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Bioavailability of phenytoin from oil suspension and emulsion in dogs

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Summary

Phenytoin as a sesame oil suspension or emulsion was administered orally to beagle dogs to study improvement of its bioavailability. The absorption of phenytoin by the digestive tract was better when it was given as a sesame oil suspension or emulsion than as a powder. With the dose amount of sesame oil and water fixed, the absorption of phenytoin from the emulsion was greater than that from the oil suspension, although the difference was not significant. Therefore, the absorption of phenytoin was not affected significantly by emulsifying the sesame oil. Its absorption corresponded not to the amount of water given with the dose amount of sesame oil fixed, but to the dose amount of sesame oil with the dose amount of water fixed, reaching maximum when the ratio of sesame oil to water was 1:3. Study of the influence of the type of oil in the emulsion on the absorption by the digestive tract showed that absorption was best with cod-liver oil, followed by sesame oil, and then oleic acid.

Introduction

The absorption of phenytoin from the gastrointestinal tract of patients and volunteers has been characterized as being erratic and incomplete, because it is a sparingly soluble drug (Sansom et al., 1975; Pentikainen et al., 1975; Neuvonen et al., 1977). Many investigators have reported that even if phenytoin is administered at doses of 3–6 mg kg^{-1} (Manaka et al., 1975; Shinkuma et al., 1976) to epileptic patients (Miyamoto, 1974; Watanabe et al., 1976), few show the therapeutically effective plasma concentration of 10–20 $\mu g\ ml^{-1}$ (Kutt et al., 1964; Buchthal and Lennox-Buchthal, 1972). The extent of bioavailability of this drug has also been shown to be dependent on particle size (Glazko and Chang, 1972; Lund, 1974), dosage form (Manson et al., 1975), and formulation factors (Tyrer et al., 1970;

Yamamoto et al., 1976; Sekikawa et al., 1978). Recently, improvement of the bioavailability of phenytoin has been under study (Sekikawa et al., 1978). The bioavailability after oral administration of poorly water-soluble drugs is known to be improved by co-administration of lipid (Wagner et al., 1966; Kabasakalian et al., 1970). For example,the bioavailabilities of indoxole (Wagner et al., 1966), griseofulvin (Carrigan and Bates, 1973), and dicumarol (Bloedow and Hayton, 1976) increase in dosage forms containing lipid. However, only Chakrabarti and Belpaire (1978) and Shinkuma et al. (1979) have considered this for phenytoin. Chakrabarti and Belpaire (1978) reported that the bioavailability of phenytoin in rats from corn oil emulsion and suspension was higher than that from aqueous suspension, and the maximal plasma concentration was reached more slowly with corn oil emulsion and suspension than with aqueous suspension. However, no studies have explored the various factors affecting the bioavailability of phenytoin from such dosage forms.

The purpose of this study was to examine the effect of the amount of sesame oil and water administered on the bioavailability of phenytoin in a sesame oil suspension and in an emulsion in beagle dogs. The absorption of phenytoin was also studied with the dose amounts of sesame oil or water fixed. Also, the influence of various factors on phenytoin absorption was investigated by administering it in these dosage forms.

Materials and Methods

Materials

Phenytoin powder (JP IX), a product of Fujinaga Pharmaceuticals, was passed through a 200-mesh sieve to make a fine powder. The following materials were also used: sesame oil (JP IX) of Maruishi Pharmaceuticals, oleic acid of Wako Pure Chemicals, and cod-liver oil of Hayashikane Food Industries, a polyoxyethylene derivative of hydrogenated castor oil (HCO-60) and sorbitan sesquioleate (SO-15) of Nikko Chemicals. All other chemicals were of analytical grade.

Preparation of dosage forms

Phenytoin was dispersed in an emulsion in accordance with the method of Hashida et al. (1977) with necessary modifications. Water was added to 1 g phenytoin, 7.83 ml sesame oil, 0.13 ml HCO-60 and 0.55 ml SO-15 to make 10 ml, and the mixture was treated with ultrasonic waves (Sharp Model UT-52) in a water bath at 70°C for 30 min. Phenytoin as a sesame oil suspension of phenytoin was prepared by adding sesame oil to phenytoin and treating the mixture with ultrasonic waves in a water bath at 70°C for 30 min. After preparation, these dosage forms were cooled to 37°C and administered orally to beagle dogs within 30 min.

Measurement of solubility

Excessive phenytoin was added to various oils and the mixture was treated with ultrasonic waves in a water bath at 70°C for 30 min, after which the solution was allowed to stand in a 37°C thermostated bath for 3 h, and the supernatant liquid was filtered off through a teflon Millipore filter of 0.2 μm. Next, the amount of

phenytoin in the filtrate was measured by gas chromatography (Shinkuma et al., 1976). Phenytoin in oleic acid could not be extracted with alkaline aqueous solution and was determined by high-performance liquid chromatography.

Absorption experiment

Phenytoin, 50 mg kg^{-1}, was administered orally to female beagle dogs, weighing approximately 8.5 kg, which had been fasted overnight. The amount of water taken at the time of drug administration was fixed at 2.9 ml kg^{-1}. Blood was collected from the femoral vein at regular intervals after drug administration. In determining the plasma concentrations of phenytoin, serum was separated after drawing of the blood and measurement was done with Markit (Dai Nihon Pharmaceuticals, Japan) based on enzyme immunoassay using an insoluble antibody with β-galactosidase-labeled drug and the cell wall of bacteria as the carrier (Watanabe et al., 1979; Nishihara et al., 1980). The experiment was performed at 2-week intervals by the random complete cross-over test.

Results and Discussion

Fig. 1 shows the mean plasma concentrations afer phenytoin powder sesame oil suspension and sesame oil emulsion were administered orally to dogs. Table 1 shows the mean maximum plasma concentration (C_{max}) after administration of phenytoin in each dosage form, the mean value for individual maximum plasma concentration (C'_{max}), the time required for the mean maximum plasma concentration to be reached (T_{max}), the mean value for the time required for individual maximum plasma concentration to be reached (T'_{max}), and the mean value for the area under the plasma concentration–time curve (AUC). C'_{max} stood at 1.96 μg ml^{-1}, T'_{max} at

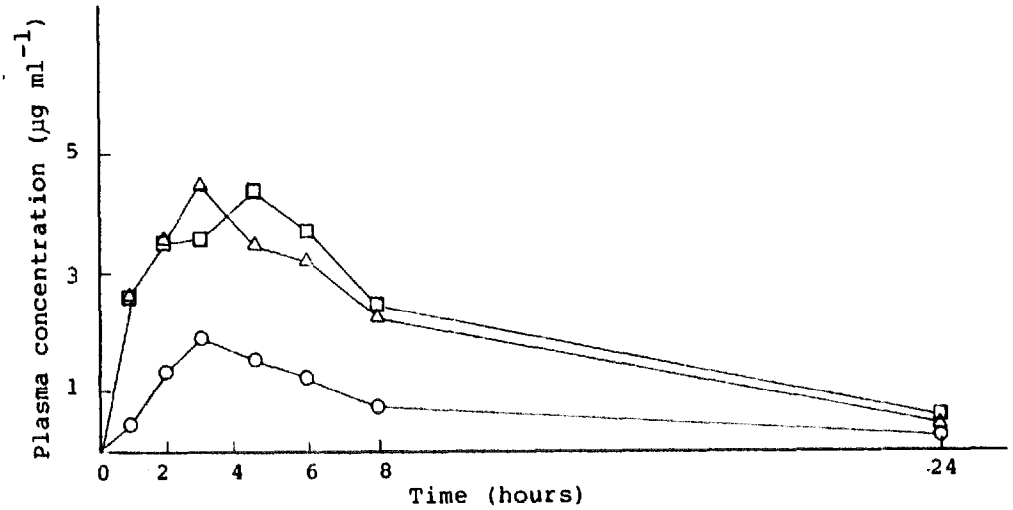

Fig. 1. Representative plasma concentrations of phenytoin following oral administration of 50 mg kg^{-1} phenytoin as a powder (○), an oil suspension (□), or an emulsion (△). Each point represents the mean result from 4 dogs.

TABLE 1

PHARMACOKINETIC PARAMETERS AND ANALYSES OF PLASMA CONCENTRATIONS OF PHENYTOIN FOLLOWING ORAL ADMINISTRATION OF 50 mg kg^{-1} PHENYTOIN IN 3 DOSAGE FORMS

Parameter	Dosage form		
	Powder	Suspension	Emulsion
C_{max} [a] ($\mu g\ ml^{-1}$)	1.91 ± 0.98	4.41 ± 1.40	4.46 ± 1.01
C'_{max} [b] ($\mu g\ ml^{-1}$)	1.96 ± 0.89	4.55 ± 0.85	4.46 ± 1.01
T_{max} [c] (h)	3	4.5	3
T'_{max} [d] (h)	3.75 ± 1.30	3.75 ± 0.75	3.00 ± 0.00
AUC [e] ($\mu g\ h\ ml^{-1}$)	16.29 ± 8.55	45.35 ± 7.49	44.08 ± 2.79
Statistical significance [f]	$P<0.001$		N.S.
		$P<0.02$	

[a] Average plasma concentration peak.
[b] Average of individual peak plasma concentrations.
[c] Time of the average plasma concentration peak.
[d] Average of individual peak times.
[e] Area under the plasma concentration–time curve to 24 h calculated by the trapezoidal rule.
[f] Determined by AUC Student's *t*-test. Each value represents the mean ± S.D. of 4 dogs.

3.75 h, and AUC at 16.29 $\mu g\ h\ ml^{-1}$ when the powder was administered. C'_{max} and AUC on administration of the sesame oil suspension or emulsion to dog increased by about 2–3 times each compared with those on administration of the powder, and the difference between the dosage forms was statistically significant at the levels shown in Table 1. These results were similar to previously observed data with rat for phenytoin in dosage forms containing lipid (Chakrabarti and Belpaire, 1978). Accordingly, the enhanced absorption of phenytoin from dosage forms containing lipid is probably due to the ability of lipid to inhibit gastrointestinal mobility and to stimulate gall-bladder evacuation (Bates and Sequeira, 1975). The plasma concentration–time curve on administration of phenytoin emulsion to dog showed the same

TABLE 2

PHARMACOKINETIC PARAMETERS AND ANALYSES OF PLASMA CONCENTRATIONS OF PHENYTOIN FOLLOWING ORAL ADMINISTRATION OF 50 mg kg^{-1} PHENYTOIN AS AN EMULSION

Parameter [a]	Phenytoin	
	Powder	Fine powder
C_{max} ($\mu g\ ml^{-1}$)	4.46 ± 1.01	7.70 ± 0.57
C'_{max} ($\mu g\ ml^{-1}$)	4.46 ± 1.01	7.70 ± 0.57
T_{max} (h)	3	6
T'_{max} (h)	3.00 ± 0.00	6.00 ± 0.00
AUC ($\mu g\ h\ ml^{-1}$)	44.08 ± 2.79	86.29 ± 2.51
Statistical significance	$P<0.001$	

[a] See Table 1.

tendency as that observed on administration of the sesame oil suspension. The same was true for AUC. A similar result was obtained by Bloedow and Hayton (1976) in an oil-in-water emulsion containing sulfisoxazole acetyl. These phenomena suggest that phenytoin suspended in sesame oil is also emulsified in the digestive tract to increase the area of contact with the mucous membrane, resulting in increased phenytoin absorption.

Table 2 shows the influence of the particle size of phenytoin in the emulsion on the absorption of phenytoin. AUC on oral administration of an emulsion of fine phenytoin powder (particle size: 4.1 μm) to dog increased by about 2-fold compared with an emulsion of commercial powder (particle size: 190 μm). The difference was statistically significant at the 1% level. The value for AUC in this case was twice as much as that for AUC on administration of powder and fine powder of phenytoin (powder: 21.2 μg h ml^{-1}, fine powder: 39.4 μg h ml^{-1}), but showed the same tendency (Shinkuma et al., 1979). Presumably, this is because the smaller particle size allows more dissolution in the digestive tract, leading to an increase in absorption (Glazko and Chang, 1972). When phenytoin dispersed in emulsion was administered orally, T'_{max} was delayed by about 2-fold for phenytoin of the small particle size compared with that of the large particle size. This is probably because small-particle phenytoin disperses well in the emulsion and adheres in many places to the wall of the digestive tract with the emulsion. Thus, it is less subjected to the influence of the gastric emptying rate and takes longer to reach the site of absorption.

Table 3 shows the influence of the kind of oil in the emulsion on the absorption of phenytoin. AUC was the largest in the case of cod-liver oil, followed by sesame oil then oleic acid. The difference was statistically significant at the 0.1% level between AUC using cod-liver oil and that using oleic acid, but no difference was observed between cod-liver oil and sesame oil or between sesame oil and oleic acid. We also measured the solubility of phenytoin in cod-liver oil, sesame oil and oleic acid. The solubility was 400–500 μg ml^{-1} and not much difference was found among the oils.

TABLE 3

PHARMACOKINETIC PARAMETERS AND ANALYSES OF PLASMA CONCENTRATIONS OF PHENYTOIN FOLLOWING ORAL ADMINISTRATION OF 50 mg kg^{-1} PHENYTOIN AS AN EMULSION

Parameter [a]	Oil used		
	Cod-liver oil	Sesame oil	Oleic acid
C_{max} (μg ml^{-1})	5.19 ± 0.15	4.46 ± 1.01	2.68 ± 0.86
C'_{max} (μg ml^{-1})	5.19 ± 0.15	4.46 ± 1.01	3.22 ± 0.91
T_{max} (h)	3	3	3
T'_{max} (h)	3.00 ± 0.00	3.00 ± 0.00	4.00 ± 1.41
AUC (μg h ml^{-1})	58.37 ± 6.52	44.08 ± 2.79	40.04 ± 3.17
Statistical significance	N.S.	$P<0.001$	N.S.

[a] See Table 1.

TABLE 4

PHARMACOKINETIC PARAMETERS AND ANALYSES OF PLASMA CONCENTRATIONS OF PHENYTOIN FOLLOWING ORAL ADMINISTRATION OF 50 mg kg^{-1} PHENYTOIN AS AN OIL SUSPENSION

Parameter [a]	Dose amount of oil		
	0.5 ml kg^{-1}	1.0 ml kg^{-1}	2.0 ml kg^{-1}
C_{max} (μg ml^{-1})	4.41 ± 1.40	7.47 ± 1.35	10.55 ± 2.93
C'_{max} (μg ml^{-1})	4.55 ± 0.85	7.47 ± 1.35	11.78 ± 2.52
T_{max} (h)	4.5	4.5	8
T'_{max} (h)	3.75 ± 0.75	4.50 ± 0.00	6.13 ± 1.24
AUC (μg h ml^{-1})	45.35 ± 7.49	104.30 ± 12.86	149.36 ± 26.11
Statistical significance		$P<0.001$	$P<0.05$
		$P<0.01$	

[a] See Table 1.

Accordingly, the solubility in oils appears to have little influence on the absorption of phenytoin, which is affected by the viscosity of the oil and by hydrolysis and emulsification in the digestive tract. The maximum plasma concentration on oral administration of phenytoin with oleic acid was low compared with that using sesame oil and cod-liver oil, and no marked peak was obtained.

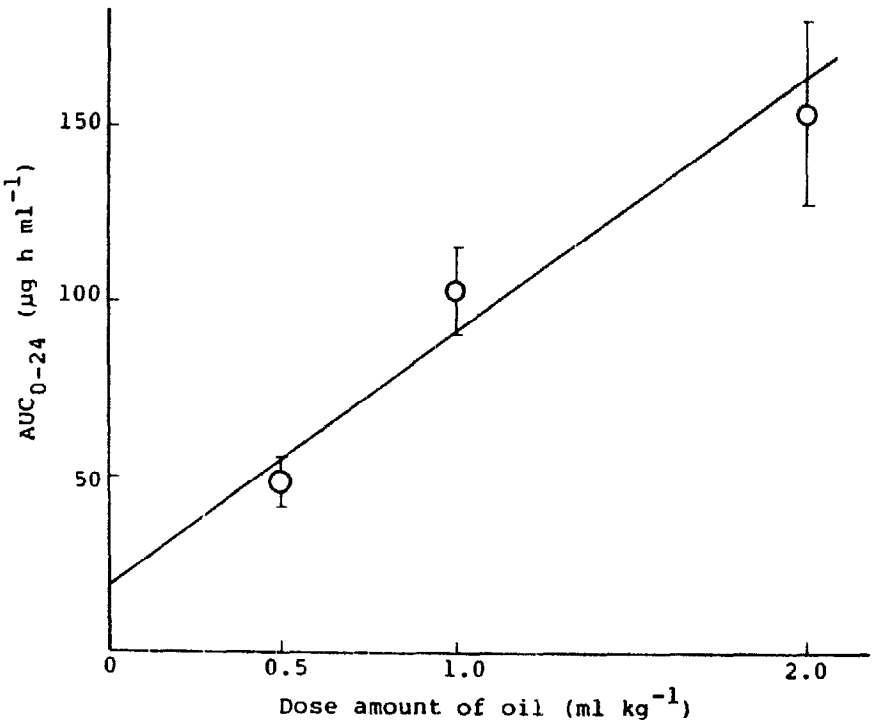

Fig. 2. The relationship between the dose amount of oil and areas under the plasma concentration–time curve from 0 to 24 h following oral administration of phenytoin as an oil suspension. Each point represents the mean result ± S.D. from 4 dogs.

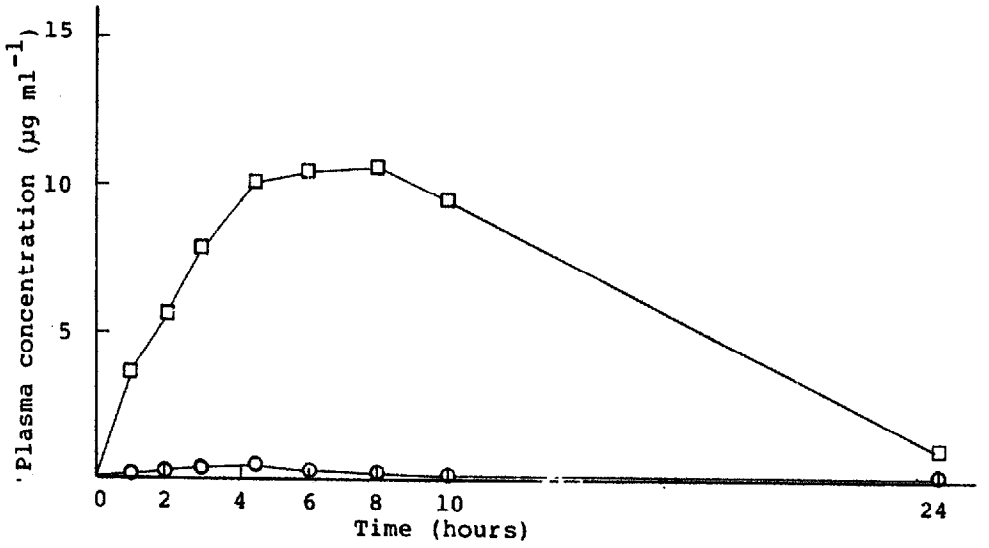

Fig. 3. Plasma concentrations of phenytoin following oral administration of 50 mg kg^{-1} phenytoin as an oil suspension (□) and 0.95 mg kg^{-1} phenytoin as a saturated oil solution (○). Each point represents the mean result from 4 dogs.

Table 4 shows the influence of the dose of sesame oil on the absorption of phenytoin as a sesame oil suspension. AUC and C'_{max} tended to increase and T'_{max} to be delayed as the dose of oil increased. In this connection, several reports indicate that the extent of bioavailability of griseofulvin in man increases with the amount of lipid (Crounse, 1961; Bates and Sequeira, 1975). On the other hand, although Bloedow and Hayton (1976) found that the extent of absorption of sulfisoxazole acetyl was not affected by the amount of lipid administered, the highest dose of lipid reduced the initial rate of drug absorption, probably by reducing the rate of drug emptying from the stomach. Differences in the volumes of lipid and water administered, the type of oil, and the strain of animal may explain the different effects observed.

TABLE 5

PHARMACOKINETIC PARAMETERS AND ANALYSES OF PLASMA CONCENTRATIONS OF PHENYTOIN FOLLOWING ORAL ADMINISTRATION OF 50 mg kg^{-1} PHENYTOIN AS AN OIL SUSPENSION AND 0.95 mg kg^{-1} PHENYTOIN AS A SATURATED OIL SOLUTION

Parameter [a]	Oil suspension	Saturated oil solution
C_{max} (μg ml^{-1})	10.55± 2.93	0.43±0.12
C'_{max} (μg ml^{-1})	11.78± 2.52	0.44±0.08
T_{max} (h)	8	4.5
T'_{max} (h)	6.13± 1.24	4.88±0.65
AUC (μg h ml^{-1})	149.36±26.11	3.74±1.45
Statistical significance	$P<0.001$	

[a] See Table 1.

Fig. 2 illustrates the relationship between the dose of sesame oil and AUC. The correlation coefficient ($r = 0.96$) and the primary function ($y = 65.87x + 22.82$) were established between AUC and the dose of sesame oil. These data suggest that the moving speed of phenytoin in the digestive tract slows down with an increase in the dose of oil, causing phenytoin to be retained longer at the site of absorption, and that the amount of phenytoin dissolved increases with an increase in the amount of oil, resulting in increased absorption of phenytoin.

Fig. 3 and Table 5 present the mean plasma concentrations after oral administration of a sesame oil suspension of phenytoin and its saturated solution (solubility: 474.9 $\mu g\ ml^{-1}$) in a dose of 2 ml kg^{-1} to the dogs. The sesame oil suspension of phenytoin was filtered through a teflon Millipore filter of 0.2 μm, and the filtrate was used as a saturated sesame oil solution of phenytoin. When the saturated sesame oil solution was administered, the dose of phenytoin (0.95 mg kg^{-1}) was about 1/50th that of the sesame oil suspension (50 mg kg^{-1}). The volume of water to be given simultaneously with oral administration of the drug was fixed at 2.9 ml kg^{-1} in order to have the volume of water exert an influence on the dissolution and absorption of the drug (Cadwallader, 1974). As a result, AUC on administration of sesame oil suspension increased about 40-fold over that on administration of the saturated sesame oil solution. On the other hand, when dicumarol was administered as an oil solution, its bioavailability was the same as that for its oil suspension (Bloedow and Hayton, 1976). Accordingly, these results suggest that the extent of dissolution of the drugs at the time of administration is not an important factor in the bioavailability. Thus, we surmise that on administration of the sesame oil suspension of phenytoin as with the saturated sesame oil solution, it takes about twice as much time for T_{max} to be reached because phenytoin not yet dissolved in sesame oil becomes dissolved and then is absorbed gradually by the digestive tract.

A study was made on the influence of the amount of water taken in on the absorption of phenytoin when its sesame oil suspension was administered. The dose of sesame oil was fixed at 1 ml kg^{-1} and the amount of water taken in was varied.

TABLE 6

PHARMACOKINETIC PARAMETERS AND ANALYSES OF PLASMA CONCENTRATIONS OF PHENYTOIN FOLLOWING ORAL ADMINISTRATION OF 50 mg kg^{-1} PHENYTOIN AS AN OIL SUSPENSION

Parameter [a]	Dose amount of water		
	1.45 ml kg^{-1}	2.9 ml kg^{-1}	4.35 ml kg^{-1}
C_{max} ($\mu g\ ml^{-1}$)	4.14± 1.02	7.47± 1.35	4.97±0.61
C'_{max} ($\mu g\ ml^{-1}$)	4.16± 1.01	7.47± 1.35	5.47±0.53
T_{max} (h)	4.5	4.5	4.5
T'_{max} (h)	5.00± 0.71	4.50± 0.00	3.17±1.02
AUC ($\mu g\ h\ ml^{-1}$)	48.30±12.90	104.30±12.86	62.22±9.40
Statistical significance	$P<0.05$	$P<0.05$	
	N.S.		

[a] See Table 1.

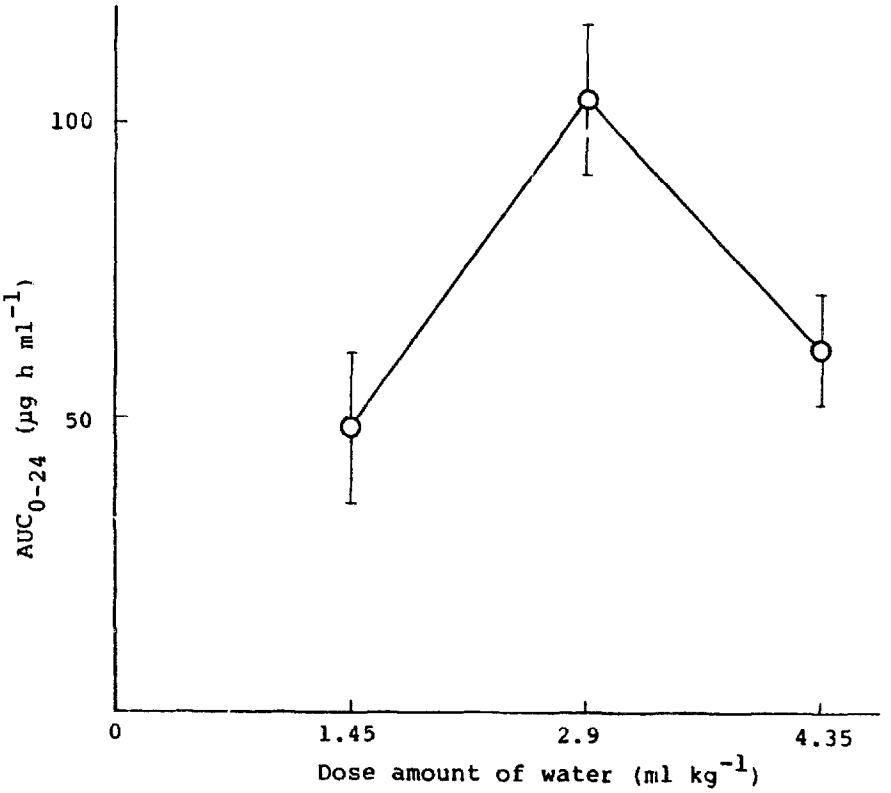

Fig. 4. The relationship between the dose amount of water and areas under the plasma phenytoin concentration-time curve from 0 to 24 h following oral administration of 50 mg kg^{-1} phenytoin as an oil suspension. Each point represents the mean result ± S.D. from 4 dogs.

The results of the study are presented in Table 6 and Fig. 4. Clearly, phenytoin absorption is not correlated with the amount of water taken in. When the amount of water taken in was increased by about 3-fold (2.9 ml kg^{-1}) over that of the dose of sesame oil, the absorption of phenytoin reached the maximum, and the difference

TABLE 7

PHARMACOKINETIC PARAMETERS AND ANALYSES OF PLASMA CONCENTRATIONS OF PHENYTOIN FOLLOWING ORAL ADMINISTRATION OF 50 mg kg^{-1} PHENYTOIN AS AN OIL SUSPENSION

Parameter [a]	Condition	
	With sodium taurocholate	Without sodium taurocholate
C_{max} (μg ml^{-1})	5.33 ± 1.88	7.47 ± 1.35
C'_{max} (μg ml^{-1})	5.75 ± 1.61	7.47 ± 1.35
T_{max} (h)	3	4.5
T'_{max} (h)	3.50 ± 1.06	4.50 ± 0.00
AUC (μg h ml^{-1})	68.43 ± 22.07	104.30 ± 12.86
Statistical significance	N.S.	

[a] See Table 1.

was statistically significant at the levels shown in Table 6. This result suggests that sesame oil is most easily dispersible in the digestive tract when the ratio of sesame oil to the amount of water taken is 1 : 3. And this dispersible state apparently increases the surface area of the oil to accelerate its hydrolysis as with administration of the emulsion, thus leading to increased absorption of phenytoin (Bates and Sequeira, 1975).

Table 7 shows the influence of taurocholic acid on the absorption of phenytoin in the sesame oil suspension. Aqueous solution of sodium taurocholate, 107 mg kg^{-1} (equimolar with the dose of phenytoin) was administered orally immediately after administration of sesame oil suspension of phenytoin. AUC following administration of taurocholic acid decreased compared with the case in which it was not administered, but the difference was not statistically significant at the 5% level.

From the above results, the dispensing state of oil and water in the digestive tract appears to be an important factor in phenytoin absorption, which is affected by the amount of water and oil given.

A comparative experiment on the absorption of phenytoin from the emulsion and the suspension was performed with the amount of sesame oil and water administered fixed. In preparing emulsions containing phenytoin at two different concentrations, 40 ml sesame oil, 0.3 ml HCO-60 and 0.7 ml So-15 were added to 1 or 2 g of phenytoin with enough water to make 100 ml and these solutions were treated with ultrasonic waves in a water bath for 30 min. Emulsions containing phenytoin (10 or 20 mg ml^{-1}) were administered orally at doses of 5 or 2.5 ml kg^{-1} to dogs, respectively. Therefore, the dose of phenytoin was fixed at 50 mg kg^{-1}. The animals were not allowed to take water other than that contained in these emulsions. With the dose of sesame oil fixed at 2 ml kg^{-1}, AUC was 171.52 μg h ml^{-1} on administration of 5 ml kg^{-1} of the emulsion (Table 8) and 149.36 μg h ml^{-1} on administration of the oil suspension (Table 4). With the dose of sesame oil fixed at 1 ml kg^{-1}, AUC was 58.66 μg h ml^{-1} (Table 8) on administration of the emulsion and 48.3 μg h ml^{-1} on administration of the oil suspension (Table 6).

TABLE 8

PHARMACOKINETIC PARAMETERS AND ANALYSES OF PLASMA CONCENTRATIONS OF PHENYTOIN FOLLOWING ORAL ADMINISTRATION OF 50 mg kg^{-1} PHENYTOIN AS AN EMULSION

Parameter [a]	Dose amount of emulsion	
	2.5 ml kg^{-1}	5.0 ml kg^{-1}
C_{max} (μg ml^{-1})	4.88± 1.47	12.40±0.43
C'_{max} (μg ml^{-1})	4.94± 1.43	12.43±0.39
T_{max} (h)	4.5	6
T'_{max} (h)	6.25± 2.25	6.67±0.94
AUC (μg h ml^{-1})	58.66±14.23	171.52±9.60
Statistical significance	$P<0.001$	

[a] See Table 1.

However, no significant difference was observed between AUC of the emulsion and the suspension. Bloedow and Hayton (1976) also reported that the extent of bioavailability of sulfisoxazole acetyl was not affected significantly by emulsifying the triolein. These results suggest that a sesame oil suspension becomes well dispersed in the digestive tract like an emulsion, thus accelerating the absorption of phenytoin.

Conclusion

When sesame oil suspension and emulsion of phenytoin were administered to beagle dogs, the absorption of phenytoin increased as the dose of sesame oil increased and a linear relationship was found between the amounts of sesame oil and AUC in suspension. The enhanced absorption of phenytoin from dosage forms containing lipid is probably due to the ability of lipid to inhibit gastrointestinal mobility and stimulate gall-bladder evacuation (Bates and Sequeira, 1975). The absorption of phenytoin reached maximum when the ratio of sesame oil to water was 1 : 3, and the absorption of phenytoin was not correlated with the amount of water given when the dose of sesame oil was fixed. With the dose amounts of sesame oil and water fixed, the absorption of phenytoin was slightly better upon administration in an emulsion than in an oil suspension, but the difference was not significant (Tables 4, 6 and 8). The extent of dissolution of phenytoin in the oil suspension at the time of administration did not affect its absorption.

The results of this study indicate that the absorption of phenytoin following oral administration as a sesame oil suspension is the same as that for its emulsion. Presumably, the sesame oil suspension may be emulsified in the digestive tract by the action of the water administered, bile salt and pancreatic lipase. Therefore, the ratio of sesame oil to water given at the time of administration is an important factor in the absorption of phenytoin in dosage forms containing lipid.

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