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EFFECT OF ANTACID CONSTITUENTS, KAOLIN AND CALCIUM CITRATE ON PHENYTOIN ABSORPTION

J.C. McELNAY, P.F. D'ARCY and O. THRONE

Department of Pharmacy, The Queen's University of Belfast, Belfast (Northern Ireland)

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SUMMARY

The effects of 4 constituents of gastrointestinal medications and calcium citrate on the absorption of phenytoin were examined in vitro using an experimental model based on the everted segment of rat intestine.

Bismuth carbonate increased phenytoin absorption by 28.2%; magnesium trisilicate reduced absorption (–6.2%) as also did light kaolin (–60.2%), activated dimethicone (–71.3%) and calcium citrate (–77.2%). The latter 3 values were significantly different from control absorption values ($P < 0.05$). Agents which decrease phenytoin absorption markedly in vitro may be implicated in poor phenytoin bioavailability in vivo.

INTRODUCTION

Drug absorption interactions involving the anticonvulsant phenytoin are potentially serious as this drug has a narrow range of effective plasma concentrations (10–20 $\mu g\ ml^{-1}$; Kutt and McDowell, 1968). This range restriction is exacerbated by the elimination kinetics of phenytoin; the drug exhibits apparent Michaelis–Menton kinetics (Arnold and Gerber, 1970; Ludden et al., 1977; Martin et al., 1977). The following parameters have been reported in man: V_{max} 10.3 ± 2.1 mg kg^{-1} day^{-1} and K_m 11.5 ± 5.0 mg l^{-1} (Martin et al., 1977).

A clinically important absorption interaction involving phenytoin occurred in Australia in 1968 and resulted in an outbreak of anticonvulsant intoxication. All the patients affected were taking one brand of phenytoin and in 87% of them its plasma levels were above the therapeutic range. The cause of the interaction was a change by the manufacturer of the excipient in phenytoin capsules from calcium sulphate to lactose. This change in formulation resulted in plasma levels of phenytoin 2.5–5.5 times greater than those produced by the capsules formulated with calcium sulphate (Tyrer et al., 1970).

Kutt (1975) has suggested that antacids may also alter phenytoin plasma levels and the

work of Kulshrestha et al. (1978) has indicated that a mixture of magnesium trisilicate and aluminium hydroxide when adminstered in therapeutic doses with phenytoin caused a small but statistically significant fall in phenytoin plasma levels in a number of patients. They also studied the effects of calcium carbonate on phenytoin absorption but found that absorption was unchanged. O'Brien et al. (1978) reported two cases of epileptic patients being admitted into hospital because of poor control of fits by phenytoin; the onset of fits coincided with the consumption of antacids for dyspepsia. Withdrawal of antacids in both patients resulted in improvement of control; however, a follow-up study in 6 volunteers showed that magnesium and aluminium hydroxides did not alter phenytoin absorption.

The aim of the present investigation was to examine further the effects of gastrointestinal medications and calcium on the absorption of phenytoin.

MATERIALS AND METHODS

The work was carried out with an experimental model based on the use of everted segments of rat intestine. This technique has been shown to correlate well with human studies on drug interactions in the gut involving the tetracycline antibiotics (D'Arcy et al., 1976) and has also been used successfully to study digoxin (McElnay et al., 1979a) and warfarin (McElnay et al., 1979b) absorption interactions. The model, which involves absorption across a physiological membrane may yield data more predictive of the in vivo situation than simple adsorption tests which were not presently carried out.

Male albino Wistar rats were fasted for 24 h prior to each experiment with drinking

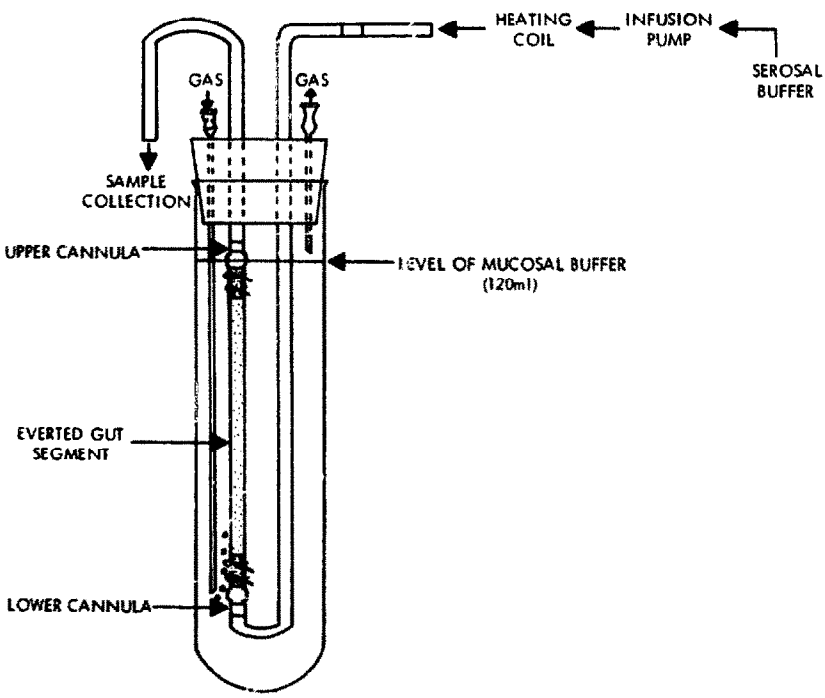

Fig. 1. Intestinal perfusion apparatus.

water allowed ad libitum. Each rat was killed with an inhalation overdose of anaesthetic ether, a method reported to prolong the structural integrity of the intestine (Levine et al., 1970). After removal of the entire small intestine it was everted on a glass rod and placed in a petri dish containing an isotonic phosphate buffer. The initial 15 cm portion of the proximal end of the intestine was discarded to ensure the use of the jejunum (Mayersohn and Gibaldi, 1971) and to prevent the inclusion of the bile duct in the segments to be used. Two consecutive segments (control and test) were then tied in position (to expose 7.5 cm of gut) on each of the two sets of intestinal perfusion apparatus, one of which is shown in Fig. 1. The segments were bathed in a buffer solution (pH 8); this pH was necessary to keep the phenytoin sodium in solution. Amounts of phenytoin absorbed across the two segments were collected separately by the infusion of 10 ml buffer samples through the segments at 10 min intervals for 100 min. The control chamber contained phenytoin sodium alone (36 mg in 120 ml) while the test segment buffer contained the same amount of phenytoin plus one of the possible interactants, i.e. activated dimethicone, bismuth carbonate, magnesium trisilicate or calcium citrate. The constituents were tested in approximately half-unit dose quantities while the amount of calcium citrate used was equivalent to the approximate calcium content of a glass of milk (250 ml).

The collected samples were assayed for phenytoin content by a spectrophotometric technique (Svensmark and Kristensen, 1963). Each interaction study was done 3 times and the averaged cumulative absorption values for phenytoin (over the 100-min period) in the presence of the possible interactants were compared with control absorption values found for phenytoin alone (taken as 100%).

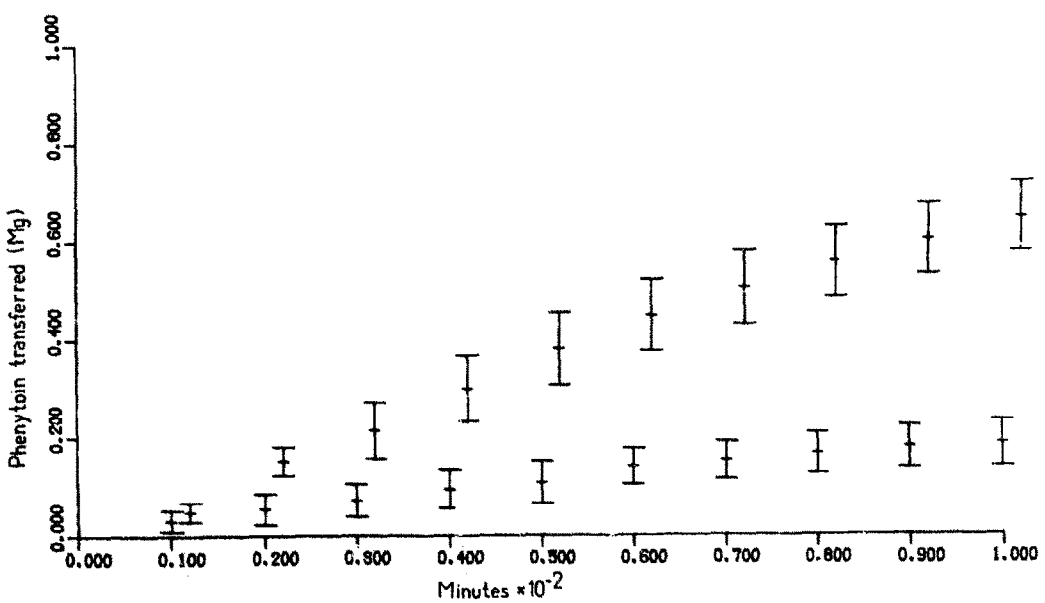

Fig. 2. Cumulative absorption profiles of phenytoin alone and while in combination with activated dimethicone. (Each point represents the mean ± S.E. of triplicate determinations in segments from 3 individual rats. Control data in all cases have been displaced 2 min to the right.)

TABLE 1

EFFECTS OF THE INVESTIGATED CONSTITUENTS ON THE ABSORPTION OF PHENYTOIN IN VITRO (USING THE EVERTED RAT INTESTINE TECHNIQUE DESCRIBED IN THE TEXT)

Constituent	Amount of constituent used in test absorption chamber	Change in total phenytoin absorbed (%)	$P <$
Dimethicone (activated) *	150 mg	−71.3 ± 4.6	0.01 **
Bismuth carbonate	250 mg	+28.2 ± 15.9	0.2
Magnesium trisilicate	250 mg	−6.2 ± 5.3	0.4
Light kaolin	1 g	−60.2 ± 9.6	0.05 **
Calcium citrate	2.47 g	−77.2 ± 8.5	0.02 **

* Activated dimethicone was used in the form of a commercially available aqueous emulsion.
** Test absorption data significantly different from control absorption data using paired *t*-test analysis.

Corrections for the possible presence of non-specific substances which absorb in the ultraviolet region of the spectrum were made for all samples tested by subtracting from their data the absorbance values of blank experimental runs using buffer alone.

RESULTS

A typical absorption profile obtained for phenytoin, for example, in the presence or absence of activated dimethicone using the everted rat intestinal model is shown in Fig. 2.

The results for all interactants are summarized in Table 1; all the constituents examined produced changes in phenytoin absorption over the 100-min time period. Bismuth carbonate caused an increased transfer of phenytoin (+28.2%). All the remaining agents agents caused decreased absorption of phenytoin although the change with magnesium trisilicate (−6.2%) was negligible and therefore should not affect the in vivo bioavailability of the anticonvulsant. Large decreases in phenytoin transfer were found with kaolin (−60.2%), dimethicone (−71.3%) and the calcium salt (−77.2%) and these may suggest that a clinically significant reduction in phenytoin availability may be caused by such interactions in vivo. The experimental results for kaolin, dimethicone and calcium citrate were significantly different from control values ($P < 0.05$) while those changes in absorption noted for bismuth carbonate and magnesium trisilicate were not significant ($P > 0.05$).

DISCUSSION

The result obtained for bismuth carbonate was unexpected and the underlying mechanism of interaction is presently unknown. The result, however, was not statistically significant and would not be expected to give rise to significant absorption changes in vivo. An increased absorption of phenytoin, if it did occur, would not be hazardous as phenytoin is normally well absorbed from the gastrointestinal tract (approximately 90%;

Jusko et al., 1976). Increased rates of absorption would, however, give rise to a shortening of t_{max} (time to reach peak plasma concentration Cp_{max}) and increased Cp_{max} values, i.e. larger than normal fluctuations in phenytoin plasma levels would occur.

The interactions which gave decreased absorption of phenytoin are likely to be of more importance since they may lead to poor seizure control in patients. This is especially so with the antiflatulent agent, activated dimethicone, which gave a large decreased absorption in vitro and might be predicted to cause decreased bioavailability in vivo. The mechanism of this interaction is unknown but it may be due to an adsorption of phenytoin onto silicone residues of this constituent. Kaolin almost certainly acts by adsorbing the phenytoin.

The bioavailability of phenytoin is known to be decreased by calcium sulphate although the mechanism is unclear. Calcium carbonate (Kulshrestha et al., 1978) and calcium gluconate (Chapron et al., 1979) do not, however, lead to changed absorption of phenytoin. A marked decrease (–77.2%) in phenytoin absorption was noted in this present study while in the presence of calcium citrate.

Recent data from our department utilizing calcium chloride, and indeed the work of others (Glazko and Chang, 1972; Chapron et al., 1979) suggest that the calcium/phenytoin interaction is not due to an ionic or chelation interaction between phenytoin and calcium ions. The mechanism of interaction presently observed, although unclear, may be due to the membrane tightening effect described by Manery (1969). Examination of the effects of a range of calcium salts on the absorption of phenytoin both in vitro and in vivo is currently being undertaken in our laboratories. Until the results of these investigations are available we support the cautionary remarks of Herishanu et al. (1976) that the calcium content of the diet might modify the absorption of phenytoin. We would also advise that concomitant administration of phenytoin with dimethicone or kaolin should be avoided or alternatively that dosages should be spaced such that approximately 4 h be allowed between doses of phenytoin and these medicaments.

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