state plasma phenytoin concentrations may be a more sensitive index than changes in single dose kinetics.

On the basis of our data however, it does not appear that antacids given in therapeutic doses will alter the absorption of phenytoin.

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INTERACTION BETWEEN PHENYTOIN AND ANTACIDS

Interaction between phenytoin and other drugs is common (Richens, 1977). Since phenytoin has a low therapeutic index and is metabolized by a saturable enzyme system (Richens & Dunlop, 1975), interaction readily leads to a change of steady-state serum phenytoin concentration.

Antacids have been shown to interfere with the absorption of tranquillizers (Fann, Davis, Janowski, Sekerke & Schmidt, 1973; Greenblatt, Shader, Harmatz, Franke & Koch-Weser, 1976), anticoagulants (Ambre & Fischer, 1973), digoxin (Brown & Juhl, 1976) and tetracyclines (Waisbren & Hueckel, 1950), and Pippenger (quoted by Kutt, 1975) has commented upon a reduction in serum phenytoin concentration in three patients who were given an antacid concurrently.

In view of the frequency with which antacid preparations are taken by patients, either on prescription or bought over the pharmacist's counter, we considered that the possible interaction merited further study. We have therefore administered two antacid preparations, one containing calcium carbonate and the other a mixture of aluminium hydroxide and magnesium trisilicate, to epileptic patients stabilized on phenytoin therapy, and have monitored serum phenytoin concentration.

Twelve male residents at the National Hospitals-Chalfont Centre for Epilepsy, Chalfont St Peter, Buckinghamshire, consented to take part in the study, the nature of which was fully explained to them. Their ages ranged from 20 to 63 years. Each was receiving phenytoin sodium tablets BP in a dose of 300–350 mg daily divided into two doses, and this treatment had been stable for at least six months. Blood samples (10 ml) were collected into plain tubes between 11.00 h and 12.00 h on days 1, 6 and 9 of the study in order to measure the baseline serum phenytoin concentration. From days 10–16 inclusive an antacid

was administered in addition to the phenytoin. Six patients received 30 ml (10 g) of a homogeneous suspension of calcium carbonate in vanillin-flavoured water daily, divided into two doses and administered with each dose of phenytoin. The remaining six patients received 15 ml of Gelusil suspension (magnesium trisilicate, 620 mg plus dried aluminium hydroxide gel, 310 mg/5 ml) with every 100 mg of phenytoin. On days 15 and 16, further blood samples were taken to determine the effect of the antacid on serum phenytoin concentration, and a further sample on day 23 (1 week after discontinuing the antacid).

Serum phenytoin concentration was measured by a gas chromatographic method involving flash methylation of the drug with trimethylphenylammonium hydroxide, and the use of 5-*p*-methylphenyl-5-phenylhydantoin as an internal standard (Houghton & Richens, 1974). The specimens were measured in duplicate at the end of the study after they had been coded and randomized.

The results are given in Tables 1 and 2. The readings on pretreatment days (1, 6, 9) were pooled as were those on treatment days (15, 16) and an analysis of variance was carried out to assess the significance of differences in serum phenytoin concentrations at the different times of treatment with the two antacid preparations.

On the fifth and sixth days of calcium carbonate treatment (study days 15 and 16) there was no change in the group mean serum phenytoin concentration. One week after discontinuing the antacid there was again no change. There was no alteration in fit frequency in any of the patients. On the fifth and sixth day of Gelusil treatment there was a slight but statistically significant fall in serum phenytoin concentration ($t=2.68$, $P<0.02$). Again, no change in fit frequency was observed.

In this study, we have used doses of antacids which

Table 1 Serum phenytoin concentration in six epileptic patients before, during and after calcium carbonate

Patient number	Serum phenytoin concentration ($\mu\text{mol/l}$)							
	Pre-antacid				With antacid			Post-antacid
	1	Trial day 6	9	Mean	Trial day 15	16	Mean	Trial day 23
1	29	25	26	26.7	22	26	24	24
2	35	36	36	35.7	36	30	33	44
3	22	22	20	21.3	19	21	20	21
4	58	60	62	60.0	63	67	65	65
5	10	12	10	10.7	13	*	13	11
6	28	22	28	26.0	28	22	25	34
Group mean	30.3	29.5	30.3	30.1	30.2	33.2	31.5	33.2

* No specimen.

Table 2 Serum phenytoin concentration in six epileptic patients before, during and after Gelusil

Patient Number	Serum phenytoin concentration ($\mu\text{mol/l}$)							
	Pre-antacid				With antacid			Post-antacid
	1	Trial day 6	9	Mean	Trial day 15	16	Mean	Trial day 23
1	39	37	27	34.3	37	27	32	34
2	48	51	44	47.7	40	42	41	39
3	23	24	22	23.0	22	26	24	33
4	74	79	60	71.0	69	66	67.5	63
5	49	43	49	47.0	36	34	35	43
6	18	22	18	19.3	10	16	13	20
Group mean	41.9	42.7	36.7	40.4	35.7	35.1	35.4*	38.7

* Significant fall in serum phenytoin from the pre-treatment level ($t=2.68$, $P<0.02$)

would be used in patients who have severe peptic ulcer symptoms. We chose to study a calcium-containing antacid because, when used as an excipient in phenytoin capsules, calcium sulphate impaired the absorption of the drug (Bochner, Hooper, Tyrer & Eadie, 1972) although the reason for this is unclear. Also, phenytoin has been shown to reduce calcium absorption in isolated gut loops in the rat (Caspary, 1972) so there were grounds to suspect that calcium carbonate might influence phenytoin absorption in man. However, no such effect could be demonstrated in this study.

Gelusil is a commonly-used mixture of magnesium trisilicate and aluminium hydroxide, and when administered in therapeutic doses in combination with phenytoin it caused a small, but statistically significant, fall in serum phenytoin concentration in our patients. We cannot say which of the constituents is responsible for the interaction and there are several possible mechanisms. Aluminium ions can chelate tetracyclines (Waisbren & Hueckel, 1950) as can ferrous and magnesium ions (Kunin & Finland, 1961) but *in vitro* studies with phenytoin have shown that

chelate formation does not occur with magnesium, ferrous and calcium ions, although it does with copper (Glazko & Chang, 1972). Aluminium hydroxide and magnesium trisilicate form gels in the gastrointestinal tract and adsorption on the surface of these could explain the reduced phenytoin absorption. These antacids will increase the pH of the upper part of the gastrointestinal tract and this would tend to increase the ionization and hence reduce the absorption of a weak acid such as phenytoin. However, the duration of the change in pH would be brief and perhaps insufficient to reduce the absorption of a drug such as phenytoin, which is relatively slowly absorbed. Finally, aluminium salts may reduce gastrointestinal motility, and this could delay absorption if not reduce the amount absorbed (van Rees & Roach, 1973). The change in phenytoin levels that we have demonstrated in the short duration of this study is small, but with prolonged antacid treatment the reduction might be of clinical importance in some patients.

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CLINICAL PHARMACOLOGY AND COMMUNICATION ON NEW DRUGS

The study of the action of drugs on experimental animals or on the healthy volunteer human subject is 'pure' pharmacology. Though such studies may have implicit clinical applications they are not part of clinical pharmacology. Nonetheless because of the probable clinical implications it is highly appropriate that they should be reported in a journal of clinical pharmacology. The main aim of clinical pharmacology however is the application of pharmacological knowledge to the treatment of the sick patient. Or to reduce the matter to the approach of the clinician in charge of the patient, the aim of the clinical pharmacologist ought to be to ensure that all the patients for whom he has any responsibility receive those drugs in appropriate dosage which will most rapidly lead to a reversal of the disease process and the most rapid possible recovery.

The clinical pharmacologist however frequently does not have direct access to many patients, for the majority of drug treatment in a hospital or in general practice is carried through by others. The clinical pharmacologist's responsibility is then to ensure that other doctors have the necessary information which enables them to pick out the drug appropriate to the patient's condition and to give it in the proper dosage for the appropriate period. There is however one school of thought within the country which starts from

the premise that the vast majority of doctors do not possess adequate knowledge of clinical pharmacology and are therefore liable if not likely to prescribe inappropriate drugs in an inappropriate dosage. It is also tacitly assumed that drugs are being prescribed which are necessarily more expensive and that money is thus being wasted. There is also a suggestion that one reason why drugs are inappropriately used is that their virtues are all too often sung of loudly by representatives from commercial firms whose aim is of course primarily to sell the drugs and make profits for their employers. This argument has political overtones and many doctors will want to keep out of such a field.

There is in fact plenty of evidence that more and more expensive drugs are being prescribed for patients but what is not available is evidence that expensive drugs are being inappropriately prescribed. Some come into use as a result of fashions in medicine. For example, ten years ago barbiturates were almost universally prescribed in hospital for night sedation for the patient who was unable to sleep simply because of his unfamiliar surroundings. Then there arose a cry that barbiturates were habit-forming, though this had been known for years. What was new was a realization that a very small minority of the population did themselves great harm by injecting themselves intravenously with barbiturate preparations not intended