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SITES AND MECHANISMS OF DRUG INTERACTIONS II. PROTEIN BINDING, RENAL EXCRETION AND PHARMACODYNAMIC INTERACTIONS

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INTRODUCTION

It was proposed in the first part of this review (McElnay and D'Arcy, 1980) that drug interactions may be divided into 3 categories, i.e. pharmacokinetic, pharmacodynamic and a miscellaneous group. In that first section consideration was given to pharmacokinetic interactions occurring in vitro, in the intestine and due to changes in enzyme systems. This second and final part concludes discussion on the pharmacokinetic sites of interaction, i.e. at protein binding sites and in the kidney; it also presents comment on pharmacodynamic and miscellaneous-type interactions together with an assessment of the clinical implications of drug interactions.

PHARMACOKINETIC DRUG INTERACTIONS (continued)

(iv) DISPLACEMENT INTERACTIONS FROM PLASMA AND TISSUE PROTEINS

Albumin is the major plasma and tissue protein responsible for the binding of most drugs. The extent of drug binding to the macromolecules of both plasma and tissues will depend on the unique physicochemical properties of the agent concerned and of the macromolecule itself (Jusko and Gretch, 1976). The strength and capacity of the binding to various biological materials may markedly affect the distribution volume of drugs. Drug displacement interactions most commonly occur at plasma and tissue binding sites by simple competition.

If two drugs are bound at the same sites on the macromolecules then there is a simple competition between the drugs for these sites in much the same way as agonists and blockers compete for receptor sites in the autonomic nervous system. Furthermore, one drug by its binding to, for example albumin, may change the physical chemistry of the macromolecule giving rise to tertiary conformational changes in the albumin itself which may change the shape of specific binding sites of other groups of drugs. This leads to a non-competitive displacement interaction (Koch-Weser and Sellers, 1976).

Drugs themselves may not give rise to albumin displacement while their metabolites

may be involved in such an interaction. This was clearly demonstrated by the chloral hydrate-warfarin interaction. Original data suggested that increased anti-coagulation was due to displacement of warfarin from its albumin binding by chloral hydrate; it was subsequently discovered, however, that it was not the chloral hydrate but its metabolite trichloroacetic acid, which gave rise to warfarin displacement (Sellers and Koch-Weser, 1970).

Aspirin influences the binding of certain other drugs by an unusual mechanism; it is capable of acetylating lysine residues on albumin molecules. This acetylation is permanent and modifies the albumin binding of acetrizoate, flufenamic acid and phenylbutazone. The binding of other anionic drugs may also be changed (Pinckard et al., 1973).

(a) Drug displacement from plasma binding sites

The most important displacing agents at plasma albumin binding sites are acidic compounds (Sellers and Koch-Weser, 1971). These compounds often have a high affinity for albumin and accumulate in the plasma. The displacement of one drug by another will depend on the displacer drug's concentration and its affinity for albumin; compounds with high affinity displace drugs of lower affinity at the same binding sites. Mutual displacement of both interacting drugs usually takes place to differing extents; however, usually the displacement of only one drug is clinically important. The latter is termed the 'displaced drug' (Koch-Weser and Sellers, 1976) while the other component of the interaction is termed the 'displacing agent'.

The displacement of a highly bound drug will give rise to an increase in the free fraction of drug in the plasma. However, it is often assumed, incorrectly, that if the percentage free value of a drug is doubled then this free, unbound drug concentration in the plasma will be doubled. The doubled free concentration often quickly distributes throughout the body and when equilibrium is again reached any remaining increases in free drug concentration in the serum and extracellular fluid will depend on the new apparent volume of distribution of the drug. This means that displacement interactions are often of a transient nature. The total drug concentration in the plasma will fall after displacement and redistribution; this will be hazardous if drug dosage is adjusted according to monitored total drug plasma concentrations.

Elevated free drug levels, if present, will also cause an increased free drug concentration at sites of metabolism and elimination and this compensatory mechanism also minimizes the expected increased therapeutic effect of the displaced drug. Any increase in metabolite levels produced as a result of this increased metabolism may further complicate the interaction if such metabolites are also highly bound to proteins.

One very important facet of drug displacement interactions at plasma protein binding sites is that the substance which causes displacement may resemble the displaced drug closely and thus may also block active transport systems in the kidney or drug metabolizing enzymes in the liver and other organs. Thus, after repeated administration of both displaced and displacer agents, the steady-state plasma level of unbound drug could increase, not because of drug displacement but because the compensatory elimination mechanism is inhibited (Gillette, 1973).

(b) Drug displacement from tissue binding sites

Tissue binding of drugs often plays a role in a drug's kinetic profile. Intersubject variability in tissue binding remains relatively unexplored; however, Jusko and Weintraub (1974) found a positive correlation between postmortem myocardial digoxin to serum digoxin ratios and antemortem creatinine clearances in 15 patients. This may explain the relatively small volume of distribution of digoxin found in patients with impaired renal function. Drugs may also compete for tissue binding sites in a similar way to their competition for serum albumin binding sites. Tissue displacement interactions may decrease the apparent volume of drug distribution and possibly give rise to elevated free plasma levels in the equilibrium state.

Tissue binding may also be affected by endogenous substances. Differences in the plasma protein binding of warfarin in rats were paralleled by qualitatively similar differences in the tissue binding of the drug. Rats which showed relatively high plasma binding of warfarin also showed relatively high tissue binding (Gibaldi and McNamara, 1977). Other workers have found that the fraction of warfarin unbound to liver homogenates correlated very well with the fraction of warfarin unbound to serum in the same animals (Yacobi and Levy, 1975). A common factor may therefore be responsible for the inter-animal variation of warfarin binding in the plasma and tissues of rats; a similar factor may also govern intersubject sensitivity to drug–drug interactions at both plasma and tissue binding sites. Endogenous materials are discussed in more detail below.

(c) Endogenous materials and drug displacement

The involvement of endogenous materials in drug displacement from protein binding is often ignored. A number of reports of their involvement have appeared; for example,

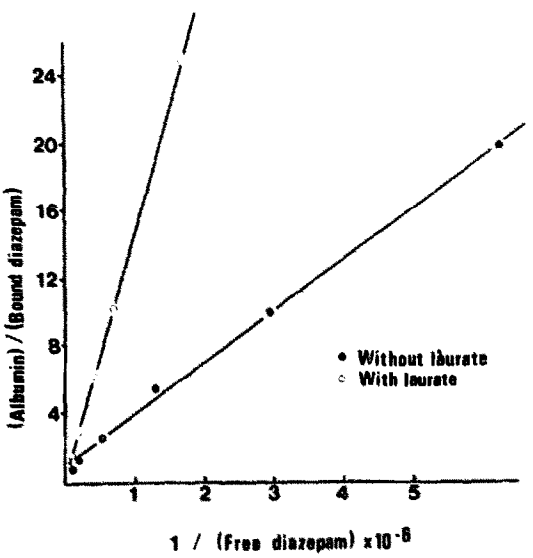

Fig. 1. Binding of diazepam to human serum albumin and the inhibiting effect of laurate. Albumin 0.5% (w/v), 7.46×10^{-5} M; laurate, 3.5×10^{-4} M. Both ordinates are calculated on the basis of molarities (after Tsutsumi et al., 1975).

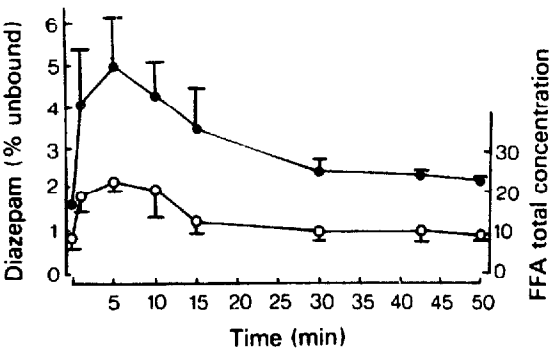

Fig. 2. Time course of change in per cent of unbound diazepam (•) and of total free fatty acids (○) after 100 units of heparin administered intravenously (after Desmond et al., 1980).

endogenous fatty acids compete with diazepam for binding. Tsutsumi et al. (1975) have shown that, at therapeutic concentrations of diazepam, about 14% of the drug was displaced by the laurate anion. This displacement effect is depicted in Fig. 1.

These authors therefore suggested that if a drug is highly bound to plasma proteins this type of endogenous competition should not be ignored. It has also recently been found (Desmond et al., 1980) that heparin affects the plasma binding of benzodiazepines. In normal non-fasting subjects heparin caused a rapid 150-250% rise in the free fraction of diazepam, chlordiazepoxide and oxazepam but no change with lorazepam. The change in free fraction occurred within 90 sec of administration of heparin and binding returned to the baseline by 30–45 min (Fig. 2). This decreased benzodiazepine binding was mediated via a two-fold rise in plasma free fatty acids after only 100 units of heparin. The authors therefore concluded that the use of heparin during drug disposition studies might affect the estimation of pharmacokinetic parameters and possibly pharmacological effects which were dependent on the circulating unbound blood level.

(d) Drug binding in disease states

An interaction mechanism involving endogenous materials is of particular relevance in the diseased patient whose plasma make-up may be disturbed by the disease process. An effect of this type is seen in patients with alcoholic liver disease in whom there is decreased binding of fluorescein, dapsone, quinine and triamterene; phenytoin binding, however, was normal or near normal in most of the plasma samples examined (Table 1; Affrime and Reidenberg, 1975), although it was decreased in patients with acute viral hepatitis (Blaschke et al., 1975).

Such decreases are only partially explained by decreased serum albumin levels and hence endogenous material displacement or perhaps variations in the albumin molecules themselves may be important.

Drug binding is often subnormal in patients with acute or chronic renal disease (Ehrnebo and Odar-Cederlöf, 1975; Mussche et al., 1975). An example of this is the decreased binding of cardiac glycosides in patients with renal disease (Kramer et al., 1974). Again such decreased binding, although correlating with the degree of hypoalbuminaemia, is not fully explained by it. The binding of diazepam is also decreased in

TABLE 1

BINDING OF DRUGS IN PLASMA OF PATIENTS WITH CIRRHOSIS (AFTER AFFRIME AND REIDENBERG, 1975)

Patient	Serum			% unbound drug			
	Albumin (g/dl)	Total protein (g/dl)	Total bilirubin (mg/dl)	Fl	DPH	Qu	Tri
1	1.5	6.2	24.5	21.5	10.5	3.2	–
2	3.0	9.2	1.3	14.5	9.0	41	22
3	1.2	5.6	–	22	–	62	–
4	3.5	9.3	1.8	18	–	33	–
5	1.5	7.7	4.8	30	–	41	31
6	2.6	8.5	5.1	20	–	43	32
7	1.1	7.7	10.8	37	5.8	49	–
8	2.0	6.2	2.5	35	26.0	44	–
9	3.2	8.0	4.5	21	7.7	41	–
10	2.2	6.0	3.7	–	10.0	–	–
11	2.3	7.5	5.1	37	11.7	58	–
12	2.4	8.2	9.3	–	13.0	–	–
13	4.0	8.1	1.9	–	–	–	39
14	2.9	7.7	6.8	–	–	–	41
Mean ± S.D.				25.6 ± 8.3	11.7 ± 6.2	41.5 ± 16.0	33.0 ± 7.5
Normal mean ± S.D.				13.8 ± 2.3	8.3 ± 0.8	14.1 ± 4.6	19.3 ± 2.9
n				18	9	7	7
P				<0.001	<0.2	<0.001	<0.01

Fl, fluorescein; DPH, diphenylhydantoin; Qu, quinidine; Tri, triamterene.

patients with poor renal function and it has been suggested that this may increase its effect in such patients (Kangas et al., 1976). The changes in binding, outlined in the above examples, will further complicate drug–drug competition for binding.

A few examples of the many known displacement interactions at protein binding sites have been used to outline this mechanism of interaction. Lists of important protein binding parameters may be found in the literature, for example, by Meyer and Guttman (1968) and Vallner (1977).

What becomes evident, however, from all such studies is that the strong binding of drugs by plasma and tissue proteins influences drug kinetics, drug–drug interactions and hence drug effectiveness. For these reasons it is important that all new drugs should be assessed as to whether or not they fall into the category of highly bound agents. It should, however, be stressed that protein binding displacement, per se, is not an important mechanism of drug interaction due to redistribution of displaced drug. When displacement, however, is combined with interaction mechanisms involving decreased elimination it will greatly increase the seriousness of the adverse effects obtained.

(v) DRUG INTERACTIONS DURING RENAL EXCRETION

Most drugs are eliminated via the kidneys, either in the form of metabolites or unchanged drug. This renal elimination takes place in one of two ways; either by simple glomerular filtration or by active secretion across the proximal tubular epithelium. As blood passes through the glomeruli low molecular weight drugs or other substances which are not protein-bound filter across the glomerular membrane. Further along the tubule lie sites of active secretion and these sites remove certain drugs and other xenobiotics. This active secretion, unlike the filtration, is independent of whether or not the substance is bound to plasma proteins. Reabsorption may occur even further along the tubule. This reabsorption will be of very small water-soluble substances or of lipid-soluble materials. Most reabsorption occurs by simple passive diffusion; however, active reabsorption also occurs in much the same way as active secretion.

If a substance is filtered in the kidney or secreted and is not reabsorbed it is lost from the body in the urine; the reabsorption process is therefore important as far as elimination is concerned.

(a) Effects of pH

The reabsorption of a drug will depend on its state of ionization, which in turn will depend on the pK_a of the drug and the pH of the glomerular filtrate. The stronger an acidic compound, the more it is ionized in neutral aqueous solution and the lower is its pK_a; the stronger a base the more it is ionized in neutral aqueous solution and the higher is its pK_a value. Most substances used in medicine have pK_a values falling between 1 and 11 (Newton and Kluza, 1978). Thus weakly acidic drugs are excreted more rapidly at high pH when they are in the largely ionized, water-soluble form. Conversely, weak bases will be excreted slowly at high pH when they remain largely unionized, lipid-soluble and easily reabsorbable across the lipid membrane by passive diffusion. Under normal circumstances, however, changes in urinary pH are not important causes of drug interactions.

The effect of pH on drug excretion is, however, utilized in cases of drug overdosage and urinary pH can be changed to increase drug elimination from the body after overdosage with an acidic drug (e.g. aspirin, nalidixic acid or phenobarbitone); the clearance of the drug is enhanced by making the urine more alkaline with sodium bicarbonate. Similarly, the clearance of weakly basic drugs (e.g. amphetamine, morphine and pethidine) can be accelerated by acidifying urine by administering ammonium chloride. This accelerated clearance is not only important in overdosage but can also be used in the diagnosis of drug addiction, for example, morphine is eliminated more rapidly in an acid urine. Exercise and dietary intake also influence pH of urine and hence drug elimination. Antacid therapy may increase urinary pH.

(b) Active transport mechanisms in the kidney

Active secretion and reabsorption mechanisms in the kidney are often troublesome as far as drug interactions are concerned. The retention or loss of drugs, which are actively secreted or reabsorbed, can be changed by other drugs when they compete for the same transport systems. This interaction mechanism has been used to advantage, for example, with probenecid which actively blocks the tubular secretion of penicillin. Probenecid was

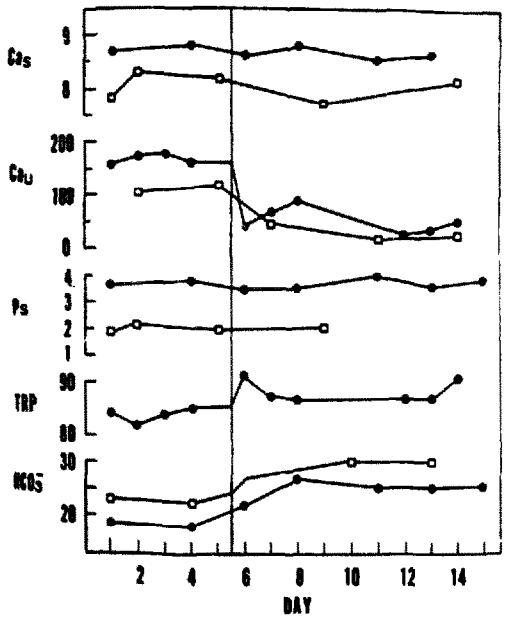

Fig. 3. Metabolic changes resulting from discontinuation of acetazolamide; drug stopped on day 5; other drugs continued in same dosages. Note concentrations of calcium (Ca_S, mg/100 ml), phosphate (P_S, mg/100 ml) and bicarbonate (HCO_3^- mEq/liter) in venous blood drawn after overnight fast, rate of renal excretion of calcium Ca_u, mg/24 h), and per cent tubular reabsorption of phosphate (TRP) (case 1, closed circle; case 2, open square; after Mallette, Arch. Int. Med., 137 (1977) 1013–1017; Copyright 1977, Am. Med. Ass.).

given concomitantly with penicillin in the early days of this antibiotic's use when it was expensive and in scarce supply. Ninety per cent of penicillin's loss into the glomerular filtrate is by active secretion and hence the use of probenecid was very helpful in maintaining blood levels of the antibiotic. Probenecid and similar compounds can also block the active secretion of other acidic drugs, however, basic drugs remain unaffected. Agents are also known which will block the excretion of basic drugs; these compounds are toxic and are not used therapeutically. Further drug interactions occurring due to changes in active secretion are the slowing of renal secretion of penicillin by oxyphenbutazone and the retardation of chlorpropamide secretion by dicoumarol.

Changes in tubular reabsorption may also give rise to problems; for example, acetazolamide has been shown to accelerate anticonvulsant-induced osteomalacia in two patients who were receiving long-term treatment with phenytoin, phenobarbitone and acetazolamide (Fig. 3).

Discontinuation of acetazolamide in these patients produced an immediate 3-fold drop in the level of urinary calcium excretion and a slight rise in tubular reabsorption of phosphate. Increased renal calcium excretion was therefore the proposed mechanism for this accelerated osteomalacia (Mallette, 1977).

Uricosuric agents promote the excretion of urates in the urine; uric acid is normally filtered in the glomerulus but is later reabsorbed actively with only a small amount being re-excreted into the filtrate. Probenecid, in therapeutic dosage, gives both decreased secre-

tion and reabsorption; however, the net result is a loss of uric acid. Other drugs used in the treatment of gout act by similar mechanisms and often the pharmacological effects of two such drugs are additive, for example, sulphinpyrazone with phenylbutazone. However, in certain cases the effects are antagonistic, for example, salicylates with phenylbutazone, and such combinations must be avoided.

A further example of a drug interaction involving the kidney is that between digoxin and quinidine. When quinidine is added to an established digoxin regimen the serum digoxin level rises and, in one patient, it increased from 2.2 to 4.1 ng ml^{-1} during quinidine treatment (Leahey et al., 1978). The mechanism of this interaction may be a displacement of digoxin from tissue binding sites (Hager et al., 1979) although Dahlquist (1979) found decreased renal digoxin clearance (57–84%) in some patients on the combined treatment. This decreased clearance seemed too large to be fully explained by an inhibition of active renal secretion of digoxin, although patients receiving quinidine did show a significant reduction in creatinine clearance. Similar results have been reported by Risler et al. (1980); however, these clinicians found that increasing quinidine dosage from 500 to 1000 mg did not give further effect on digoxin or creatinine clearances. This indicates that the digoxin–quinidine interaction on the kidney might be saturable.

(c) Drug-induced changes in urine volume

The drugs most commonly implicated in changed urinary output are the diuretics; ethacrynic acid and hydrochlorthiazide increase the urinary secretion of chloramphenicol and its metabolites. Glomerular filtration rates did not change in the subjects (creatinine clearance remained relatively constant) and the influence of these diuretics on chloramphenicol excretion was explained by decreased water reabsorption by the tubules (Schuck et al., 1978).

Reductions in urinary output may also be involved in drug interactions. A recent report describes a manic depressive patient who developed symptoms of lithium toxicity while receiving spectinomycin for the treatment of gonorrhoea. Spectinomycin can reduce urine output and therefore may have caused inhibition of normal lithium excretion (Int. Drug Ther. Newsl., 1978).

A broad classification of the sites and mechanisms of pharmacokinetic drug interactions has been outlined. It must, however, be stressed at this point that drug interactions can occur by more than one mechanism simultaneously either at the same site or at different sites. Drug absorption interactions with antacids illustrate the former situation, e.g. aluminium hydroxide gel may lead to the malabsorption of drugs by decreasing gastric emptying rate but may also change absorption via changes in gastric pH. Many antacids including aluminium hydroxide gel also act as adsorbents and can adsorb drug on to their surface, thus preventing absorption; activated charcoal, antidiarrhoeals, e.g. kaolin, and certain tablet excipients, e.g. bentonite, will also be involved in adsorption interactions.

The fact that interactions can occur at different sites has been illustrated by the digoxin–quinidine interaction which may be due to decreased tissue binding (Hager et al., 1979) and also decreased renal tubular secretion (Dahlquist, 1979) of digoxin.

PHARMACODYNAMIC DRUG INTERACTIONS

Drug combinations are often used to take advantage of interactions between drugs affecting the same receptor sites or physiological systems. Certain undesirable interactions may also occur giving rise to another important area of interest in the drug interaction field.

Drugs used together in this way will interact either by summation or synergism. Summation is the additive effect of two or more drugs on the same target organ or cell, the total effect equalling the sum of effects of the individual drugs given separately. This pharmacological summation implies that the drugs involved act via the same receptor sites or by the same mechanism. Synergism, on the other hand, takes place when two or more drugs are given together and the effect on the target organ or cell is greater than the sum of their separate effects. This implies that the drugs achieve the same pharmacological effect by differing mechanisms.

(a) Drugs acting on the autonomic nervous system

The action of many drugs is due to a competition with natural substances at receptor sites, for example, atropine has no intrinsic activity but competes with acetylcholine for receptors at the post-ganglionic parasympathetic nerve ending. The β-blockers (e.g. propranolol, oxprenolol, sotolol, timolol, and atenolol) occupy β-adrenergic receptors so blocking the action of catecholamines. Suxamethonium antagonizes the effects of acetylcholine at neuromuscular junctions in skeletal muscle. A similar pharmacological effect is seen with d-tubocurarine. The mechanism of action of the two drugs, however, is very dif-

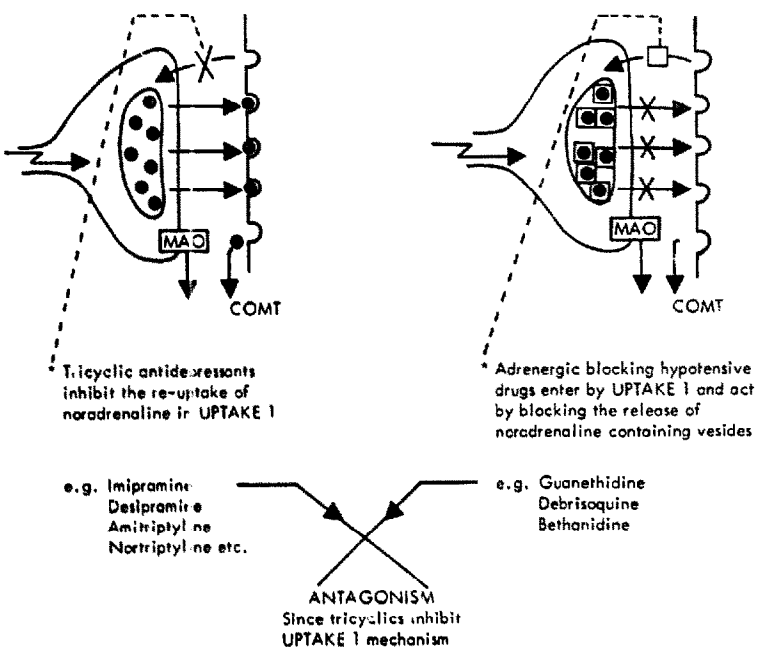

Fig. 4. Interaction between tricyclic antidepressants and adrenergic blocking drugs at the adrenergic nerve terminal (after Griffin and D'Arcy, 1979).

ferent. Suxamethonium is itself an agonist and hence causes a depolarizing block while curare, in a similar way to propranolol, blocks by competition with the agonist for the receptor site. An anticholinesterase will therefore reverse a curare block while potentiating a block achieved with suxamethonium. The use of ecothiopate iodide eyedrops would therefore potentiate a suxamethonium block, as lack of cholinesterase would give rise to increased acetylcholine levels and hence further depolarization (Wade and Beeley, 1976).

The adrenergic blocking drugs guanethidine and bethanidine are concentrated in the adrenergic nerve terminal by the same amine pump as endogenous catecholamines. Tricyclic antidepressants inhibit this uptake mechanism (Fig. 4) and hence will inhibit the hypotensive effect of the blocking drugs. The tricyclic antidepressants, phenothiazines, tranquillizers, antihistamines and the anticholinergic drugs used for Parkinsonism all inhibit acetylcholine giving atropine-like side-effects. These atropine effects are increased if an anticholinergic drug is given to prevent the extrapyramidal side-effects of phenothiazines (Wade and Beeley, 1976).

There are also many examples of drug interactions involving synergism and again many interactions between drugs by this mechanism can be used to therapeutic advantage, for example, propranolol may be used with hydrallazine in the treatment of hypertension. The hydrallazine produces vasodilatation while the propranolol prevents reflex tachycardia which would normally occur due to the vasodilatation. Thus there is a greater fall in blood pressure when the two drugs are used together (Guevara et al., 1977). Practolol (which is now used only as an i.v. injection in hospitalized patients) has been shown to be useful in combination with digoxin in the treatment of atrial fibrillation. Practolol induces significant decreases in ventricular rate and hence combination with other antiarrhythmic drugs, possessing a depressant action on atrioventricular conduction, may be used beneficially with digoxin in cases of tachyarrhythmic atrial fibrillation (Cargnelli et al., 1977).

(b) Chemotherapeutic agents

Synergism is very important in the chemotherapy of cancer and infections. In addition to the enhanced pharmacological effect, it is often possible to use smaller doses of the drugs so avoiding the toxicity with higher individual drug dosages. In cancer chemotherapy antisera may also be used together with drugs; bronchial carcinoma may respond better when antineoplastic agents are used together with tumor-specific immunoglobin (Newman et al., 1977). A synergistic effect was seen when fosfomycin was combined individually with 15 other antibiotics in differing strains of pathogenic organisms (Daza et al., 1977) while the use of antibiotic combinations improved the treatment of Gram-negative rod bacteraemia (Anderson et al., 1978). Antagonism between antibacterials can also occur; penicillins act by inhibition of bacterial cell wall synthesis and are ineffective if cell growth is prevented by, for example, chloramphemicol, tetracyclines or aminoglycosides.

(c) Centrally acting drugs

The CNS is often affected by pharmacodynamic-type interactions. Many drugs produce CNS depression either as a side-effect or as a therapeutic effect. Depression will therefore be increased if two such drugs are used in combination. Alcohol is important in this respect if taken with sedatives, antihistamines or antidepressants; for example, resid-

Fig. 5. Mean kinetic visual activity scores obtained in volunteers after alcohol alone on 3 successive days, and with or without alcohol on 3 successive days after a single dose of Mandrax. Mandrax was taken at 22.30 h on day 1. Sessions I, II and III refer to 17.30 h on each of the next 3 evenings. The tests were carried out 30 min after consumption of the alcohol (after Roden et al., 1977).

ual concentrations of methaqualone, 3 days after ingesting a therapeutic dose of Mandrax, enhanced the depressant action of alcohol (Roden et al., 1977). Four cases of self-poisoning in chronic alcoholics who were being treated for depression with chlormethiazole edisylate have been reported (Horder, 1977). The author suggested that the hazards of drinking alcohol while taking the drug should be stressed since its action was enhanced by alcohol.

(d) Oral anticoagulants

The action of the coumarin anticoagulants depends on a competitive interaction with vitamin K for the hepatic synthesis of various clotting factors. Dietary vitamin K should therefore be kept at a relatively constant level during anticoagulant therapy in order that a constant therapeutic effect is obtained. Vitamin K can be given to overcome the effects of anticoagulation due to coumarin overdosage.

As can be seen, however, from the few examples given to illustrate interactions of this type, the underlying mechanisms are predictable on the basis of known pharmacology and although serious in nature could be relatively easily prevented.

MISCELLANEOUS DRUG INTERACTIONS

There are a few types of drug interactions which do not fit well into the previous two groups of pharmacokinetic and pharmacodynamic interactions. These include those in which a drug may evoke a hypersensitivity reaction to radiation treatment and also those interactions in which a drug can interfere with drug assay results or upset the measurements obtained using biochemical tests.

TABLE 2

EFFECT OF IRRADIATION ON COMEDOGENICITY (AFTER MILLS ET AL., 1978).

Substances	Grades *									
	Non-irradiated					Irradiated				
	1	2	3	4	5	1	2	3	4	5
Rabbit										
Cocoa butter	2	2	2	2	2	3	3	3	3	3
1% coal tar	2	2	3	2	3	3	3	3	3	3
Human sebum	1	1	1	1	1	2	2	3	3	3
Noxzema skin cream	1	1	2	1	2	2	3	3	3	2
2% sulphur	2	2	2	2	2	3	3	3	3	3
Squalene	2	2	1	2	1	3	3	2	3	2
Hydrophilic ointment	0	0	0	0	0	0	0	0	0	0
Human										
15% coal tar	2	2	2	2	2	3	3	3	3	3
Noxzema skin cream	1	1	1	1	1	2	2	2	2	2
Squalene	1	2	1	1	1	2	2	2	1	2
Hydrophilic ointment	0	0	0	0	0	0	0	0	0	0

* Degree of comedo formation was assessed histologically on a 4 point scale: 0 = none; 1 = slight; 2 = moderate; and 3 = strong.

(a) Drugs and radiation

A report by Utley et al. (1977) described a 54-year-old woman who was receiving 200–600 mg of chloroquine daily; she then received radiation therapy and subsequently exhibited a severe radiation reaction, with chest wall necrosis. Experiments in rats by this reporting group have shown that the reaction to radiation was more severe in rats treated with chloroquine.

The use of combined drug treatment and ultraviolet radiation in the treatment of acne has increased over recent years. Problems again may arise due to the drug sensitizing the patient's skin to the radiation therapy, although it is more usual that the interaction between the drug and the radiation is beneficial. Mills et al. (1978) have shown, however, that ultraviolet radiation enhanced the comedogenicity of coal tar and squalene in man. Ultraviolet radiation also enhanced the capacity of human sebum, sulphur and cocoa butter to produce comedones in the external ear canals in rabbits, the conjecture being that in certain patients sunbathing may aggravate acne by augmenting the comedogenicity of sebum.

(b) Drug interference with assay results

Drugs which interfere with assay procedures, which are thought specific for the drug being measured, give rise to difficulties in the construction of dosage regimens for patients. Like all drug interactions these will be particularly important for a drug which has a narrow therapeutic range, for example, digoxin. Spironolactone and canrenoate

have been shown to give rise to falsely high digoxin plasma levels as measured by a commercially available [^{125}I]digoxin radioimmunoassay kit. Intravenous canrenoate potassium gave an immediate effect while the effects of spironolactone showed a continuing increasing influence for 5 days when the recorded digoxin value was increased by 81%. It was therefore concluded that canrenoate, spironolactone and its metabolites (which include canrenoate) were affecting the assay specificity (Lichy et al., 1977). This apparent increase in digoxin concentration may lead to therapeutic digoxin levels being mistaken for toxic levels. This would give rise eventually, after dosage adjustment, to digoxin undertreatment.

Interaction between various other drugs and the digoxin-'specific' radioimmunoassay may be an important reason why patients often do not respond well on the various dosage nomograms, as the patients' plasma level may have been incorrectly monitored. Johnston and McDevitt (1979) have, in fact, shown that none of the 6 prescribing aids which they investigated were more satisfactory than the physicians' intuitive choice in determining satisfactory digoxin dosage.

Various drugs have also been shown to interfere with the spectrophotometric procedure for the determination of theophylline (Banner et al., 1977); barbiturates, phenytoin and acetaminophen gave rise to falsely low values. Hydroxyzine and large doses of thiamine produced falsely high values while salicylates totally masked the spectrum. This means that undetectable levels may be found in patients with actual therapeutic blood levels or conversely therapeutic blood levels may be assayed when, in fact, they have reached a toxic level.

(c) Drug interference with biochemical tests

Drugs can also change laboratory biochemical analyses. An example worthy of note is in the estimation of alkaline phosphatase; indeed a table has been drawn up of drugs that decrease alkaline phosphatase measurement by interfering directly with the laboratory test procedure (Sher, 1977a). Failure to determine that a patient is using an oral contraceptive can also lead to numerous errors in evaluating and interpreting the results of laboratory tests. Plasma hormone levels particularly of cortisol and thyroxine may be affected (Fig. 6). Both increases and decreases in serum protein levels may be seen reflecting altered hepatic protein synthesis, while increases in serum cholesterol, triglycerides and total lipids can seriously complicate diagnosis and treatment of hyperlipidemias (Sher, 1977b).

Briggs (1976) has compiled a comprehensive table of the biochemical effects of oral contraceptives in women and further discussion on the subject is given by Harkness (1980). A comprehensive list of drug-induced modifications of laboratory test values has been compiled by Constantino and Kabat (1973).

CLINICAL IMPLICATIONS OF DRUG INTERACTIONS

Fortunately few drug interactions currently known are disabling or life-threatening and this is not really surprising since relatively few patients appear to die as a result of therapeutic endeavour, and most of those that do, have been treated with powerful drugs given to delay the progress of otherwise fatal disorders (Br. Med. J., 1977). Since drug

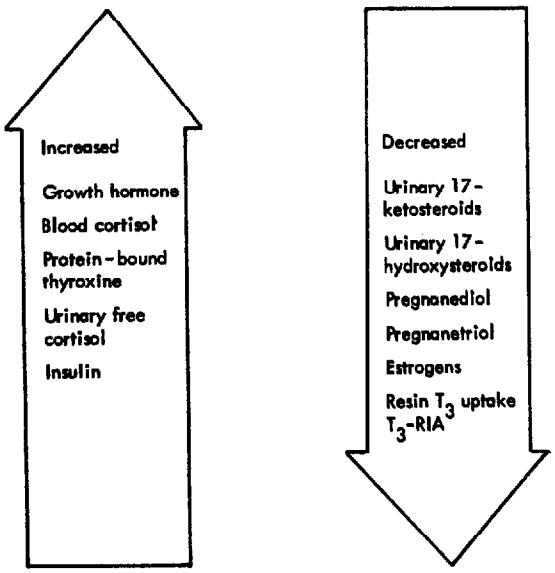

Fig. 6. Changes in concentration of hormones resulting from the use of oral contraceptives (after Sher, 1977b).

interactions are only one facet of the wider problem of adverse reactions to drugs, it is appropriate in this context to review in brief detail some of the recent findings on drug-induced fatalities.

Studies by the Boston group (Armstrong et al., 1976; Porter and Jick, 1977) and others in America (Caranasos et al., 1976; Irey, 1976) on medical or surgical in-patients have clearly shown that deaths associated with therapeutic drugs are uncommon and usually occur in the terminally ill. In particular, the study by Porter and Jick (1977) monitored more than 26,000 acutely ill patients in 7 countries and recorded 24 drug-related deaths. Most of the patients who died from drug therapy were suffering from severe terminal illness such as cancer, leukaemia, pulmonary embolism or cirrhosis. Viewed retrospectively (Br. Med. J., 1977) only 6 out of 24 deaths occurring in 26,500 consecutive patients could have been prevented, and in only 3 cases did death result from treatment of patients who were otherwise only mildly unhealthy.

Information on patients other than medical in-patients is admittedly sparse and only details from spontaneous reports to official agencies are available. Without doubt these official figures are an understatement of the true frequency of the hazard. Swedish data are probably the most reliable since in that country reports on adverse drug reactions are mandatory. The pattern of side-effects of therapy is similar in Sweden (Böttiger et al., 1974) to that in the United Kingdom (Girdwood, 1974) and haematological, thrombo-embolic and anaphylactic events account for most drug-related deaths in out-patients.

Sparse as available data are, they do none-the-less indicate that life-threatening emergencies due to therapeutic drugs are relatively rare. Since most epidemiological surveys would have included drug interactions within adverse drug reactions, it may thus be logical to conclude, at least on the basis of evidence currently at hand, that relatively

few drug interactions cause fatalities although there is of course no way of assessing the life-threatening emergencies that have been near misses. It is salutary with such observations to quote Ballin (1974) who commented that there will always be an irreducible minimum number of people who get 'ill' from drugs.

Assessments of the proportion of adverse drug reactions attributable to drug interactions vary. In the early days of the Boston Collaborative Drug Surveillance Program, Borda et al., (1968) reported 405 (48.8%) adverse reactions in 830 patients of which 22% were thought to be due to a drug interaction. In 1972 (BCDSP, 1972), these Program workers re-examined their data on 9900 monitored patients; there were 3600 (36.4%) adverse reactions of which 6.9% were attributed to a drug interaction. This lower frequency to that previously reported was thought to be due to the fact that all of the 9 hospitals added to the group study since the initial report had been acute diseases hospitals.

Emphasis has been given by other groups to qualitative rather than quantitative aspects of drug interaction and attempts have been made to pinpoint those areas of prescribing in which drug interactions are most likely to cause dangerous results (Pearson and Harvard, 1974; Crooks et al., 1977; Koch-Weser and Greenblatt, 1977).

As a result therefore of exhaustive research, many clinically important drug interactions have come to light and the effects of drugs within a new situation are becoming more predictable. If polypharmacy must be used in a patient either because of different disease processes within the patient or to treat different symptoms of the same disease, untoward consequences of using several drugs simultaneously are generally preventable primarily by making appropriate dosage adjustments (Koch-Weser and Greenblatt, 1977). The clinical problems caused by drug interactions has perhaps been over-estimated, especially in cases where reactions are considered only as a direct result of animal studies. Extrapolation of such data to the clinical situation must be made with extreme caution. This is especially true in the case of metabolism experiments in animals as there are often profound differences between species in the metabolic fate of many drugs. This means that many pharmacokinetic drug interactions which can be demonstrated in animals may be of no clinical relevance in man (Conney et al., 1972).

The occurrence of adverse drug interactions is of prime importance to the clinician when they influence the effectiveness or safety of drug therapy. The criteria which decide whether a drug will fall into this category do not depend only on the intensity of the interaction but also, and more importantly on the slope of the dose–response curves, the therapeutic ratios of the interacting substances (Koch-Weser and Greenblatt, 1977) and the *milieu* (drug–disease environment) of the patient. The slope of the dose–response curve must be relatively steep for an intensive interaction to occur. In such a case a small change in plasma drug concentration will give rise to a marked change in pharmacological response. Similarly for a clinically hazardous drug interaction to occur the therapeutic index of the drug should be narrow. A small change in plasma concentration will then mean that the drug no longer lies within the therapeutic range resulting in either under-treatment of disease symptoms or overactivity of the medicament, giving rise to toxicity.

Few drugs satisfy these criteria but important examples do exist. These include oral anticoagulants, cardiac glycosides, antiarrhythmics, sympathomimetic amines, certain antihypertensives, anticonvulsants, oral hypoglycaemics and cytotoxic drugs. Drug inter-

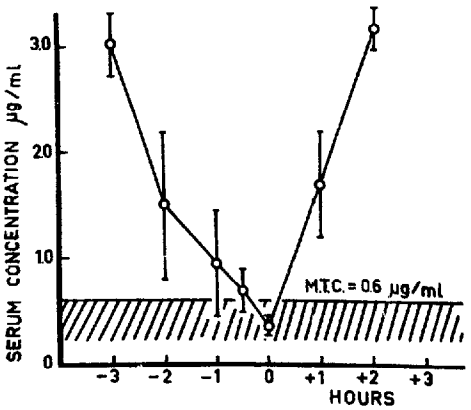

Fig. 7. Graphic presentation of the iron tetracycline interaction. Ordinate: mean serum concentration 3 h after a single dose of 500 mg tetracycline. Abscissa: interval between intake of tetracycline and 600 mg ferrous sulphate (left side, iron taken before; right side, iron taken after tetracycline; after Gothoni et al., 1972).

actions involving these drugs may be disabling or indeed life-threatening, giving rise to haemorrhages, cardiac arrhythmias, severe hypo- or hypertension convulsive seizures or hypoglycaemia.

Other drug interactions involving other drug categories will fall into second rank behind the above groups of drugs and the interactions experienced will be of a lesser magnitude. This does not, however, detract from their importance. An example is the interaction between tetracyclines and iron in which absorption of the antibiotic was decreased and tetracycline plasma levels fell by 50% and, even more importantly, in the case of doxycycline by 80–90% (Neuvonen et al., 1970). The serum levels of the antibiotics fell in that study to levels usually accepted as being below their minimum inhibitory concentration. This decreased effect may not be as life-threatening as hypertensive or haemorrhagic complications, however, to ignore such interactions would be sheer folly. Further studies (Gothoni et al., 1972) with tetracyclines have shown that the interaction did not occur if the ferrous sulphate was taken 3 h before or 2–3 h after the tetracycline (Fig. 7). Such data clearly demonstrate that when a drug interaction is identified (and the mechanism elucidated) the interaction may be avoided in the clinic. All interaction data must therefore be treated critically if real progress is to be made.

Physicians and pharmacists, both in hospitals and in general practice, should make it their duty to familiarize themselves with drug interactions involving drugs which they commonly prescribe or dispense and then either attempt to avoid or indeed overcome possible adverse consequences. Out-patients should also be counselled on the dangers of self-medication with certain proprietary medicines which may upset the clinical outcome of their prescribed treatment. Such an approach should surely decrease further the incidence of adverse drug interaction in both the hospital setting and in the community.

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