Drug Interactions With Psychoactive Drugs

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Introduction

In 1970 more than 219 million prescriptions were filled in American drug stores for psychoactive drugs. They accounted for 17 percent of all prescriptions filled that year. In most instances the psychoactive medication was prescribed in combination with other non-psychoactive drugs. The extensive use of psychoactive drugs — especially in drug combinations — can be explained only in part by the rather high prevalence rate of psychiatric disorders in the general population, and the fact that physical illness, which requires pharmacological intervention, frequently occurs in the course of psychiatric disease. Probably more important is that psychopathological manifestations which can be symptomatically controlled by psychoactive medication are often present in physical illness (Ban 1973). As a result there is an increasing number of drug interaction manifested, mostly in adverse, but occasionally also in desirable clinical effects.

Drug interaction is commonly defined as modification of the action of a drug by another exogenous chemical (usually referred to as "interactant"), regardless whether the modification of the action produces beneficial or adverse effects. It is present in infra- and supra-addition, but not in simple summation in which the combined effects of two or more drugs are equal to the sum of the individual effects produced when the component drugs are administered alone (Martin 1971).

Mechanisms of Drug Interactions

It has been recognized that in drug interactions with psychoactive drugs one or more of the following four mechanisms are involved: Alteration of absorption, modification of action at receptor sites, modification of biotransformation and alteration of excretion.

Alteration of Absorption

Although the principles involved in the various drug interactions are simple, species differences and the disease — diet — drug interplay modify the results of multiple drug regimens, and therefore findings in animal experiments cannot be applied directly to man. Nevertheless, it would appear that antacids and oral resins may modify the effect, by altering the absorption of psychoactive drugs. Thus, the frequently used alkalis for the treatment of indigestion, e.g. aluminum hydroxyde gel (Amphojel) and the increasingly employed ion exchange resins, e.g. cholestyramine (Questran) for the treatment of hypercholesterolemia, by impairing the absorption of antipsychotic and antidepressant drugs, may call for an adjustment in the dosage of the concommitantly administered psychoactive drug to prevent relapse in the course of maintenance treatment (Rosenoer and Gill 1972).

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Modification of Action at Receptor Sites

It has been established that norepinephrine (NE) is synthesized in the terminals of adrenergic neurons, stored there in minute vesicles and inactivated intracellularly by oxidative deamination — the enzyme responsible for this reaction is monoamine oxidase (MAO) — to form vanylmandelic acid (VMA). When NE is released by a stimulus to the adrenergic neurons, however, the freed NE is inactivated only in part by O-methylation — the enzyme responsible for this reaction is catechol-O-methyl transferase — to form normetanephrine, while in another part it is inactivated by reuptake into the neuron. Since the binding of the freed NE to postsynaptic NE receptor sites results in elevation of blood pressure, combined administration of an MAOI antidepressant (antihypertensive agent) or tricyclic antidepressant with an NE releaser, via rendering more NE available at postsynaptic NE receptor sites by either interfering with its intracellular catabolism (MAOIs) or interfering with its reuptake into the neuron (tricyclics), may result in "hypertensive episodes." Among the most frequently encountered MAOIs in this reaction are phenelzine (Nardil), pargyline (Eutonyl) and tranylcypromine (Parnate); among the most frequently encountered tricyclic antidepressants in this reaction are desipramine (Pertofrane), nortriptyline (Aventyl) and protriptyline (Triptil) (since the secondary amines have greater specificity to noradrenergic neurons than the tertiary amines) and among the most frequently encountered NE releasers in this reaction are the salicylates (e.g. acetylsalicyclic acid — Aspirin), tyramine (e.g. food staff such as cheese, beer, Chianti wine, pickled herring, snail), Rauwolfia alkaloid (e.g. reserpine — Serpasil) and amphetamine and its congeners (e.g. phenylpropanolamine — Propadrine) and other sympathomimetics (frequently present in decongestants and in other over-the-counter cold preparations). Since after the combined administration of an MAOI antidepressant (or antihypertensive agent) with tyramine, neither the releaser of NE (i.e. tyramine) nor the intraneuronal NE is inactivated, "hypertensive crisis"

may occur (Azarnoff and Hurwitz 1970). Nevertheless, while a proprietary cough remedy containing a small dose of phenylpropanolamine (Propadrine) caused a rapid and potentially dangerous rise in blood pressure, in a patient receiving an MAOI, an obviously adverse drug interaction, the combined administration of an MAOI and cheddar cheese (i.e. tyramine) was successfully used in the treatment of severe, therapy refractory, orthostatic hypotension. Similarly, while the addition of acetylsalicyclic acid (Aspirin), reserpine (Serpasil), or an MAOI to tricyclic antidepressant treatment may infrequently give rise to central adrenergic signs, including hypertension (with a possible fatal outcome), more frequently the same preparation produces a potentiation of the mood lifting effect of the psychoactive drug.

It has been recognized that various psychoactive drugs including tricyclic antidepressants and neuroleptic antipsychotic agents (i.e. phenothiazines, thioxanthenes or butyrophenones) block the activity of the adrenergic membrane transport system. Accordingly, they not only interfere with the reuptake of NE into the storage vesicles but also with the reuptake of guanethidine (Ismelin) and its congeners such as bethanidine (Esbaloid) and debrisoquine (Declinax). Since guanethidine (Ismelin) and its congeners exert their antihypertensive effect via accumulation within the adrenergic neuron by inhibiting the release of NE from the storage vesicles, a slow reversal of the hypotensive effect occurs if a tricyclic antidepresasant or a neuroleptic antipsychotic drug is added to the treatment regime. The same also explains that while hypotensive shock may follow the withdrawal of tricyclic antidepressant or neuroleptic drugs in the course of treatment with guanethidine (Ismelin), the addition of guanethidine (Ismelin) or its congeners to tricyclic antidepressant or neuroleptic treatment remains without any measurable blood pressure change.

Modification of Biotransformation

Alteration of biotransformation by one drug of another includes both enzyme induction and inhibition. In this context it is of practical importance that alcohol accelerates, via enzyme induction, the metabolism, and consequently diminishes the activity of numerous widely used drugs. Because of this, pharmacotherapy of alcoholics — irrespective of the condition — presents special problems. The same applies to the sedative barbiturates and to the anxiolytic benzodiazepines and propanediols. Among the barbiturates, phenobarbital (Luminal) alone has been shown to stimulate more than 60 chemicals including the phenothiazines, digitoxin (Digoxin) and diphenylhydantoin (Dilantin). This explains, that addition of phenobarbital (Luminal) to phenothiazine treatment lowers blood level — and consequently the clinical effect, including sedation — of the phenothiazine (Curry et al 1970). It also explains the need for an increase of the dosage of digitoxin (Digoxin) and/or diphenylhydantoin (Dilantin) when phenobarbital (Luminal) (also diazepam — Valium) is added to the treatment. Furthermore, since phenobarbital (Luminal) (also meprobamate — Equanil) induces not only the metabolism of cortisol, but also that of androgens, estrogens and progesterone, the possibility of an interference (i.e. decrease of effectiveness) with oral contraceptives was raised (Conney 1969). Finally, since phenobarbital (Luminal) (also ethchlorvynol — Placidyl and meprobamate — Equanil) induce the metabolism of oral anticoagulants, discontinuation of administration of any of these drugs in the course of anticoagulant treatment may lead to severe bleeding episodes (Macdonald and Robinson 1968).

Self-induction refers to a special form of enzyme induction, i.e. when a drug stimulates its own metabolism. It may explain the tolerance which develops to barbiturates, glutethimide (Doriden) and meprobamate (Equanil). It may also explain that there is only a transient increase in the sedative effect with combined diphenhydramine (Benadryl) and phenobarbital (Luminal) treatment, i.e. treatment with two "enzyme inducer" drugs, which then is progressively replaced by a decrease of sedative action.

In contrast to the "enzyme inducers," the "enzyme inhibitors" retard the catabolism of the affected drugs. Thus, the psychostimulant methylphenidate (Ritalin) has been shown to retard the breakdown of anticoagulants, antidepressants and phenothiazines. This explains, that addition of methylphenidate (Ritalin) to phenothiazine or tricyclic antidepressant treatment increases the blood levels — and may also the clinical effect — of the antidepressant or of the neuroleptic (Garrettson, Perel and Dayton 1969). It also explains the not infrequent need to decrease the dosage of the anticoagulant and/or anticonvulsant when methylphenidate (Ritalin) is added to the treatment regime.

Alteration of Excretion

Modification of the action of a drug by another "exogenous chemical" may occur at the site of excretion. This is the case with lithium, an antimanic agent, the primary choice of treatment in manic-depressive disease. Accordingly it was noted, that decrease of serum sodium (Na) concentration, below the normal level, in lithium-treated patients, was followed by a selective tubular (renal) reabsorption of the substance with a rapid increase in serum lithium. This explains that administration of an anti-diuretic agent, e.g. chlorothiazide (Diuril) which produces salt (NaCl) depletion promptly, to a lithium-treated patient, may increase serum lithium concentration beyond the therapeutic level (i.e. 2.0 mEq/L) and result in toxic confusional state (or even coma and death) (Schou 1968).

Americans are now spending well over $500 million each year for anxiolytic sedative drugs — commonly called tranquilizers or minor tranquilizers — to control a wide variety of symptoms and conditions gathered loosely together under the name of psychoneuroses. On

the basis of psychodynamic considerations, anxiolytic sedative benzodiazepines are frequently prescribed in combination with antidepressant drugs. While there is no evidence that the combination would result in significantly superior therapeutic action in the treatment of psychoneurotic or depressed patients than its component drugs alone, there are indications that associated administration of chlordiazepoxide (Librium) and a tricyclic antidepressant may produce mutual enhancement of sedation and anticholinergic side effects. Furthermore, addition of amitriptyline (Elavil) to chlordiazepoxide (Librium) treatment may intensify, instead of alleviate, depressive psychopathological symptoms and has led to a clinical picture that simulated brain damage.

While anxiolytic sedatives remain the most extensively employed drugs in the psychoneuroses, neuroleptics are the most widely used drugs in the treatment of schizophrenias. On the basis of clinical considerations neuroleptics are frequently prescribed in combination. While there is no evidence that combined administration of various neuroleptics would enhance clinical effectiveness and lower the incidence of side effects (Freeman 1967), there are indications that addition of nylidrine (Arlidin), a cerebral vasodilator substance (Lehmann et al 1964), methyl-p-tyrosine (H44/68 Hassle, Molndal), a tyrosine hydroxylase inhibitor and methyldopa (Aldomet), a dopa-decarboxylase inhibitor, may potentiate the therapeutic effect of neuroleptics. Other drug interactions with neuroleptics with practical significance include the potentiation of the effect of antipyretics, e.g. dipyrone (Direma) and the inhibition of the effect of hypoglycemic agents. Nevertheless, the administration of orphenadrine (Norflex citrate), a hypoglycemic agent has resulted in severe hypoglycemia in chlorpromazine-(Largactil)-treated patients.

While there is no evidence that tricyclic antidepressants would enhance the therapeutic activity of anxiolytic sedatives there are indications that they may potentiate the therapeutic effect of neuroleptic drugs (Rafaelsen 1973). Nevertheless, the fact remains that the addition of a tricyclic antidepressant to the therapy of a patient treated with a neuroleptic —and an antiparkinsonian preparation — may aggravate constipation and lead to paralytic ileus (Warnes, Lehmann and Ban 1967). Furthermore, while no clear-cut evidence was presented that antidepressant combinations of the same group, i.e. tricyclic with another tricyclic or MAOI with another MAOI, were superior to their component drugs, there are indications that the therapeutic activity of tricyclic antidepressants may be potentiated by the addition of an MAOI (Dally 1967, Sargant 1966; Schuckit, Robins and Feighner 1971), methylphenidate (Ritalin) (Wharton et al 1971), dexamethasone (Decadron) (McClure and Cleghorn 1968), dessicated thyroid (Earle 1970) liothyronine (Cytomel), or thyroid stimulating hormone (Prange et al 1971).

Concluding Remarks

According to corticovisceral theory, development of the irreversible, organic phase of an illness is preceded by a functional "neurogenic" phase of the disease in which conditional reflex activity in general, and especially in relationship to the affected organ, is disturbed. On the basis of this theory, combined administration of psychoactive medication — with a prevailing effect on conditional reflex behavior — and specific drugs for the particular disorder, are recommended, in a ratio which depends on the developmental stage of the disease. Acceptance of this theoretical framework would vastly extend the area of medical practice in which drug interactions with psychoactive drugs may occur.

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