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COMPARISON OF THE BIOAVAILABILITY OF ORAL AND RECTAL FORMS OF DIPHENYLHYDANTOIN SODIUM

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ABSTRACT

The bioavailabilities of single 100-mg oral and rectal doses of diphenylhydantoin sodium were studied in five healthy volunteers. The rectal form used was prepared at laboratory conditions and the oral form was a commercial preparation. Blood samples were analysed over a 72-hr period. Evaluation of the AUC, t_{max} and C_{max} values have shown that the total absorption after the two routes of administration was the same while the C_{max} and t_{max} differed.

INTRODUCTION

Diphenylhydantoin is a commonly used anticonvulsant since 1937 when it was first introduced into use for the treatment of seizure disorders(1). The average therapeutic plasma concentration of phenytoin lies within the range of 10-15 μg/ml. This is usually maintained with a daily dose of 300-400 mg, 2-4 times a day(2).

Diphenylhydantoin sodium (DPH·Na) is one of the clinically important drugs because of its difficulty in predicting the dose needed to achieve the desired plasma levels. It was reported by Lund(3) that the sodium salt of DPH showed much better bioavailability than the free acid. Not the excipient but the particle size of DPH was decided to affect the bioavailability. However,

Eadie et al(4) stated that the interaction of the drug with the excipient is needed for the absorption of DPH.

Many authors have reported the bioavailability of different commercial preparations of DPH·Na(5,6,7,8,9,10,11). The results of these numerous studies show that there is a possible change in the absorption of dosage forms. DPH has received attention because of its narrow therapeutic ratio which makes accurate dosage adjustment important and the largeness of the intersubject variation in serum concentration(12).

There is no linear relationship between the dose and serum concentration. The half-life of phenytoin depends on the dose and is 13 hours at lower plasma levels, but may rise up to 46 hours when maximum therapeutic limit is reached(13). The average half-life after oral administration is 22 hours while shorter after intravenous administration ranging from 10 to 15 hours(1).

Suppositories are indicated for systemic action when there is drug inactivation in the upper GI tract or the liver; the patients who are comatose and cannot tolerate oral medication (14). DPH·Na is sometimes needed to be administered rectally for a rapid absorption when the patient is in status epilepticus.

Since there are consequences of the bioinequivalences of different preparations and the problem seems to continue to occur, our study was conducted to investigate the bioequivalence of the oral and rectal dosage forms.

MATERIALS AND METHOD

This study was conducted in five normal volunteers who were healthy as determined by history and routine laboratory tests. None had a history of adverse drug reactions. The weights of the volunteers were within a range of 48-62 kg and among them four were females.

Single oral and rectal doses of 100-mg of DPH.Na were administered in the morning after an over-night fasting. The food intake was permitted after 1 hour following administration. The oral doses were given in the form of "EPDANTOIN" tablets (EMBIL-Turkey). The rectal form was prepared , using Imhausen H 15 as an excipient, under good and precise laboratory conditions. When selecting the suppository base, the general concept of choosing a lipophilic base for water soluble compounds for rapid and complete release, was accepted.

Blood samples were taken at time 0, 0.25, 0.5, 1, 2, 4, 6,12, 24, 48 and 72 hours. The determination of DPH·Na in blood was achieved using a benzophenone procedure(15). This procedure was chosen, among the many methods(16,17,18,19), in the light of reducing the sample volume requirement and overall procedure time and the removal of non-specific interference.

The standard curve of DPH·Na was drawn and used all through the experiments. The correlation coefficient of the curve was 0.9987 and the regression equation was $y=0.1165x + 7.7256x10^{-3}$, where x is the concentration and y, the absorbance.

The 200 ml blood samples were placed in heparinised tubes and used in the extraction of DPH·Na(15). The solvents used in the extraction procedure were of analytical grade. The quantitation was achieved at 248 nm, spectrophotometrically (Shimadzu UV 240-Graphicord). The absorbance of the reagent blank was subtracted from the sample values.

The relative bioavailabilities of the two preparations were compared by estimating the areas under the plasma concentration-time curves. Peak plasma levels (C_{max}) and the time to reach these levels (t_{max}) were measured.

RESULTS AND DISCUSSION

The plasma concentrations of DPH·Na-time following oral and rectal dosing were recorded in Table 1. The mean plasma concentration-time curves of the single 100-mg dose studies were shown in Figure 1.

The time course of absorption of DPH·Na was irregular as shown in Figure 1. Most of the subjects showed an initial absorption peak at 0.5-2 hr and a secondary peak at 10-15 hr after an oral administration. Previous investigations(7) have also shown that the time course of absorption is irregular and there is a secondary absorption peak probably due to the dissolution of an appreciable fraction of the residual dosage form when food is ingested.

The fact that DPH·Na is an extremely important drug for the bioavailability and thus for the therapeutic efficacy and risk of side-effects can be predicted looking at the intersubject variation shown in Table 1. This variation is reported to be due to the genetic influences and to the saturation of the enzyme system of subjects.

When the cumulative plasma concentration values were applied to Kolmogorov-Smirnov Two Samples Test, it could be estimated that there is no difference between the group distributions of the two routes of administration (D_{max}=0.416989; p>0.05).

Area under the curve of plasma concentration-time of both dosage forms were calculated using the normal AUC calculations and given in Table 2. AUC values do not seem to differ significantly for either preparation. This means the total absorption, after a single dose, is almost the same for oral and rectal forms. However the C_{max} reached and t_{max}, differ for both preparations. C_{max} of the oral form is about 0.8944 μg/ml at time 2 hr, while the C_{max} of the rectal form

TABLE 1

Plasma Levels of DPH·Na Following Administration of 100-mg as Oral or Rectal Forms.

Time (hr) / Subject	Plasma DPH·Na level (μg/ml)					
	K.A.	I.C.	Ö.T	G.V.	Y.Y.	Mean
ORAL						
0.25	0.599	0.345	0.882	0.539	0.796	0.6322
0.50	0.710	0	0	0.796	1.054	0.512
1	1.054	1.740	0	0.624	0	0.6836
2	1.654	2.427	0.024	0	0.367	0.8944
4	0	0.367	0.539	0.195	0.195	0.2592
6	0	0	0.109	0	0	0.0218
12	0.109	0.281	0.139	0.968	0	0.3993
24	0	0.912	0.453	0.084	0	0.2898
48	0.195	0	0	0.654	0.024	0.1746
72	0.105	0.109	0	0	0	0.0428
RECTAL						
0.25	0	0.281	0	0.281	1.654	0.4432
0.5	0	4.058	0.968	1.397	2.341	1.7528
1	0.195	0.195	0.624	0	0	0.2028
2	0.367	0	0.367	0	0	0.1468
4	0.195	0	0	0	0	0.039
6	0.281	0	0	0	0	0.0562
12	0.1075	0	0	0	0	0.0215
24	1.054	0	0	0	0	0.2108
48	0.796	0	0	0	0	0.1592
72	0.311	0	0	0	0	0.0622

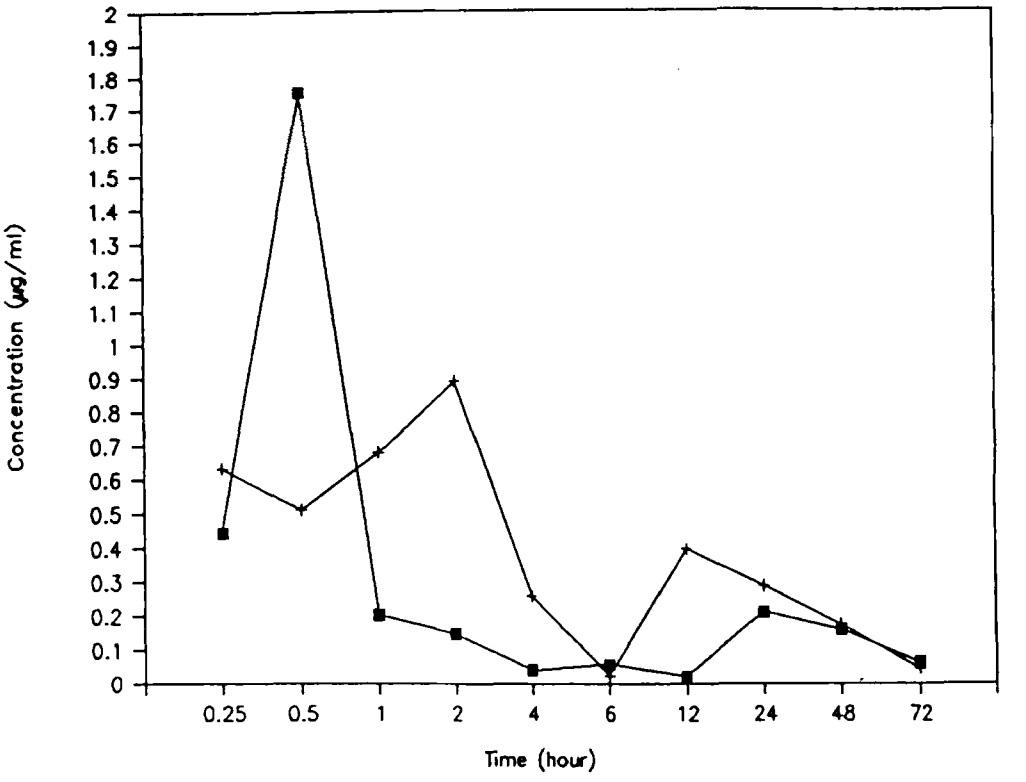

FIGURE 1

Blood Concentrations of DPH·Na as a Function of Time After Oral (+) and Rectal (■) Administration of a Single 100-mg Dose.

appears to be 1.7528 µg/ml at time 0.5 hr. The C_{max} reached following the rectal administration is almost twice as much when compared with the C_{max} of the oral administration. And this level is reached in one-fourth of the time of the latter.

The experimental plasma concentrations were applied to the linear, hyperbolic and parabolic regressions using the computer. The values seem to fit best to parabolic regression. The parabolic regression equation for the rectal administration is $y=0.49792-0.02445\ x + 0.0003\ x^2$; where x, is the time and y, the plasma concentration. The equation is $y=0.55656-0.01647\ x + 0.0001\ x^2$ for the oral administration. The values calculated using those equations are given in Table 3 and plotted in Figure 2.

TABLE 2

Area Under the Curve of Plasma Concentration-Time After a Single Dose of 100-mg of DPH·Na.

Time (hr)	AUC(oral) µg/ml/hr	AUC(rectal) µg/ml/hr
0.25	0.1617	0.1432
0.50	0.2927	0.7096
1	0.4675	0.7752
2	0.6963	0.8226
4	0.7626	0.8352
6	0.7681	0.8534
12	0.8703	0.8603
24	0.9444	0.9285
48	0.9891	0.9799
72	1	1
Mean	0.7908	0.6953

TABLE 3

The Plasma Concentrations of DPH·Na Calculated Using the Parabolic Regression.

Time (hr)	Plasma Conc. (oral) µg/ml	Plasma Conc. (rectal) µg/ml
0.25	0.5525	0.4918
0.50	0.5484	0.4858
1	0.5402	0.4737
2	0.5242	0.4501
4	0.4929	0.4045
6	0.4627	0.3611
12	0.3788	0.2439
24	0.2407	0.0689
48	0.0838	0.0441
72	0.0857	0.1587
Standard Deviation	0.2470	0.5503

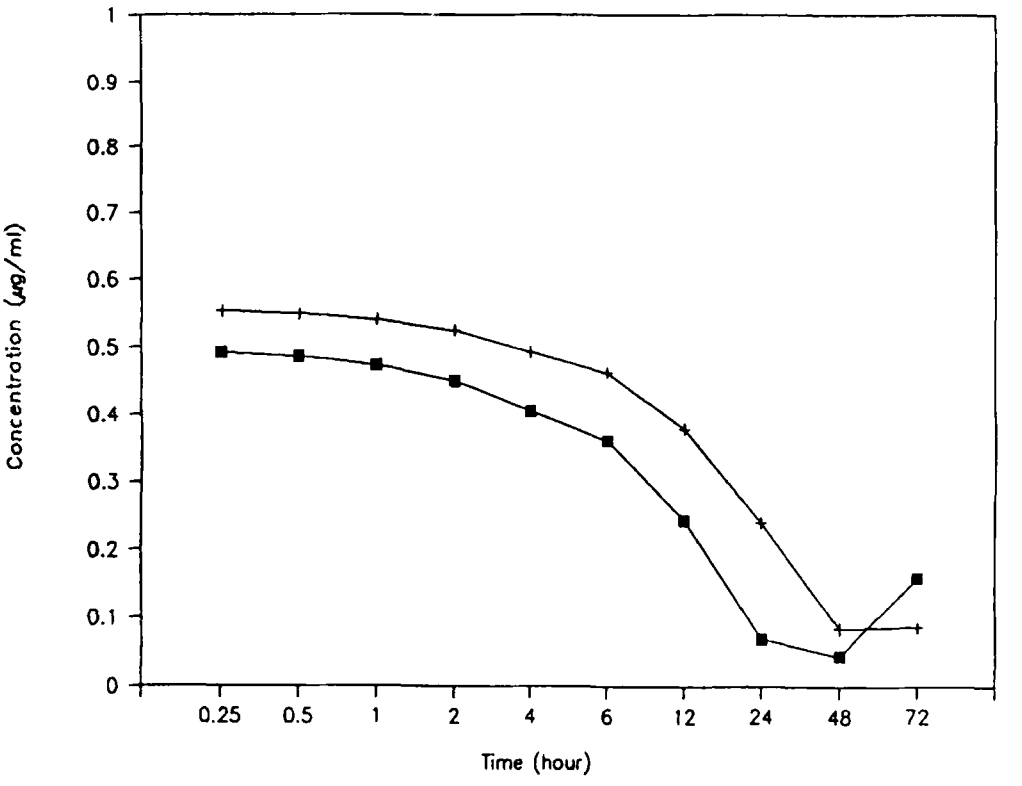

FIGURE 2

Plasma Concentration-Time Curve of DPH·Na Calculated Using the Parabolic Regression (+ Oral, ■ Rectal).

All of the data obtained clearly indicate that the total absorption of DPH·Na following oral and rectal administration do not differ significantly. The suppository base selected appears to be good for rapid release of DPH·Na. In the light of those results, further dose- determination studies may be carried on for the accurate dosage of rectal administration bioequivalent to the oral administration.

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