DRUG INTERACTIONS IN THE GUT INVOLVING METAL IONS

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1. INTRODUCTION

Drug interactions can occur at many different sites in the body and indeed all pharmacokinetic processes from absorption, distribution and metabolism, to elimination are susceptible to drug interactions. Interactions can also take place outside the body when, for example, a particular compound included in a drug formulation can influence the drug release characteristics from a dosage form.

Before moving on to specific mechanisms of interactions in the gastrointestinal tract it is worthwhile to summarise the stages in drug absorption from the gut. When a drug is given by the oral route in a solid dosage form or suspension the drug must first dissolve in the gastrointestinal contents before drug absorption can take place. In the case of solid dosage forms (with the exception of certain sustained release products) the dosage unit must disintegrate before significant dissolution can take place. The dissolution rate of a particular drug may vary markedly depending on the formulation, the particle size, the salt used and the pH of the gastrointestinal contents.

The absorption of most drugs takes place in the small intestine by the process of passive diffusion of unionised molecules (lipid soluble form). Changes in gastric emptying rate will therefore obviously change the time post administration at which the drug is presented to its site of absorption and therefore change the overall rate of drug absorption. With certain drugs, metabolism can take place within the intestinal wall during the absorption process or within the liver during the "first-pass", before the drug reaches the systemic circulation. Such a metabolic degradation effectively decreases the plasma concentrations of a drug obtained for a given dosage and can greatly decrease the therapeutic effect obtained if the metabolites themselves are not pharmacologically active.

Drug interactions in the gut can take place at many stages of the absorption process /1-3/. Changed gastrointestinal pH can influence formulation disintegration and drug dissolution. It will also influence drug ionisation which in turn will change passive diffusion processes. Changed pH can be due to co-administration of antacid products which commonly contain salts of aluminium, magnesium and calcium. Antacids can also alter gastrointestinal motility, e.g. aluminium and calcium ions decrease gastrointestinal motility whereas magnesium ions increase motility. Taking a solid dosage form with food or fluids can also influence its bioavailability (rate and extent of absorption) as food de-

creases gastric emptying rate while fluid has the opposite effect. Metal ions present in antacids and certain foodstuffs, e.g. dairy products can form insoluble or poorly absorbable drug complexes and chelates. Antacids and certain metal containing clays also have high adsorption properties and can physically adsorb large amounts of susceptible drugs, thus hindering their absorption. Drug interactions can also take place during drug metabolism in the gastrointestinal wall; however, such latter interactions are unlikely to involve metal ions.

As mentioned previously, the term bioavailability explains both the rate and extent of drug absorption. In drug absorption studies the rate of drug absorption is commonly quoted as the time taken to reach peak plasma concentrations (t_{max}) after an oral dose of the drug. Extent of drug absorption is quantified as the area under the plasma concentration time curve (AUC).

In this present review consideration is given to drug absorption interactions involving metal ions. Interactions involving metal containing antacids have also been included, although with the latter, malabsorption of drug is often due to changed gastrointestinal pH, adsorption phenomena or changed gastric emptying rate rather than to ionic interactions between metal ions and a particular drug.

The review has been divided into three sections. Firstly, formulation interactions which involve metal containing compounds are described and this is followed by an account of the published interactions involving antacids. The final section examines the influence that drug interactions have on drug kinetics and dynamics and the clinical significance of these changes on drug therapy.

2. DRUG-FORMULATION INTERACTIONS

Two drugs, namely phenytoin and tetracyclines, are the major agents with which drug formulation interactions involving metal constituents have been described.

2.1 Tetracyclines

The absorption of tetracyclines and the effect on this of concomitantly administered agents has been the subject of research by many groups over a considerable time. As early as 1957, Sweeney *et al.* /4/ examined the effect of various fillers and adjuvants on the absorption of orally administered tetracycline. One of the most important and interesting findings from their study was that dicalcium phosphate de-

creased tetracycline absorption. This finding has since been supported by many other reports; indeed it is now firmly established that decreased absorption of tetracyclines results from their interaction not only with Ca^{2+}, but also with many other metal ions, notably Fe^{2+}, Mg^{2+} and Al^{3+}.

The accepted mechanism of the interactions is chelation of drug giving rise to a poorly diffusible product /5/. Chelation has been defined as the formulation of a compound between a metallic ion and an organic molecule having two groups spatially arranged so as to form a ring structure with the metal /6/. By comparing the spectral characteristics of the parent drug with the drug-ion complex Stoel *et al.* /7/ have characterised metal ion complex formation with anhydrotetracycline. Circular dichroism spectra were utilised by Newman and Frank /8/ to follow complex formation of tetracycline with Ca^{2+} and Mg^{2+}. Their results indicated that calcium formed a 2:1 metal ion : ligand complex and that the magnesium complex formed at a 1:1 ratio. Recent studies by Riaz and Pilpel /9/ indicated that Cu^{2+} and Ni^{2+} form 2:1 complexes with oxytetracycline and 1:1 complexes with desmethylchlortetracycline. Fe^{2+}, Zn^{2+}, Mg^{2+} and Ca^{2+} form weaker 1:1 complexes with both drugs. Although this complex formation is undoubtedly of importance in the interaction of tetracyclines with di- and trivalent metal ions, work by Poiger and Schlatter /10/ has led to the suggestion of an alternative mechanism for the absorption interactions. They suggested that binding of tetracyclines to organic macromolecules within the gut is increased by calcium ions and probably also by other di- and trivalent ions. These latter authors felt that this was the main reason for the impaired permeation across the absorbing epithelium. Certainly this latter explanation is meaningful especially since Kakemi *et al.* /11/ showed that the tetracycline - Ca^{2+} complex was more lipophilic than tetracycline alone. Ethylenediaminetetraacetic acid (EDTA) prevents the interaction between tetracycline and calcium. The decreased absorption of the antibiotic which occurs in the presence of milk (calcium ions) can be overcome by the simultaneous administration of EDTA /12/.

As indicated above, it is not only metal ions in formulation excipients which interfere with tetracycline absorption, but also ions from other sources, notably dairy produce and iron preparations. The calcium ions present in milk, butter and cheese, for example, have been shown to lead to a considerable reduction in the absorption of tetracyclines. The serum concentrations of demeclocycline have been shown

to be decreased by some 80% if the antibiotic is taken with milk as compared with the same dosage swallowed with water /13/. Buttermilk decreased the absorption to a lesser degree than did fresh milk; cottage cheese also gave rise to a much reduced tetracycline absorption.

Neuvonen *et al.* /14/ in a single dose study, found that the serum concentrations of oxytetracycline and tetracycline were reduced by 40% - 60% and those of doxycycline and methacycline by 80% - 90% when the antibiotics were given together with ferrous sulphate (Figure 1). The tetracycline iron interaction is dependent upon the nature of the iron salt used in the combination; it was found that the inhibition of tetracycline absorption by iron salts was as follows:- with ferrous sulphate 85%, with ferrous fumerate, succinate or gluconate 70% - 80%; with ferrous tartrate 50% and with ferric sodium edetate 30% /15/.

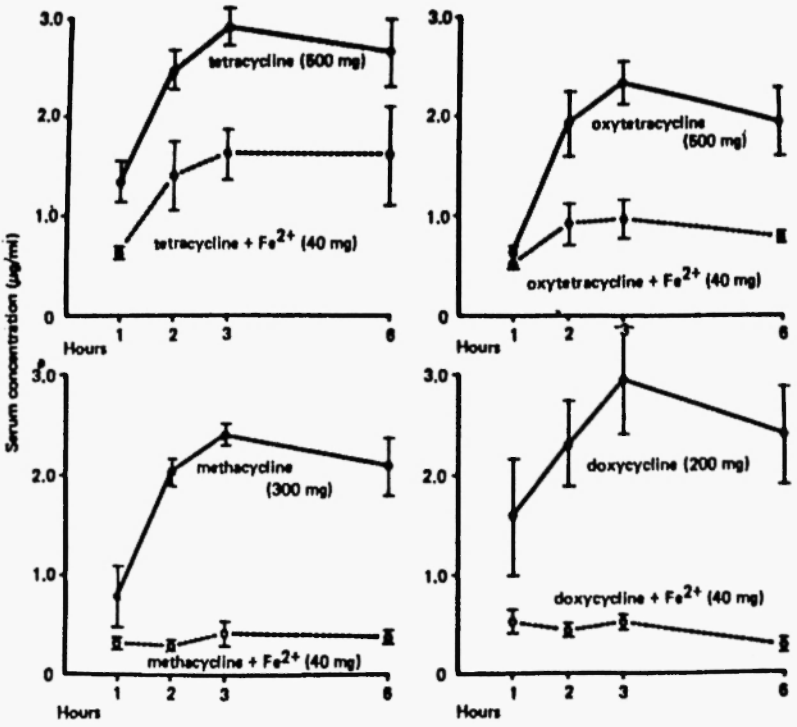

Figure 1. Effect of concomitant administration of ferrous sulphate (40 mg Fe^{2+}) on the serum concentrations of tetracyclines, both drugs given orally (after Neuvonen *et al.* /14/).

Zinc has also been shown to inhibit the gastrointestinal absorption of tetracyclines /16/. It is therefore important that tetracycline products do not contain metal ions in their formulation and that metal ions from any source are not permitted to come into intimate contact with them in the gut if decreased absorption is to be avoided.

2.2. Phenytoin

Drug absorption interactions involving the anticonvulsant phenytoin are potentially serious, as this drug has a narrow range of effective plasma concentrations (10 - 20 $\mu g ml^{-1}$; /17/). This range restriction is exacerbated by the elimination kinetics of phenytoin as the drug exhibits apparent Michaelis-Menton kinetics /18-20/. 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} /20/. A clinically important absorption interaction involving phenytoin occurred in Australia in 1968 and resulted in an outbreak of anticonvulsant intoxication /21-24/. All patients affected were taking one brand of phenytoin and in 87% of them the plasma phenytoin concentrations were above the therapeutic range. The cause of the interaction was a change by the manufacturer of the excipient in 100 mg phenytoin sodium capsules from calcium sulphate to lactose. There had also been a slight increase in the content of both magnesium silicate and magnesium sterate in the capsule formulation. Direct evidence for the interaction was obtained in one patient whose medication was changed from a phenytoin-lactose preparation to a phenytoin-calcium sulphate preparation and finally back to a lactose-containing product. His serum phenytoin concentration fell sharply when the calcium sulphate-containing product was introduced and rose again when the lactose-containing capsule was reinstated /25/. The mechanism of the interaction is unclear. Data from our own laboratory utilising calcium chloride and indeed the work of others /26, 27/ suggest that the calcium/phenytoin interaction is not due to an ionic or chelation interaction between phenytoin and calcium ions. Calcium gluconate, for example, does not lead to changed absorption of phenytoin /27/.

Using a stirred flask method Bastami and Groves /28/ investigated the dissolution behaviour of formulations containing phenytoin sodium. When the lactose was replaced by calcium sulphate dihydrate as diluent, there was a reduction in the release rate of phenytoin. The release of phenytoin from the calcium sulphate preparation was incomplete, with

only 80% - 90% of the drug dissolving. These workers also showed that magnesium sulphate prevented the release of phenytoin and concluded that phenytoin was perhaps capable of forming insoluble salts with calcium and magnesium ions. Since phenytoin is capable of forming a chelate with copper but not with calcium, magnesium or ferrous ions /26/, the true interaction mechanism of this historic interaction still remains uncertain. The interaction can be avoided simply by not using calcium or magnesium sulphates as excipients in phenytoin formulations.

3. GASTROINTESTINAL ABSORPTION INTERACTIONS INVOLVING ANTACIDS

Gastric antacids are probably the largest group of agents involved in drug interactions occurring during absorption from the gastrointestinal tract. The mechanisms of drug-antacid interaction are numerous and include elevation of gastrointestinal pH, changed gastric emptying rate, the formulation of non-absorbable chelation products and adsorption of drugs thus preventing their absorption. A large number of drugs have been implicated in drug interactions of this type either via anecdotal case reports, via controlled clinical trials or *in vitro* analyses.

In the present review eight drugs or groups of drugs have been chosen for detailed discussion while a synopsis of the available literature is given in Table 1. The drugs receiving a more detailed analysis are antiarrhythmics, cardiac glycosides, chloroquine, cimetidine, oral anticoagulants, phenytoin, tetracyclines and finally theophylline. Two criteria have been used in selecting these agents, namely a large bulk of information available on the interactions and/or interactions involving drugs with a narrow therapeutic range. The latter parameter is of utmost importance since, with such drugs, changed drug absorption from the gastrointestinal tract could have very marked effects on the therapeutic outcome of a patient's treatment. The drugs are presented in alphabetical order and not in order of clinical importance.

3.1. Antiarrhythmics

The effect of aluminium hydroxide gel on the absorption of quinidine has received attention from two research groups. Romankiewicz *et al.* /29/ found that the antacid did not influence quinidine's kinetics. Proving the absence of an interaction is important since aluminium hydroxide gel has been given to treat the diarrhoea associated with

TABLE 1. Drug absorption interactions involving metal salts or metal-containing antacid preparations

Drug Involved	Interactant	Result of Interaction	Reference
Ampicillin	Magnesium hydroxide	Peak serum ampicillin levels depressed more than 50% in mice by concomitant antacid.	/73/
Aspirin	Magnesium and aluminium carbonates	Buffering agents significantly increase rate of aspirin dissolution from solid dosage giving faster peak plasma levels	/74/
Atenolol	Aluminium hydroxide	Bioavailability of atenolol reduced by average 33%	/75/
Atropine	Aluminium hydroxide magnesias	Adsorption of atropine onto antacid	/76/
Betamethasone	Magnesium trisilicate; aluminium hydroxide	Drug adsorbed and dissolution rate altered	/77/
Bishydroxycoumarin	Magnesium hydroxide	Increased peak drug concentration	/54/
Chlordiazepoxide	Magnesium aluminium hydroxide gel	Decreased rate of absorption of orally administered chlordiazepoxide	/78/
Chloroquine*	Magnesium trisilicate	Decreased *in vivo* absorption. Also decreased absorption *in vitro* by a range of antacids.	/44;45;46/
Chlorpheniramine	Magnesium trisilicate; aluminium hydroxide	Drug adsorbed and dissolution rate altered	/77/
Chlorpromazine	Magnesium-aluminium hydroxide gel. Magnesium trisilicate-aluminium hydroxide	Although it has been reported that the first antacid mixture decreased mean urinary concentrations of chlorpromazine /79/, Pinell *et al.* /80/ have shown no clear indication of changed serum concentrations. The second mixture decreased serum concentrations of chlorpromazine.	/79;80;81/
Cimetidine*	Aluminium-magnesium hydroxide; magnesium trisilicate	Although some early work /47/ demonstrated a lack of interaction with antacids recent data indicate an interaction leading to decreased absorption of cimetidine.	/47;48;49;50;51/
Copper	Dietary zinc	Inhibitory effect of high dietary zinc on copper absorption	/82/

TABLE 1 / cont.

Drug Involved	Interactant	Result of Interaction	Reference
Dexamethasone	Magnesium trisilicate	Significant decrease in dexamethasone absorption; probably due to its adsorption onto surface of antacid.	/83/
Digoxin / Digitoxin*	Aluminium hydroxide; magnesium hydroxide; magnesium trisilicate; magnesium perhydrol	Conflicting data are available as to whether the absorption of cardiac glycosides is decreased by various antacids. Digoxin is decomposed by hydrogen peroxide liberated from magnesium perhydrol by gastric juice.	/36;37;38;39 40;41;42/
Indomethacin	Aluminium-magnesium hydroxide	Decreased indomethacin bioavailability	/84/
Isoniazid	Aluminium hydroxide gel	Decrease in peak blood levels of isoniazid; probably due to decreased gastric emptying rate caused by the aluminium hydroxide.	/71,85/
Levodopa	Magnesium-aluminium hydroxide	Enhanced levodopa absorption in humans	/71,85/
Lithium Carbonate	Copper sulphate	Copper sulphate given orally in an emetic dose decreased the absorption of aspirin and lithium carbonate more than was expected judging from drug recovery in the vomit.	/87/
Metoprolol	Aluminium hydroxide	Bioavailability of metoprolol increased by average 11%.	/75/
Mexiletine	Magnesium-aluminium silicate hydrate	Slightly slowed absorption rate of the mexiletine.	/33/
Naproxen	Range of antacids	Changed bioavailability patterns of naproxen seen with a range of antacids.	/88/
Nitrofurantoin	Magnesium trisilicate	The antacid decreased both the rate and extent of nitrofurantoin absorption. This was due to adsorption effects. Other antacids have been shown to be free from interaction.	/89;90/
Oral contraceptives	Dried aluminium hydroxide gel; magnesium trisilicate	The two antacids adsorb norethisterone acetate; this may affect its absorption and also its contraceptive action.	/91/

TABLE 1 / cont.

Drug Involved	Interactant	Result of Interaction	Reference
Penicillamine	Magnesium-aluminium hydroxide; dimethicone	Decreased absorption of penicillamine when taken together with antacid. Also decreased absorption in the presence of ferrous sulphate.	/92/
Pentobarbitone	Aluminium hydroxide; aluminium salts; trivalent cation lanthanum	Antacids retarded gastrointestinal absorption of sodium pentobarbitone, lowering its concentration in blood and preventing or delaying sleep in rats.	/93/
Phenytoin*	Calcium sulphate; aluminium hydroxide-magnesium hydroxide; magnesium trisilicate; calcium carbonate; light magnesium oxide-activated dimethicone	A range of antacids have been shown to decrease phenytoin availability.	/25;57;58;59;60;61/
Prednisone	Aluminium-magnesium hydroxide	Significant decrease in prednisone absorption.	/94/
Procainamide	Aluminium phosphate	Decreased procainamide bioavailability.	/32/
Propranolol	Aluminium hydroxide gel	Antacid caused decreased bioavailability of propranolol in four out of five male adults. Interaction not due to adsorption or chelation.	/95;96;97/
Proquazone	Magnesium-aluminium hydroxide	Decreased rate but similar extent of absorption of this non-steroidal, anti-inflammatory caused by antacid.	/98/
Pyrimethamine	Calcium carbonate; magnesium trisilicate	Decreased pyrimethamine absorption *in vitro* across everted rat intestine.	/44/
Quinidine*	Aluminium hydroxide gel	Although extent of absorption is unchanged, rate of absorption may be decreased.	/29;30/
Riboflavin	Aluminium magnesium hydroxide	Decreased rate but similar extent of drug absorption.	/99/

TABLE 1 / cont.

Drug Involved	Interactant	Result of Interaction	Reference
Salicylate	Magnesium-aluminium hydroxide	Steady state salicylate levels decreased during concomitant antacid therapy.	/100/
Sulphonamides	Antacids	Antacids which raise gastric pH sufficiently can increase dissolution of the acid form of sulphonamide increasing its absorption rate.	/71/
Tetracyclines*	Di- and tri-valent metal ions; sodium bicarbonate	Absorption decreased by forming non-absorbable complexes. Decreased absorption also caused by bismuth subgalate, zinc sulphate and iron salts. Changed pH caused by sodium bicarbonate prevents complete dissolution of tetracyclines and hence its absorption.	/13;14;16;101;102;103; 104;105;106/
Theophyllines*	Magnesium-aluminium hydroxide; magnesium carbonate	Changed absorption in particular from some sustained release products.	/18;68;69/
Valproic acid	Aluminium magnesium hydroxide	Possible increase in valproic acid bioavailability.	/107/

* Further details of these interactions are given in the text.

(After D'Arcy and McElnay /108/. The reader is also referred to two early review articles on drug-antacid interactions /71;109/).

quinidine administration. A further study by Ace *et al.* /30/ confirmed the lack of a clinically relevant interaction between quinidine and aluminium hydroxide gel, however, there was a significant increase in the time taken to reach maximum plasma concentrations (t_{max}) of quinidine; the extent of drug absorption remained unchanged. Based on these results aluminium hydroxide gel appears to be a good choice in the treatment of diarrhoea associated with quinidine therapy especially since the drug is adsorbed by the commonly used antidiarrhoeal agent kaolin /31/.

A French group have examined the bioavailability of procainamide and disopyramide both in the presence and the absence of the antacid agent aluminium phosphate /32/. The absorption of procainamide, as measured by the area under the plasma concentration vs. time curve ($AUC_{0-\infty}$), decreased when the drug was taken together with the antacid, whereas no significant differences between control (drug alone) and test (drug plus antacid) data were found with disopyramide.

Herzog *et al.* /33/ have examined the effects of Gelusil liquid® (magnesium-aluminium-silicatehydrate) on the absorption of mexiletine. The antacid, when administered one hour prior to the antiarrhythmic drug, slightly increased the t_{max} but did not change its overall availability.

A common explanation for drug interactions of this type in which absorption is slowed, is the slowing effect of aluminium ions on gastric emptying rate. Hurwitz *et al.* /34/ showed quite clearly that aluminium hydroxide gel delays gastric emptying in rats and man. This is likely to be due to the relaxing effect of aluminium on gastric smooth muscle /35/. It is unclear, however, why some drugs should be affected more than others; perhaps more than one interaction process is occurring simultaneously.

3.2. Cardiac glycosides

Digoxin and digitoxin are the two major cardiac glycosides in clinical usage. Digitoxin is lipid soluble and readily absorbed from the gastrointestinal tract, whereas the polar structure of digoxin makes it poorly soluble and less readily absorbed. On account of this many substances can interfere with the absorption of digoxin; also its entry into the systemic circulation is very dependent on the physical characteristics of the tablet /36/.

In one study in healthy volunteers the effect of antacids and kaolin-pectin on the bioavailability of digoxin was examined /37/. Cumultative

six day urinary digoxin excretion (expressed as the percentage of a 0.75 mg dose recovered) was: control, 40.1 ± 3.0 (S.E.); aluminium hydroxide, 30.7 ± 2.9; magnesium hydroxide, 27.1 ± 2.4 and magnesium trisilicate 29.1 ± 1.7. The test values were highly significantly different from the control values indicating that the antacids significantly decreased digoxin absorption. Earlier work by Binnion /36/ has shown that about 20% of digoxin was adsorbed by the antacid Maalox® (aluminium-magnesium-hydroxide) while Khalil /38/, in simple *in vitro* adsorption studies, found that magnesium trisilicate adsorbed digoxin and digitoxin. At an initial concentration of 0.25 mg% both glycosides were completely adsorbed by 1 g of magnesium trisilicate. Other antacids showed a relatively weaker adsorptive effect, the extent of which did not exceed 25%. Similar data were obtained by McElnay *et al.* /39/ when they examined the effects of antacid on the transfer of digoxin across everted segments of rat intestine. Ascione and Poirier /40/ have also discussed the possible interaction between simultaneously administered digitalis glycosides and antacids containing aluminium or magnesium compounds. They have pointed out both the supportive and conflicting evidences of interaction. Cooke and Smith /41/, for example, found that the *in vivo* absorption of digoxin was unchanged when the glycoside was administered with magnesium trisilicate in the clinical setting. It appears therefore that adsorbed digoxin can become "desorbed" from the antacid during its passage down the gastrointestinal tract.

Magnesium perhydrol reduces the bioavailability of digoxin by a different mechanism. Digoxin is decomposed by hydrogen peroxide which is liberated from magnesium perhydrol on exposure to gastric juice /42/.

The effect of antacid on the bioavailability of β-acetyldigoxin has also been examined /43/. No significant difference in bioavailability was found for β-acetyldigoxin alone and that of the combination with a combined aluminium magnesium hydroxide product (Alucol®).

It appears therefore that the possibility of interaction between cardiac glycosides and antacids has been overestimated based on *in vitro* adsorption findings. Since the agents have long half-lives, and need only be given once daily, doses of antacid and digoxin need not be given at exactly the same time; their administration could be conveniently separated by two or three hours and this would help prevent them coming into direct contact within the gut, and would therefore minimise the likelihood of an interaction.

3.3. Chloroquine

Although chloroquine is used only occasionally in western Europe in the treatment of autoimmune diseases, its use is extensive in countries where malaria is endemic, e.g. in the Sudan chloroquine accounts for some 90% of the country's expenditure on malaria chemotherapy. *In vitro* /44/ and *in vivo* data /45/ have shown that antacids and kaolin can change the absorption of chloroquine. AUC data showed that magnesium trisilicate decreased chloroquine absorption by 18.2% in six healthy Negro-Arab volunteers (see Figure 2 for the chloroquine serum

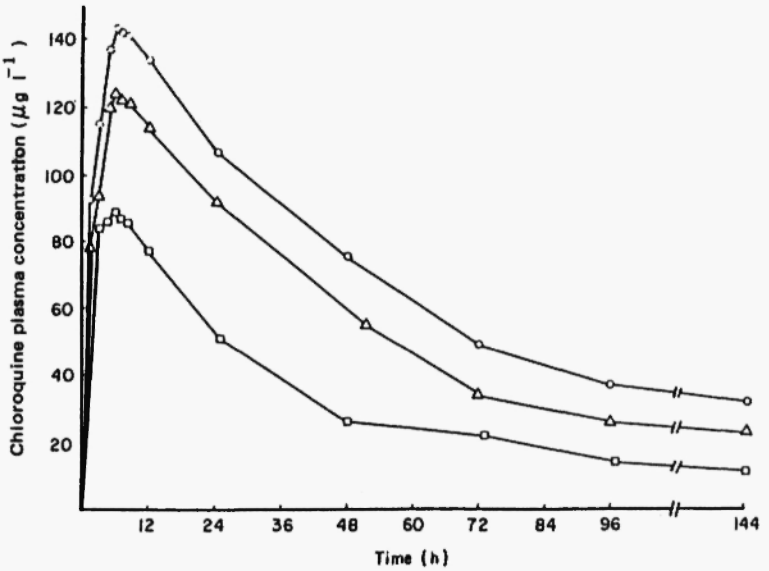

Figure 2. Effect of magnesium trisilicate (-△-) and kaolin (-□-) on the absorption of chloroquine compared to control data.(-o-). (After McElnay *et al.* /45/).

profiles obtained in a representative volunteer). The *in vitro* studies, which involved the monitoring of chloroquine transfer across everted rat intestine while in the absence and presence of antacids, indicated that calcium carbonate, gerdiga, kaolin and magnesium trisilicate decreased chloroquine absorption by 30 - 50%. Similar data were obtained for pyrimethamine, another commonly used antimalarial agent. Gerdiga is a crude clay material used as an antacid in rural areas of the Sudan. It consists of hydrated silicates chemically related to other antacids and

adsorbents together with sodium and potassium carbonates and bicarbonates. The mechanism of interaction is likely that of adsorption of the drug by the antacids. Khalil /46/, for example, has shown that monolayer adsorption of chloroquine to magnesium trisilicate takes place followed at higher concentrations by multilayer adsorption. Interactions of this type are important since gastrointestinal upset is a common symptom of malaria and in the Sudan, for example, it is common practice to take antimalarial drugs and an antacid preparation as a combined treatment.

It is clear therefore that to obtain reproducible and complete absorption of chloroquine, concomitant therapy with antacids should be avoided, or alternatively the administration of the two medicaments should be spaced by four hours to reduce the possibility of them interacting in the gastrointestinal tract. Inadvertent coadministration of gastrointestinal medicaments should also be considered in studies comparing the efficacy of different chloroquine dosage regimens, as decreased bioavailability caused by such agents may introduce an experimental artifact which may not always be considered or indeed realised /45/.

3.4. Cimetidine

The treatment of peptic ulcer disease often involves the use of H_2-receptor blockers and antacids, e.g. cimetidine given with meals and at bedtime and antacids taken between meals and at bedtime. As both medications will therefore be taken together at bedtime it is important to ascertain whether or not the bioavailability of cimetidine is changed by antacids.

Burland *et al.* /47/ found that both a calcium carbonate-magnesium carbonate and an aluminium-magnesium hydroxide product did not change cimetidine AUC values for up to four hours after drug administration, indicating the absence of an interaction. Bodemar *et al.* /48/, however, in a study involving nine patients found that in fasting patients administration of an antacid suspension (containing aluminium hydroxide and magnesium hydroxide) together with cimetidine decreased the absorption of the H_2 blocker. The mechanism of the interaction is uncertain since *in vitro* adsorption studies have shown that cimetidine is significantly adsorbed by activated charcoal, kaolin, talc, and magnesium trisilicate but that adsorption is virtually non-existent with magnesium hydroxide and aluminium hydroxide /49/.

In a further clinical study the absorption of cimetidine was investigated when given alone, together with 60 ml of an aluminium-magnesium hydroxide containing antacid liquid preparation, and together with liquid metoclopramide (14 mg) to eight healthy volunteers. The antacid significantly reduced the cimetidine AUC values; on average metoclopramide reduced the bioavailability by an average of 22%. The authors suggested that cimetidine and antacids should not be given together, and that the dose of cimetidine may have to be increased if it is administered concomitantly with metoclopramide /50/.

Recent American data indicated that antacids containing magnesium and/or aluminium hydroxide inhibited the absorption ($\geqslant$50%) of cimetidine in fasting normal subjects and in patients with duodenal ulcer. In addition, a magnesium and aluminium hydroxide combination (Mylanta II®) inhibited the absorption of cimetidine when the two were taken together with food, but not when the antacid was taken one hour after food. The authors suggested that antacids and cimetidine should not be taken together; however, taking antacids one hour before or after cimetidine in the fasting state or one hour after the drug in the postprandial state, should not interfere with the full suppressive effect of cimetidine on gastric acid secretion /51/. This appears to be prudent advice and indeed since twice daily dosing with cimetidine is now common in the treatment of duodenal ulcer disease, the ability to space dosing of the two gastrointestinal medications should present no difficulties.

3.5. Oral anticoagulants

Warfarin and the other coumarin anticoagulants are drugs on which patients are stabilised for prolonged periods of time with deviation from stability leading to serious consequences including thrombosis or haemorrhage. It has been suggested on theoretical grounds that antacids may influence the gastrointestinal absorption of warfarin /52/. Robinson *et al.* /53/, however, showed that an antacid mixture of aluminium and magnesium hydroxides did not alter plasma warfarin concentrations. Peak concentrations in plasma of bishydroxycoumarin have been shown to be increased by 75% when given with magnesium hydroxide. Bishydroxycoumarin concentrations were not affected by the coadministration of aluminium hydroxide while warfarin absorption was not affected by either of the antacids /54/. These workers showed that the magnesium chelate of bishydroxycoumarin is absorbed more rapidly than its sodium salt. This suggested that the increased absorption of

this anticoagulant in the presence of magnesium hydroxide was due to chelate formation. The chelate has a 2:1 ligand-metal stoichiometry with two moles of water associated with the complex /55/. McElnay *et al.* /56/ found that the absorption of warfarin across everted rat intestine was slightly decreased while in the presence of some antacids. Bismuth carbonate decreased warfarin transfer by 6.9% while magnesium trisilicate led to a 19.3% decrease in absorption. It could be concluded that the use of large doses of magnesium trisilicate concomitantly with warfarin may decrease its bioavailability. The probable mechanism of the interaction is adsorption. If antacid therapy is required in a patient stabilised on warfarin, magnesium hydroxide or aluminium hydroxide products should be used since they have been shown to be free from interaction with this widely used anticoagulant.

3.6. Phenytoin

Formulation problems with phenytoin have already been discussed in this review (see Section 2.2); the effect of antacids on the absorption of this important antiepileptic agent has also been studied. O'Brien *et al.* /57/, in a study in six healthy male volunteers, showed that the t_{max} and AUC values did not change when phenytoin sodium (100 mg) was given alone or during treatment with an aluminium hydroxide gel and magnesium hydroxide mixture. Calcium carbonate was also shown not to influence phenytoin absorption /58/. Gelusil®, a commonly used mixture of magnesium trisilicate and aluminium hydroxide, did lead to a small but statistically significant fall in serum phenytoin in patients given combination therapy /58/. The authors of this latter study concluded that, although the demonstrated change in phenytoin levels was small, prolonged antacid treatment might lead to a clinically important interaction in some patients.

In a small study involving only two volunteers, Chapron *et al.* /27/ examined the effect of calcium gluconate and two antacids (magnesium and aluminium hydroxide mixture; aluminium hydroxide-magnesium trisilicate mixture) on the bioavailability of a single dose of phenytoin. Neither the rate nor the extent of phenytoin absorption was altered by the treatments. It should be pointed out, however, that two subjects is an unacceptable number for a valid clinical trial and indeed later work /59/ involving eight subjects, in a randomised cross-over trial, showed that aluminium-magnesium hydroxide and calcium carbonate significantly decreased the mean AUC obtained after a 600 mg dose of

phenytoin. An aluminium hydroxide-magnesium trisilicate mixture exhibited a similar trend but did not reach statistical significance. The authors suggested that antacids administered in a peptic ulcer regimen may decrease the AUC of a single dose of phenytoin and that patients should be cautioned against concomitant use of antacids and phenytoin.

McElnay *et al.* /60/ found that the AUC values were decreased in five of six volunteers who took part in a clinical trial of phenytoin bioavailability in the absence and presence of Asilone Suspension® (Figure 3). This product contains activated dimethicone, dried aluminium

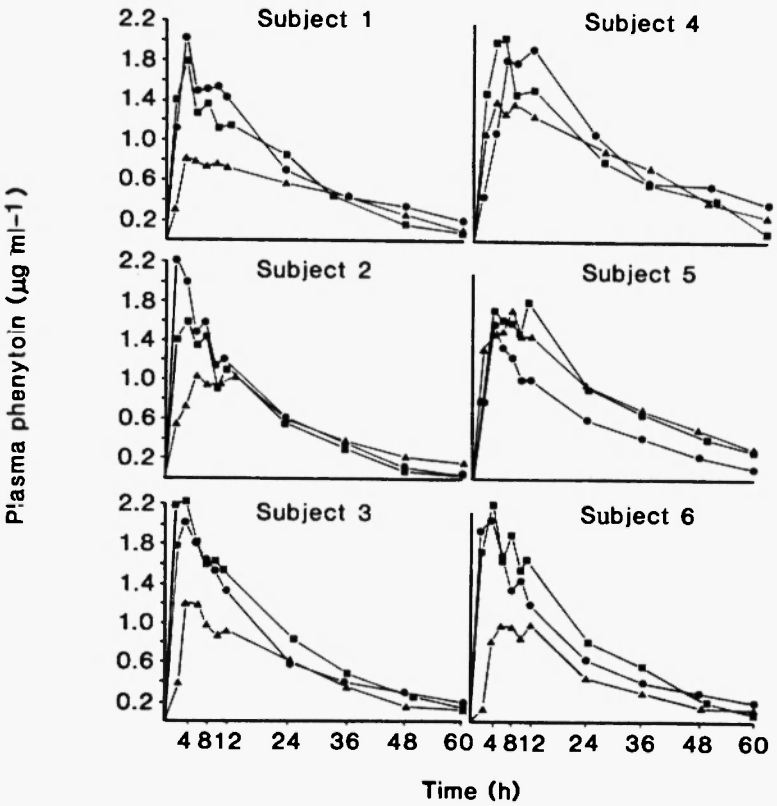

Figure 3. Phenytoin plasma concentration vs time profiles of six volunteers while receiving phenytoin alone (–•–) phenytoin plus Asilone® (–▲–) and phenytoin plus dimethicone (–■–). (After McElnay *et al.* /60/).

hydroxide and light magnesium oxide. The decrease in AUC values was greater than 30% in three subjects. Activated dimethicone was also administered to the volunteers, and although this decreased phenytoin absorption *in vitro* /61/, the *in vivo* absorption was not changed.

In conclusion, although there are a few studies which indicate a lack of effect of antacids on phenytoin bioavailability, the bulk of the information suggests that phenytoin absorption can be decreased by antacids. It would therefore appear prudent that the administration of antacids and phenytoin, when both are required by a patient, should be separated by several hours to avoid their direct contact in the gut.

It nas also been suggested that the calcium content of the diet may modify the absorption of phenytoin /62/, perhaps by the direct effect of calcium ions on the intestinal membrane causing a "membrane-tightening" effect /63/. Phenytoin itself may also influence the absorption of metal ions from the diet. Weismann *et al.* /64/ have shown that the anticonvulsant increases the absorption of zinc in the rat. Studies in epileptic patients have shown that phenytoin does not affect serum levels of magnesium /65/.

3.7. Tetracyclines

Di- and tri-valent metal ions decrease tetracycline absorption(see Section 2.1). Although the metal compounds present in antacids are relatively insoluble, metal ions are released within the gastrointestinal tract and therefore interfere with absorption of the antibiotics. Antacids and tetracyclines should therefore not be taken at the same time; their administration should be separated by several hours. A comprehensive discussion on the mechanism of the interaction is included in the section "Drug-Formulation Interactions", while references to specific studies involving antacids are given in Table 1.

3.8. Theophylline

Like digoxin, the oral anticoagulants and phenytoin, the serum levels of theophylline must be carefully controlled in order to obtain maximum benefit from the therapy without toxicity. The therapeutic range for theophylline is 10-20 $\mu g ml^{-1}$ in serum /66/. Theophylline is a weak base at physiologic pH and therefore it has been suggested that antacids could lead to changed theophylline absorption /67/. Arnold *et al.* /18/ have carried out a study involving antacids in healthy volunteers where theophylline was administered to 12 adults either with or without

Maalox® (aluminium-magnesium hydroxide). Serum theophylline concentrations drawn over 24 hours were significantly different at the 0.67 and 1.0 hour time periods indicating that the rate of absorption was decreased by the antacid. The extent of absorption and elimination rate constant, however, remained the same and the interaction was therefore deemed not to be clinically significant. The latter study involved theophylline given as aminophylline in a normal release dosage form. Shargel *et al.* /68/ have examined the effect of antacid on the bioavailability of theophylline from both normal release and timed release drug products. A magnesium-aluminium hydroxide suspension was given concurrently with either theophylline anhydrous tablets or theophylline anhydrous timed-release capsules to 13 volunteers using a four-way crossover design. AUC values were unchanged as were the absorption rate constants indicating a lack of interaction. More recent data involving two different sustained release theophylline products (Neulin Depot® and Theo-Dur®) and an antacid suspension containing magnesium hydroxide, magnesium carbonate and aluminium hydroxide, however, indicated an interaction /69/. Anatacid did not influence the serum theophylline levels in the Theo-Dur® treatment period in the volunteers whereas in the Neulin Depot® treatment period the antacid caused a significantly larger increase in serum levels of theophylline after drug intake (Figure 4). The difference between morning and peak concentrations were also much higher with the combination. The reason for these differences is the fact that theophylline release from various sustained release products is pH dependent. *In vitro* analyses have indicated that theophylline release from Nuelin Depot® (Theolair Retard®) was highly pH-dependent, while this was not the case for Theo-Dur® /70/.

In conclusion, theophylline absorption from certain sustained release products may be influenced by antacids. Theophylline gives rise to hyperacidity, gastritis and heartburn in susceptible individuals and therefore the use of theophylline and antacids concomitantly is probably not uncommon. To avoid an interaction an antacid/theophylline combination which is free from interaction should be chosen from the studies above if both agents are required by a particular patient. Serum concentrations of theophylline should of course also be monitored regularly to ensure optimal therapeutic response.

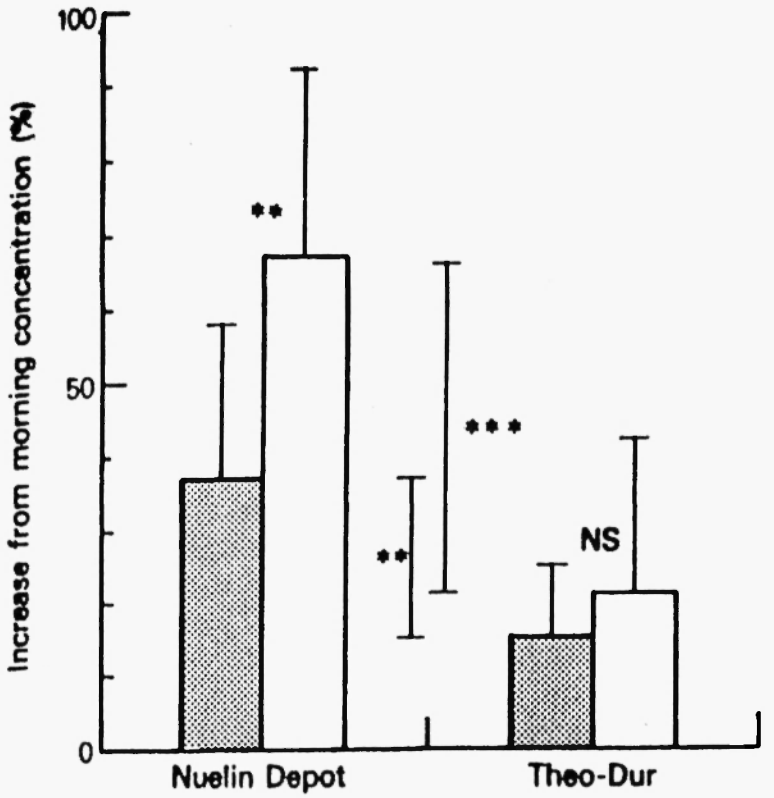

Figure 4. Mean percentage increase (± S.D.) in serum theophylline concentration from the morning to the highest value during the dose interval when treated with Theo-Dur® 300 mg x 2 or Nuelin Depot® 350 mg x 2 with (□) and without (▨) antacid. N.S. *,**, and *** denotes non-significant ($P > 0.05$), and significant differences ($P < 0.05$, $P < 0.01$, and $P < 0.001$), respectively. (After Myhre and Walstad /69/).

4. CLINICAL SIGNIFICANCE OF INTERACTIONS IN THE GUT INVOLVING METAL IONS

Much of the available human data on drug absorption interactions (and indeed all other interactions) has been obtained from studies carried out in healthy volunteer subjects given single doses of the drug being examined both in the absence and in the presence of the interactant (e.g. metal salt; antacid). Although these data are superior to *in vitro* or animal data, optimal results can only be obtained during multiple dosing in patients who would normally receive the therapies.

Altered drug bioavailability due to a drug interaction will lead to a changed rate of absorption and/or a changed extent of drug absorption. The rate of drug absorption can either be decreased or increased while the extent of drug absorption in the case of interactions involving metal ions is most commonly either unchanged or decreased.

4.1. Changed rate of drug absorption

The rate of drug absorption influences both the time taken to reach peak plasma concentrations (t_{max}) and the magnitude of the peak plasma concentration (Cp_{max}). Table 2 illustrates this point, e.g. in a type 1 interaction, in which both the rate and the extent of drug absorption is increased, both the t_{max} and Cp_{max} values increase.

The clinical significance of changed rates of drug absorption will depend very much on the drug involved. An increased rate of drug absorption will lead to larger than normal fluctuations in serum concentrations between doses. This will be particularly marked if the drug is normally absorbed slowly and has a short plasma half-life, e.g. an interaction which increases the release rate of theophylline from a sustained release theophylline product could be potentially serious.

A slowed rate of drug absorption generally gives rise to fewer problems in the clinical (multiple dosing) situation, providing the extent of drug absorption remains unchanged. Such an interaction would lead to smaller than normal fluctuations in serum concentration between dosing.

4.2. Extent of drug absorption

A changed extent of drug absorption is much more likely to give rise to a clinically important drug interaction than a changed rate of drug absorption. This was clearly illustrated by the phenytoin incident in Australia when the formulation change led to increased absorption of phenytoin and to phenytoin intoxication (Section 2.2; /25/). A decrease in the amount of phenytoin absorbed would be equally serious and would likely lead to seizures in patients normally therapeutically well controlled. The pharmacokinetic effects of changed extent of drug absorption are also shown in Table 2.

4.3. Drugs involved in clinically important drug interactions

In order to elicit a serious drug absorption interaction the change in drug absorption must be marked and/or the drug involved must have a

TABLE 2. Effects of changed absorption patterns on drug plasma profiles and drug interactions (after D'Arcy and McElnay /108/)

Type	AUC∞ (extent of drug absorption)	Rate of drug absorption	Resulting t_{max}	Resulting Cp_{max}	Possibility of interaction
1	Increased	Increased	Decreased	Increased	Yes
2	Decreased	Decreased	Increased	Decreased	Yes
3	No change	No change	No change	No change	No
4	Increased	Decreased	Increased	Uncertain	Yes
5	Decreased	No change	No change	Decreased	Yes
6	No change	Increased	Decreased	Increased	Yes
7	Increased	No change	No change	Increased	Yes
8	Decreased	Increased	Decreased	Uncertain	Yes
9	No change	Decreased	Increased	Decreased	Yes

narrow therapeutic range. Otherwise the drug interaction is of interest but not of immediate clinical importance since, with drugs of a wide therapeutic range, the changed serum levels which would result from changed absorption would lead to little change in therapeutic effect in the patient. In this respect drug interactions during absorption have been overemphasised and overstated. Drugs with a narrow therapeutic range with which relatively minor changes in drug absorption could lead to clinically important changes in pharmacological effects include anti-arrhythmic agents, anticoagulants, anticonvulsants, cardiac glycosides, lithium salts, antidiabetic agents, psychotropic agents and theophylline. It is also important to consider agents like H_2-receptor antagonists because they will commonly be used together with antacids. The combination of e.g. isoniazid and antacids would be much less common and an interaction between these two agents /71/ is of little more than theoretical interest.

In conclusion, many drugs enter into drug absorption interactions with antacids and metal salts; however, not all those recorded will give rise to clinically significant changes in a patient's treatment. A knowledge of common interactions of this type is important to the prescribing physician and pharmacist. An informed judgement can then be made (based both onthe drug dynamics and kinetics discussed) as to the advice to give to patients in which an interaction is likely or suspected.

Finally it should be remembered that many drug interactions in the gastrointestinal tract can be prevented simply by avoiding the adminis-

tration of interacting agents at exactly the same time. This fact was clearly demonstrated by Gothoni *et al.* /72/ who showed that the interaction between oral iron and tetracyclines could be avoided by simply spacing the separate administration of these drugs by two or three hours.

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