International Journal of Pharmaceutics, 5 (1980) 167–185

Review Article

SITES AND MECHANISMS OF DRUG INTERACTIONS I. IN VITRO, INTESTINAL AND METABOLIC INTERACTIONS

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(Received February 25th, 1980)

Over the past decade there has been increasing concern about the interaction of one drug with another as many patients receive more than one drug simultaneously. Combinations of drugs, however, are often necessary in patient therapy, for example, a patient may suffer from more than one disease or perhaps have different symptoms of a single disease which may require separate and different treatment.

An understanding of drug interactions can best be approached by considering the mechanisms by which, and the sites at which, the interactions take place. All drug interactions can be divided into three major categories: (a) pharmacokinetic drug interactions in which one drug changes the pharmacokinetic profile of another drug concomitantly administered; (b) pharmacodynamic drug-interactions in which two drugs interact giving either summation, potentiation or antagonism of pharmacological effect; and (c) miscellaneous drug interactions – this group contains those interactions which do not fit well into the two previous classifications.

(a) PHARMACOKINETIC DRUG INTERACTIONS

The mechanisms by which this type of drug interaction takes place must by definition complicate the time-dependent changes in serum concentration, or the total amount of drug and its metabolites in the body. Mechanisms involved in pharmacokinetic drug interactions are as follows:

(i) in vitro drug interactions (drug interactions occurring outside the body);
(ii) drug interactions in the intestine;
(iii) interactions involving metabolizing enzyme systems;
(iv) displacement interactions from plasma protein and tissue binding sites; and
(v) drug interactions during renal excretion.

These sites are shown diagrammatically on Fig. 1.

(i) IN VITRO DRUG INTERACTIONS

This category accounts for those interactions which may occur in the intravenous infusion fluid container, in the syringe or due to changes in the bioavailability of medicines

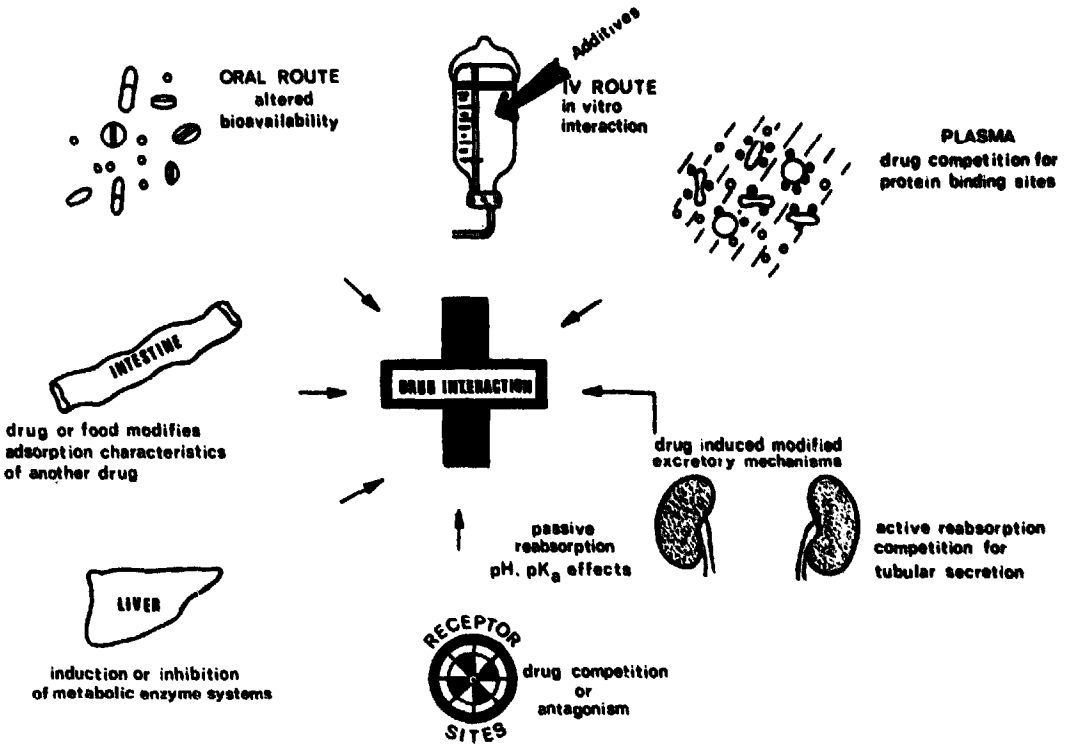


Fig. 1. The possible sites of drug interactions (after Griffin and D'Arcy, 1979).

when their formulation is altered. Such interactions may be either physical or chemical in nature.

Problems may occur, for example, when drugs are added to the containers of intravenous infusion fluids. Thus a drug may be unstable in the medium to which it is added or it may be incompatible with another drug or chemical within the infusion. The incidence of such additions is high, for example, D'Arcy and Thompson (1974), in a survey of Ulster hospitals, found that 39.2% of infusions had drugs injected into the container. Similar results have been found by other workers. Harrison and Lowe (1974) have shown that 44% of i.v. solutions used in a ward study contained additives, 17–24% of which were multiple. Brodlie et al. (1974) have found that single drugs were added to fluids for medical patients whereas for surgical patients 15% of the additives contained two or more drugs. A summary of several drug additive surveys is given in Table 1.

Certain fluids to which no drug should be added have been documented by Griffin and D'Arcy (1979) and include blood, fluids containing amino acids, fat emulsions and 20 or 25% mannitol solutions.

Drugs may become inactive in i.v. fluids, for example, benzylpenicillin loses 10% of its activity in 4–8 h in dextrose and dextrose saline while under similar conditions ampicillin loses 10% activity in 2–4 h. Drug–drug incompatabilities also occur, demonstrated, for example, by the precipitation of gentamicin in infusions containing heparin sodium.

A more subtle problem associated with additives is the changed pharmacokinetic profile of a drug given over a long period instead of the more usual rapid intravenous or

TABLE 1

COMPARISON OF DATA FROM SEVERAL DRUG ADDITIVE SURVEYS

Authors	Number of infusion with additives (%)	Common drug additives	Multiple drug additives (%)	Maximum number
D'Arcy and Thompson (1974) Ulster	39.2	KCl Heparin Oxytocin Lignocaine Ampicillin	1.6	4
Hughes (1973) Kent	14.3	–	3.4	3
Brodlie, Henney and Wood (1974) Dundee	*	KCl Ampicillin Cephaloridine Tetracycline	Medical 0 Surgical 15	4
Harrison and Lowe (1974) ** London	44.0	KCl Heparin Comp. Vitamins Ampicillin	17–24	4
Timoney and Harte (1974) Eire	21.2	KCl Ampicillin Hydrocortisone Heparin	–	–

* 15% incompatibilities recorded overall.

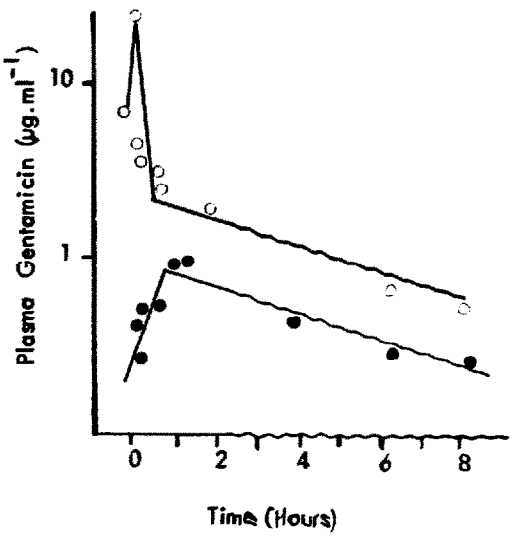
** Three cases of incompatibility recorded.

intramuscular injection. French (1972) showed that both peak and plateau blood levels of gentamicin were greatly depressed when infused over one hour as compared to a 5-min period (Fig. 2). In addition, sterility and pyrogenicity is a matter for concern with i.v. infusion fluids and therefore drug additions should only be made using aseptic technique and under conditions which are suitable for such techniques to be practised.

Another, and quite different, type of in vitro drug interaction may occur during the formulation of medicinal products, giving rise to changes in bioavailability of the active constituent(s). The 3 best documented examples of this type of interaction concern the tetracyclines, phenytoin and digoxin. Calcium phosphate used as a filler in tetracycline capsules gave rise to the formation of a poorly absorbed drug complex while the change from calcium sulphate to lactose in phenytoin tablets produced increased dissolution rates and a resultant outbreak of phenytoin intoxication in Australia in patients who received the new formulation (Tyrer et al., 1970).

The digoxin incident involved a change in particle size of the medicament; Lanoxin tablets manufactured after May 1972 contained a smaller particle size (and thus more readily absorbed) digoxin (Johnson et al., 1973). This gave rise to overdigitalization in patients already stabilized on established regimens of the old drug formulation. As a result of these incidents, stricter controls have been introduced by national drug regulatory bodies to ensure comparable biological availability between batches of the same drug product and that of competing proprietary products.

More recently, formulation studies have shown that the bioavailability of digoxin can be further improved by encapsulating a solution of the glycoside rather than using the



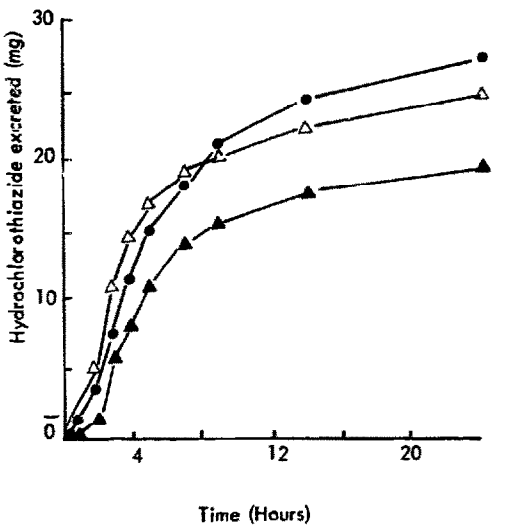


Fig. 2. Plasma levels of gentamicin when administered by intravenous infusion at different rates; 60 mg gentamicin infused over 5 min (○); 60 mg gentamicin infused over 1 h (●). (after French, 1972).

Fig. 3. Mean cumulative amounts of hydrochlorothiazide excreted (mg) at various times after ingestion of 100 mg of drug in capsule formulations containing hydrochlorothiazide–PVP 10,000 co-precipitate (●); hydrochlorothiazide–PVP 10,000 mechanical mixture (△); and hydrochlorothiazide alone (▲) (after Corrigan et al., 1976).

normal compressed tablets. Longhini et al. (1977) demonstrated that such capsules produced a bioavailability 26.1% better than tablets. Similar findings using encapsulated digoxin solution have been reported by Lindenbaum (1977).

Formulation changes have also been used to increase the bioavailability of hydrochlorothiazide (Corrigan et al., 1976) thus inclusion of polyvinylpyrolidone in the capsules increased bioavailability (Fig. 3).

This interaction mechanism should, however, give rise to few problems unless manufacturing changes are made without warning prescribers about possible bioavailability changes.

(ii) DRUG INTERACTIONS IN THE INTESTINE

Drug interactions at this site can affect either the rate at which a drug is absorbed and/or the total amount of drug absorbed. Those interactions which give rise to decreased total drug absorption will generally give greater problems as the interaction will effectively be equivalent to the administration of the drug in reduced dosage.

Certain factors will effect this absorption of drugs, for example, changes in gastric pH, altered motility of the gastro-intestinal tract, the amount and consistency of food ingested at the same time as the drug, whether or not antacid therapy is being taken, ionic interactions in the intestine and malabsorption syndromes.

(a) Changes in gastric pH. The ionization of a drug is dependent on the pH of its environment and its pK_a value. The unionized form of a drug is less polar and hence more lipid soluble than the ionized form and will therefore be more readily absorbed across the cell membranes of the gastric mucosa. The pH of the gastro-intestinal tract varies from region to region; the pH in the stomach is about 1.0 while that of the duodenum is approximately 6.6. Weak acids, for example acetylsalicylic acid and phenylbutazone, will be more readily lipid-soluble at lower pH when they will be in their unionized forms. Alkali administered together with these drugs may therefore decrease their rate of absorption. Changes in pH of the gastro-intestinal tract, theoretically, should produce changes in the absorption of weak acidic or basic drugs, but such changes do not seem to give rise to clinically significant drug interactions. This may be due to the vast surface areas within the gastro-intestinal tract which are available for drug absorption.

The change of pH of the gastro-intestinal tract as well as causing absorption changes directly, as an effect of ionization, will also change the dissolution rates of drugs. Such an effect was reported by Barr et al. (1971) who observed a decrease of about 50% in the amount of tetracycline absorbed from a capsule when given together with sodium bicarbonate. Absorption was found to be normal if the tetracycline was given in solution form with the alkali. The decrease in the absorption was therefore due to a decreased dissolution of the drug in the higher pH medium. The converse would be expected to take place for the weak acid, aspirin, as the dissolution rate of this agent would be increased at higher pH. The acidity of the stomach may also affect the absorption of ferrous sulphate. A delayed response to iron therapy in two anaemic patients was thought to be caused by the prolonged reduction of gastric acid secretion caused by high doses of cimetidine (Esposito, 1977).

(b) Altered motility of the gastro-intestinal tract. The majority of drugs are absorbed

from the upper regions of the small intestine and so substances changing the rate of stomach emptying would be expected to affect the rate of drug absorption. Nimmo et al. (1973) have shown that propantheline, which delays gastric emptying, gave rise to reduced rates of paracetamol absorption while metoclopramide, which increases gastric emptying, increased the rate of paracetamol absorption. The absorption rate of the anti-arrhythmic drug, mexiletine, was also increased by metoclopramide without altering its relative bioavailability (Wing et al., 1979). However, if a drug is poorly soluble, a decreased stay within the stomach may decrease dissolution of the drug, and this may be the cause of decreased digoxin absorption in presence of metoclopramide and increased absorption in the presence of propantheline (Manninen et al., 1973). Anticholinergic drugs and the opiates decrease gastric emptying and hence may also change drug dissolution and absorption rates. Purgatives, taken concomitantly, may reduce the efficacy of oral contraceptive agents.

(c) Interaction with foodstuffs. The presence of foodstuffs within the gastro-intestinal tract may delay gastric emptying and this can affect the rate of drug absorption. There are, however, many specific interactions between drugs and foodstuffs.

Foods, especially milk products interfere significantly with the absorption of erythromycin, oleandomycin, tetracyclines and most of the oral penicillins (Bartelink, 1974). Whole milk and soft cheeses contain calcium caseinate; the calcium ions form non-absorbable complexes with the tetracycline group of antibiotics. This interaction has the same mechanism as the interaction discussed earlier between tetracycline and calcium phosphate used as a capsule filler. The calcium caseinate interaction has in the past been complicated by the fact that milk was often taken with tetracycline to combat the gastric irritation caused by the drug; such an action was also effectively decreasing tetracycline absorption.

Stimulants of gastric acid secretion, for example, appetizers or aperitifs containing bitters may greatly increase the incidence of gastric bleeding and ulceration caused by drugs like aspirin. A similar potentiation may be apparent with many amino acids and meat extracts which initiate gastric acid secretion via the release of gastrin. Ethanol also gives rise to an increased acid secretion in the stomach.

The fat content of the diet is sometimes an important determinant of drug–food interactions. This has been clearly demonstrated by Crounse (1961) when the effects on the absorption of griseofulvin of different diets, containing varying degrees of fat, were examined. It was demonstrated that the rate of griseofulvin absorption was greatly increased when given together with a high fat-containing diet. This increased absorption may be a disadvantage if a drug is intended to give a local effect. The absorption of the anthelmintic tetrachloroethylene, for example, is increased in a high fat diet and this, as well as taking the drug from its site of action, may lead to hazard as this agent is toxic to both liver and kidneys. The effects of various test meals and different volumes of water on the absorption of amoxicillin has been examined by Welling et al. (1977). The data obtained (Fig. 4) indicate that serum levels were reduced in the presence of food and that the extent of this reduction was independent of the dietary components.

Food has, however, been shown to increase the bioavailability of propranolol and metoprolol. The bioavailability of both beta-blockers was increased after a normal breakfast as compared with the drugs taken on an empty stomach (Melander et al., 1977a). The

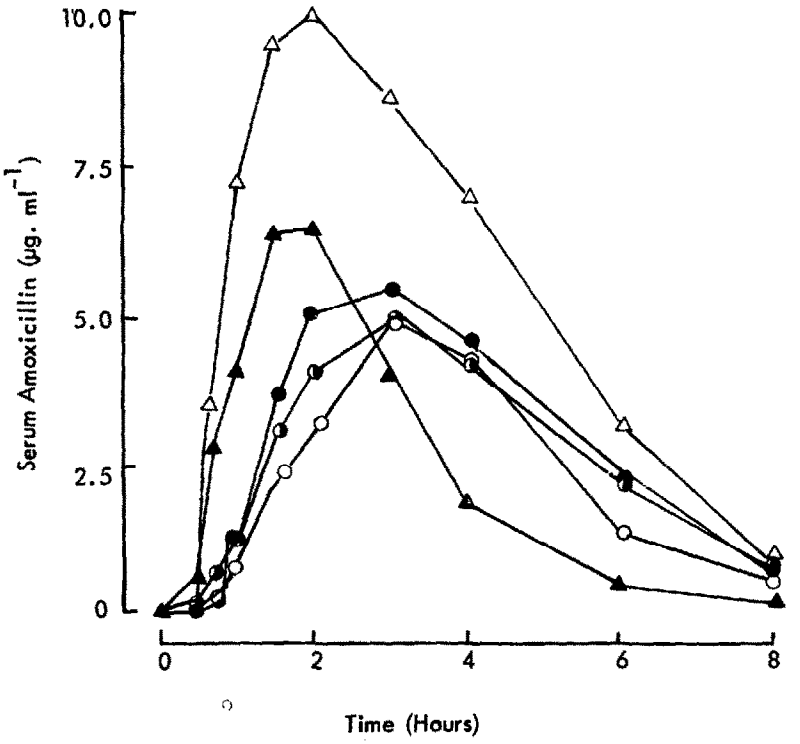


Fig. 4. Average serum levels of amoxicillin in 6 subjects receiving 500 mg amoxicillin trihydrate in capsules following high-carbohydrate (○), high-fat (●), and high-protein (◉) meals and in the fasting state with 25 ml (▲) and 250 ml (△) of water (after Welling et al., 1977).

same group of workers in a further study have shown that canrenone, the major active metabolite of spironolactone, enters the general circulation to a greater degree when ingested together with a meal (Melander et al., 1977b; Fig. 5). Food may also give rise to changes in the shape of serum–drug profiles without changing drug bioavailability. This has been shown for cephradine (Mischler et al., 1974). In their study, food had no significant effect on the urinary excretion of the antibiotic but, as can be seen from Fig. 6, the t_{max} value was shortened and the f_{max} value was increased. Changes of this nature would be important for drugs with a low therapeutic index.

Finally, tea and coffee have been implicated in the malabsorption of the neuroleptic drugs. Kulhanek et al. (1979) found that when drops of fluphenazine or haloperidol were added to a solution of tea or coffee, the neuroleptic formed an insoluble precipitate. About 90% of the drug was precipitated, bound or otherwise changed in tea, and about 10% in coffee. Fortunately, however, the majority of drugs do not seem to be affected by foodstuffs and are absorbed well regardless of dietary intake.

(d) Interaction with antacid preparations. Antacids are a group of medicinal agents often involved in drug absorption interactions; they may change the rate of drug absorption or the total amount of drug absorbed. Constituents of antacid preparations have been shown to affect the absorption of digoxin (Khalil, 1974; Brown and Juhl, 1976; Van der Vijgh et al., 1976; McElnay et al., 1979) and phenytoin (Kulshrestha et al.,

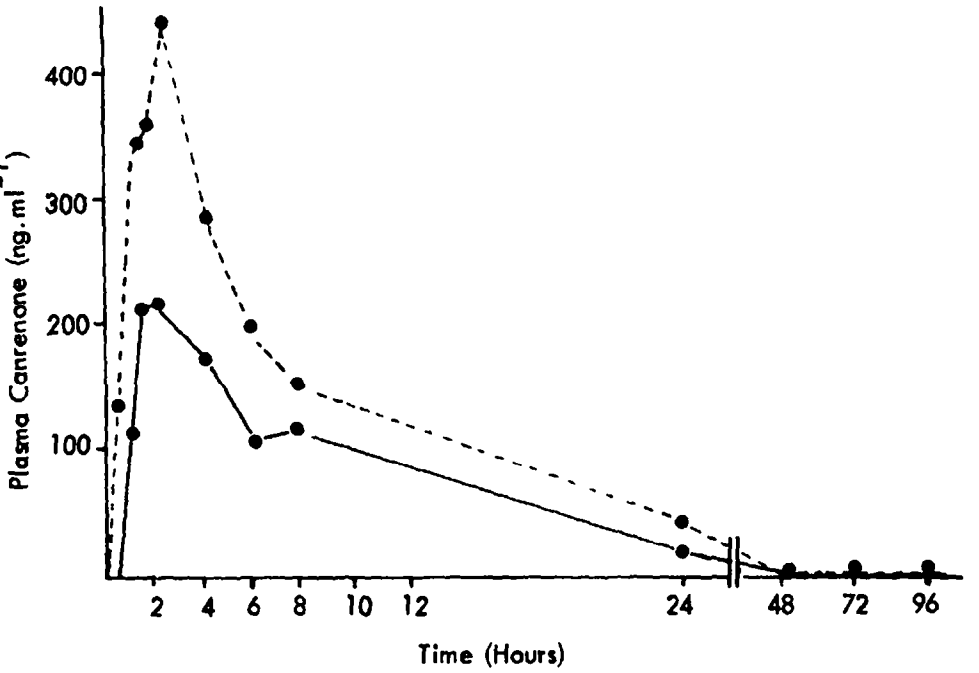


Fig. 5. Plasma levels (ng ml^{-1}) of canrenone in a healthy volunteer after a single oral dose (4 X 25 mg) of spironolactone given while fasting (●——●) and together with a standardized breakfast (●- - - - -●). Apparently, more canrenone enters the general circulation in the postprandial state (after Melander et al., 1977b).

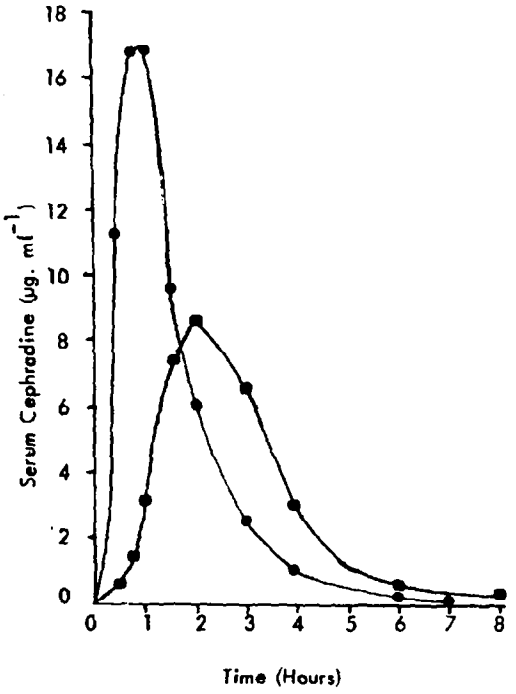


Fig. 6. Serum concentrations after oral cephradine (500 mg) given to fasting (●) and non-fasting (■) subjects (after Mischler et al., 1974).

1978), two drugs with which patient stabilization is essential.

Occurrence of this type of drug interaction is by no means new since aluminium hydroxide gel was implicated many years ago in the malabsorption and thus lowered serum levels of aureomycin (Waisbren and Hueckel, 1950). Since then a wide range of drugs have been implicated in this type of interaction. The absorption rate and peak plasma levels of chlordiazepoxide were delayed in 6 of 10 volunteers when given together with an aluminium hydroxide–magnesium hydroxide mixture, while a psychotic patient, well controlled with chlorpromazine, was noted to suffer relapse within 3 days of being placed on a regular regimen of antacid therapy (Fann et al., 1973). Aluminium hydroxide gel decreased the maximum plasma concentration of propranolol by 57% (Dobbs et al., 1977) and more recently the absorption of metoprolol and atenolol has been shown to change when these drugs were given together with an antacid preparation. The mean area under curve for metoprolol was increased by 11% while that of atenolol was decreased by 33% (Lundborg, 1979).

These findings suggest that patients should be made aware of this interaction mechanism, especially with regard to freely available non-prescription antacid preparations, and also of the fact that an interaction can often be avoided by simply allowing an interval of at least 4 h to elapse between taking the antacid and the primary drug.

(e) Ionic interactions in the intestine. The main type of ionic interaction which takes place is the interaction of various drugs with divalent or trivalent metal ions, notably Ca^{2+}, Mg^{2+}, Fe^{2+} and Al^{3+}. The interaction leads to the formation of non-absorbable complexes (Prescott, 1969). The best known interaction of this type is the tetracycline interaction with Ca^{2+}. Neuvonen et al. (1970) also showed that concomitant administration of iron tablets with antibiotics of the tetracycline group gave rise to decreased blood levels of the drugs of up to approximately 85% less than controls (Fig. 7). This interaction is on a molecular basis and hence is more pronounced with doxycycline which, being more potent, is given in lower dosage.

Levy (1970) demonstrated marked decreases in limethylchlortetracycline when given together with half a pint of milk or with a dose of aluminium hydroxide gel as compared with the single 300 mg dose of the drug given on an empty stomach. This type of interaction may be overcome by concomitant administration of the complexing agent, EDTA. Poiger and Schlatter (1978) found that ingestion of tetracycline with milk caused a marked depression of the amount of drug excreted in the urine. Simultaneous administration of EDTA with milk gave a return to near control values (Fig. 8). It is unlikely, however, that such a procedure would be acceptable clinically; avoidance of the interaction is a more sensible solution.

Tonics contain high concentrations of iron and have been shown to decrease serum levels of concurrently administered tetracyclines below the effective level of 0.6 μgm ml^{-1}. It should be borne in mind, however, that the absorption of the iron will also be decreased and the anaemia for which the iron is being administered, will remain untreated or at best undertreated.

Cholestyramine may also give rise to problems for a slightly different reason. This agent is a basic anion exchange resin which forms non-absorbable complexes with bile salts thus preventing their enterohepatic circulation. Bile acids are formed from cholesterol and, when there is depletion of bile acids, plasma cholesterol is utilized for bile acid

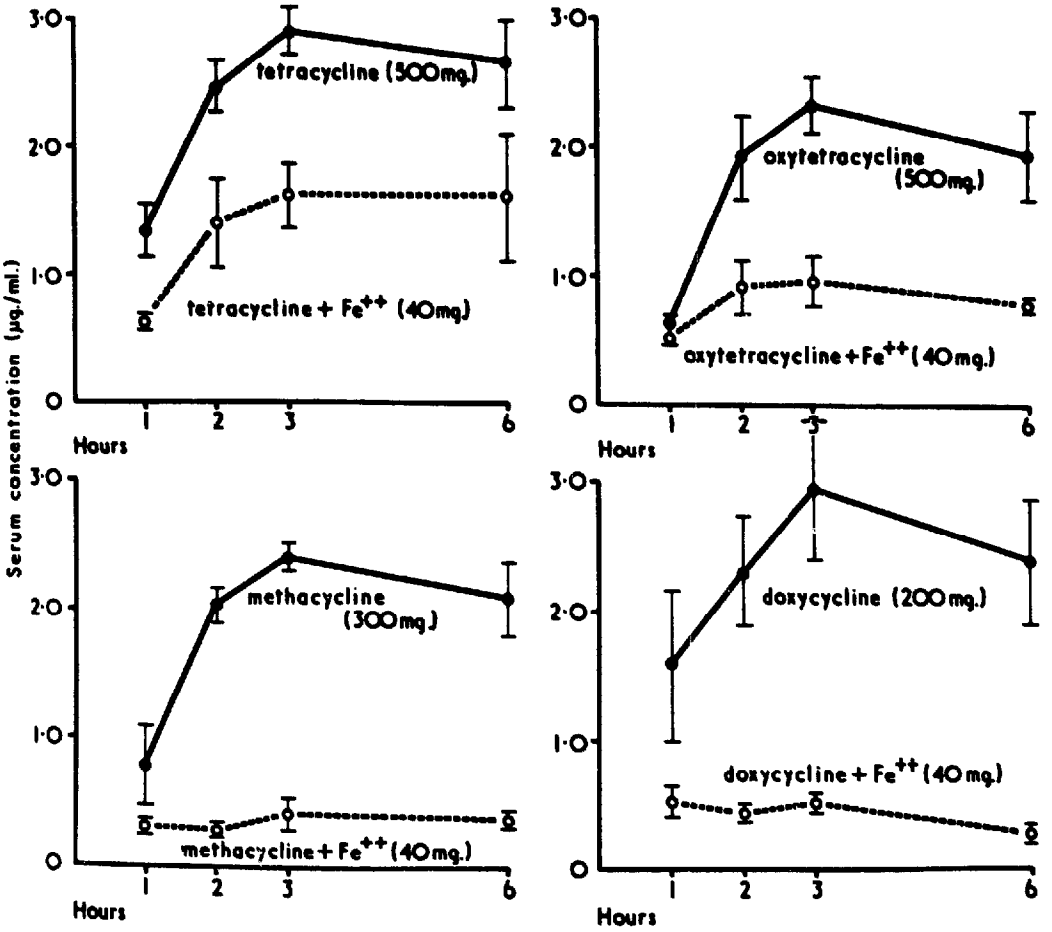


Fig. 7. The effect of concomitant administration of iron tablets on the serum concentrations of tetracyclines; both drugs given orally (after Neuvonen et al., 1970).

synthesis – hence cholestyramine is used as a cholesterol-lowering agent. Bile acids, however, are important in fat absorption and after cholestyramine administration, side-effects may include steatorrhoea and malabsorption of the fat-soluble vitamins A, D, E and K. Cholestyramine has also been shown to decrease the absorption of digoxin and digitoxin (Caldwell et al., 1971) and warfarin (Koch-Weser and Sellers, 1971). The total clearance of phenprocoumon increased 1.5–2-fold when given together with cholestyramine in 6 normal subjects (Meinertz et al., 1977). This meant that the total anticoagulant effect per dose was considerably reduced. The results suggested that cholestyramine effectively interrupted enterohepatic recycling of the phenprocoumon thus increasing its rate of elimination.

One product taken in great quantity by elderly patients, who are often preoccupied with bowel habit, is liquid paraffin. Although effects on drug absorption, or perhaps more importantly the absorption of fat-soluble vitamins has not been well documented, it is apparent that the liquid paraffin could dissolve such substances and carry them through the gastro-intestinal tract, thus inhibiting their absorption.

(f) Malabsorption syndromes. Neomycin, like cholestyramine, decreases the absorp-

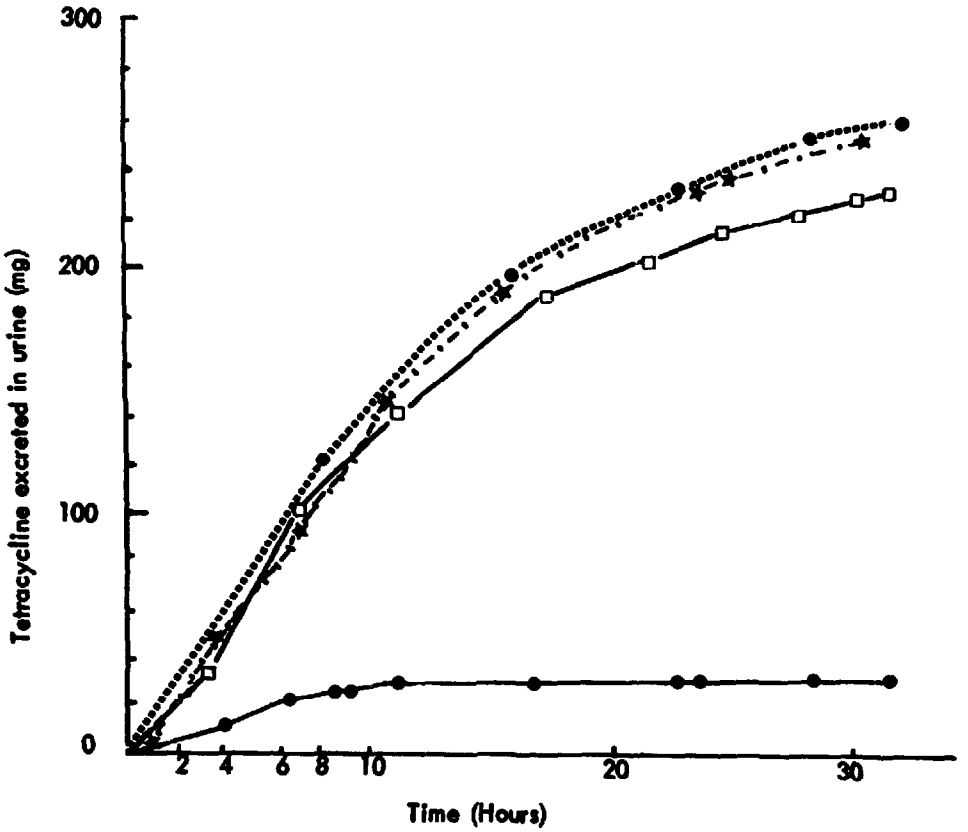


Fig. 8. Cumulative amount of tetracycline excreted in urine of one individual after receiving a 500 mg capusle alone (★– · – · –★) with 500 mg EDTA (●- - - - -●), with 200 ml milk (●———●), or with 200 ml milk and 2.3 g EDTA (□———□) (after Poiger and Schlatter, 1978).

tion of fat by precipitation of bile salts in the gut. This precipitation effect is potentiated as neomycin gives rise to changes in gut flora, the bacteroides, clostrides and certain lactobacilli being favoured. These bacteria produce an amidase which can deconjugate bile salts and also are toxic to intestinal mucosa cells. This manifests itself as a decreased activity of mucosal enzymes and can cause malabsorption of carbohydrates and proteins. Dobbins et al. (1968) have also shown malabsorption of carotene, hexose sugars, iron and vitamin B_{12} in the presence of neomycin, polymyxin, kanamycin and bacitracin. Drugs used in cancer chemotherapy which arrest mitosis, for example methotrexate, cause injury to the intestinal mucosa and hence the absorption of drugs administered concomitantly is changed.

Para-amino-salicylic acid (PAS) has been reported to decrease the absorption of rifampicin (Boman et al., 1971). This interaction is of particular importance as the two drugs are often used together in the treatment of tuberculosis. Later evidence showed, however, that the malabsorption of rifampicin was caused by the excipient, bentonite, present in the PAS granules (Boman et al., 1975).

(iii) INTERACTIONS INVOLVING DRUG METABOLIZING ENZYME SYSTEMS

Most drugs are altered chemically in the body and give rise to compounds which are more water-soluble and hence easier to excrete via the kidney. This biotransformation process is carried out mainly by microsomal enzyme systems in the liver; the plasma and kidney may also contain enzymes capable of drug metabolism. The microsomal enzyme systems in the liver are often non-specific and hence biotransform a variety of different drugs. Drug interactions can therefore occur when the activity of these enzymes is altered and this may give rise to changed drug biotransformation and hence drug elimination. Effects produced on the enzyme systems can be classified as to whether increased activity (enzyme induction) or decreased activity (enzyme inhibition) is achieved.

(a) Enzyme induction. A wide range of chemical substances are capable of increasing microsomal enzyme activity. These include not only drugs but also many insecticides, dyestuffs, hydrocarbons (such as those found in cigarette smoke) and alcohol. The alcoholic, for example, can tolerate greater quantities of alcohol than the non-drinker and this is due in part, at least, to an increased rate of alcohol metabolism; indeed Kater et al. (1969) have shown that alcohol metabolism can be doubled in alcoholics as compared with abstinent subjects. Alcohol can also give rise to increased metabolism of drugs; examples are tolbutamide, warfarin and phenytoin, 3 of the most important drugs as far as patient stabilization is concerned. The effects on tolbutamide elimination are shown in Fig. 9.

Iber (1977) also examined the rate of removal of tolbutamide from the blood of heavy-drinking male alcoholic subjects who consumed 100 g or more ethanol daily and

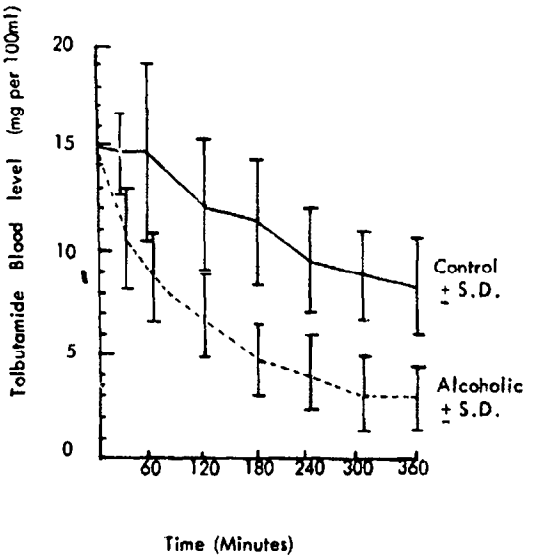


Fig. 9. Ten alcoholic subjects drinking more than 200 g ethanol daily, studied 3 days after cessation of alcohol, and 6 abstinent adults, all male and all with no history of any drug intake, were given 1 g tolbutamide intravenously at zero time and subsequent blood levels of tolbutamide were measured. All vaues (mean ± S.D.) after 3 h are significantly different ($P < 0.05$), which indicates that such alcoholic subjects remove tolbutamide from the blood faster than normal abstinent (non-drinking) subjects (after Kater et al., 1969).

found that the rate of removal of the tolbutamide was faster than in normal non-drinking subjects. This rapid rate of elimination persisted for periods of 4–9 weeks after hospitalization.

Cigarette smoking has also marked effects on the pharmacokinetic profiles of certain drugs. The tolerance to nicotine in smokers may be due to enhanced nicotine metabolism in smokers (Beckett and Triggs, 1967). The rate of metabolism of pentazocine is increased in smokers and in city dwellers, in which atmospheric pollution is suggested to increase the drug's metabolism (Kerri-Szanto and Pomeroy, 1971).

Kuntzman et al. (1977) have studied the effect of cigarette smoking on the metabolism of phenacetin in the rat and in man. Treatment of rats with 3,4-benzpyrene (a common constituent in cigarette smoke) resulted in a more rapid drug disappearance from the plasma. The metabolism of phenacetin to N-acetyl-*p*-aminophenol by the intestinal mucosa in rats was enhanced. In man, a depressed blood phenacetin level was seen in non-smokers together with an increased amount of the N-acetyl derivative. The plasma half life, however, was the same in both smokers and non-smokers. These authors therefore suggested that increased intestinal metabolism of the drug, induced by cigarette smoking, might be involved in the depressed blood levels seen in smokers.

A survey of 7 countries by Miller, of the Boston Collaborative Drug Surveillance Program (1977), examined how intensity of smoking affected drug performance. Propoxyphene was found ineffective in 10% of non-smokers, in 15% of light-smokers and in 20% of heavy-smokers. In patients receiving diazepam and chlordiazepoxide, the incidence of drowsiness decreased with increasing cigarette smoking. Similar results were found with the drowsiness associated with chlorpromazine treatment in a psychiatric population. Such data suggested that substances in cigarette smoke induced liver microsomal enzyme systems involved in the metabolism of these drugs. Other drugs have, however, been shown to be unaffected by cigarette smoking; the steady-state plasma levels of nortriptyline was similar in smokers and non-smokers (Norman et al., 1977) and the incidence of drowsiness associated with phenobarbitone was unchanged by smoking (Miller, 1977).

Hepatic microsomal enzyme induction by the polynuclear aromatic hydrocarbons in cigarette smoke is therefore not universal, meaning that these agents are selective with regard to specific enzyme systems and it is for this reason that the effects of smoking on metabolism remain relatively unpredictable.

Many drugs are inducers of microsomal enzyme systems particularly the cytochrome P 450 system. A consequence of this type of induction is a shortening of the plasma half-life of the inducing drug itself and of other drugs metabolized by a similar pathway. The induction is more commonly seen with drugs which are relatively lipid-soluble and which are themselves slowly metabolized. The main drugs which have been associated with clinically significant enzyme induction interactions include barbiturates, chloral hydrate, carbamazepine, glutethimide, griseofulvin, phenazone, phenylbutazone, phenytoin and rifampicin.

Many more drugs have been shown to induce enzymes in animals, but relatively few of these interactions seem to be important in the clinic. Drugs which are used in a daily dose of less than several hundred milligrams do not produce significant induction and this helps to explain why drugs capable of producing induction in animals fail to do so in man during normal therapy (Wade and Beeley, 1976). The enzyme induction often gives rise

to decreased steady-state plasma levels of the drug or drugs concerned. In order to get the required therapeutic effect, drug dosage must therefore be increased. All then remains well until the inducing agent is withdrawn, after which plasma levels of the primary drug increase, giving rise to toxicity. Important clinical examples of drug–drug interactions by this mechanism are the increased warfarin metabolism caused by barbiturates and other hypnotics and the increased metabolism of steroids caused by phenobarbitone and phenytoin; for example, failure of oral contraceptives in epileptic patients receiving phenytoin has been reported. Phenytoin was also thought to be involved in the increased metabolism of dexamethasone in a female craniotomy patient (McLelland and Jack, 1978). An increased phenytoin metabolism, on the other hand, may occur with phenobarbitone or with loxapine (Ryan and Matthews, 1977). Phenobarbitone is also thought to effect vitamin D metabolism which in turn effects the mobilization of body calcium. Prolonged treatment with this drug may lead to osteomalacia in the patient (Young et al., 1977). Phenytoin gives similar effects. Phenobarbarbitone has also been shown to increase the elimination rate of D-glucaric acid and salicylamide (Drzewiecki, 1977). More recently, rifampicin, a strong enzyme inducer, has been shown to decrease blood levels of clofibrate by almost 50% meaning that if both drugs are administered together, an increased dose of clofibrate would be necessary (Hovin and Tillement, 1978). There are many further examples of such interactions occurring in the clinic; however, the few examples given here outline the complexity of this interaction mechanism.

Finally, it is well known that the ingestion of certain pesticides, for example DDT, affects drug metabolism. A survey of these effects has shown that the metabolism of

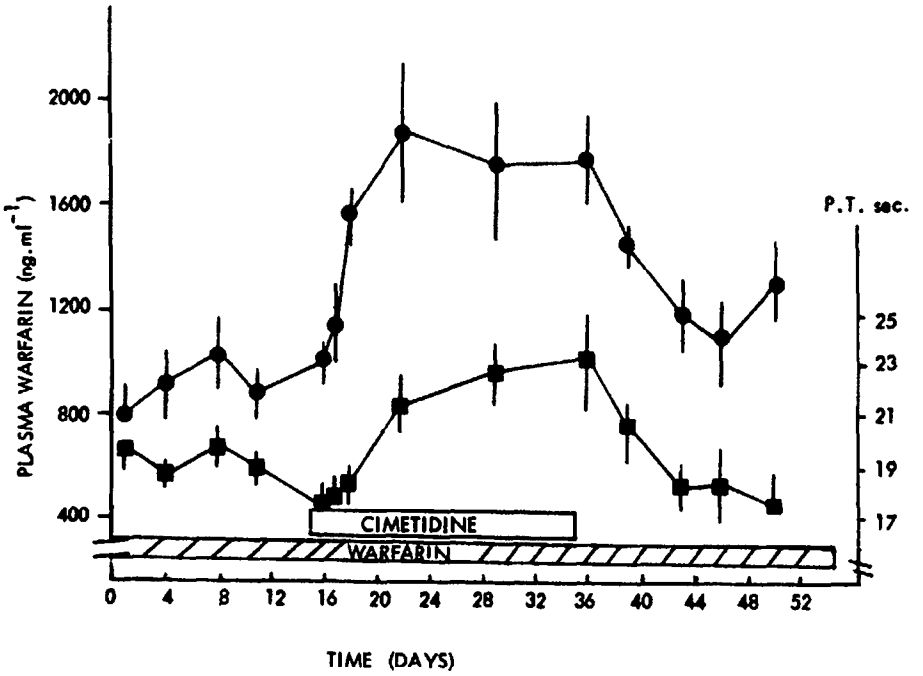


Fig. 10. Effect of cimetidine on steady-state warfarin concentration (•) and prothrombin times (▪); mean data ± S.E. in 7 volunteers (after Serlin et al., 1979).

TABLE 2

TYRAMINE OR OTHER AMINE CONTENT OF CLASSES OF FOODS KNOWN TO CAUSE HYPERTENSION IN PATIENTS TAKING MAOI DRUGS (AFTER D'ARCY AND GRIFFIN, 1980).

Product	Tyramine content range ($\mu g\ g^{-1}$ or $\mu g\ ml^{-1}$)
Alcohol	
Beer	1.8–4.4
Chianti	25
Port	NS
Reisling	0.6
Sauterne	0.4
Sherry	3.6
Broad beans	Rich in DOPA
Cheese	
Blue	49–266
Brie	180
Brie (South African)	142
Camembert	86–125
Camembert (South African)	13
Cheddar (Australian)	226
Cheddar (Canadian)	231–535
Chedder (English)	0–953
Cheddar (New York State)	1416
Cheddar (New Zealand)	417–500
Cheddar (South African)	175–775
Cheshire (South African)	297
Cottage, low fat	NS
Cottage, cream	NS
Edam	100–214
Emmenthaler	225
Gouda	54–95
Gruyère	64–516
Gruyère (South African)	30
Kraft	214
Liederkrantz	1226–1683
Limburger	204
Munster	110
Processed (American)	50
Roquefort	48
Roquefort (South African)	656
Stilton	466
Swiss	50–434
Chocolate	Rich in vanillin
Fish	
Caviar (Russian)	680
Pickled herring	3030
Fruit and vegetables	
Avocados	23
Bananas (skin)	65
Bananas (pulp)	7 (plus serotonin)
Figs (canned)	NS
Red plum	6
Tomato	4

TABLE 2 (continued)

Product	Tyramine content range ($\mu g\ g^{-1}$ or $\mu g\ ml^{-1}$)
Liver	
Beef (fresh)	50–65
Beef (stored)	274
Chicken (fresh)	NS
Chicken (stored)	94–113
Yeast products	
Barmene	157
Befit	419
Marmite	1087–1639
Marmite (salt-free)	187
Yeastrel	101
Yex	506
Yogurt and dairy products	
Yogurt	NS
Cream	Significant levels but no value given

NS = tyramine levels were not significant.

many drugs may be increased in exposed laboratory animals, in humans occupationally exposed, and in birds environmentally exposed to chlorinated organic insecticides (Azarnoff, 1977).

(b) Enzyme inhibition. A range of substances cause the opposite effect to enzyme induction and are capable of decreasing the metabolism of other drugs. If the metabolism of a drug is decreased, the retention of the drug will give rise to changed drug distribution in the body, higher plasma drug levels and hence increased risk of toxicity. One of the most widely studied interactions in this field concerns the monoamine oxidase inhibitors (MAOIs) which act via the inhibition of intraneuronal monoamine oxidase. This results in the accumulation of noradrenaline and adrenaline in adrenergic nerve terminals. These stores may be released by indirectly-acting sympathomimetic amines, for example, amphetamines, tyramine and ephedrine, giving rise to severe hypertension. Tyramine contained in foodstuffs is metabolized in the gut wall by MAO and normally does not enter the circulation. However, MAOIs also inhibit the enzyme at this site and hence absorbed tyramine gives rise to hypertensive episodes some of which have been fatal (McClure, 1962; Sjöqvist, 1965). Tyramine is found in high concentration in some foods (Table 2), for example, cheese, pickled herrings, broad bean pods, yeast extracts and Chianti wine and indeed a treatment card explaining these dietary restrictions should be given to, and carried by, all patients receiving MAOI therapy. A report concerning this type of interaction describes a patient who while receiving MAOI treatment ingested 3 or 4 heaped tablespoonfuls of Iranian caviar. This was followed 40 min later by a bursting headache, nausea, palpitations and a hot flush. On analysis some caviar was found to contain 0.68 mg g^{-1} of tyramine (Isaac et al., 1977).

Other drugs causing enzyme inhibition include chloramphenicol, para-amino-salicylic acid, isoniazid, dicoumarol, phenylbutazone, sulphaphenazole, disulfiram, allopurinol, pethidine, morphine and more recently cimetidine. A range of interactions can therefore

take place, for example, phenylbutazone and sulphaphenazole decrease tolbutamide metabolism (Pond et al., 1977) while allopurinol, a xanthine oxidase inhibitor, gives rise to the potentiation of mercaptopurine. It has been established that treatment of patients or healthy volunteers with cimetidine causes a prolongation of the prothrombin time achieved with concomitantly administered warfarin (Serlin et al., 1979; Fig. 10). Cimetidine has also been shown to increase the half-life of diazepam (Klotz et al., 1979). The mechanism of both interactions is thought to be due to an inhibition of drug metabolism by cimetidine. Cimetidine may therefore also influence the activity of other drugs metabolized by a similar metabolic pathway.

Deficiency of certain endogenous materials may inhibit drug metabolism. Nicholls and Shepherd (1978) suggested that the impaired warfarin metabolism seen in a patient could be due to the effect of iron deficiency on the heptatic microsomal cytochrome P 450 drug metabolizing system.

Phenylbutazone can both give rise to enzyme induction and enzyme inhibition and has been shown to increase the elimination of the R-isomer of warfarin while decreasing S-warfarin elimination (Lewis et al., 1974).

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