# THE FATE OF PHENOBARBITONE IN CHILDREN IN HYPOTHERMIA AND AT NORMAL BODY TEMPERATURE

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ABSTRACT

Four critically injured children receiving large doses of phenobarbitone were studied during hypothermia (30°–31° C) and at normal body temperature. The volume of distribution of phenobarbitone varied from 0.79 to 1.01 litres per kg and the serum $t_{\frac{1}{2}}$ ranged from 36.8 ± 9.4 to 86.2 ± 10.5 hrs. The percentage of dose recovered in urine in 16 days ranged from 40.5 to 65.5 per cent: 2.7 to 12.4 per cent as hydroxyphenobarbitone, 1.7 to 19.7 per cent as conjugated hydroxyphenobarbitone, 6.0 to 22.4 per cent as phenobarbitone-N-glucoside and 17.8 to 23.1 per cent as unchanged drug. After the body temperature was allowed to return to normal the rate of excretion of metabolites increased substantially and the rate of excretion of the unchanged drug decreased markedly. It is concluded that reduction in body temperature influences the volume of distribution, rate of metabolism and excretion of phenobarbitone.

KEY WORDS: PHARMACOKINETICS, Phenobarbitone, hypothermia.

SEVERAL REPORTS indicate that the combination of hypothermia and barbiturate administration is essential for brain salvage of near-drowning patients who remain comatose after resuscitation. During the first five years after the introduction of this treatment regimen the incidence of mortality and permanent brain damage was significantly reduced among patients admitted to The Hospital for Sick Children of Toronto with hypoxic or traumatic brain damage.[1-3] The doses of phenobarbitone administered are extremely high and numerous questions were raised regarding the necessity of such large doses. Slowly accumulating case studies indicate that chances of total recovery are best when body temperature is maintained at 30°–31° C and phenobarbitone serum concentration above 75 μg per ml during

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treatment.[3] To predict with any assurance the dose required to achieve and maintain this serum level it was necessary to investigate the fate of phenobarbitone in the body of patients undergoing such treatment. Information available from the literature is limited to doses sufficient to control seizures or is concerned with accidental or intentional poisonings.[4-13] In addition, attention was focused in these studies on phenobarbitone and one primary metabolite only, the free and conjugated p-hydroxyphenobarbitone. Recently it was shown that phenobarbitone-N-glucoside (N-β-D-glucopyranosyl-phenobarbitone) is another major metabolite of this drug,[14] and a mass spectrometric method was devised to measure its concentration in urine. The data presented here were obtained from four critically injured children and include the serum concentration of phenobarbitone, the urinary excretion of the unchanged drug and the two metabolites, all measured during hypothermia and at normal body temperature.

The medical assessment and management of similarly treated patients was discussed in detail in previous publications and therefore is not included here.[1-3]

## MATERIALS AND METHODS

Four boys between the ages of 5 and 15 years suffered from trauma-induced hypoxic brain

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damage and were treated according to the regimen outlined in detail by Conn, et al.[3] On admission they were comatose. Their age and body weights are listed in Table I. It was concluded after careful evaluation that they would benefit from the combination treatment. As part of the standard procedure, a Richmond screw was positioned on the top of the forehead under general anaesthesia for continuous monitoring of the intracranial pressure. Electroencephalograph (EEG) and electracardiograph (ECG) leads were attached and thiopenthone, d-tubocurare and a loading dose of phenobarbitone sodium were administered intravenously. The respiration was controlled by artificial means. The body temperature was lowered to 30–31° C and maintained there for six to nine days. Venous and arterial catheters and a nasogastric tube were placed according to need. The medical team's efforts were concentrated to deal with the following problems: hyperhydration, hyperventilation, hyperpyrexia, hyperexcitability and hyperrigidity. The following drugs were administered during the treatment in addition to those already mentioned: intravenous fluids, sodium bicarbonate, pancuronium, dexamethasone, furosemide, cimetidine, acetaminophen, diazepam, diphenhydramine, phenytoin, isoproterenol, propranolol, atropine, morphine, ampicillin, cefamandole, cephalotin, gentamycin, methicillin, ampicillin, penicillin G and mannitol. Not all the patients received all the drugs and some were administered only once as needed. After four or more days the temperature was allowed to return to normal, but if the intracranial pressure increased over a certain critical point the hypothermia and drug administration was extended for three or more days.

The loading dose of 33 to 75 mg·kg⁻¹/day sodium phenobarbitone and the maintenance dose of 10 to 25 mg·kg⁻¹/day was administered intravenously in three divided doses. One to three ml blood samples for the measurement of phenobarbitone concentration in serum were taken daily through the catheter inserted for the administration of intravenous fluids. The blood was allowed to clot and, after centrifugation the serum was separated and stored at −20° C until analyzed. Urine was collected from the bladder through a standard catheter until the patients regained consciousness and were able to void on their own. The total urine volume was measured in 24 to 48 hour batches and 15 to 25 ml aliquots were stored at −20° C until analyzed.

The concentration of phenobarbitone (PB) in serum was determined by high performance liquid chromatography (HPLC). To 0.1 ml serum was added 0.05 ml saturated ammonium sulphate [(NH$_4$)$_2$SO$_4$] solution and 0.2 ml dichloromethane (CH$_2$Cl$_2$) containing 40 μg amylobarbitone as internal standard. After thorough mixing for 20 seconds, the mixture was centrifuged for 5 minutes at 5000 rpm and 0.1 ml of the supernatant was dried with an airstream. The extract was redissolved in 0.05 ml 10 per cent 1,4 dioxane in CH$_2$Cl$_2$ and a 0.02 ml aliquot was injected into the HPLC (model 1084B, Hewlett-Packard, California, 94304) equipped with a Li Chromosorb S1 60 10 μm, 25 cm × 4.6 mm column (Hibar II, BDH, Toronto, Canada). The column was eluted with 10 per cent 1,4 dioxane in CH$_2$Cl$_2$ at the rate of 1.2 ml per min and monitored by ultraviolet detector at 254 nm.

The concentration of phenobarbitone and free hydroxyphenobarbitone (COH) in urine were determined by HPLC. To 0.2 ml urine, 0.1 ml saturated (NH$_4$)$_2$SO$_4$ solution and 1.0 ml ethylacetate containing 100 μg of amylobarbitone and 1 μg of phenacetin as internal standards was added. After mixing for 20 seconds, the preparation was centrifuged at 5000 rpm for five minutes and as much as possible from the organic layer was transferred to a dry test tube. An additional 1 ml of ethylacetate containing no internal standards was added to the aqueous mixture, and after mixing and centrifugation as before, the organic layer was separated and added to the primary extract. The pooled ethylacetate extract was dried with an airstream and the dry residue was redissolved in 0.1 ml 10 per cent 1,4 dioxane in CH$_2$Cl$_2$. A 0.02 ml aliquot was injected into the HPLC and monitored as before. Phenacetin was required as a secondary internal standard because some urine samples contained a multitude of drugs which sometimes interfered with the amylobarbitone peak.

The concentration of the glucuronic acid conjugated hydroxyphenobarbitone (COC) in urine was measured after the compound was hydrolyzed with the aid of hydrochloric acid and heat. That is 0.2 ml 12N HCl was added to the previously extracted aqueous layer and heated to 100° C for one hour. The same double extraction procedure was carried out as before and the measurement by HPLC was also the same.

The concentration of phenobarbitone-N-glucoside (PBNG) in urine was measured by a mass spectrometric method using the "Biospect" (Scientific Research Instruments, Baltimore, Md.) as described by Tang, et al.[14] To 0.1 ml

## TABLE I

PATIENTS AGE, WEIGHT, DOSE OF SODIUM PHENOBARBITONE, INITIAL VOLUME OF DISTRIBUTION, MAXIMUM SERUM CONCENTRATION, SERUM t½ AND PERCENTAGE OF METABOLITES AND UNCHANGED PHENOBARBITONE RECOVERED IN URINE

| Patient | Age (yrs) | Weight (kg) | Dose mg of Na PB Initial mg/kg | Total | Initial vol. of distrib. l/kg | Maximum serum conc μg/ml | Serum t½ (hrs ± SE) | Percentage of PB dose recovered In urine as COH | COC | PBNG | PB | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 10 | 35 | 64 | 6,175 | 0.79 | 214 | $42.0 \pm 3.7$ | 12.4 | 9.4 | 22.4 | 21.3 | 65.5 |
| 2 | 15 | 46 | 32 | 3,600 | 0.98 | 84 | $36.8 \pm 9.4$ | 6.9 | 4.3 | 13.5 | 20.4 | 45.1* |
| 3 | 5 | 20 | 75 | 3,250 | 0.88 | 133 | $86.2 \pm 10.5$ | 2.7 | 1.7 | 18.3 | 17.8 | 40.5 |
| 4 | 7 | 26 | 55 | 4,400 | 1.01 | 90 | $51.3 \pm 1.1$ | 12.4 | 19.7 | 6.0 | 23.1 | 61.2 |
|  |  |  |  |  |  |  | $\dagger 75.6 \pm 6.9$ |  |  |  |  |  |

*Collection for 13 days only.
†Serum t½ estimate 4 days after first treatment.
NaPB: sodium phenobarbitone.
COH: hydroxyphenobarbitone.
COC: glucuronic acid conjugated hydroxyphenobarbitone.
PBNG: phenobarbitone-N-glucoside.
PB: phenobarbitone.

urine, 0.01 ml saturated $(NH_4)_2SO_4$ solution and 0.05 ml of amylobarbitone-N-glucoside, 0.1 mg per ml solution as internal standard were added. The mixture was extracted twice with 1 ml ethylacetate by mixing for 20 seconds and separating the solvents by centrifugation for five minutes at 5000 rpm. The combined organic phase was evaporated to dryness by a gentle airstream and the residue was dissolved in 10 µl of pyridine and 50 µl acetic anhydride. The resulting solution was heated to 60° C for 30 min and then dried by air. The dry residue was dissolved in 0.1 ml methanol and about 6 µl of it was dried in a sample glass tube for direct probe application into the mass spectrometer. The sample was introduced into the mass spectrometer through a heated probe and masses m/e 563, 557, 503 and 497 were monitored simultaneously. In all quantitative measurements, the peak height ratio of internal standard over unknown was used to determine the concentration with the aid of a calibration curve.

All chemicals were of analytical grade obtained from Fisher Scientific Co. (Toronto, Canada). The internal standard, amylobarbitone-N-glucoside was synthesized by the method already reported.[15]



FIGURE 1a Body temperature, dose of sodium phenobarbitone administered, phenobarbitone serum concentration and percentage of metabolites and unchanged phenobarbitone excreted in urine for patient 3. COH = hydroxyphenobarbitone, COC = conjugated hydroxyphenobarbitone, PBNG = phenobarbitone-N-glucoside, PB = phenobarbitone.
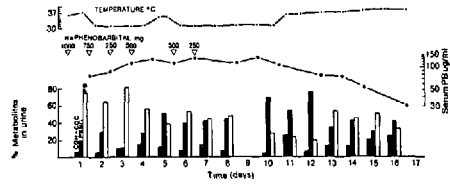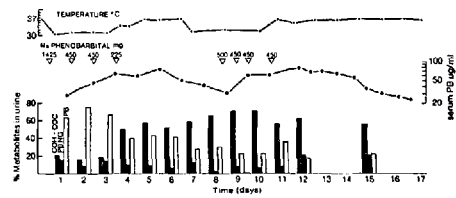


FIGURE 1b Body temperature, dose of sodium phenobarbitone administered, phenobarbitone serum concentration and percentage of metabolites and unchanged phenobarbitone excreted in urine for patient 4. COH = hydroxyphenobarbitone, COC = conjugated hydroxyphenobarbitone, PBNG = phenobarbitone-N-glucoside, PB = phenobarbitone.

## RESULTS

The therapeutically desirable concentration of at least 75 µg phenobarbitone per ml of serum was reached either after the loading dose was administered or on the second day of treatment. The initial volume of distribution (Table I) varied from 0.79 to 1.01 l/kg. With subsequent daily doses the serum concentration increased gradually reaching a maximum of 84 to 214 µg per ml depending on the dose (Table I). The EEG recordings showed the typical barbiturate-induced changes but the ECG recordings were normal. The acid-base balance in blood was adjusted several times during a 24 hour period. After the phenobarbitone administration was stopped and the body temperature was allowed to return to normal, the serum concentration increased sharply by at least 10 per cent (Figure 1a and b) for all patients, and from 52 µg per ml to 99 µg per ml for patient 2.

The terminal serum half-life estimated three to four days after the body temperature returned to normal, ranged from 36.8 ± 9.4 to 86.2 ± 10.5 hours (Table I). There is no correlation between serum t½ and the total dose of drug administered.

For patient 4, it was possible to calculate the serum t½ from values obtained half way through the treatment. Because the intracranial pressure became dangerously elevated three days after the temperature had gradually returned to normal, the combined treatment was reinstated for an additional four days. The first serum t½ was 75.6 ± 6.9 hours and at the conclusion of treatment was 51.3 ± 1.1 hours.

Urine was collected for 13 days from one patient and for 16 days from the other three patients. There was a large patient-to-patient variation in the amount of phenobarbitone metabolites eliminated in urine (Table I). Expressed as percentage of the dose, from 2.7 to 12.4 per cent was excreted as free hydroxyphenobarbitone (COH), 1.7 to 19.7 per cent as conjugated hydroxyphenobarbitone (COC) and 6.0 to 22.4 per cent as phenobarbitone-N-glucoside (PBNG). The amount of unchanged drug excreted showed only minor variation, from 17.8 to 23.1 per cent of the dose.

The duration of hypothermia ranged from six to nine days and for patient 4 a total of nine days,

TABLE II

RATE OF URINARY EXCRETION OF PHENOBARBITONE AND ITS METABOLITES AT 30°–31° C AND AT NORMAL
TEMPERATURE. THE AVERAGE PERCENTAGE OF METABOLITES AND UNCHANGED PHENOBARBITONE EXCRETED
AT 30°–31° C AND AT NORMAL BODY TEMPERATURE

| Metabolite | Mean ± SE rate of secretion μmol/hr temperature | | F-test | | Average percentage of metabolites in urine at body temperature | |
|---|---|---|---|---|---|---|
| | 30°–31°C | Normal | Low/normal | Interaction patient/ Low/normal | 30°–31°C | Normal |
| COH | 1.87 ± 0.71 | 4.50 ± 1.90 | 15.53* | 0.72 | 14.4 | 21.7 |
| COC | 1.67 ± 0.75 | 2.72 ± 1.96 | 1.97 | 1.56 | 14.6 | 19.8 |
| COH + COC | 3.81 ± 1.65 | 7.98 ± 3.90 | 14.06* | 0.64 | — | — |
| PBNG | 6.12 ± 1.42 | 13.13 ± 2.69 | NA | NA | 20.9 | 35.7 |
| PB | 12.01 ± 3.38 | 6.25 ± 1.25 | 6.20† | 0.83 | 52.1 | 22.8 |

*p    0.005.
†p    0.05.
NA = not applicable.
COH = hydroxyphenobarbitone.
COC = conjugated hydroxyphenobarbitone.
PBNG = phenobarbitone-N-glucoside.
PB = phenobarbitone.

i.e. treatment was interrupted by a four day period of near normal body temperature. By comparing the average hourly rate of elimination of metabolites and phenobarbitone during hypothermia with that observed during normal body temperature the variation due to the uneven time distribution becomes less important (Table II). In hypothermia the rate of metabolite excretion was low but, after the temperature returned to normal, it increased by 141 per cent for COH, 63 per cent for COC and 114 per cent for PBNG. At the same time, the rate of phenobarbitone excretion decreased by 48 per cent. The rates obtained at low and normal temperatures were compared by analyses of variance of the logarithmically transformed observations. Logarithms were justified and required because first, the ratios of measurements in the patients were quite similar in spite of their differing magnitudes (this is reflected by the statistically not significant interaction terms) and, second, the standard deviations of the untransformed readings were proportional to the corresponding means. The PBNG excretion appeared to be inhibited by furosemide, therefore, the data were not subjected to a similar calculation.

The temperature induced change in the urinary excretion rate of the various metabolites and of phenobarbitone are reflected in their relative concentrations in urine. The average values in Table II show that during hypothermia 52 per cent of the urinary metabolite constituted the unchanged drug but at normal temperature PBNG was present in the highest concentration.

Body temperature, dose of phenobarbitone, serum concentration of phenobarbitone and the relative concentration of phenobarbitone and its metabolites found in urine are illustrated in Figure 1a for patient 3 and 1b for patient 4. The serum concentration of phenobarbitone increased in accordance with the dose, and after the body temperature was allowed to return to normal, a secondary increase was observed although no phenobarbitone was administered for more than 24 hours. The decline of the serum concentration in the terminal phase is compatible with first-order kinetics. The change in the relative concentration of phenobarbitone and metabolites in urine was influenced primarily by the body temperature. For both patients the unchanged drug was the major urinary metabolite especially during the first 5 or 6 days of treatment. For patient 3, PBNG was the major urinary metabolite during hypothermia and at normal body temperature. The relative amounts of COH and COC excreted were low but increased gradually after day 10. For patient 4, COH and COC were the major urinary metabolites at normal temperature and during the second phase of treatment. PBNG was only a minor metabolite for patient 4.

The cumulative urinary excretion of phenobarbitone and metabolites is illustrated in Figure 2a for patient 3 and 2b for patient 4. Both
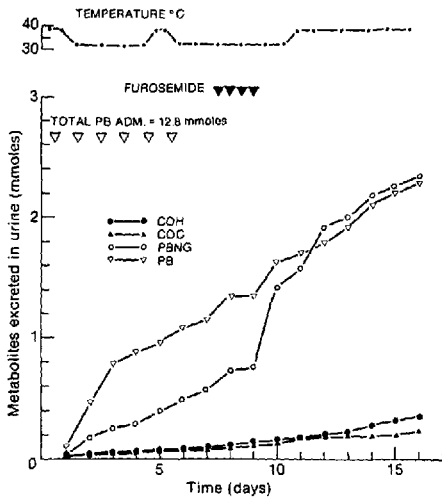
FIGURE 2a   Body temperature, furosemide administration, phenobarbitone administration and cumulative urinary excretion of phenobarbitone and its metabolites for patient 3. COH = hydroxyphenobarbitone, COC = conjugated hydroxyphenobarbitone, PBNG = phenobarbitone-N-glucoside, PB = phenobarbitone.

patients excreted large amounts of the unchanged drug during hypothermia, especially during the early phase. For patient 3, PBNG was the major metabolite and COH and COC were eliminated in low concentrations only. For patient 4, COC and COH were the major metabolites present. During furosemide administration the rate of PBNG excretion was reduced for both patients.

### DISCUSSION

The fate of phenobarbitone was investigated in four critically injured children who received the drug as part of their treatment. All four survived with minimum brain damage and were receiving rehabilitation therapy at a chronic care institution at the time this report was completed.

The initial apparent volume of distribution of phenobarbitone estimated from the serum concentration after the full loading dose was administered, is consistent with values reported by other investigators.[5,7,8,11] A tendency to higher volume of distribution was noticed for those patients who had their temperature lowered to 30°C for several hours before the whole dose was administered. During hypothermia, the apparent volume of distribution following the administration of the daily maintenance dose
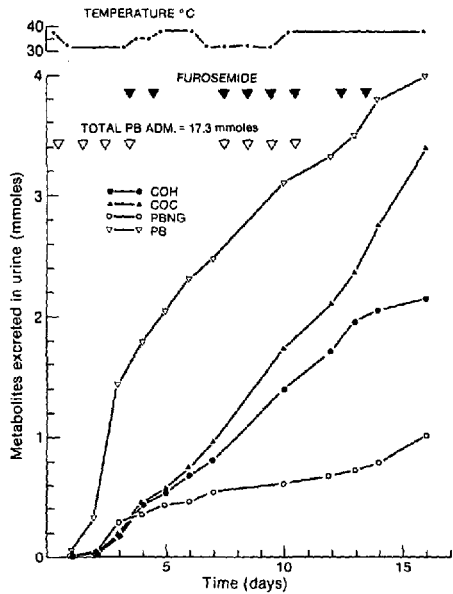


FIGURE 2b   Body temperature, furosemide administration, phenobarbitone administration and cumulative urinary excretion of phenobarbitone and its metabolites for patient 4. COH = hydroxyphenobarbitone, COC = conjugated hydroxyphenobarbitone, PBNG = phenobarbitone-N-glucoside, PB = phenobarbitone.

was between 1.05 to 1.25 litres per kg. An apparent increase in size of the storage compartment at lower than normal body temperature was evident for every patient and the increased serum concentrations observed after the body temperature was allowed to return to normal is the result of backflow of the drug into the central compartment. Cooling of the tissue might increase binding capacity as described by Kinniburg and Boyd[16] for in vitro binding of phenytoin to serum proteins. The estimates of volume of distribution in hypothermia were poorly reproducible because sodium bicarbonate solution was administered frequently to adjust the blood pH, and only half of the customary volume of intravenous fluids were given in order to lower the risk of pulmonary oedema.

The phenobarbitone serum half-life observed in these patients is in good agreement with results of other investigators using much smaller doses.[7,8,10–12] Since these values were calculated from the serum concentration ten to sixteen days after the initial dose was administered, the mixed-function oxidases in liver were probably

in a fully induced state. For one patient the estimated serum $t\frac{1}{2}$ half way through the treatment, was 47 per cent longer than the terminal $t\frac{1}{2}$. The serum concentrations of phenobarbitone and the body temperatures were similar during the periods when the two estimates were taken; therefore enzyme induction was most likely responsible for the shorter half-life.

The percentages of unchanged drug and metabolites eliminated in urine are in good agreement with the observation of other investigators.[4,5,8,9,11,14] The amount of free and conjugated hydroxyphenobarbitone eliminated by patient 3 was unusually low in comparison with the other patients but the PBNG elimination was better than average. The serum half-life was the longest in this patient indicating that hydroxylation is an important factor in the elimination of the drug.

It is quite possible that the rate of metabolism and elimination of phenobarbitone was influenced by the simultaneous administration of the other drugs. No attempt was made to change either the dose or the frequency of administration of any of the drugs. The observation that furosemide appears to interfere with the excretion of PBNG was made several months after the patients were discharged and urine analyses completed. At the present time there is no evidence to suspect any major life-threatening drug interaction in this clinical situation.

The percentage of dose recovered in urine as unchanged drug and metabolites is in good agreement with the result of other investigators.[5,8,9,11,12] In this study, the total dose was administered not at once or in one day but over a period of several days; therefore, strict comparisons are not possible. Because of cost of hospitalization it was not practical to extend urine collection beyond sixteen days. Minor metabolites described by other investigators[8] constitute only a small percentage of the dose; therefore, no attempt was made to measure their concentration. With further refinement of the analytical technique we hope to be able to measure all metabolites in future studies.

A significant temperature-dependent change occurred in the urinary excretion rate of phenobarbitone and metabolites. For all four patients after the temperature was allowed to return to normal, the urinary excretion rate of the unchanged drug decreased by almost 48 per cent, for COH increased by 145 per cent and for COC by 62 per cent. The 62 per cent increase was statistically not significant because of the large daily variation in the excretion rate as the result of possible drug interaction.

The recently discovered phenobarbitone-N-glucoside metabolite[14] excretion was extremely erratic and this made any elaborate statistical calculation meaningless. Previous studies in normal healthy adult volunteers using amylobarbitone as a test drug indicated that the rate of formation and the presence or absence of this metabolite is genetically controlled.[17,18] Further studies showed that it is a particularly prominent amylobarbitone metabolite in the majority of Oriental subjects.[17,18] The four children were of Caucasian origin and their drug metabolism pattern is in agreement with that race. Most of the depression in the excretion rate during hypothermia and at normal body temperature coincided with the administration of furosemide. The urine flow increased under the influence of the diuretic as expected but the excretion of PBNG decreased or was almost completely inhibited. Whether this interaction occurred in the kidneys or in the liver is not clear yet but with further improvement in the sensitivity of the analytical procedure it will be possible to measure the concentration of this metabolite in serum.

In summary, this study indicates that for children the volume of distribution of intravenously administered phenobarbitone may range from 0.79 to 1.01 litres per kg, after the body temperature is reduced to 30°–31°C, it may increase to 1.25 litres per kg. During hypothermia about 10 to 15 per cent of the dose is eliminated in urine in 24 hours as unchanged drug and metabolites. A loading dose of 75 mg per kg on the first day of treatment administered in three divided doses would produce the clinically desirable serum concentration and 7.5 to 10 mg per kg per day would be sufficient to maintain it.

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RÉSUMÉ

On a étudié quatre jeunes blessés graves recevant du phenobarbitone à hautes doses en hypothermie (30°–31°C) et à température normale. Le volume de distribution du phénobarbitone a varié de 0.79 à 1.01 litre par kg et la t½ sérique s'est située entre 36.8 ± 9.4 et 86.2 ± 10.5 heures. Le pourcentage de la dose recouvrée dans l'urine en 16 jours a été de 40.5 à 65.5 pour cent: 2.7 à 12.4 pour cent sous forme d'hydroxyphenobarbitone, de 1.7 à 19.7 pour cent sous forme d'hydroxyphenobarbitone conjugué, de 6.0 à 22.4 pour cent sous forme de phenobarbitone-N-glucoside et de 17.8 à 23.1 pour cent sous forme inchangée. Lorsqu'on a laissé la température revenir à la normale, la vitesse d'excrétion des métabolites a augmenté substantiellement alors que l'excrétion sous forme inchangée a subi une baisse importante. On en conclut que la baisse de température de l'organisme a influencé le volume de distribution, la vitesse du métabolisme et de l'excrétion du phenobarbitone.