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Safer Prescribing

A Guide to some problems in the use of drugs

Second edition

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a guide to some problems in the use of drugs

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Contents

Drug interactions

Drug interactions are of two kinds:
1 Pharmacodynamic interactions occur between drugs which compete for the same receptor site or act on the same physiological system. They can also occur indirectly when a drug-induced disease or change in fluid or electrolyte balance alters the response to another drug.
2 Pharmacokinetic interactions occur when one drug alters the absorption, distribution or elimination of another drug such that the amount which reaches the site of action is increased or decreased.

It is generally true that pharmacodynamic interactions demonstrated with one drug should be anticipated with related drugs. Pharmacokinetic interactions, on the other hand, cannot be extrapolated to combinations of pharmacologically related drugs unless the pharmacokinetics are known to be similar.

From the therapeutic point of view the result of a drug interaction can be harmful, unimportant or useful. The following tables list those interactions which have been shown to be or are potentially harmful in man during normal clinical use of the drugs concerned. They are not intended to be comprehensive lists of all possible interactions and therapeutically useful interactions are not included.

In most of the tables the drug whose action is affected is listed in column 1 and drugs are arranged by body system or pharmacological group, as seemed most appropriate. Column 2 lists the drugs which interact with the primary drug, and column 3 states the mechanism and result of the interaction.

Because only the drug affected appears in column 1, when using the tables to check whether any interaction is likely to occur between drugs prescribed for a patient each drug must be looked for in column 1 and the presence of the others sought in column 2.

The table of drug interactions with alcohol differs from the others as it contains all drug–alcohol interactions regardless of whether it is the effect of the drug or the effect of alcohol which alters.

CARDIOVASCULAR SYSTEM

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
Cardiac glycosides, digoxin, digitoxin, medigoxin, etc.	Diuretics: thiazides frusemide bumetanide ethacrynic acid	Toxicity increased by hypokalaemia.
	Carbenoxolone Amphotericin B	
	Cholestyramine	Reduced absorption of digitoxin.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
	Antacids	Have been shown to reduce the absorption of digoxin. Clinical importance not known.
	Phenobarbitone Phenytoin Phenylbutazone	Reduced effect of digitoxin due to increased metabolism.
Lignocaine	Phenytoin Quinidine	Sino-atrial arrest.
Mexiletine	Narcotic analgesics	Delayed absorption. Can be overcome by giving a larger (oral) loading dose of mexiletine.
Verapamil	Beta-blockers	Increased risk of asystole.
Beta-blockers	Prenylamine	Increased negative inotropic effect. Prenylamine produces catecholamine depletion in the myocardium.
	Ergotamine	Increased peripheral vasoconstriction. Raynaud's Phenomenon may occur.
Nitrates	Antihypertensive drugs Alcohol	Increased postural hypotension.
Antihypertensive drugs		
All	Anti-inflammatory analgesics e.g. phenylbutazone, indomethacin	Hypotensive effect antagonised by drugs causing fluid retention or hypertension.
	Carbenoxolone Corticosteroids, ACTH Oral contraceptives	

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
	Alcohol Sedatives and hypnotics	Potentiation. These drugs all produce hypotension as a side effect.
	Tranquillisers Antidepressants (but see below)	
	L-dopa Fenfluramine Nitrates	
Guanethidine Bethanidine Debrisoquine	Tricyclic antidepressants Indirect sympathomimetic amines e.g. amphetamines phenylpropanolamine (present in proprietary common cold remedies)	Antagonism. Neuronal uptake to site of action is prevented.
	Chlorpromazine (large doses)	May occasionally antagonise hypotensive effect.
Clonidine	Tricyclic antidepressants	Antagonism. Probably a central effect.
	Beta-blockers	May potentiate withdrawal hypertension. When changing from clonidine to a beta-blocker several days should be left between stopping clonidine and starting the beta-blocker.
Vasoconstrictors		
Noradrenaline Adrenaline	Tricyclic antidepressants	Potentiation due to inhibition of neuronal uptake. Hypertension, tachycardia, arrhythmias may occur.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
	Guanethidine Reserpine	Potentiation due to increased receptor sensitivity ("denervation supersensitivity").
Metaraminol Phenylephrine	Guanethidine Reserpine Debrisoquine	Potentiation of direct vasoconstrictor effect. Hypertension may occur. N.B. Phenylephrine is present in many proprietary common cold remedies.
Diuretics		
Thiazides Frusemide Bumetanide Ethacrynic acid	Corticosteroids, ACTH Carbenoxolone	Increased urinary potassium loss
	Anti-inflammatory analgesics, e.g. phenylbutazone indomethacin Carbenoxolone Oestrogens Corticosteroids, ACTH	Diuretic effect antagonised by fluid retention.
Thiazides	Cholestyramine	Reduced absorption. Avoided by giving them at least 2 hours apart.
Spironolactone	Aspirin	Inhibition of natriuretic effect—mechanism unknown.
ORAL ANTICOAGULANTS		
Coumarins		
Warfarin Ethylbiscoumacetate Nicoumalone	Cholestyramine	Cholestyramine interferes with the absorption of warfarin and of vitamin K. Either inhibition or potentiation is possible.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
	Barbiturates Primidone Dichloralphenazone Glutethimide Methaqualone Phenytoin Carbamazepine Rifampicin Griseofulvin	Reduced anticoagulant effect due to increased metabolism. Overdose and bleeding may occur when interacting drug is stopped.
	Chloramphenicol Metronidazole Alcohol (acute intoxication) ? Allopurinol	Increased effect due to inhibition of coumarin metabolism.
	Distalgesic	Recent reports suggest that potentiation may occasionally occur. Dextropropoxyphene inhibits the metabolism of warfarin.
	Co-trimoxazole and possible other sulphonamides	Increased effect. Probably due partly to inhibition of metabolism and partly to displacement from protein binding.
	Azapropazone	Potentiation has been reported.
	Phenylbutazone, oxyphenbutazone	Increased effect due to inhibition of metabolism and displacement from protein binding. Serious risk of haemorrhage.
	Mefenamic acid Chloral hydrate, triclofos Nalidixic acid	Displacement from protein-binding occurs but the increased effect is transient and will usually be unimportant.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
	Clofibrate	Increased effect. Mechanism not established but evidence suggests an interaction at the receptor site.
	Anabolic steroids e.g. oxymetholone, norethandrolone, ethyloestranol, stanozolol	Increased effect—possibly due to decreased receptor affinity for vitamin K.
	Neomycin	Increased effect due to impaired absorption of vitamin K—probably secondary to steatorrhoea.
	Oral broad spectrum antibiotics	They are said to potentiate anticoagulants by reducing bacterial synthesis of vitamin K, but significant vitamin K deficiency is very unlikely to occur unless dietary vitamin K is also reduced and treatment is continued for many weeks.
	Aspirin Dipyridamole	Increased risk of bleeding due to antiplatelet effect. A single dose of aspirin can prolong the bleeding time for up to 5 days, and large doses also have a hypoprothrombinaemic effect.
	Oral contraceptives	Reduced effect due to increased synthesis of vitamin K-dependent clotting factors.
	Vitamin K	Reversal of anticoagulant effect due to competitive inhibition.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
		N.B. Some proprietary chilblain preparations contain sufficient vitamin K to inhibit oral anti-coagulants (e.g. Pernivit, Amisyn.

Indanediones—Phenindione

The indanedione anticoagulants do not appear to share all the interactions of coumarins. They can be expected to interact in the same way as the coumarins with the following drugs:

Clofibrate
Anabolic steroids
Neomycin
Aspirin
Dipyridamole
Oral contraceptives
Preparations containing vitamin K

ANALGESICS AND DRUGS USED IN ARTHRITIS AND GOUT

Aspirin	Alcohol	Increased risk of gastro-intestinal bleeding.
	Metoclopramide	Increased rate of absorption. Higher blood levels.
Paracetamol	Metoclopramide	Increased rate of absorption. Higher blood levels.
	Cholestyramine	Reduced absorption.
	"Enzyme inducers" e.g. barbiturates chronic alcoholism	Increased risk of hepatotoxicity after paracetamol overdose.
Indomethacin	Probenecid	Reduced excretion and higher blood levels of indomethacin. May increase therapeutic and side effects.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
Phenylbutazone	Cholestyramine	Reduced absorption of phenylbutazone
Penicillamine	Oral iron	Reduced absorption of penicillamine. Give at least 3 hours apart.
Probenecid Sulphinpyrazone	Aspirin	Inhibition of uricosuric effect. In a dose of less than 2 g daily aspirin also causes uric acid retention.

CENTRAL NERVOUS SYSTEM

Hypnotics and sedatives

Barbiturates Other hypnotics Benzodiazepines e.g. nitrazepam flurazepam diazepam chlordiazepoxide	Alcohol Narcotic analgesics Antihistamines Tranquillisers Antidepressants	Increased CNS depression.

Major Tranquillisers

Phenothiazines Haloperidol	Metoclopramide	Risk of increased extra-pyramidal side effects.
Chlorpromazine	Aluminium hydroxide Magnesium trisilicate	Absorption of chlorpromazine is significantly reduced. Clinical importance unknown.

Antidepressants

Tricyclic antidepressants e.g. imipramine amitriptyline	Barbiturates	Increased metabolism and reduced blood levels. Clinical importance unknown.
	Alcohol	Potentiation of sedative effect, especially during first few days of treatment.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
Monoamine oxidase inhibitors e.g. tranylcypromine phenelzine N.B. interactions can occur up to 2 weeks after stopping MAOI	Food containing tyramine or dopamine e.g. cheese, bovril	Hypertensive crisis – severe headache – risk of cerebral haemorrhage.
	Indirect sympathomimetic amines: amphetamine ephedrine phenylpropanolamine phenylephrine metaraminol	
	L-dopa	
	Tricyclic antidepressants	CNS excitation, hypertension, and convulsions.
	Pethidine (and possibly other narcotics	CNS excitation, hypertension or hypotension, coma.
	Reserpine	CNS excitation and hypertension.
Lithium carbonate	Sodium bicarbonate Acetazolamide Aminophylline	Increased excretion of lithium. Clinical importance unknown.
	Sodium chloride	Large doses increase lithium excretion and reduce blood levels. Sodium depletion increases lithium toxicity.
	Diuretics	Increased risk of toxicity due to sodium depletion. Lithium excretion is reduced in patients on long-term thiazides.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
Anticonvulsants		
All	Phenothiazines Tricyclic anti-depressants	Antagonism—these drugs lower the convulsive threshold.
	Methotrexate Co-trimoxazole Pyrimethamine Oral contraceptives	Potentiation of folate deficiency is a theoretical possibility.
Phenytoin	Isoniazid Sulthiame Dicoumarol Chloramphenicol Pheneturide Sulphaphenazole Disulfiram	Potentiation and increased toxicity due to inhibition of phenytoin metabolism.
	Diazepam	Increased blood levels and phenytoin toxicity have been reported.
	Phenobarbitone Carbamazepine Chronic alcoholism	Increased phenytoin metabolism. Clinical importance probably small.
	Phenylbutazone Tolbutamide Aspirin Sodium valproate	Displace phenytoin from protein binding. Potentiation will usually be transient but toxicity has been reported.
Phenobarbitone Primidone	Phenytoin Pheneturide Sodium valproate	Inhibition of phenobarbitone metabolism. Increased blood levels of phenobarbitone and increased sedation.
Carbamazepine	Phenobarbitone Phenytoin	Increased metabolism and lower blood levels of carbamazepine. Clinical importance probably small.

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
Drugs used in Parkinsonism		
Anticholinergic drugs e.g. benzhexol orphenadrine benztropine	Tricyclic anti-depressants Phenothiazines Monoamine oxidase inhibitors Antihistamines	Increased anticholinergic side effects—dry mouth, blurred vision, urinary retention, constipation.
	Tricyclic anti-depressants Monoamine oxidase inhibitors Amantadine	Excitement, confusion and hallucinations—additive central anticholinergic effects.
L-dopa	Phenothiazines Reserpine Haloperidol Methyldopa	Antagonism. These drugs have extrapyramidal side effects.
	Benzodiazepines	Deterioration has been reported in patients on l-dopa who were given diazepam or chlordiazepoxide.
	Metoclopramide	Increased absorption and higher blood levels of l-dopa. Metoclopramide can produce extrapyramidal effects but does not seem to antagonise the effect of l-dopa.
	Anticholinergic drugs e.g. propantheline benzhexol benztropine	Reduced absorption and lower blood levels of l-dopa. Clinical importance unknown.
	Pyridoxine (present in many proprietary multi-vitamin preparations and in Optimax)	Antagonism. Probably due to increased peripheral metabolism of l-dopa. (Pyridoxine has no effect if a dopa decarboxylase inhibitor e.g. carbidopa is used.)

DRUGS AFFECTED	DRUGS WHICH INTERACT	RESULT OF INTERACTION
DRUGS USED IN ANAESTHESIA		
Anaesthetics		
All	Antihypertensive drugs	Potentiation of hypotensive effect.
	Beta-blockers, e.g. propranolol oxprenolol	Potentiation of hypotensive effect. Loss of compensatory reflex tachycardia.
	Chlorpromazine	Potentiation of hypotensive effect. Vasopressors ineffective because chlorpromazine blocks α-receptors.
Halothane Cyclopropane Trichlorethylene (Methoxyflurane)	Adrenaline Isoprenaline	These anaesthetics increase the sensitivity of the myocardium to sympathomimetic amines. Cardiac arrhythmias may occur.
	L-dopa	Increased risk of cardiac arrhythmias due to dopamine. L-dopa should be stopped 12 hours before surgery.
Methoxyflurane	Tetracyclines	Increased risk of polyuric renal failure.
Muscle relaxants		
All	Colistin, Polymixin B Quinidine Propranolol (large doses)	Increased or prolonged paralysis. These drugs have neuromuscular blocking activity. Not reversed by neostigmine.
Competitive neuromuscular blockers tubocurarine gallamine pancuronium	Aminoglycoside antibiotics Magnesium salts	Increased neuromuscular block. Partially reversed by neostigmine and calcium.