Pharmacokinetic characteristics of phenobarbital in hyperbilirubinemic neonates

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ABSTRACT

Current knowledge has brought to light some of the pharmacokinetic characteristics of phenobarbital during the neonatal period. We measured plasma levels of total phenobarbital and its free fraction 24, 48, 72, 96 and 120 h after a single dose of the drug in 12 neonates with hyperbilirubinemia. The pharmacokinetic characteristics of the samples, which were closer to normality than in most of the reference models used to date, e.g. anoxia and convulsions, are discussed in the light of earlier studies.

INTRODUCTION

The increase in available pharmacological information has made it possible to establish the pharmacokinetic profile of a number of drugs in different age groups. Important differences between preterm infants, term neonates and young children have come to light. However, because it is often extremely difficult to establish rational dosages in the neonate, surveillance of plasma levels should be considered an integral part of therapy[1,2]. The main problem in neonatal care is the non-existence of a cohort of healthy 'volunteers' to serve as controls in studies of pharmacokinetics. The information published to date is based mostly on groups of patients who received some form of treatment.

Although phenobarbital is widely used in pediatrics, its pharmacokinetic properties in the neonatal period have not been thoroughly investigated. The studies published to date have involved different treatments and reported different pharmacokinetic patterns and were neither conclusive nor systematic. Moreover, earlier research has been limited to neonates with convulsions, acute fetal distress and/or anoxia. The administration of phenobarbital to pregnant women before delivery has been thought to decrease the frequency of intracranial hemorrhage in preterm infants[3].

The constant anatomical and physiological modifications that take place in the neonate mean that data from this group are not entirely comparable with data obtained from children and adults. Characteristics such as the increase in blood pressure, the greater organ volume (macrosplanchnia), acid pH (tendency to acidosis), the greater body water volume and the smaller adipose panniculus, give rise to pharmacokinetic variations in processes of drug absorption, distribution metabolism and elimination. Awareness of these variations is of prime importance in designing rational pharmacotherapy for neonatal patients[4–7].

The aim of this study was to identify the principal pharmacokinetic characteristics of phenobarbital during the neonatal period.

METHODS

The study was carried out in the Neonatology Service, University of Granada Hospital. The subjects were 12 neonates with a mean weight of 3121.6 g (SD, 500 g) 3120 (524) g, with 38.7 (1.1) weeks of gestational age and 3.7 (1.3) days of life. None of the mothers had an

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obstetric history of diseases. Birth weight was normal for gestational age in 83.3% of the subjects, and was below and above the normal range for gestational age in subjects 4 and 3, respectively.

Because of the difficulties inherent in studies of this type in neonates, and because some of the subjects had pathological conditions that could affect the results, we selected the subjects on the basis of the absence of congenital diseases, mainly endocrine and metabolic disorders. The sample included one patient with transitory hypoglycemia that did not affect the findings of this study. Normal hepatic function was defined as first, the absence of signs and symptoms of hepatic insufficiency; and second, normal results in coagulation tests (prothrombin activity). In the entire sample, neonatal vital signs were normal, with a 5-min Apgar score higher than 8 in all subjects. Good hemodynamic status was documented by normal heart rate, arterial pressure and diuresis (2.64 ml/kg per h). Electrolyte balance was satisfactory in all subjects, as confirmed by adequate hydration and oral feeding. In all neonates, the administration of phenobarbital was necessary because of hyperbilirubinemia. All subjects were treated in accordance with the Declaration of Helsinki, and due authorization for all procedures was obtained from the parents and our hospital's research ethics committee.

Each patient was given a dose of 7.5 mg/kg of phenobarbital intravenously, and blood samples were drawn 24, 48, 72, 96 and 120 h later. Plasma levels of phenobarbital were measured with an Autolab 5000 EMIT system specially designed for enzyme immunoassays in the clinical laboratory. The free fraction, i.e. the amount of drug not bound to proteins and hence pharmacologically active, was measured with an Amicon MPS-1 micropartition system based on the separation, by ultrafiltration, of free and protein-bound fractions in small volumes of serum, plasma, or other biological fluids, at physiological pH. The protein-free ultrafiltrate is obtained by a single 5–10-min centrifugation step. The half-life was calculated as the time needed for the concentration of the drug to fall by half. In first-order kinetics, the time required for a given amount of drug to be reduced by half is always constant. The elimination constant was calculated as the slope of the elimination curve, and expressed as unit time 1. Clearance (Cl) was expressed as the amount of plasma that became free of the drug per unit time, and was calculated by the formula:

$$Cl = K \times V_d$$

where K is the elimination constant and V_d the distribution volume. The apparent distribution volume, a theoretical concept with no actual physiological equivalence, represented the theoretical amount of body water in which the drug was distributed within the organism.

RESULTS

A standard criterion was used to establish the single experimental dose of 7.5 mg phenobarbital/kg intramuscularly. Depending on body weight, the total dose ranged from 15.5 mg (subject 4, 2100 g) to 30 mg (subject 3, 4040 g). The mean dose for the entire sample was 22.6 (SD 3.8) mg (Table 1).

The relationship between plasma concentration of phenobarbital and time was examined by correlating the mean concentrations in the entire sample (Table 2) and considering five pairs of values, which were plotted against time (Figure 1). Plasma concentration showed a significant direct linear correlation ($r = 0.99$, $p < 0.001$), from which we derived a polynomial equation that explained the relationship between these two variables: $y = 1.023 - 3.26E - 0.3x$. Plasma levels of total (TPB) and free phenobarbital (FPB) were found from the data in Table 2. The mean values and standard deviations of TPB at five different times (in pg/ml) were: T_1, 8.60 (SD 1.39); T_2, 7.47 (SD 1.14); T_3, 6.43 (SD 1.4); T_4, 4.95 (SD 1.03); T_5, 4.29 (SD 0.99). Corresponding values for the free fraction (FPB) (in pg/ml) were: T_1, 6.025 (SD 1.08); T_2, 5.21 (SD 0.94); T_3, 4.54 (SD 1.0) T_4, 3.42 (SD 0.89); T_5, 2.88 (SD 0.92). Figure 2 is a scattergram of all determinations of TPB and FPB, with the overall correlation coefficient ($r = 0.88$, $p < 0.001$), and the regression equation that predicts the values of the dependent variable as a function of the value of the independent variable (x = total drug): $y = 9.58E - 0.2 + 0.6x$. The maximum concentration at time 0 (Table 3) was determined by extrapolation of each of the regression lines that related time with plasma concentration of phenobarbital. Peak

Table 1 Dose and plasma concentration of phenobarbital (PB)

Case	Weight (g)	Dose (mg/kg)	Plasma total PB (μg/ml)	Plasma free PB (μg/ml)	Diuresis (ml/kg per h)	Plasma urea (mg/dl)	Bilirubin (mg/dl)
1	3340	7 5	9 93	6 66 (67 1%)	2 5	48	10 7
2	2600	7 5	6 35	4 63 (72.9%)	3	20	11
3	4040	7 5	10.82	6 80 (62.8%)	2 7	15	10 5
4	2100	7.5	8 05	6 83 (84.8%)	2 5	20	11
5	3260	7.5	7 13	5 13 (71.9%)	2	25	12 7
6	3620	7.5	11.04	7.62 (69%)	2 5	20	13 5
7	3250	7.5	7.81	5.14 (65.8%)	2.5	20	19 7
8	2600	7 5	8.25	4 55 (55.2%)	2 8	14	13
9	3000	7 5	8 75	5.40 (62.7%)	2 9	34	17
10	3050	7 5	7.95	6.70 (84.3%)	2.7	30	13
11	3600	7.5	8.55	7.40 (86 5%)	2.8	35	17
12	3000	7 5	8.70	5.45 (62.6%)	3	15	13
Mean	3121 6	7 5	8 61	6 02	2 64	24 6	13.5
SD	500	0	1 39	1 08	0.27	10 2	3.05

Table 2 Plasma concentration (μg/ml) of total and free (total/free) phenobarbital at different times

Case	24 h	48 h	72 h	96 h	120 h
1	9 93/6.66	8.31/5 13	6.38/3.14	4.79/2.38	4 43/2 38
2	6 35/4 63	6 07/4 59	5.67/4.32	3 34/2 87	3.53/2.52
3	10 82/6 80	9 41/6 18	8 90/5 68	6 55/4 07	6.46/3.82
4	8 05/6 83	7 16/4.70	7 55/4 83	5 73/3 71	4.39/2 69
5	7 13/5 13	6.36/5 04	5.13/3 62	4 01/2 74	3.48/2 31
6	11 04/7 62	8 84/6 18	6.80/5 04	4 98/3 37	4.53/3 67
7	7.81/5 14	6 13/4 70	5 17/3 83	3 26/2 90	2 61/2 06
8	8 25/4 55	6 75/3.65	5 25/2.85	5 00/2 30	3 95/1 95
9	8 65/5 40	6 40/4 15	5 75/3.35	4 90/2 95	3 75/4 55
10	7 95/6 70	7 95/6 35	6 30/5 80	5 80/4 95	5 30/4 55
11	8 55/7 40	8 00/6 65	6.95/5.90	6 15/5 20	5 00/4.25
12	8 70/5.45	8 35/5 20	7 40/4 20	4 95/2 95	4 05/2 00
Mean	8 60/6 02	7.47/5 21	6 43/1 14	4 95/1 03	4 29/0.99
SD	1 39/1 08	1 14/0 94	1 14/1 00	1.03/0 89	0 99/0 92

concentration was expressed as pg/ml at time 0; the mean value was 10.6 (SD 0.5) μg/ml, with a range of 8.2 (subject 2) to 13.9 μg/ml (subject 6). The elimination constant for phenobarbital (Table 3) ranged from 0.005/h (subject 10) to 0.012/h (subject 7), with mean values of 7.75×10^{-3} (SD 6×10^{-3})/h.

The estimated half-life of the drug in plasma (Table 3) was 96 (SD 7.7) h, with a range from 58.9 h (subject 7) to 147.7 h (subject 10). The distribution volume (Table 3) was greater than 2 l/kg in all subjects except subject 4 (1.6 l/kg), subject 6 (1.5 l/kg) and subject 12 (1.9 l/kg). The mean distribution volume was 2.2 (SD 0.1) l/kg, and ranged from 1.5 (subject 6) to 2.7 l/kg (subject 5). The mean plasma clearance (Table 3) was 3.67×10^{-3} ml/h, with a range from 0.002 to 0.006 ml/h.

DISCUSSION

The differences in the distribution of drugs at different ages in pediatric patients are mediated by a number of factors, including the relative size of the

Table 3 Pharmacokinetic characteristics of phenobarbital in the newborn (single dose of 7.5 mg/kg)

Case	Dose (mg)	Peak concentration (μg/ml)	Elimination constant *K* (per h)	Half-life (h)	Distribution volume (l)	Mean plasma clearance (ml/h)
1	25.5	12 4	0 009	76.8	2 1	0 004
2	18 0	8.2	0 007	93 7	2 2	0 003
3	30 0	12 5	0 006	119.3	2.4	0.002
4	15.5	9 9	0 006	115 8	1 6	0 004
5	24.0	8.9	0 008	87 7	2.7	0 003
6	21 0	13 9	0 01	70.6	1 5	0.006
7	24 0	10 8	0 012	58.9	2.2	0.005
8	20.0	9 6	0 007	93.8	2.0	0.004
9	22 5	10 1	0 008	85.8	2.2	0.004
10	23.0	9 2	0.005	147 7	2.5	0 002
11	26.5	10 2	0.006	124 5	2.6	0.002
12	22.5	11 9	0 009	81.0	1 9	0 005
Mean	22 7	10 6	$7\ 75 \times 10^{-3}$	96.3	2 2	$3\ 67 \times 10^{-3}$
SD	3 8	0 5	6×10^{-3}	7 7	0 1	$3\ 9 \times 10^{-3}$

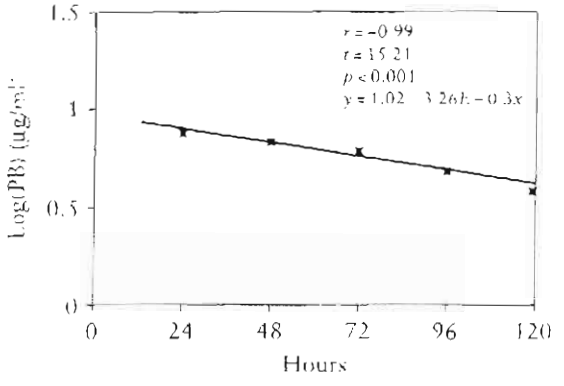

Figure 1 Statistical analysis of the relationship between mean concentration of phenobarbital (PB) and time (logarithm of mean PB concentration in 12 neonates in each period) reveals a significant negative correlation ($r = -0\ 99$, $p < 0\ 001$). The equation that predicted changes in plasma PB concentration as a function of time was $y = 1.02 - 3\ 26E - 0\ 3x$

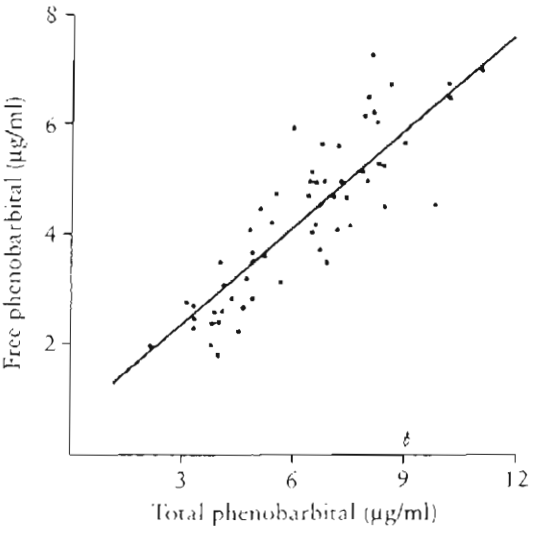

Figure 2 Correlation between concentration of total phenobarbital (PB) and free fraction. The points represent pairs of values in each of five determinations in 12 neonates. Linear fit was good, with $r = 0.88$, $p < 0\ 0001$. The linear equation was $y = 9\ 58E - 0\ 2 + 0\ 6x$

different organic water compartments, the binding capacity of plasma proteins, circulating factors, the strength of the blood–brain barrier and the specificity of tissue receptors.

Based on the most elementary model of kinetics, the newborn organism can theoretically be considered as a single compartment, where drug distribution is assumed to occur rapidly in comparison with absorption and elimination, and to be relatively uniform. According to this model, the distribution volume of the drug is that volume which the drug would occupy under conditions of equilibrium if the concentration were the same as that in plasma. Thus, at high tissue concentrations of the drug, the apparent distribution volume may be much greater than the total volume of body water. In general, the distribution volume in neonates is estimated to be larger than in adults.

Many studies have reported the distribution volume of phenobarbital in the neonatal period, the

values given in the literature ranging widely from 0.41 µl/kg[8] to 2.25 µl/kg[9]. Painter and colleagues[10] and Pitlick and colleagues[11] related distribution volume to gestational age and birth weight, and found no significant differences between several groups of neonates ranging in gestational age from 27 to 40 weeks, who were treated with phenobarbital for convulsions.

The values we obtained were higher than those reported by most other authors; with a mean of 2.2 (SD 0.11) µl/kg (95% CI 1.98–2.41). The considerable difference may be because hyperbilirubinemia in our sample of neonates limited the binding of phenobarbital to plasma proteins, making the free fraction larger; this in turn would increase the distribution volume. However, earlier studies were not illuminating on this point.

Other factors, sometimes overlooked, are also involved in drug distribution. Such influences include the patient's clinical status, blood flow, hemodynamic status, acid–base equilibrium, hypoproteinemia and the presence of other drugs. Specifically, the distribution of phenobarbital (pK_a 7.4) can be significantly affected by variations in blood pH, as is often the case in patients with post-anoxic convulsions[12]. These factors are closely related to the pharmacological and therapeutic effects of the drug. The variability in body compartments in adults, children and infants leads to different pharmacokinetic and pharmacological results. In the neonate, the total water content is relatively greater, the ratio between extracellular and intracellular water is higher, fat tissue is scarcer (15% in relation to muscle mass) and musculoskeletal mass is lower than at more advanced ages. In contrast, the brain and liver are proportionately larger (macrosplanchnia), hence blood flow to the brain is more rapid than in children and adults. These features, together with functional variations as noted above (clinical and hemodynamic status, acid–base equilibrium or hypoproteinemia) should be taken into account when the dose is calculated, to optimize the therapeutic effects.

Significant differences between neonates, children and adults have also been described in the elimination rate of drugs, this process tending to become faster with age[13]. The evidence accumulated to date suggests that enzymatic processes related to drug metabolism are less active in the neonate and require varying periods to reach adult levels of activity. In general, the neonate's capacity for drug elimination is low, a limitation of great clinical significance during the first weeks of life. Conjugation with glucuronic acid is diminished, which is translated as lower concentrations of glucuronyl transferase and uridine diphosphate dehydrogenase, which break down glucuronic acid. Therefore, the limited production in the neonate of the glucuronic acid-conjugated metabolites of phenobarbital seems to be compensated by the efficient excretion of unaltered drug and its unconjugated metabolites. The clinical significance of the decreased capacity to metabolize the drug may thus depend on the presence of alternative routes of metabolism and elimination.

Processes of conjugation with sulfate, in contrast, appear not to be diminished in the neonate, oxidative metabolism being the most important pathway for many drugs. Both hydrolysis and hydroxylation of esters are decreased, especially in the preterm infant. These pathways have been shown to be related, to some extent, to the patient's degree of development and maturation.

In addition to metabolism and renal excretion, other factors such as plasma protein binding may also affect the rate of elimination. In a sample of ten neonates, Gold and co-workers[14] found a half-life of 238 h and an elimination constant of 0.00029 h after an intravenous load of 20 mg/kg. According to Nau and associates[15], the half-life of phenobarbital in neonates was slightly less than 113 h. Morselli and co-workers[12] emphasized the differences in half-life between neonates (100–500 h) and adults (64–120 h), and Donn and colleagues[16] recorded a half-life of 148 (SD 55) h after phenobarbital administration at an intravenous dose of 30 mg/kg, in ten neonates with severe asphyxia. Jalling[17] noted that, in most cases, phenobarbital was eliminated by first-order kinetics, the half-life decreasing after the first week to approximately 100 h, and falling to 30–100 h, i.e. significantly shorter than in adults, by 4 weeks after medication. Shikey[13] studied the differences in half-life after a fixed dose of phenobarbital as a function of age, and noted a steady decrease from 115 h in neonates younger than 7 days to 78 h in neonates older than 7 days, and a further

decrease to 67 h in infants between 1 and 12 months of age.

The elimination rate, influenced by the patient's clinical status, renal function and gestational age, as well as by the administration of other drugs or pH, varies widely from one day to another. In a sample of 17 preterm neonates and five term neonates, Kossmann and colleagues[18] recorded a half-life of 106 h after a single dose of 10 mg/kg, noting that, during the first 7 days, elimination was variable, becoming constant thereafter. They concluded that in neonates the elimination of phenobarbital during the first 15 days of life does not follow classical linear models, but rather shows a biphasic curve. The rate of elimination is slow during the first phase (4–5 days), with a half-life of 409 h and probably with zero-order kinetics, and accelerates during the second phase (7–15 days), the elimination rate becoming faster and showing a linear relationship proportional to concentration (first-order kinetics). During the second phase, the overall elimination constant is 0.0066.

The elimination constants found by Royer and colleagues[19] in full-term, intrauterine growth-restricted (0.0081–0.007 ml/h) and preterm neonates (0.0063 ml/h) were higher than our findings (0.003 ml/h). The authors concluded that full-term and preterm neonates could be given the same dose of phenobarbital. Boreus and co-workers[20] found elimination constants ranging from 0.0040 to 0.0133 (mean 0.0073) in four neonates and noted an inverse relationship between plasma concentration and renal excretion. In contrast, the elimination constant found by Gold and colleagues[14] was closer to our value; the half-life in their group of ten neonates was 238 h. Butler[21] suggested that hydroxylation is the most important pathway for the inactivation of phenobarbital, and showed that almost half the *p*-hydroxy-phenobarbital recovered in urine was unconjugated. Similar findings have also been reported by Raun-Jonsen and associates[22]. The type of conjugation has not been determined. Butler[21] was unable to demonstrate a glucuronic metabolite and assumed the presence in humans of a sulfate conjugate of *p*-hydroxy-phenobarbital. Another study[23] provided evidence that *p*-hydroxy-phenobarbital is conjugated in humans mainly with sulfate. The pattern of excretion in neonates during the first 8 days after administration is similar to that in adults; thus, unmetabolized and *p*-hydroxy-phenobarbital appear in neonate urine in the same amounts relative to dose as in adult urine. In neonates, unmetabolized drug represented 18%, and *p*-hydroxy-phenobarbital 10% of the dose. Neonates eliminate 32% of the dose during the first 8 days, whereas adults eliminate 39%; these differences would probably disappear if the observation period were longer.

The poor capacity of neonates to conjugate drugs seems to be the main handicap to drug metabolism during this period of life. In a classical study, Vest[24] corroborated this notion with regard to glucuronide conjugation of paracetamol. As demonstrated, the low elimination constant of conjugated phenobarbital metabolites was compensated by the efficient elimination of unconjugated metabolites and unmetabolized phenobarbital.

An important point to emphasize is the fact that clinical characteristics of the neonate appear to influence drug metabolism and may in fact be more important than age differences. The better the patient's clinical status, the more efficiently is phenobarbital eliminated. We should underline, however, that our sample of neonates is not directly comparable to the patients described in earlier studies, since neonates with hyperbilirubinemia are generally considered to be more similar to the healthy infant than to the neonate with anoxia or convulsions.

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