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PHENYTOIN ABSORPTION IN PATIENTS WITH ILEOJEJUNAL BYPASS

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1 The absorption and elimination of phenytoin was studied after a 200 mg oral dose was administered to seven patients with ileojejunal bypass and nine control patients.

2 Analysis of the area under the plasma concentration time curve showed the absorption of phenytoin was decreased in the subjects with ileojejunal bypass ($P < 0.005$).

3 The half life of elimination of the drug was shorter in the bypass group (15.1 h) than in the controls (17.8 h, $P < 0.05$).

4 Subjects with an ileojejunal bypass receiving phenytoin are likely to require increased oral dosages to achieve an optimal plasma concentration. There is probably malabsorption of other poorly soluble drugs and parenteral therapy may be necessary to ensure adequate bioavailability.

Introduction

Surgically induced ileojejunal bypass is designed to produce malabsorption of nutrients and is reserved for the management of the morbidly obese. Since its introduction in the early 1960s, there have been a number of modifications to the surgical technique, the most significant of which has been altering the site of drainage of the blind loop from the colon to the terminal ileum. The procedure described by Payne & de Wind (1969) is most commonly employed and involves anastamosis of 35 cm of proximal jejunum with 10 cm of terminal ileum.

Several important medical complications of the procedure have been recognized including arthritis, nephrolithiasis and impairment of hepatic function which may be severe enough to necessitate reversal of the bypass. However, the degree to which the induced malabsorption state also affects the absorption and efficacy of orally administered medications is not known but clearly important. The present study was designed to investigate the absorption of phenytoin, a drug with poor and variable absorption in healthy subjects.

Methods

Subjects and procedures

Seven patients, aged 21–45 years, who had undergone ileojejunal bypass were studied 13 days–20 months after surgery. Details of the subject's weight, and the time of the study after surgery are seen in Table 1. The control group consisted of nine healthy volunteers of a similar age group (21–36 years) with normal haematological and biochemical profiles.

After an 8 h overnight fast, 2 × 100 mg capsules of phenytoin sodium (Dilantin) were administered with 100 ml water. Water was allowed *ad lib* but no food was allowed for 3–4 h. Blood samples (10 ml) were collected in E.D.T.A. veneject tubes at 0, 1, 2, 4, 8, 12, 24, 36 and 48 h after dosing and the plasma stored at −20°C until analysis.

Measurement of phenytoin in plasma

Phenytoin was measured by radioimmunoassay using a commercially available antibody to phenytoin (Wein Laboratories, Succassunna, New Jersey). Duplicate aliquots of plasma (0.1 or 0.5 ml) were diluted 1:100 or 1:400 with phosphate buffer (0.1M, pH 7.4). The diluted plasma was then mixed with [^{3}H]-phenytoin solution (0.05 ml containing between $30–40 \times 10^3$ d/min), 0.05 ml phenytoin antibody solution and 1 ml sodium phosphate buffer (0.01M, pH 7.4 containing bovine serum albumin, 6.0 g/l). After incubation for 1 h at 0°C, activated charcoal (0.05 ml) suspension (containing 3.125 g activated charcoal, 0.31 g dextran 4.26 g NaCl and 0.69 g $Na\ H_2\ PO_4.H_2O$ in 500 ml pH 7.4) was added, the tubes mixed and reincubated for 10 min at 0°C. The tubes were then centrifuged and the supernatant added to P.C.S. scintillant (Amersham, Searle) and counted in a Packard Tri-Carb scintillation counter with due correction for quenching. The lower sensitivity for the assay was 0.1 μg/ml.

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Table 1 Subject details

Control group

Subject	*Age (years)*	*Sex*	*Weight (kg)*
J.R.	27	M	68
W.C.	36	F	50
S.T.	24	F	64
D.B.	24	F	57
P.D.	21	M	89
S.L.	23	M	70
R.L.	22	M	72
E.C.	24	F	58
P.H.	23	M	93

Bypass group

Subject	*Age (years)*	*Sex*	*Weight (kg)*		
			Prior to surgery	*Time of study*	*Months post-surgery*
P.D.	22	F	120	92	5
P.O.'R	29	M	161	102	20
N.D.	37	F	127	102	14
V.A.	21	F	89	87	13 (days)
W.H.	45	F	94.4	72	18
P.W.	31	F	143	76	17
P.O.	40	F	114.5	71	20

Table 2 Pharmacokinetic parameters

Subject	*Peak plasma concentration (μg/ml)*	*Time to peak height (h)*	*AUC* (μg ml^{-1} h^{-1})*	$T_{\frac{1}{2}}$† *(h)*
Bypass group				
P.D.	1.71	8	46	17.3
P.O.'R	1.35	4	30	15.5
N.D.	1.4	4	26	12.3
V.A.	1.36	13	39	17.9
W.H.	1.87	1	44	16.9
P.W.	0.91	2	16	10.6
P.O.	1.07	12	40	14.7
Mean	1.38	6.2	34.4	15.1
s.e. mean	0.13		4.11	1.03
Controls				
J.R.	3.5	4	126.8	17.3
W.C.	3.95	4	66	10.0
S.T.	3.28	8	102	17.8
D.B.	5.35	4	151	21.1
P.D.	3.0	2	77.5	12.8
S.L.	4.75	4	153	26.7
R.L.	3.55	2	71	19.1
E.C.	4.34	8	138	15.7
P.H.	3.34	4	89.2	20.3
Mean	3.89	4.4	108.3	17.8
s.e. mean	0.26		11.5	1.61

* AUC measured by trapezoidal rule

† calculated by the formula $T_{\frac{1}{2}} = \frac{0.693}{K_{el}}$ where K_{el} was derived from the log linear portion of the decline in the plasma level time curve.

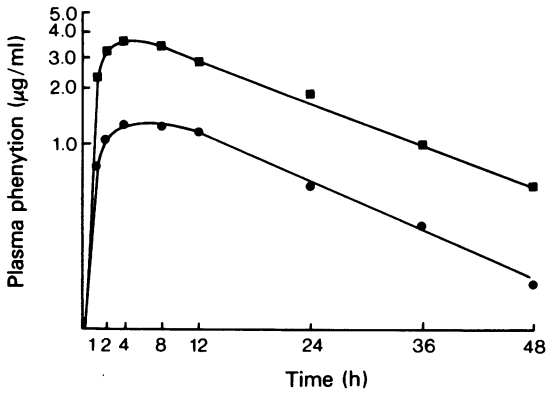

Figure 1 The mean plasma phenytoin concentration-time course in control (■) and bypass (●) subjects.

Results

The mean plasma concentration time course in both the control and bypass subjects is shown in Figure 1, and the measured pharmacokinetic parameters are shown in Table 2. The plasma levels at each time interval were significantly lower in the bypass group when analysed by unpaired Student's *t*-test ($P < 0.005$). The rates of elimination of phenytoin were faster in the bypass group ($P < 0.05 > 0.01$).

Discussion

Peterson & Zewig (1974) reported the need to increase the daily dose of phenytoin in one patient after ileojejunal bypass from 300 to 500 mg/day so as to maintain optimal therapeutic effect but concluded there was good absorption of the drug. Decreased plasma concentrations of d-norgestrel were reported after bypass in seven women receiving oral contraceptives but it was suggested that this was due to lowered levels of 'sex steroid' binding globulin rather than the malabsorption state (Johansson & Krai, 1976). In a recent investigation, the pharmacokinetics of digoxin was studied in seven patients before and after surgery (Marcus, Quinn, Horton, Jacobs, Pippin, Stafford & Zutoski, 1977). These authors concluded that the absorption of digoxin, at the dose of 0.5 mg/day, was unimpaired after the procedure as the bioavailability of digoxin was only slightly decreased but this difference was not significant at the $P = 0.05$ level. It was also found that the elimination kinetics of digoxin after dosing to steady state was unimpaired.

The decreased absorption of phenytoin found in the present study was associated with a marked malabsorption state induced by the shortening of the small bowel by some 10 m. It is likely that the difference between digoxin and phenytoin is due to the less complete absorption of phenytoin, which in healthy subjects, has an absolute bioavailability of between 57 and 86.6% (Gugler, Manion & Azarnoff, 1976). On the other hand, the digoxin preparation used in the study conducted by Marcus *et al.* (1977) had an availability of 89%. It has been shown that in the case of digoxin the most important determinant of absorption in patients with malabsorption states is the bioavailability of the preparation employed (Hall, Doherty, Gammill & Sherwood, 1974). The greater the bioavailability the better the absorption.

The findings of the shorter half-life of elimination in the bypass group is more difficult to explain. It could be due to faster biotransformation of the smaller absorbed dose, as the $T_{\frac{1}{2}}$ of phenytoin is dose dependent (Kutt & Louis, 1972). Alternatively, there may be a change in the enteric circulation of the drug. However, the difference was small and a larger number of patients would be needed to be certain this difference was real.

The implications of these findings seem clear. Epileptics treated with phenytoin who undergo bypass procedures should be carefully monitored and are likely to require an increased dosage to maintain an optimal plasma concentration of the drug. Furthermore, the absorption of other drugs, with poor or variable bioavailability, is very likely to be similarly decreased. Larger doses than usual and careful monitoring are likely to be necessary to achieve an optimal response. In any emergency situation, it would be wise to administer important drugs by a parenteral route.

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