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BIOPHARMACEUTICS OF RECTAL ADMINISTRATION OF DRUGS IN MAN 7. ABSORPTION RATE AND BIOAVAILABILITY OF PHENOBARBITAL AND ITS SODIUM SALT FROM RECTAL DOSAGE FORMS

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SUMMARY

In this report it will be shown that rectal administration of phenobarbital and its sodium salt can be looked upon as an alternative route of administration.

Plasma phenobarbital concentrations were measured in 6 volunteers after a single oral dose (219 mg) of sodium phenobarbital and after single rectal doses of phenobarbital (200 mg) or sodium phenobarbital (219 mg). In the case of the rectally administered aqueous dosage forms of phenobarbital no distinct difference in absorption rate occurred whether the sodium salt or the free acid was used. Rectal administration of both types of micro-enemas results in absorption which is less rapid than after oral administration of the sodium salt. However, the final and total absorption of phenobarbital and its sodium salt after 6.5 h is practically complete, compared with oral administration. The in vitro release of phenobarbital from fatty suppositories using a coarse powder (125–250 μm) of sodium phenobarbital and with a fine powder (<20 μm) of phenobarbital showed marked differences. The rectal absorption profile of the aqueous and fatty dosage forms of sodium phenobarbital in vivo was quite similar. A much slower absorption rate was observed if the free acid was used in the fatty suppository dosage form.

INTRODUCTION

Phenobarbital is still a widely used anticonvulsant. The therapeutic plasma concentration for that purpose is of the order of 10–25 μg/ml, judging from clinical and EEG evidence (Buchthal and Lennox-Buchthal, 1972). In most cases such levels are reached 3 weeks after a regular use of phenobarbital in doses of 1.0–2.5 mg/kg in adults. Leucuta and Pop (1978) concluded that pharmacokinetics in man after an intravenous dose can be adequately described by a two-compartment model. The plasma elimination half-life varied widely from 2 to 6 days (Maynert, 1972); the apparent volume of distribution

ranged from 0.7 to 1.0 l/kg, while the plasma clearance was reported to be about 0.004 liters/kg/h (van der Kleijn, 1975). After a single oral dose of 200 mg phenobarbital in different dosage forms, peak plasma levels were reached after 1–3 h (Jälling, 1974; Leucuta et al., 1978).

Quantitative absorption data after rectal administration of phenobarbital are scarce. From studies in rats Boyd and Singh (1967) concluded that phenobarbital administered in aqueous solutions was readily absorbed from the rectum; the absorption rate was found to be at least as fast as that following oral administration. From studies in dogs Leucuta et al. (1977) concluded that absorption oral administration of solutions, suspensions or tablets was superior compared with the rectal route using suppositories with lipophilic and hydrophilic excipients. From a rectal study in children it was concluded that absorption rate was significantly increased if sodium phenobarbital instead of phenobarbital was applied in fatty suppositories (Heimann et al., 1978). No attempt was made to establish whether this was due to differences in the release of the drug from the suppository or to an unequal absorption rate via the rectal mucosa. No further human studies were available on measurement of plasma concentrations of phenobarbital after rectal administration.

Human studies were therefore planned to determine the rectal absorption rate of phenobarbital and its sodium salt, by measuring plasma concentrations of phenobarbital after administration in micro-enemas and fatty suppositories. To establish differences in relative bioavailability a comparison was made with an orally administered solution of sodium phenobarbital.

EXPERIMENTAL

Dosage forms

Phenobarbital (PH.Ned.VII) and sodium phenobarbital (British Pharm., 1973) were used. The oral dosage form was a 200 ml aqueous solution, containing 219 mg of sodium phenobarbital.

For rectal use a solution was prepared containing 219 mg of sodium phenobarbital dissolved in 20 ml of a medium, which consisted of 0.5% methylcellulose 400 cP (Ph. Ned. VI) in distilled water. The pH of the solution was 9.3. The recetal dosage form for phenobarbital (free acid) was made by suspending 200 mg of a micronized fraction (<20 μm) in 20 ml of the same medium. The pH of this suspension was 6.3. A coarse (125–250 μm) fraction was separated by sieving and a micronized (<20 μm) fraction was prepared by grinding the drugs under study in a jet mill. The powders were mixed with a molten base Witepsol H 15 (Interpharm), poured into brass moulds (3 ml) and stored in the refrigerator for at least one night before use. Their weight was adjusted to 3.0 g and each of them contained 219 mg of sodium phenobarbital or 200 mg of phenobarbital.

In vitro determinations

A release model with a variable release surface, as described by Schoonen et al. (1976) was used. The results are given as the mean values of 4 runs.

Human experiments

Six healthy human subjects, female and male, ranging in age from 20 to 32 years and

in body weight from 51 to 75 kg, participated in the cross-over study. No drugs were taken for two weeks prior to or during the study. The experiments were initiated in the morning and the volunteers did not take any food during the experiments. They were asked to remain in a sitting position. No discomfort following application of any rectal dosage forms was reported by the volunteers. Both micro-enemas were administered using a plastic disposable syringe to which a plastic application tube was connected. The tube was introduced in the rectal lumen enabling quantitative emptying of the syringe into the rectum

Blood samples of 10 ml were taken using Venoject tubes (Terumo Corporation) with 15 mg EDTA-sodium granules at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 6.5 h after administration.

Plasma was obtained by centrifugation of blood samples and was frozen until the time of analysis.

Determination of phenobarbital in plasma

Phenobarbital concentrations in plasma were estimated by high-pressure liquid chromatography (HPLC) as described by Westenberg and De Zeeuw (1976).

Standard solutions. A 3 M solution of sodium dihydrogen phosphate 1-hydrate (Merck) in distilled water was prepared. The pH was 3.8.

An internal standard solution was prepared by dissolving nitrazepam (Hoffmann-La Roche) in dichloromethane (Merck) in a concentration of 0.4 μg/ml. The dichloromethane was half saturated with water, in order to eliminate differences in water content of the organic phase, which can lead to variable results.

Apparatus. A liquid chromatograph (Waters Associates) was used in this study, equipped with an UV detector (model 440) set at 254 nm. The column (15 cm × 3.0 mm) was packed with silica gel (LiChrosorb Si 100-10, Merck). Analyses were performed using a mobile phase of 3% tetrahydrofuran (Merck) in dichloromethane at a flow-rate of 1.5 ml/min.

Procedure. To 0.50 ml plasma in a 10 ml tapered stoppered tube, 0.10 ml phosphate solution and 2.0 ml of the internal standard solution were added. After shaking for 10 min the content of the tube was centrifuged during 5 min at 4000 rpm and the aqueous phase was removed by aspiration; 100 μl of the resulting dichloromethane phase was injected into the HPLC. The retention times of phenobarbital and nitrazepam were 2.5 and 5.0 min, respectively. The ratio of the peak area of the sample component to that of the internal standard was used to calculate concentrations of phenobarbital, based on calibration curves prepared from spiked plasma samples (Table 1). The overall recovery from plasma was determined for 5 different concentrations and was found to be at least 95%. With 0.50 ml plasma samples the method can be used to determine concentrations as low as 0.5 μg/ml.

Pharmacokinetic parameters

The plasma concentrations in the present experiments were only followed up to 6.5 h after drug administration, since the aim of our rectal study was to compare the differences in absorption rate from the various dosage forms. As a result of the extremely long elimination half-life of phenobarbital the absorption rate can be reliably characterized by

TABLE 1

OVERALL RECOVERY OF PHENOBARBITAL FROM PLASMA

Concentration added (μg/ml)	Number of determinations	Calculated concentrations ± S.D. (μg/ml)	Coefficient of variation	Recovery (%)
2.0	5	1.9 ± 0.09	4.2	95
4.0	5	3.9 ± 0.15	3.8	97
6.0	5	5.9 ± 0.17	3.2	98
8.0	5	7.8 ± 0.21	2.7	97
10.0	5	9.7 ± 0.26	2.7	97

the peak concentration (C_{max}) and the peak concentration time (t_{max}). The area under the plasma concentration curve (AUC) from $t = 0$ to $t = 6.5$ h was determined by the trapezoidal rule. Relative bioavailability was determined using the equation:

$$F_{rel} = \frac{AUC_{rectal}}{AUC_{oral}} \times \frac{Dose_{oral}}{Dose_{rectal}}$$

Statistical analysis

Differences in plasma phenobarbital levels after administration of the various dosage forms were tested for statistical significance by the Student's *t*-test ($P < 0.05$ two sided). In pairs, the concentrations of phenobarbital were compared after it had been established that these concentrations were normally distributed applying the Shapino–Wilk's test ($P < 0.05$).

RESULTS AND DISCUSSION

Oral administration

A representative example of the difference in oral absorption rate between sodium phenobarbital and phenobarbital in one individual is given in Fig. 1.

After oral administration the sodium salt, dissolved in 200 ml of water, phenobarbital will be precipitated in the acid medium of the stomach as very fine particles with a large intrinsic surface, resulting in rapid dissolution and a fast absorption, Sjögren et al. (1965) demonstrated this phenomenon for several barbiturates.

In the case of oral administration of barbiturates in the form of the free acid pharmaceutical factors, such as the wettability and crystal size may influence the rate of absorption (Svensmark and Buchthal, 1963; Breimer, 1974). In addition the slow dissolution rate of the large particles of the free acid results in a dissolution rate of phenobarbital which is less than the dissolution rate of the free acid, precipitated from the sodium salt. These factors may explain the observed absorption differences after oral administration of the suspension of the free acid and the solution of the sodium salt of phenobarbital.

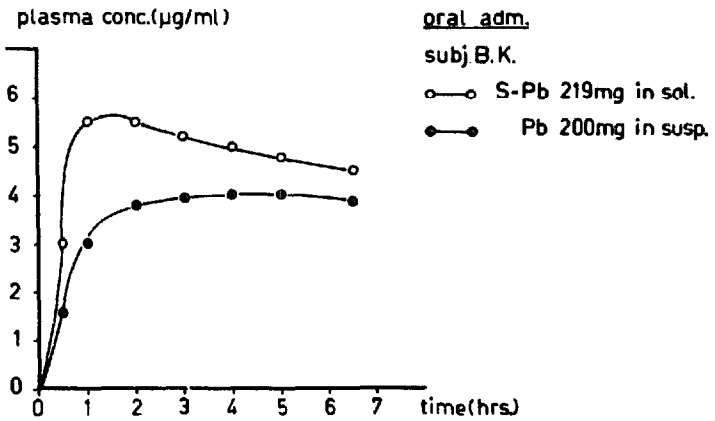

Fig. 1. Plasma concentrations of phenobarbital after oral administration of doses of 219 mg sodium phenobarbital (S-Pb), dissolved in 200 ml of water and 200 mg phenobarbitol (Pb), suspended in 200 ml of water, to subject B.K.

Rectal aqueous dosage forms

The mean plasma concentrations of phenobarbital after rectal administration of a single dose of 200 mg micronized phenobarbital suspended in 20 ml of medium, or 219 mg sodium phenobarbital dissolved in 20 ml of medium, in 6 volunteers, are given in Fig. 2 and Table 2.

The $AUC_{0-6.5h}$ did not differ significantly ($P < 0.05$) compared with the oral dosage form. For the free acid relative bioavailability was found to be about 97% of that after oral dosing. For the sodium salt this value was 87%. Thus the extent of rectal absorption

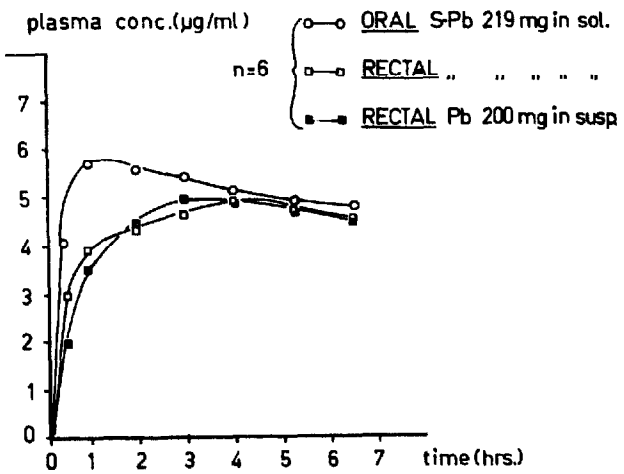

Fig. 2. Mean plasma concentrations of phenobarbital after oral and rectal administration of doses of 219 mg sodium phenobarbital (S-Pb) and 200 mg phenobarbital (Hb) in different aqueous dosage forms in 6 subjects.

TABLE 2

ABSORPTION CHARACTERISTICS AND RELATIVE BIOAVAILABILITY OF S-Pb AND Pb (MEAN ± S.D.) FROM DIFFERENT DOSAGE FORMS AFTER ORAL AND RECTAL ADMINISTRATION

	Oral	Rectal			
	S-Pb 219 mg in sol. of 200 ml	S-Pb 219 mg in sol. of 20 ml	Pb 200 mg in susp. of 20 ml	S-Pb (125–250 μm) 219 mg in supp. (3 ml)	Pb (<20 μm) 200 mg in supp. (3 ml)
Plasma conc. (μg/ml) at different t's					
t': 0.5 (h)	4.0 ± 1.7	3.0 ± 1.6	2.0 ± 1.1	1.2 ± 0.7	0.2 ± 0.1
1.0	5.7 ± 1.5	3.9 ± 1.7	3.5 ± 0.9	2.7 ± 0.8	1.0 ± 0.5
2.0	5.5 ± 1.3	4.3 ± 1.3	4.4 ± 1.1	3.9 ± 0.8	2.8 ± 1.5
3.0	5.4 ± 1.3	4.6 ± 1.1	4.9 ± 1.0	4.3 ± 1.0	4.0 ± 1.8
4.0	5.1 ± 1.1	4.8 ± 0.9	4.8 ± 0.8	4.5 ± 1.1	4.3 ± 1.8
5.25	4.9 ± 1.1	4.7 ± 0.9	4.7 ± 0.8	4.4 ± 0.8	4.4 ± 1.7
6.5	4.8 ± 1.0	4.5 ± 0.8	4.6 ± 0.7	4.2 ± 0.7	4.3 ± 1.6
Number	6	6	6	6	6
C_{max} ($\mu g \cdot ml^{-1}$)	5.7 ± 1.5	5.0 ± 1.2	5.6 ± 0.9	4.6 ± 0.9	4.5 ± 1.7
t_{max} (h)	1.4 ± 0.8	3.5 ± 1.6	3.7 ± 0.9	4.4 ± 0.8	4.1 ± 1.1
$AUC_{0-6.5\ h}$ ($\mu g \cdot ml^{-1} \cdot h$)	1800 ± 420	1560 ± 420	1625 ± 345	1380 ± 300	1290 ± 540
F_{rel}	1.00	0.87	0.97	0.77	0.72

of phenobarbital and its sodium salt is practically complete after 6.5 h. Yet, with respect to the absorption rate, the data indicate that, compared with the plasma curves following orally administered sodium phenobarbital, the peak of the plasma curves after rectal application of both micro-enemas occurred later and was only reached 3–4 h after administration. The peak plasma concentration after administration of the oral dosage form was often reached within 2 h. The difference was found to be significant ($P < 0.05$) No significant difference in C_{max} between the three dosage forms was measured.

In a previous study we concluded that the limited rectal absorption surface might explain the observed difference in absorption rate after oral and rectal route of administration (Moolenaar et al., 1979). This factor may play a role in spite of the fact that a relatively large volume of 20 ml was chosen in order to establish an optimal absorption surface.

In addition to the limited rectal absorption surface it was considered that the pH differences between the gastrointestinal lumen and the rectal lumen could explain differences in absorption rate, assuming that absorption occurs according to the pH-partition hypothesis. Since the pK_a value of phenobarbital is 7.4 and the physiological pH in the rectum fluid is 7–8, about 50% of the drug will be in the non-ionized form so that the absorption conditions for phenobarbital in the rectum would be rather favourable.

However, the pH of the micro-enema, containing the sodium salt, was 9.3 and therefore it is likely that the rate of uptake will be limited as the result of dissociation of the drug in the rectum lumen. In the case of rectal administration of an aqueous suspension of the free acid, pH conditions may be more favourable but in this case absorption rate is probably dissolution rate-limited. Therefore, apart from differences in absorption surface the use of both types of rectal micro-enemas results in absorption rate conditions which are less favourable than after oral administration of the sodium salt.

Suppositories

From experiments in which suppositories were used we concluded that, dependent on the water solubility of the drugs under study, particle size of a drug suspended in a fatty suppository base, can affect the release rate in vitro (Schoonen et al., 1976) and the absorption rate in vivo (Stuurman-Bieze et al., 1978). The release characteristics in vitro of phenobarbital and its sodium salt from Witepsol H 15 suppositories with two classes of particle size, are given in Fig. 3.

In view of the difference in water solubility of the drugs under study it might be expected that reduction in particle size from 125–250 μm to micronized (<20 μm) particles would have less effect on the in vitro release rate of phenobarbital free acid than on the release of its sodium salt. In the case of the freely soluble sodium salt, particle size reduction reduces the transport rate of the particles through the base or across the base/water interface (Schoonen et al., 1976). On the other hand the free acid is more soluble in fat (1 in 250) than in water (1 in 1000) and therefore the diffusional–convective transport of solute away from the interface in water is the rate limiting step, a

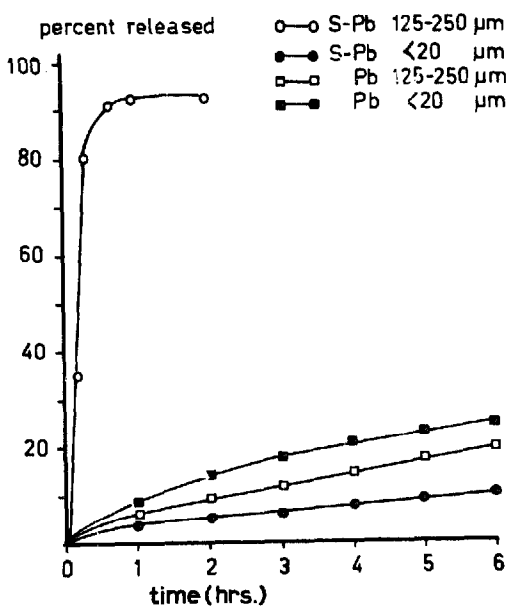

Fig. 3. Effects of particle size on release rate of sodium phenobarbital (S-Pb) and phenobarbital (Pb) from Witepsol H 15. The results are mean values of 4 runs.

process which is much less dependent on the size of the particles. This is indeed illustrated by the results in Fig. 3.

On the ground of these in vitro results the volunteers received suppositories with a coarse powder (125–250 μm) sodium phenobarbital and a fine (<20 μm) powder phenobarbital. The latter formulation was especially chosen because it was learned from a rectal study with the slightly water-soluble paracetamol (acetaminophen) that, after melting, particle size reduction results in a more homogeneous distribution of suspended particles in the fatty base compared with coarse particles, thereby enlarging the area of release and consequently the absorption rate (Moolenaar et al., 1979).

The following observations were made (Fig. 4 and Table 2).

(a) A substantial lag time was found when the micronised phenobarbital suppository was administered in vivo. In addition a considerable intersubject variation occurred using this dosage form.

(b) Absorption from the coarse sodium phenobarbital suppository occurred more rapidly than from the free acid suppository. However, 3 h after administration no significant ($P > 0.05$) differences were found for the plasma concentrations. In addition the t_{max} and C_{max} of the two administered suppositories did not differ significantly ($P > 0.05$).

(c) Compared with the two micro-enemas dosage forms no distinct difference in absorption profile could be detected after administration of the coarse sodium phenobarbital suppository. Differences in C_{max} and t_{max} were not significantly ($P > 0.05$) different.

(d) Relative bioavailability of both administered suppositories did not differ significantly ($P < 0.05$). However, there was a significant ($P < 0.05$) difference in bioavailability after 6.5 h between the fine particle phenobarbital suppository and the orally administered solution of sodium phenobarbital.

One of the most striking results of the present study is the difference in rectal absorp-

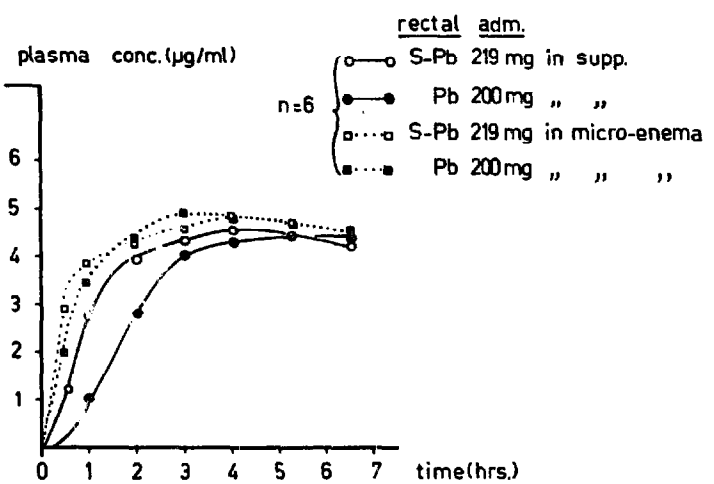

Fig. 4. Mean plasma concentrations of phenobarbital after rectal administration of doses of 219 mg sodium phenobarbital (S-Pb) and 200 mg phenobarbital (Pb) in different dosage forms to 6 subjects.

tion rate between a suspension of micronized phenobarbital (free acid) in 20 ml of aqueous medium and a suspension of micronized phenobarbital in 3 ml of fatty suppository base, whereas no such difference was found if the sodium salt was used (Fig. 4). It is likely that due to the small water solubility of the free acid the transport across lipid/water interface of the suppository is rate determining, whereas a rectal aqueous dosage form already possesses the saturation concentration, resulting in a higher uptake rate for phenobarbital.

In contrast, the absorption profile of the aqueous and fatty dosage forms of sodium phenobarbital did not show distinct differences. It is likely that after rectal administration of the suppository the release area of the molten base is smaller than the absorption area for the administered micro-enema, but this may be compensated for by a higher concentration of dissolved sodium phenobarbital in the rectum fluid, due to the rapid release of the sodium salt from the suppository base.

Taking into account the relative bioavailability after 6.5 h, it is remarkable, however, that there was no significant difference in this parameter between both suppositories, although in vitro only 30% of phenobarbital was released in 6.5 h. Spreading of the fine particles in the rectum with the fatty mass result in a larger release area in vivo as compared with the situation in vitro.

A relatively large intersubject variation was found for the suppository with the fine particles of phenobarbital. Earlier observations in our laboratory indicated that after administration of this dosage form the absorption may be influenced by various factors, such as the resistance at the lipid/water interface, due to agglomeration of particles, and the extent of spreading of the particles with the fatty mass (Stuurman-Bieze et al., 1978).

THERAPEUTIC CONSIDERATIONS

For the treatment of epilepsy chronic administration of phenobarbital is commonly applied to achieve steady-state concentrations. It can be argued that for this purpose it is not relevant whether absorption occurs very fast or not and that it is of importance that bioavailability of an administered dosage form of phenobarbital or its sodium salt is sufficient. Compared with oral administration of the aqueous solution of sodium phenobarbital, the peak concentrations of the micro-enemas and the suppositories did not differ significantly ($P > 0.05$). Also, statistical analysis did not show a significant difference in intersubject variation at C_{max} after administration of the oral solution and three of the rectal dosage forms. Therefore we concluded that rectally administered phenobarbital can be looked upon as an alternative route of administration in anticonvulsive therapy. If a micro-enema dosage form is chosen both the free acid and the sodium salt of phenobarbital can be used. If a suppository dosage form is used the sodium salt may be preferred because of less variability.

Phenobarbital and its sodium salt are often included in analgesic and tranquillizing preparations. In this case absorption rate may be of greater importance. In our study the volunteers felt drowsy 2–3 h after administration of a single rectal dose in the form of micro-enemas, but not after administration of the fine particle phenobarbital suppository. Our results, therefore, may indicate that only for the micro-enemas is rectal absorption sufficiently rapid to achieve sedative levels in the central nervous system.

This is in agreement with the results of Jälling (1974) who observed that after a single oral dose sedation appeared in many of the children during the ascending phase of the plasma curves of phenobarbital.

However, sedative effects of barbiturates have reported to disappear with continuous use, due to development of tolerance. Therefore the use of phenobarbital for sedation in either dosage form should be restricted to short term application.

CONCLUSIONS

After oral administration of phenobarbital the use of sodium salt promotes a fast absorption as compared with the free acid form. After rectal administration of aqueous dosage forms no distinct difference in absorption rate occurs whether the sodium salt or the free acid are used. Administration of both types of rectal micro-enemas results in absorption conditions which result in slower absorption but equal bioavailability after 6.5 h, compared with oral administration of the sodium salt. The rate of rectal uptake of sodium salt may be limited as a result of dissociation of the drug in the rectum lumen. In the case of the free acid the absorption rate is probably dissolution rate-limited.

Differences in release rate in vitro between phenobarbital and its sodium salt, suspended in a fatty suppository mass, are reflected in the absorption profile in vivo.

From the point of view of therapeutics it is concluded that rectally administered phenobarbital can be looked upon as an alternative route of administration in anticonvulsive therapy. It is important to emphasize that, if a micro-enema dosage form is chosen, both the free acid and the sodium salt of phenobarbital can be used. If a suppository dosage form is used the sodium salt may be preferred because of less variability.

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