DRUG INTERACTIONS WITH MONOAMINE OXIDASE INHIBITORS, TRICYCLIC ANTIDEPRESSANTS AND ANTIHYPERTENSIVES

by

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Drug interactions involving monoamine oxidase inhibitors, tricyclic antidepressants and antihypertensives, are very much related and will be discussed together.

A. INTERACTIONS OF MONOAMINE OXIDASE (MAO) INHIBITORS

One of the early reports on drug interaction was about interaction of monoamine oxidase inhibitor with food substance—"cheese reaction". Cheese produced hypertensive crisis in patients on MAO inhibitor therapy. The reports that followed brought the problem of drug interaction to the limelight and led to an extensive study of the mechanisms involved.

Monoamine oxidase (MAO) is an enzyme (or a group of enzymes) whose function is to break down biologically active monoamines like noradrenaline, adrenaline, dopamine and 5-hydroxytryptamine. The enzyme is present in most cells and is essentially an intracellular enzyme.

MAO inhibitors produce inhibition of the enzyme by forming a stable complex with it. Tranylcypromine however produces a reversible complex. Both the antidepressant activity of the MAO inhibitors and their interactions with other drugs or with food substances are as a consequence of the enzyme inhibition which results in the accumulation of the monoamines normally inactivated by the enzyme.

1. With Food Substances Containing Tyramine

Serious hypertensive crisis is known to occur in people who ingest food substances of high tyramine content during therapy with MAO inhibitor.

Tyramine is an indirectly acting sympathomimetic amine and thus can raise the blood pressure by releasing noradrenaline from its stores in the adrenergic neurones and other sites.

During treatment with MAO inhibitor, the enzyme (MAO) is inhibited and this results in the accumulation of monoamines like noradrenaline in the stores. When food or drink containing tyramine is taken, the tyramine produces a marked release of noradrenaline from the stores. This results is a marked rise in blood pressure (hypertensive crisis).

Under normal conditions (i.e. without MAO inhibitor), the effect of tyramine in these food substances is not important. This is because there is a high content of MAO in the gut and in the liver. The tyramine absorbed from the food is inactivated by MAO present in the gut and in the liver and thus does not reach the general circulation. However when the MAO enzyme is inhibited, the tyramine absorbed reaches the circulation to induce a rise in blood pressure.

The amount of tyramine in the food determines the interaction and certain food substances are known to have high tyramine content (1) e.g. cheese, pickled herring, some meat and yeast extracts like marmite and oxo, and some drinks like chianti wine. To guard against any interaction of MAO inhibitor with food substances or drugs, the Pharmaceutical Society of Britain and the British Medical Association have prepared a warning card—"MAO Inhibitor Warning Card"—which is issued to all patients on MAO inhibitor therapy in Britain.

THE MAO INHIBITORS WARNING CARD (2)

TREATMENT CARD

Carry this card with you at all times. Show it to any doctor who may treat you other than the doctor who prescribed this medicine, and to your dentist if you require dental treatment.

INSTRUCTIONS TO PATIENTS

Please read carefully

While taking this medicine and for 10 days after your treatment finishes you must observe the following simple instructions:-

1 Do not eat CHEESE, PICKLED HERRING OR BROAD BEAN PODS.

2 Do not eat or drink BOVRIL, OXO, MARMITE or ANY SIMILAR MEAT OR YEAST EXTRACT.

3 Do not take any other MEDICINES (including tablets, capsules; nose drops, inhalations or suppositories) whether purchased by you or previously prescribed by your doctor, without first consulting him.

NB *Cough and cold cures, pain relievers, tonics and laxatives are medicines.*

4 Drink ALCOHOL only in moderation and avoid CHIANTI WINE completely.

Report any severe symptoms to your doctor and follow any other advice given by him.

This has considerably reduced the incidence of this type of interaction in Britain.

2. With Indirectly Acting Sympathomimetic Amines

Like tyramine, other sympathomimetics with indirect action also produce their effects by release of biological amines (noradrenaline, adrenaline etc.) from the stores. Thus they can also produce hypertensive crisis when taken during treatment with MAO inhibitor. These sympathomimetic amines include:

amphetamine
dexamphetamine
ephedrine
methylphenidate
phenylephrine (also directly acting)
metaraminol
phenylpropanolamine

It must be remembered that many preparations for cold and cough contain sympathomimetics and can therefore interact with MAO inhibitors.

Also certain drugs like procarbazine (an antineoplastic) furazolidone or its metabolite (an anti-infective agent, important when taken for more than 5 days), and debrisoquine (Declinax—an antihypertensive) have some MAO inhibitory activity and can interact with the above sympathomimetics and also with tyramine.

It has been suggested that the interaction of phenylpropanolamine with MAO inhibitors can also arise from the ability of MAO inhibitors to retard its metabolism in the liver. Thus large amounts of phenylprepanolamine are spared to act on the adrenergic neurones.

3. With Reserpine-like Drugs

Reserpine produces its effect by depletion of amines stores, both on the brain and in the periphery. Thus during treatment with MAO inhibitor, biological amines will accummulate as stated above. Administration of reserpine will cause a sudden release of large amount of noradrenaline and other amines leading to the effects observed in this type of interaction like disorientation, illusions and delirious agitation and epileptiform convulsions (3). This interaction occurs only when MAO inhibitor and reserpine-like drug are given concurrently or sequentially. If the reserpine is given before the course on MAO inhibitor, no interaction is expected to occur.

4. With Levodopa

Levodopa (an anti-parkinsonism drug) is converted in the body to dopamine and noradrenaline. It also occurs in large amount in broad beans (see MAOI—warning card). Its interaction with MAO inhibitors is thought to be as a result of the formation of dopamine in the liver which causes release of noradrenaline from the adrenergic neurone. Thus the interaction resembles that of the indirectly acting sympathomimetics and is similarly treated.

5. With Barbiturates

There has been reports that MAO inhibitors enhance and prolong the effect of barbiturates in animals. It is not known how often this type of interaction occurs in man. This interaction is probably due to the inhibition by MAO inhibitor of the barbiturate metabolising enzymes in the liver. It is thus wise to avoid combining the two types of drug.

6. With Hypoglycaemic Agents

MAO inhibitors enhance the effect of hypoglycaemic agents. This has been shown to occur with insulin or chlorpropamide and mebanazine. The mechanism for this interaction is not fully understood but may be due to direct stimulation of insulin release by MAO inhibitor or the impairment of sympathetic activity which MAO inhibitors are known to produce.

7. With Pethidine

Pethidine has been shown to cause excitation, restlessness and tremor and at times respiratory depression when given to partients on MAO inhibitor. This does not occur in all patients. It is not known for certain the mechanism of this interaction. However MAO inhibitors depress the activity of many enzymes including those concerned with the biotransformation of pethidine. Thus the metabolic intermediate may be responsible for the reaction.

8. With Tricyclic Antidepressants

Severe adverse reaction has been observed during therapy with MAO inhibitor and tricyclic antidepressants. Some workers have been able to combine the two types of antidepressants without any adverse effect. This means that any such combination should be done with caution.

9. With MAO Inhibitors

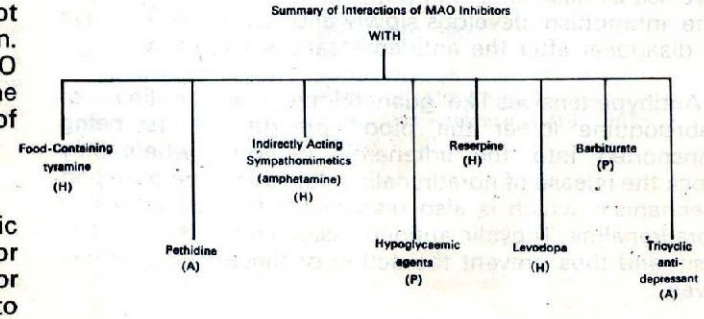
Some MAO inhibitors like tranylocypromine, phenelzine and pheniprazine which have also amphetamine-like action can produce hypertensive crisis when given alone or in combination. It is suggested that this is as a result of the two properties of the drug viz, MAO inhibition and amphetamine-like activity.

10. With Dextromethorphan

Dextromethorphan (present in some cough preparations) has been reported to cause hyperpyrexia, with restlessness and dilated pupil when combined with MAO inhibitor (phenelzine). The mechanism of this interaction is not known and it is not unlikely that the reaction will occur with other MAO inhibitors.

Examples of MAO Inhibitors

Iproniazid	Pargyline
Isocarboxid	Phenelzine
Mebanazine	Pheniprazine
Nialamide	Tranylcylpromine



KEY

H = Hypertensive crisis

P = Potentiation of the drug effect by MAO inhibitor

A = Enhanced adverse effects of the drug.

B. INTERACTIONS OF TRICYCLIC ANTI-DEPRESSANT

The action of noradrenaline released from adrenergic nerves is terminated mainly by an up take mechanism which returns it to the nerve. Only a small amount of the released noradrenaline (about 10%) is metabolised by catechol-O-methyltransferase (COMT). Tricyclic antidepressants block this uptake of noradrenaline at the adrenergic neurones and will therefore prolong and also enhance the action of noradrenaline.

1. With Sympathomimetics

Noradrenaline or adrenaline contained in local anaesthetics has been known to produce unexpected rise in blood pressure when the local anaesthetic was given to patients on tricyclic antidepressant.

The action of injected noradrenaline is terminated mainly by the uptake mechanism. Tricyclic antidepressants block the uptake mechanism as stated above and thus will enhance and prolong the action of noradrenaline or adrenaline contained in the local anaesthetic.

It has been demonstrated in animals that the pressor effect of tyramine (an indirectly acting sympathomimetic) is reduced by tricyclic antidepressant. The indirectly acting sympathomimetics produce their effect by releasing noradrenaline from the adrenergic neurones. The tricyclic antidepressants block the uptake of the indirectly acting sympathomimetic (e.g. tyramine) into the neurones and thus prevent the release of noradrenaline. In this way the pressor effect of the tyramine is reduced or prevented.

In a similar way the action of amphetamine will be reduced. There is however evidence that tricyclic antidepressant inhibit the metabolism of amphetamine and thus enhance its action.

2. With Antihypertensives

The antihypertensive effect of guanethidine was reversed by desipramine in patients on combined therapy. The antagonism develops slowly and also takes 5-7 days to disappear after the antidepressant is withdrawn.

Antihypertensives like guanethidine, bethanidine or debrisoquine lower the blood pressure by first being transported into the adrenergic neurones where they block the release of noradrenaline. It is this same transport mechanism which is also responsible for the uptake of noradrenaline. Tricyclic antidepressants block this mechanism and thus prevent the action of these antihypertensives.

It is said that this antagonism is very much less marked with doxepin (4 & 5) than with other antidepressants. However when a high dose of doxepin (300mg daily) is used, significant antagonism with guanethidine will occur.

3. With Atropine-like drugs

Tricyclic antidepressants have as their side effects, anticholinergic activities. These side effects like blurring of vision, dryness of mouth, constipation and in the elderly, urinary retention, will be enhanced by atropine-like drugs (e.g. benzhexol) or drugs known to have atropine-like side effects (e.g. diphenhydramine). Thus patients on combined therapy of tricyclic antidepressant and anticholinergic drugs must be carefully watched for the possible side effect due to interaction of the two drugs.

4. With Alcohol

The possible interaction of alcohol and some tricyclic antidepressant has been mentioned (6). They interact to produce enhanced CNS depression (which may affect driving skill) and also decreased gut motility. It is therefore best to avoid alcohol during therapy with antidepressants.

5. With Thyro-active Agents

Thyro-active agents (Tri-iodothyronine and thyroxine) have been shown to enhance the action tricyclic antidepressant. It has been suggested that these thyro-active agents act by increasing the sensitivity of the adrenergic receptors in the central nervous system to noradrenaline Since the antidepressant blocks the uptake mechanism of noradrenaline, the amount of noradrenaline in the receptor area will be increased. This together with the increased sensitivity of the receptors due to the thyro-active agents will lead to enhanced antidepressant effect.

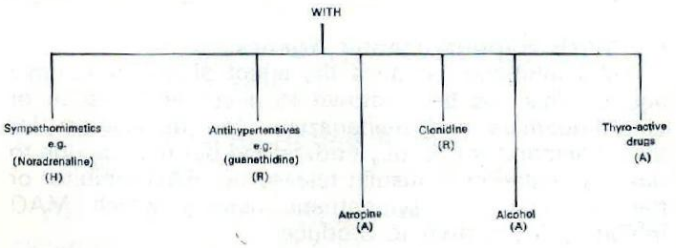
6. With Clonidine

Tricyclic antidepressants (imipramine) seems able to antagonise the hypotensive effect of clonidine. This may happen with other antidepressants. The mechanism of this effect is not known for certain but it has been suggested that probably the antidepressant prevents the uptake of the clonidine into adrenergic neurones which is essential for the hypotensive effect.

Examples of Tricyclic antidepressants

Imipramine
Amitriptyline
Trimipramine
Desipramine
Clomipramine
Doxepin
Dibenzepin
Iprindole
Protriptyline
Nortriptyline
Opipranol

Summary of Interactions of Tricyclic Antidepressants



KEY

H = Hypertension

R = Reversal of antihypertensive effect

A = Enhanced adverse effect.

C. INTERACTIONS OF ANTIHYPERTENSIVES

Drugs which are used to lower the blood pressure in hypertensives produce this effect by various mechanisms. The mechanism of action determines the types of drugs with which each can interact.

1. Guanethidine and the directly acting sympathomimetics.

Guanethidine and drugs acting like it, will enhance the pressor effects of sympathomimetics like adrenaline and noradrenaline. This is because guanethidine blocks the noradrenaline uptake mechanism and this increases the concentration of noradrenaline around the receptors Also guanethidine blocks adrenergic nerve transmission and thus produces "pharmacological denervation" of the adrenergic nerve. This results in sensitization of the receptors.

2. Guanethidine-like drugs and indirectly acting sympathomimetics

The antihypertensive effect of guanidines (guanethidine, bretylium, bethanidine and debrisoquine) will be prevented or reversed by indirectly acting sympathomimetics like amphetamine, tyramine, ephedrine and hydroxyamphetamine. These amines actually compete with the guanidines for the receptor sites. Thus ephedrine and guanidines for the receptor sites. Thus ephedrine and probably phenylephrine and phenylpropanolamine which are used as decongestants and which are sold without restriction can reverse the antihypertensive effect of guanethidine-like drugs.

3. Guanethidine and hypoglycaemic agents.

Guanethidine seems to have some hypoglycaemic effect. It reduces the insulin requirement in the diabetic. Thus caution should be exercised whenever guanethidine is to be added or withdrawn from the therapy of a patient taking hypoglycaemic agent, in order to prevent any disastrous consequences.

4. Guanethidine and antipsychotic agents

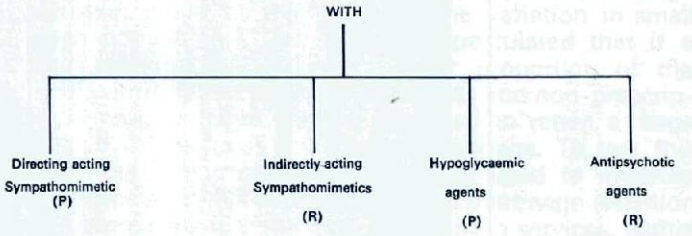
There is a report that chlorpromazine reversed the antihypertensive effect of guanethine. This may be as a result of the inhibition of guanethidine uptake into the adrenergic neurones by chlorpromazine. It is not known whether this interaction will occur in all patients.

Similar reversal has been reported with haloperidol and thiothizene.

5. With oral contraceptives.

It has been reported that patients on oral contraceptives are often refractory to guanethidine-type of antihypertensive. The mechanism of this interaction is not known.

Summary of Interactions of Antihypertensives.



KEY

P = Potentiation of the sympathomimetic or hypoglycaemic effect.

R = Reversal of the antihypertensive effect.

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