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EFFECT OF A BULK FORMING LAXATIVE ON THE BIOAVAILABILITY OF CARBAMAZEPINE IN MAN

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The influence of a bulk forming laxative consisting of 3.5g. Ispaghula Husk (Plantago seeds) on the bioavailability of Carbamazepine from commercial tablets was studied in four healthy male volunteers. The drug was administered as a single oral dose of 200 mg. Evaluation of the absorption was done by means of the plasma concentration measurements. Seven blood samples were collected over a 24-h period following carbamazepine administration and the drug plasma concentrations were determined by HPLC. The data were statistically analyzed by the t-test for paired observations and were subjected to a stripping computer program to obtain the relevant bioavailability values.

INTRODUCTION

Carbamazepine (5-carbamoyl-5h-dibenz[b,f]azepine) is an antiepileptic agent which is useful in patients with generalized tonic-clonic and both simple and complex partial seizures (1). It is also an effective agent for the treatment of patients with trigeminal neuralgia (2). It is slowly but fairly completely absorbed from the gastro intestinal tract (3). Numerous studies have demonstrated the influence of other drugs on the plasma concentrations of carbamazepine. Fluoxetine (4) and isoniazid (5,6) increased significantly the plasma concentrations of the drug due to inhibited metabolism. The simultaneous administration of isoniazed was shown to cause several cases of clinical toxicity (6). A study in paediatric patients has documented the occurrence of toxicity due to erythromycin coadministration and it was concluded that children receiving carbamazepine should not be given erythromycin except in circumstances allowing careful monitoring (7). The combination of these two drugs represents a clinically significant drug interaction and should be avoided where possible (8). Examples of other drugs which were reported to increase carbamazepine serum levels include primidone (9) and danazole (10). On the other hand, the serum levels of

carbamazepine were significantly lower in patients receiving cimetidine (11), and phenytoin (12), than the serum levels in patients receiving carbamazepine alone. Since much emphasis has been placed on the interactions of other drugs with carbamazepine, the influence of a bulk forming laxative on the bioavailability of the drug was investigated.

MATERIALS

The following chemicals were used as received from the manufacturers : Methanol, HPLC grade, Romil Chemicals CO., Liece, UK; 5-(-p-methylphenyl)-5-phenyl-hydantoin (BP), Alexandria Pharmaceuticals, Alexandria, Egypt; carbamazepine 200mg. tablets, tegretol, batch No. 358 and expiry date 2/1997 produced by Ciba-Geigy, Egypt, under the licence of Ciba-Geigy Limited, Basle, Switzerland, and Ispaghula Husk B.P. 3.5 g. sachet, fybogel, batch No. 645 and expiry date 7/95 produced by Reckett & Colman, UK.

METHODS

Design of the In-vivo Study

Four healthy male volunteers participated in this study after obtaining their signed consent. Their ages ranged from 29-33 years and their weights from 59 to 76 kg. Each volunteer swallowed one carbamazepine tablet with 200 ml of water (treatment A) or one tablet and one Ispaghula Husk sachet suspended on 200 ml of water (treatment B) at 8 a.m. following defaecation and an overnight of fasting which was continued for 4 h post drug administration.

Blood samples (3 ml each) were collected in heparinized vacutainer tubes (Becton, Dickinson - France, each containing 143 units of USP heparin sodium) at zero and 1,2,3,4,6,8 and 24 h after drug administration. Blood samples were centrifuged and the collected plasma was separated and frozen at -20 C pending analysis. The volunteers abstained from any other medication one week before and during the study weeks.

Analytical Procedure :

The HPLC conditions were developed in the Pharmaceutics Service Unit of the Department of Pharmaceutics for plasma monitoring of anticonvulsants. A reversed phase C-18 column (Partisil ODS, 5μ, Whatman) and a HPLC unit (Waters Model 441, Waters Associates, USA) were used. The mobile phase consisted of 55% (v/v) methanol in water. Detection was carried out at 254 nm. 5-(-p-methylphenyl)-5-Phenylhydantoin was used as internal standard (i.s.). Retention times were 8 and 10m for carbamazepine and i.s., respectively, at a

flow rate of 1.2 ml/m. Necessary spiked recovered standards and blanks were prepared in blank (zero time) plasma and processed along with the samples. The processing of plasma samples involved precipitating plasma proteins with acetonitril followed by vortex and centrifugation.

Preparation of Plasma Samples and Standards :

Five Hundred µl of each plasma sample were placed in a glass tube. Fifty µl of i.s. solution in methanol were added followed by 1.25 ml acetonitril. The tubes were vortexed for 3 m then centrifuged for 5 m. Twenty five µl were injected onto the column. Standards were prepared for each set of samples in zero time plasma. Three standards together with a blank were processed and injected with each set of samples.

Calculations :

Peak heights of carbamazepine and the internal standard were measured and peak height ratios were calculated. Concentration of carbazamepine in each sample was calculated from peak height ratios using the corresponding linear regression equation relating peak height ratios of standards to their concentrations.

RESULTS and DISCUSSION

The carbamazepine plasma concentration profiles following the administration of carbamazepine either alone or in combination with Ispaghula Husk for each subject as well as for the mean is shown in Fig. 1. It is obvious from the figure that the concurrent ingestion of Ispaghula Husk with carbamazepine resulted in a decreased level of absorption throughout the test hours in each of the 4 volunteers. Comparison of the mean plasma concentrations after treatment (A) with the corresponding values after treatment (B) by paired student's t-test revealed statistical significance at $p=0.1$ ($t = 2.452$). Some bioavailability data were further calculated using the stripping computer program (Dept. of Pharmacodynamics, College of Pharmacy, University of Illinois at Chicago) and the results are presented in Table I. It is obvious from the results that Ispaghula Husk induced appreciable reduction in the AUC in treatment B ($AUC_{0\text{-}24h}$ = 25.03µg. h/ml) compared to treatment A ($AUC_{0\text{-}24h}$ = 45.43µg. h/ml). It is also clear, from the results of Table 1, that Ispaghula Husk caused a marked decrease in the calculated maximum carbamazepine concentration (C_{max}) from 2.33 to 1.11µg/ml. In addition, the time to reach this maximum (T_{max}) was also increased from 5.52h to 24.14h after the simultaneous administration of the drug with the bulk laxative. The above results demonstrate that Ispaghula Husk reduces appreciably both the rate and the extent of carbamazepine absorption which could induce subclinical levels of the drug.

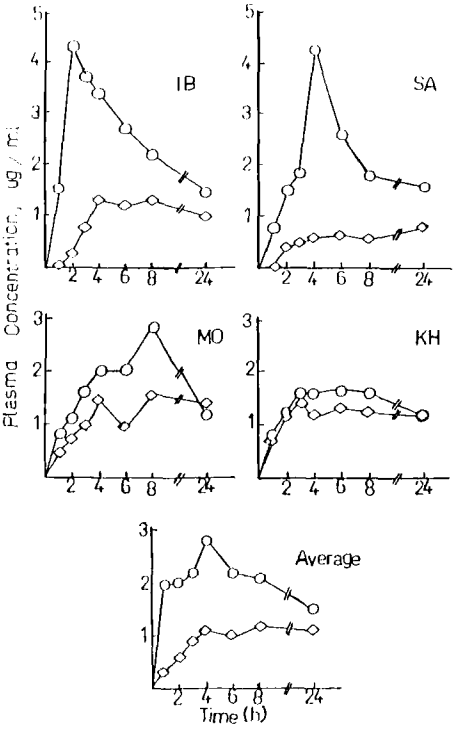

FIGURE 1

Plasma concentrations of carbamazepine following the administration of 200 mg of carbamazepine alone (O-O) or with Ispaghula Husk (◇—◇) to healthy volunteers.

Recent studies have demonstrated the effect of Ispaghula Husk on the absorption of some drugs. Ispaghula Husk was found to have no effect on digoxin plasma concentrations in geriatric inpatients (13). However, it has reduced the plasma concentrations of lithium salts and it was concluded that Ispaghula Husk may inhibit their absorption from the gastrointestinal tract (14).

Several factors might explain the reduction in carbamazepine absorption by Ispaghula Husk. The bulky and water-absorbing nature of the laxative would decrease or delay the absorption by decreasing the amount of the biological fluid available in the gastrointestinal tract and thereby reducing the dissolution rate of the drug from the tablet (15). This could be the rate limiting factor in the absorption process due to the very poor solubility of the drug. Moreover, the formation of a viscous solution or gel (16), by the bulk forming laxative could

TABLE 1

Bioavailability of Carbamazepine Following the Oral Administration of 200 mg Carbamazepine Tablet Alone (Treatment A) and in Combination with 3.5 gm Sachet of Ispaghula Husk (Treatment B).

Parameter \ Treatment	Treatment A	Treatment B
AUC (μg.h/ml) 0 - 24 hr	45.43	25.03
Calculated C_{max} (μg / ml)	2.33	1.11
T_{max} (h)	5.52	24.14
Lag time (h)	No lag time	0.38
% Bioavailability	--------	55.1 %

possibly retard both the dissolution rate and the diffusion of the dissolved drug. Singha and Singh (17), reported a prolongation in the release rates of tetracycline capsules due to the gel forming fraction of Plantago seeds. In addition, solids or semisolid components may act as a mechanical barrier preventing drug movement towards the mucosal surface of the gastrointestinal tract (18). Bulk forming laxatives may also influence drug absorption more directly by the adsorption onto their surfaces. Utilizing the AUC values, the % bioavailability of carbamazepine in presence of the fibres relative to carbamazepine alone was lower and was found to be 55% (Table 1).

An explanation of the reduced bioavailability in addition to the above mentioned factors may reside in the fact that these fibres lower the transit time through the intestine and stimulate peristalsis (16), and thereby decrease the time available for complete absorption of the drug.

It could be concluded from the above discussion that Ispaghula Husk reduces the bioavailability of carbamazepine. Therefore, ingestion of carbamazepine and

of a bulk forming laxative like Ispaghula Husk should be separated in time as far as possible. However, since the potential of such interaction is great, it warrants individual monitoring of the plasma levels of the drug especially in those patients who are taking Ispaghula Husk or other similar bulk forming laxatives.

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