1 $\pm$ 0.6
Plasma DPH concentration (mg/l)			
Mean	11.0†	2.2	2.0
SD	9.6	1.2	1.5
Range	0.9-28.6	0.6-3.8	0.5-5.7

*Age refers to the time at which steady-state plasma concentrations were measured.

†This value excludes the 2 preterm infants, M and O, in whom Cp^{ss} on day 8 were 37.0 and 51.8 respectively (Fig. 5).

postnatal age. The results again reflect the slow and variable drug elimination in the first week. The mean doses received were not significantly different (unpaired t-test); however at 8 days of age the mean Cp^{ss} was 11.0 ± 9.6 mg/l ($44 \pm 38.4 \mu\text{mol/l}$), compared to 2.2 ± 1.2 ($8.8 \pm 4.8 \mu\text{mol/l}$) and 2.0 ± 1.5 ($8 \pm 6 \mu\text{mol/l}$) at 14-25 days and 5-96 weeks, respectively. The difference in Cp^{ss} observed between group I and group II and/or III was significant ($P < 0.01$, Mann-Whitney U test). The difference between groups II and III was not significant (unpaired t-test).

Plasma protein binding of DPH as a function of age.

Impaired binding of DPH to cord plasma protein (Ehrenbo *et al.*, 1971) and displacement of the hydantoin by bilirubin (Rane *et al.*, 1971) and fatty acids (Fredholm *et al.*, 1975) have been reported. Since the plasma concentration of unbound drug is likely to correlate better than total drug with pharmacological effect (Booker and Darcey, 1973), it is important to ascertain protein binding throughout childhood in order to interpret the significance of observed total plasma DPH concentrations. In fact, diminished protein binding could contribute to observed low steady-state concentrations in infants more than 2 weeks of age (Table 3). Unfortunately, sample volume considerations prevented detailed study of binding in the plasma of infants less than 3 months old (except for cord plasma), but the data in Table 4 show that, at a

Table 4 Plasma protein binding of DPH assessed by ultrafiltration at 37°C and a total DPH concentration of 15 mg/l

Patient groups	Percent unbound DPH mean $\pm$ SD (no.)	P value*
Adult	12.6 $\pm$ 1.6 (16)	—
Newborn (cord plasma)	19.8 $\pm$ 2.6 (28)	<0.001
Infants 3 m–2 yr	14.7 $\pm$ 3.4 (8)	0.05
Children		
2 yr–4 yr	14.8 $\pm$ 1.1 (10)	0.01
5 yr–16 yr	14.0 $\pm$ 2.3 (19)	>0.05

*Unpaired t-test (two-tailed), compared to adult.

total DPH concentration of 15 mg/l (60 μ mol/l) the impaired binding seen neonatally had approached adult values by 3 months of age. The binding of DPH throughout childhood differed slightly from adults. These differences are of borderline statistical and of no clinical significance.

Discussion

DPH elimination in man occurs largely via the hepatic microsomal mixed function oxidase reaction with subsequent glucuronidation and excretion of the hydroxylated derivatives, mainly HPPH (Chang and Glazko, 1972). In adults the oxidation of DPH exhibits saturability at high plasma concentrations (Arnold and Gerber, 1970). Horning *et al.* (1975) have found HPPH (5-p-OH phenyl, phenylhydantoin) and its glucuronide, as well as the dihydrodiol derivative, in the urine of infants who had been exposed to DPH transplacentally or after birth. Identical metabolites have been found in adult urine. Indeed, the relative proportions of DPH, HPPH, and conjugated HPPH in urine from neonates who had acquired DPH (and perhaps, metabolites) transplacentally resemble those seen in urine from adult man (Reynolds and Mirkin, 1973; Rane, 1974).

Pharmacokinetic investigations of DPH in infants have been reported by Mirkin (1971, 7 newborns, transplacental acquisition), Rane *et al.* (1974, 7 newborns, transplacental acquisition), Baughman and Randinitis (1970, 1 newborn, transplacental acquisition), and Jalling *et al.* (1970, steady-state plasma concentrations in 6 infants, 5 of whom were more than 3 weeks old). The interpretation of events in each study and the method of data analysis have influenced conclusions. Mirkin (1971), though noting that elimination was 'very slow on postpartum days 1 and 2, and increased markedly on postpartum day 3', pooled data and derived an average plasma half-life of about 60 hours. Rane *et al.* (1974) thought the early slow phase of elimination reflected saturation kinetics; analysis of the subsequent first order decay curves omitted the events of the first few days

and yielded plasma half-lives (6.6–34 h) similar to adult values. Jalling *et al.* (1970) observed surprisingly low steady-state plasma concentrations of DPH after multiple intramuscular or oral doses in older infants. The data presented here are consistent with each set of observations.

The single intravenous dose studies suggest that the low steady-state plasma concentrations observed after 2 or 3 weeks of age reflect primarily the shorter half-life in young infants relative to the adult. The data probably reflect maturation of drug oxidative activity (Neims *et al.*, 1976). Indeed, when the half-lives derived for the term infants reported here are combined with estimates calculated from reported data (Baughman and Randinitis, 1970; Jalling *et al.*, 1970; Mirkin 1971; Rane *et al.*, 1974), mean DPH plasma half-lives of about 80, 15, and 6 hours are found for the age groups 0–2, 3–14, and 15–150 days, respectively (Fig. 6). Large intersubject

Fig. 6 Plasma DPH half-life in infants grouped according to postnatal age. Each infant received the drug either transplacentally (●) or as an initial therapeutic dose (■). Some half-lives were calculated from steady state plasma DPH concentrations (▲). Means and SDs are shown. Data were obtained from several published studies (see text).

variability is seen during the first few postnatal days with half-lives ranging from <10 to >100 hours; the variability diminishes with age. Since many of the infants in these series also received phenobarbitone, the influence of the latter on the developmental pattern cannot be excluded. Nonetheless, there was no correlation between phenobarbitone exposure, transplacentally or postnatally, and DPH half-life. Previous studies have shown that in the first few days of life the oxidative metabolism of certain other drugs is also slow compared to that of the adult; for example, tolbutamide (Nitowsky

et al., 1966), acetanilid (Vest and Streiff, 1959), diazepam (Morselli *et al.*, 1973), phenobarbitone (Wallin *et al.*, 1974; Boréus *et al.*, 1975), and amylobarbitone (Draffan *et al.*, 1976).

The observed clearance of DPH per unit body weight in young infants beyond the neonatal period is considerably higher than that reported in adults (Glazko *et al.*, 1969). This phenomenon has been observed not only with DPH (Svensmark and Buchthal, 1964) but also with phenobarbitone (Heinze and Kampffmeyer, 1971), theophylline (Loughnan *et al.*, 1976), phenylbutazone, and antipyrine (Alvares *et al.*, 1975).

Clinical trials based on reported data, and comparing the efficacy and toxicity of available anti-convulsants are needed to determine optimal therapy for the newborn and young infant. In the absence of pharmacodynamic data in this age group, an appropriate therapeutic plasma DPH concentration must be selected. Data reported in adults and older children suggest that plasma concentrations of 10–20 mg/l (40–80 μ mol/l) are effective (Buchthal *et al.*, 1960). The impaired protein binding seen with cord plasma may persist through the first weeks of life, as has been shown for bilirubin (Kapitulnik *et al.*, 1975). Such impaired binding in the newborn would indicate a higher concentration of unbound DPH at any given total plasma concentration. A therapeutic concentration range of 6–14 mg/l (mean 10 mg/l, total drug; 24–56 μ mol/l, mean 40) may therefore be more appropriate in the immediate neonatal period. An intravenous loading dose of 8 mg/kg phenytoin sodium would be expected to achieve rapidly a mean plasma DPH concentration of 10 mg/l (40 μ mol/l) in all age groups studied. No toxicity has been noted using a 15-minute infusion of 12 mg/kg which produced a mean C_p of 15 mg/l (60 μ mol/l).

The selection of a maintenance dose rate is difficult because of the rapidly changing and variable elimination of DPH after birth. Certainly the maintenance dose rate used in this study, 8 mg/kg per 24 h, resulted in potentially toxic accumulation in some infants during the first postnatal week (Fig. 3); other infants of the same age showed subtherapeutic concentrations (Fig. 4). The mean kinetic data for term infants less than 1 week of age indicate that a maintenance dose rate of 5.9 mg/kg per 24 h (phenytoin, free acid) would achieve a mean, but variable, steady-state plasma DPH concentration of 10 mg/l (2.4–21.0 mg/l) (40; 5.76–84 μ mol/l). However, because of this marked individual variation it is impossible to recommend a fixed dosage regimen in this group. Clinical assessment and, when possible, plasma concentration measurements, are necessary. In particular, a plasma DPH concentration

measured 36–48 hours after starting therapy would be of value. We emphasize that these difficulties exist only in the case of the maintenance dose in the first week of life for term infants and possibly longer for the preterm. The loading dose at all ages and the maintenance dose in older infants are more clearly defined in the data presented.

By the second week most infants will require a dosage increase to at least 8 mg/kg per 24 h and in view of the half-life at this age, a shorter dosage interval of 6–8 hours may be necessary to prevent undue fluctuations in plasma concentrations between doses. The present data suggest that a much higher dose may be required, namely 15.4 mg/kg per 24 h, for a mean plasma concentration of 10 mg/l, range 6.2–19.1 mg/l (40; 24.8–76.4 μ mol/l). This calculated dose (15.4 mg/kg per 24 h) is *not* now recommended because saturation kinetics may occur (Arnold and Gerber, 1970). Such zero-order kinetics, though not evident in this study (Fig. 1), cannot be confidently excluded with the doses and methodology used. When such low plasma concentrations are documented in infants with inadequate seizure control, the dosage should be increased with monitoring of plasma concentration of DPH.

We gratefully acknowledge the assistance of the nursing staff of the Newborn Intensive Care Unit, Montreal Children's Hospital, and the medical and nursing staff of the Neonatal Unit, Royal Children's Hospital, Melbourne; Dr. A. Sherwin who performed gas chromatographic analyses of DPH; Mme. Lori Bonet for technical assistance; Sylvia Cohen and Norma Downey for secretarial help. We are indebted to Dr. C. E. Cook of Research Triangle Park, who developed and supplied the materials necessary for radioimmunoassay of DPH under US National Institute of Health Contract No. PH-43-NIGMS-65-1057.

P. M. L. holds a Fellowship in Clinical Sciences (Clinical Pharmacology), National Health and Medical Research Council of Australia. Presented in part at the Society for Pediatric Research, Denver, Colorado, April 1975.

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