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Pharmacokinetics of Phenobarbital in Childhood

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Summary. In 14 neonates 1–4 weeks old, 30 babies aged 1–12 months, and 7 infants of 1–5 years of age, the serum levels of phenobarbital were determined by a gas chromatographic micro-method after intravenous injection of phenobarbital 5–10 mg per kg body weight. It was possible to calculate the pharmacokinetic parameters using a two compartment open model. The distribution volumes within the individual age groups and the rate constants k_{12} and k_{21} showed no significant differences, but the elimination half-life was significantly longer in neonates (118.6±16.1 h) than in babies (62.9±5.2 h) or infants (68.5±3.2 h).

Key words: Phenobarbital, pharmacokinetics, neonates, infancy.

Little is known about the pharmacokinetics of phenobarbital in childhood despite the frequent use of this compound in paediatrics. Findings in adults [1, 2, 3, 4] are of only limited relevance to newborns and babies, since in this age range certain unique pharmacokinetic characteristics of the distribution, metabolism and elimination of drugs have to be considered [5].

The few published pharmacokinetic studies of phenobarbital in childhood [6, 7, 8, 29, 30, 31, 32] have only determined the elimination half-life from blood levels, assuming that the elimination of phenobarbital is proportional to its plasma concentration and that it follows a simple exponential function, i. e. that the organism could be regarded as a single-compartment system. The published findings are contradictory. While some authors [6] have found an elimination half-life in neonates comparable to that in adults, others have reported either prolonged [29, 30, 31] or considerably more rapid elimination [8, 9]. Direct comparison of these findings, however, is difficult, since the route of administration of phenobarbital was different. Some authors have studied elimination of phenobarbital after i. m. injection [29, 30, 31, 32] and others after oral administration of pulverized tablets [29, 30] given in milk; some neonates have been investigated whose mothers had been treated with phenobarbital before delivery [30, 6]. In addition, several different analytical methods have been employed.

It was the objective of this study, therefore, to determine kinetic data for phenobarbital elimination in the newborn, baby and infant after a single i. v. injection, using a gas chromatographic micro-method of analysis, in order to derive pharmacokinetic models of general validity.

Patients and Methods

51 patients were investigated: 14 mature neonates with a birth weight greater than 2500 g (mean 3250 g) and a normal gestational age were treated with phenobarbital 7.5 mg (range 5–10 mg) per kg body weight. The therapy was clinically necessary because of convulsions. 30 babies, whose ages ranged from 2–12 months, and 7 infants 2–5 years old received phenobarbital[1] 10 mg per kg body weight to induce sedation during vomiting and febrile convulsions. All the patients had normal renal function and disorders of acid-base balance were excluded. After intravenous injection of phenobarbital, which was diluted 1:10 in isotonic NaCl solution, 4 capillary blood samples were taken from the finger tip or heel during the succeeding 60 minutes.

[1] Luminal®, Bayer, Leverkusen, GFR

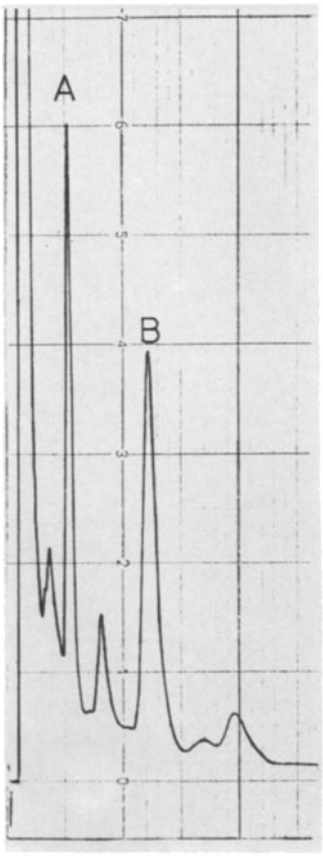

Fig. 1. Gas chromatogram after injection of 1.0 µl reaction mixture. **A:** N,-N'-dimethylphenylethyl-barbituric acid. The peak represents 87.7 ng. **B:** Internal standard C_{17} margarinic acid methylester 100 ng. The retention time for A was 1.71 min and for B 4.48 min

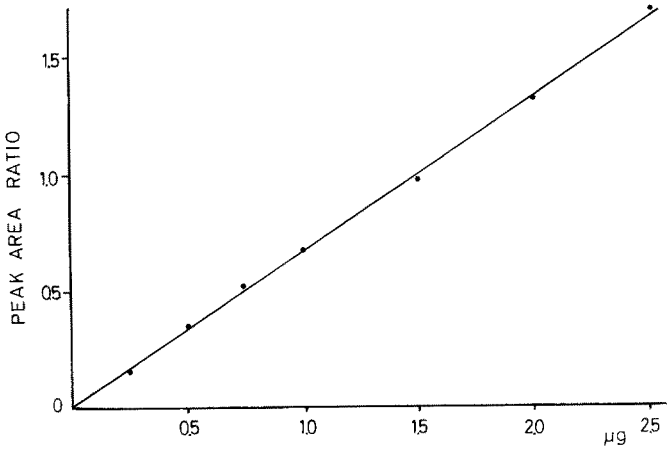

Fig. 2. Peak area ratio of C_{17}-margarinic acid methylester (internal standard) to N,N'-dimethyl phenobarbital as a function of the amount of phenobarbital added to 50 µl serum. The mean values of 8 determinations are shown. The peak areas were determined by an integrator (Hewlett-Packard 3370 B)

Two samples were taken each day for the next 8 days.

Since repeated venous or arterial samples could not be obtained from newborns and small infants, a gas chromatographic method of high sensivity was developed for determination of phenobarbital in 50 or 100 µl serum samples. The principle of the method was transformation of phenobarbital to its N, N'-dimethyl derivative using methyl iodine as the alkylating agent and potassium carbonate as the condensing agent [10]. A modification of the technique of Dünges and Bergheim was used [11]. The advantages of this method over other techniques, for instance "on-column" methylation, are discussed in detail elsewhere [11].

a. Reagents:

1. 1 N HCl (Merck, Darmstadt No. 9057)
2. Acetone p. a. (Merck, Darmstadt, No. 12) was dried over potassium carbonate (Merck, Darmstadt, No. 4926)
3. Potassium carbonate (Merck, Darmstadt, No. 4926) was dried in vacuo at 170° C over phosphorus pentoxide
4. Methyl iodine p. a. (Merck, Darmstadt, No. 6064) was redistilled before use
5. Benzol, (Merck, Darmstadt, No. 1785)
6. C_{17}-margarinic acid methylester (Merck, Darmstadt, No. 9754)

b. Apparatus:

1. GLC 5700 (Hewlett-Packard) with FID
2. Integrator (Hewlett-Packard) No. 3370 B

c. Analytical Procedure

Serum 50 µl was acidified with 1 N HCl 10 µl and was twice extracted with ether-chloroform (8:2) 400 µl.

The extracts were combined in a pasteur pipette, which was melted at the tip (micro-reflux-condense), and evaporated to dryness. After addition of acetone 100 µl, methyl iodine 100 µl and potassium carbonate 1–2 mg methylation was carried out putting the micro-reflux-condense 1 cm into a water bath at 56° C and cooling the remaining part (4° C). After complete reaction (30 minutes), the solution was evaporated to dryness in a desiccator and then dissolved in benzol 50 µl containing C_{17}-margarinic acid methyl-ester as an internal standard (1 µg/ml). 1 µl of the solution was injected into the GLC and was analysed under the following conditions: detec-

tor temperature 250° C, injection port temperature 200° C, N_2 30 ml/min, H_2 30 ml/min, air 240 ml/min. A 50 cm steel column was used (temperature 140° C), filled with 1.5% UCC-W 982 on Chromosorb WHP 80–100 mesh. A typical gas chromatogram is shown in Figure 1.

d. Quantitative Results

The yield of derivatisation was 98%±6% (S. D.; 11). Calibration curves have been established with authentic N, N'-dimethyl phenobarbital. The reproducibility has been tested analysing 7 different concentrations on eight separate occasions. Using the t-test, the reproducibility expressed in standard deviations was 4.1%. The recovery from serum was 98.2±2.8% (S. D.), the miniumum detectable serum concentration of phenobarbital was 0.2 µg per ml serum. A standard curve is shown in Figure 2.

e. Statistical Methods

A digital computer program was used for calculating the hybrid constants A, α, B and β, from which the pharmacokinetic parameters of the two-compartment open model can be determined [12].

Results and Discussion

The concentration-time-curve measured in serum after i. v. injection of phenobarbital showed a very rapid decrease during the first 30 to 60 min, followed by a much slower decline over a period of several days (Fig. 3). The two elimination phases can clearly be distinguished. They indicate that elimination of phenobarbital, like that of other barbiturates [13], follows a model with at least two different compartments.

Injection and distribution of phenobarbital in the central compartment clearly followed a rapid flow (α-phase) into a peripheral compartment. The central compartment accounts for the much slower elimination (β-phase) of phenobarbital, which is characterised by biotransformation in the liver [14] and elimination of free barbituric acid and its metabolites via the kidney [15]. This kinetic model may be described by the equation (I):

$$C = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \qquad (I)$$

defining serum concentration C as the sum of two exponential functions at time (t) [16, 17, 18, 19]. The hybrid constants A, B, α and β in this equation

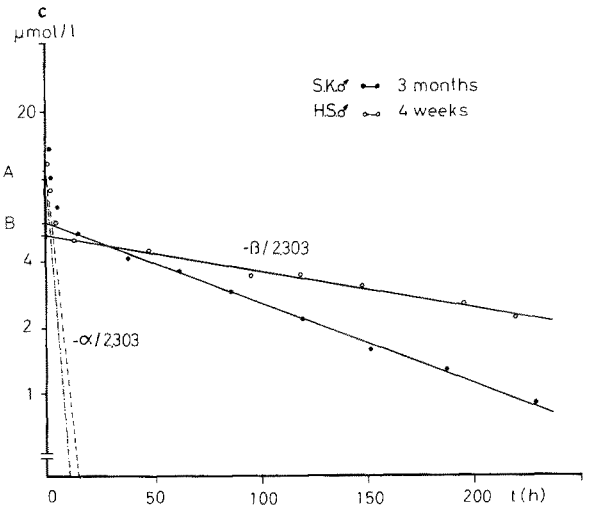

Fig. 3. Serum concentration of phenobarbital after intravenous administration of 10 mg/kg body weight plotted on a semilogarithmic scale. The hybrid constants of the two compartment open model A, B, the rapid α- and slow β-slope were calculated by a computer program (12); (○; ●) = experimentally determined values; (——) = regression line calculated for the β-phase; (– – – –) = regression line calculated for the residuals of the α-phase. Two representative concentration curves are shown from a neonate and an older infant. Statistical analysis of the age-dependent kinetic parameters is shown in Tables 1–3

were determined by means of the computer program mentioned above. Serum concentration at time t = 0, total metabolic clearance, rate constants k_{12}, k_{21}, and k_{el} of the open 2-compartment model and the values of the distribution volumes can be calculated with these constants (for the corresponding equations II–IX see Appendix).

The kinetic parameters of phenobarbital elimination in children of different age groups determined according to an open 2-compartment model are summarised in Tables 1–3. The value of α (Table 1), representing the rapid flow of phenobarbital from the central into the pheripheral compartment, did not show a significant difference between the newborn baby and infant. Constant β, however, which reflects the much slower elimination, showed significant age-dependent changes (Table 1; $p<0.05$). In neonates the elimination half-life (118.6±16.1 h) was significantly longer than in older babies (62.9±5.2; 63.2±4.2 h, respectively) or in infants (68.5±3.2 h).

Total metabolic clearance calculated according to equation IX (see Appendix) shows similar behaviour. In newborns it was clearly lower per kg body weight than in older children (Table 1). In accordance with these data, the rate constant k_{el} of the postulated 2-compartment model describing elimination from the central compartment was signifi-

Table 1. Kinetic parameters ($\bar{x} \pm$ S. D.) of phenobarbital elimination from serum in different age groups using an open two compartment model; see Equation (I)

Age	n	A	B	α	β	Elimination-half-life	Cl_{tot}/kg
		µmol/l	µmol/l	(h^{-1})	(h^{-1})	(h)	(ml · h^{-1})
0–4 weeks	14	27.99±4.51	38.14±3.48	1.336±0.132	0.0067±0.0008	118.6±16.1	$5.71 \cdot 10^{-4}$
2–3 months	16	39.68±3.44	55.9 ±4.51	1.465±0.650	0.0196±0.0009	62.9± 5.2	$9.59 \cdot 10^{-4}$
4–12 months	14	53.36±5.41	67.89±3.52	1.406±0.304	0.0115±0.0006	63.2± 4.2	$7.01 \cdot 10^{-4}$
>12 months	7	62.65±18.0	71.25±7.09	1.177±0.665	0.0102±0.0005	68.5± 3.2	$8.12 \cdot 10^{-4}$
		$\bar{x}$±S. D.	$\bar{x}$± S. D.	$\bar{x}$± S. D.	$\bar{x}$± S. D.	$\bar{x}$± S. D.	$\bar{x}$

Table 2. Hybrid constants ($\bar{x} \pm$ S. D.) of the open two compartment model in different age groups

Age	n	$k_{12}(h^{-1})$	p	$k_{21}(h^{-1})$	p	$k_{el}(h^{-1})$	p
0–4 weeks	14	0.553±0.09	>0.05	0.777±0.09	>0.05	0.012±0.0021	<0.025
2–3 months	16	0.646±0.32		0.809±0.32		0.024±0.0018	
4–12 months	14	0.397±0.16		0.756±0.13		0.020±0.0011	
>12 months	7	0.516±0.34		0.739±0.32		0.018±0.0019	
		$\bar{x} \pm$ S. D.		$\bar{x} \pm$ S. D.		$\bar{x} \pm$ S. D.	

Table 3. Distribution volumes of the steady state V_{dss}, the central compartment V_1 and peripheral compartment V_2 in the different age groups ($\bar{x} \pm$ S. D.)

Age	n	V_{dss} (l/kg)	V_1 (l/kg)	V_2 (l/kg)
0–4 weeks	14	0.850±0.059	0.496±0.044	0.353±0.048
2–3 months	16	0.857±0.089	0.496±0.046	0.361±0.046
4–12 months	14	0.570±0.046	0.342±0.026	0.237±0.024
>12 months	7	0.666±0.073	0.396±0.052	0.270±0.043
		$\bar{x} \pm$ S. D.	$\bar{x} \pm$ S. D.	$\bar{x} \pm$ S. D.

cantly lower in neonates (0.02 h^{-1}) than in older babies (0.020 h^{-1}) or infants (0.018 h^{-1}).

It is striking that for all age groups the apparent distribution volume in steady state (V_{dss}; Table 3) related to body weight in kg was clearly higher than the age-dependent volume of total body fluid, which accounts for 80% of body weight in newborns, 60 to 75% in babies, and 55 to 65% in infant age [20]. The distribution volume of the central compartment V_1, or the initial dilution volume, was 2 to 3 times smaller than the distribution volume in steady state V_{dss}. According to these findings phenobarbital, like other barbiturates [13], becomes distributed in tissue due to its lipophilic properties.

Comparison of the distribution volumes within individual age groups showed almost equal values related to body weight, and there was a true difference only between the neonates and babies of 4 to 12 months of age (Table 3). There were also no significant differences between individual age groups in rate constant k_{12} reflecting the flow of phenobarbital from the central to the peripheral compartment, and k_{21} which represents reflux into the central compartment. In accordance with the different sizes of the distribution volumes of the central and peripheral compartments (Table 3) k_{12} was somewhat smaller than k_{21} in all age groups.

Since the apparent distribution volumes (V_{dss}) in steady state, as well as those in the central (V_1) and peripheral (V_2) compartments, were not subject to age-specific change, there must be other causes for the significant differences in elimination half-life or k_{el} between neonates and older babies. Specific attention should be paid to age-dependent limited function of organs like liver and kidney, which play a role in metabolism and elimination [5]. The functional performance of these organs is important for elimination, since 50–75% of phenobarbital is metabolised into p-hydroxy-phenobarbital in the liver [21], which reduces its pharmacological efficacy [15]. Subsequently this metabolite is eliminated very rapidly via the kidney [14], whilst non-metabolised phenobarbital is eliminated via the kidney in the form of free acid, and sulphate or glucuronide [14, 15]. The limitation of certain enzymatic liver functions in newborns, as well as reduced glomerular filtration and tubular secretion of the kidney, could

be the reason for delayed elimination of phenobarbital in newborns.

Studies by Boreus and coworkers [22], however, have excluded a lower metabolic rate in the liver. In urine from neonates they found comparable fractions of p-hydroxy-phenobarbital and the glucuronides to those in adults [22]. Thus, the delayed elimination of phenobarbital has to be ascribed to the limited renal elimination in newborns. Elimination of phenobarbital is delayed until the 3rd or 4th week of age and so it shows good coincidence in time with the age-dependent glomerular filtration rate for thiosulphate, which also reaches the value found of older children or adults in this age range [23]. The influence of the pH of urine on the rate of tubular absorption, which is increased by non-ionic diffusion, is probably of importance in the first days after birth; in neonates and young babies urinary pH is normally more acid than in older children and adults [24], i. e. the tubular reabsorption rate is faster than at later age.

Kinetic data determined with the 2-compartment model demonstrate that in neonates elimination from the central compartment is slower than in older children, which cannot be ascribed to changes in the distribution volume. This confirms the previous finding of a longer elimination half-life in neonates than in older children [7]. Other results describing shorter half-life in 5 newborns than in adults [8] have not been confirmed.

Certain dosage recommendations for phenobarbital in childhood have been based on measurement of plasma levels after long-term medication [9], or on determination of the sleeping period as a function of age and dosage [25]. From these came the recommendation for administration of a relatively larger dose to babies, but it is not consistent with the pharmacokinetic data of age-dependent phenobarbital elimination. Clinical experience showing that in younger babies a higher dose was required for a persistent sleep-inducing effect might be due to diminished responsiveness of the central nervous "receptor" [26, 27]. Present pharmacokinetic data demonstrate, however, that phenobarbital, like many other drugs, shows delayed elimination during the newborn period. As regards the dosage of phenobarbital in childhood, it may be concluded that there is a great danger of accumulation in newborns, particularly after repeated doses. A single daily dose of 5 mg/kg body weight only causes a rise in plasma concentration without reaching a steady state [22], and after 5 days of treatment plasma concentrations between 20 and 30 μg/ml are reached [22].

If the kinetic data on age-dependent elimination of phenobarbital are neglected, undesirable and intolerable side-effects, such as drowsiness, reduced drinking and even respiratory depression [26], must be anticipated. They usually occur at plasma concentrations higher than 30 μg/ml [28].

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Appendix

1. Serum concentration at time t = o

$$C = A + B \tag{II}$$

2. Hybrid constants of the 2-compartment open model

$$k_{el} = \frac{C}{\frac{A}{\alpha} + \frac{B}{\beta}} \tag{III}$$

$$k_{21} = \frac{\alpha \cdot \beta}{k_{el}} \tag{IV}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{el} \tag{V}$$

3. Distribution volumes
Distribution volume of the central compartment (D = Dose)

$$V_1 = \frac{D}{C} \tag{VI}$$

Distribution volume of the peripheral compartment

$$V_2 = V_1 \cdot \frac{k_{el}}{\beta} \cdot \frac{k_{12}}{\alpha} \tag{VII}$$

Distribution volume of the steady state (19)

$$V_{dss} = V_1 \cdot \frac{k_{21} + k_{12}}{k_{21}} \tag{VIII}$$

4. Total clearance

$$Cl_{tot} = k_{el} \cdot V_1 \tag{IX}$$