MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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DRUG INTERACTIONS IN CLINICAL MEDICINE

I. HYPNOTICS AND SEDATIVES:

A. A number of sedatives have been shown to induce hepatic drug-metabolizing enzymes and thereby to stimulate the metabolism of other drugs. Relatively well documented examples in man include:

Inducer	Stimulates metabolism of
Phenobarbital, 60-120 mg/day (3,4,5,10) Heptabarbital, 400 mg/day (1) Butabarbital, 60-120 mg/day (9) Glutethimide (Doriden), 1 g (8) Chloral hydrate, 0.5 g (6) Chloral betaine, 1.7 g (8) Ethchlorvynol (Placidyl), 0.5 g (7)	Bishydroxycoumarin (Dicumarol) (1,3,4,6) Biscoumacetate (Tromexan) (1) Warfarin (Coumadin) (5,7,8,9,10) Phenprocouman (Liquamar) (9)
Phenobarbital, 120 mg/day (3)	Diphenylhydantoin (Dilantin) (3)
Phenobarbital, 90 mg/day (2)	Griseofulvin (2)

B. Animal studies indicate that the following compounds may also stimulate drug metabolism: barbital, carisoprodol (Soma), chlorbutanol, meprobamate, orphenadrine (Norflex), pentobarbital, and thiopental.

Drugs metabolized more rapidly after pretreatment with these compounds include the following: aminopyrine, carisoprodol (Soma), meprobamate, phenylbutazone (Butazolidin), coumarin anticoagulants, and pentobarbital. The insecticides chlordane and DDT also stimulate the metabolism of barbiturates, anticoagulants, and phenylbutazone in animals. The many possibilities suggested by these studies have not yet been tested critically in man.

C. Secobarbital used as a sedative in a dose of 100 mg at bedtime probably does not interfere with anticoagulant therapy (6).

II. ANTICOAGULANTS:

A. Rates of metabolism and therefore dosage requirements of the coumarin anticoagulants are increased by the sedatives listed above.

B. The following drugs are also said to increase the dosage requirement for anticoagulants (mechanism unidentified):
Haloperidol (Haldol) (16)
Griseofulvin (19)

C. A number of drugs potentiate the effect of coumarin anticoagulants and therefore decrease the dosage requirements for anticoagulants. This may result from one of several mechanisms (all examples documented in man):
1. Drugs which compete with coumarin anticoagulants for binding sites on plasma proteins and thereby increase the plasma concentration of free anticoagulant:
Clofibrate (Atromid-S), 2 g/day (11, 14, 22, 24)
Phenylbutazone (Butazolidin), 400-600 mg/day (21,24, 26)
Oxyphenbutazone (Tandearil), 400 mg/day (17)
(Part of the antiprothrombinemic effect of salicylates may be via this mechanism.)

2. Drugs which inhibit the metabolism of both coumarin anticoagulants and phenindione:
   Phenyramidol (Analexin), 0.8-1.6 g/day (18,20,24).

3. Drugs which increase the effect of coumadin anticoagulants but alter neither the metabolism nor the binding of the anticoagulant -- postulated interaction at receptor site:
   Norethandrolone (Nilevar), 10 mg/day (22)
   Methandrostenolone (Dianabol), 10 mg/day (15)
   d-Thyroxin, 4 mg/day (13,22,23,24).

4. Drugs with intrinsic hypoprothrombinemic activity sufficient to produce bleeding when given to patients on a stable dose of anticoagulant:
   Salicylates, 3-6 g/day (12)
   Quinidine, 0.8-1.2 g/day (25)

D. Bishydroxycoumarin has been reported to prolong the half-life of diphenylhydantoin (27) and of tolbutamide (28).

E. Phenindione does not alter the metabolism of diphenylhydantoin or tolbutamide (27,28), and it is said that phenobarbital does not alter the metabolism of phenindione (29); but these advantages do not offset the serious hypersensitivity reactions (skin, liver, and kidney) produced by phenindione (11).

III. ANTICONVULSANTS:

A. The rate of metabolism of diphenylhydantoin is increased by phenobarbital, 120 mg/day (3).

B. Metabolism of diphenylhydantoin is inhibited by bishydroxycoumarin (26) and by disulfiram (Antabuse), 400 mg/day (29). Disulfiram does not inhibit the metabolism of phenobarbital (30).

IV. ORAL HYPOGLYCEMIC DRUGS:

A. The hypoglycemic effect of tolbutamide (Orinase) is increased by bishydroxycoumarin (28), phenylbutazone (32), and sulphaphenazole (32), an antibacterial agent not marketed in the U.S. This is due to inhibition of the metabolism of tolbutamide (28,32) and, in the case of phenylbutazone and sulphaphenazole, also to displacement of tolbutamide from serum proteins (32).

B. The blood level and hypoglycemic effect of chlorpropamide (Diabinese), and possibly also of tolbutamide, are enhanced by large doses of aspirin (6 g/day) (31); the mechanism is not identified.

C. Phenylbutazone, 400 mg/day, increases the hypoglycemic effect of acetohexamide (Dymelor) by an unusual mechanism. The conversion of acetohexamide to hydroxyhexamide is not impaired; however, this metabolite is a biologically active hypoglycemic agent and its excretion is impaired by phenylbutazone (33).

V. ANALGESICS AND ANTIINFLAMMATORY DRUGS:

A. Phenylbutazone (Butazolidin), 400-800 mg/day, increases the rate of metabolism of aminopyrine in man (34). In animals phenylbutazone stimulates the metabolism of a number of compounds: aminopyrine, phenylbutazone, hexobarbital, meprobamate, carisoprodol, and zoxazolamine (57, 59, 64).

B. Phenylbutazone, 400-800 mg/day, potentiates the actions of tolbutamide (32) and of coumarin anticoagulants (21,26) by competing for binding sites on plasma protein and by inhibiting their metabolism. Oxyphenbutazone (Tandearil), 400 mg/day, will probably do the same thing (17).

C. Phenylbutazone potentiates the effect of acetohexamide by a different mechanism (see IV C above).

VI. SULFONAMIDES:

A. Certain acidic drugs are highly bound to plasma proteins and compete with each other for binding sites; these include phenylbutazone analogues, coumarin anticoagulants, tolbutamide, salicylates, penicillin, and the sulfonamide antibacterials. These drugs potentiate each others' actions, since the administration of any one in the group will increase the concentration of free drug molecules of any other in the group already in the body. (17, 21, 24, 26, 28, 32, 36, 37, 38, 56, 61)

B. Sulfonamide antibacterials and salicylates (and probably the whole above group) compete with bilirubin for binding sites on plasma protein (36-38, 56). Sulfonamides increase the incidence of kernicterus in newborns (35) by this mechanism (36).

C. Acidic drugs which do not compete with the above group include barbiturates, probenecid (Benemid), and phenyramidol (24, 56).

VII. MONOAMINE OXIDASE INHIBITORS:

A. The MAO inhibitors pargyline (Eutonyl), isocarboxazid (Marplan), nialamide (Niamid), phenelzine (Nardil), and tranylcypromine (Parnate) all increase the norepinephrine content of adrenergic nerve endings and inhibit MAO in the liver, kidney, and intestinal mucosa. The pressor action of some sympathomimetic amines is potentiated by the following mechanisms:

1. Tyramine, dopamine, phenylephrine (Neosynephrine), phenylpropanolamine (Propadrine) and phenylpropylmethylamine (Vonedrine) act, to greater or lesser degrees, by releasing endogenous norepinephrine from nerve endings and also are substrates of MAO. These compounds are potentiated many-fold by MAO inhibitors, especially when given orally (39, 51, 55, 58). Major sources of these agents include wine, yeast products, nose drops, cheese, and proprietary cold remedies (42, 45-48, 51).

2. Amphetamine, methamphetamine, and ephedrine all act in part by releasing endogenous norepinephrine, but they are not substrates of MAO. Potentiation of these drugs by MAO inhibitors is less pronounced than with the above agents, but deaths have been reported (41, 51, 55, 58). Metaraminol (Aramine) and mephentermine (Vasoxyl) are also in this group and in theory carry the same hazard.

3. The MAO inhibitors tranylcypromine and phenelzine, and the CNS stimulant methylphenidate (Ritalin), while not sympathomimetic amines, can release norepinephrine from nerve endings. Hypertensive reactions and deaths from these agents have been reported (44, 55, 58).

4. Norepinephrine (Levophed), epinephrine, and isoproterenol (Isuprel) act directly on adrenergic receptors, and MAO does not participate significantly in terminating their pharmacological effects. MAO inhibitors potentiate these drugs only slightly (39, 51, 55).

B. The combined use of tranylcypromine or phenelzine with tricyclic antidepressants such as imipramine (Tofranil) or amitryptyline (Elavil) has produced in sporadic instances severe reactions characterized by excitation, sweating, hyperpyrexia, delirium, and convulsions (43, 55, 58). The mechanism is obscure.

C. The effect of meperidine may be prolonged in patients treated with MAO inhibitors; hypotension, hyperpyrexia, and shock may occur (49, 55, 58). The mechanism is not identified.

D. Reactions to the following drugs have been reported in patients on MAO inhibitors: barbiturates, droperidol, phenothiazines, methyldopa, reserpine, anti-parkinson drugs, and insulin (40, 50, 55, 58).

VIII. GUANETHIDINE:

A. The hypotensive action of guanethidine may be reversed by the acute oral administration of non-pressor doses of the following drugs (53):

d-amphetamine, 10 mg
methylphenidate (Ritalin), 20 mg
ephedrine, 90 mg
nialamide, 50 mg

B. The effect of guanethidine can also be reversed by the chronic oral administration of the following:

imipramine (Tofranil), 75 mg/day (52)
desipramine (Pertofrane), 50-75 mg/day (54)
protryptyline (Vivactil), 20 mg/day (54)
(probably any tricyclic antidepressant)

C. Reversal of the effect of guanethidine by these drugs is probably due to inhibition of the uptake and/or binding of guanethidine by adrenergic nerve endings. The side effects, as well as the hypotensive action, of guanethidine are reversed (52, 53).

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