A REVIEW OF THE DANGERS OF MONOAMINE-OXIDASE INHIBITORS, WITH SPECIAL REFERENCE TO ANAESTHESIA

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Although this article was designed primarily for the guidance of anaesthetists, it should be of equally great concern to surgeons, obstetricians, physicians, psychiatrists and general practitioners.

The subject of anaesthesia has expanded tremendously in the last decade or two, and concurrently there have been great developments in other fields as well, notably in that of psychiatry. It is most important for anaesthetists to keep abreast of developments in other fields, as they often have a very close bearing on their own. The perils which they face daily, are continually increasing with the introduction of new drugs affecting anaesthesia, and possible iatrogenic catastrophes should figure prominently in their minds.

The association between anaesthetists and psychiatrists has always been a fruitful one, particularly since Bennett first used curare to soften the convulsions of electroconvulsive therapy. However, this association is purchased at a price, often considerable and, unfortunately, sometimes supreme. During recent years anaesthetists have been faced with a new menace in the form of a group of drugs used by psychiatrists, as well as by physicians and general practitioners. These drugs, known as the monoamine-oxidase (MAO) inhibitors[1] have been instrumental in great strides being made in the treatment of mental depression,[2, 3] but at the same time they offer nothing to the anaesthetist and merely add to his daily burden. To ignore them would be sheer folly, and in view of the fact that very little mention has been made in respect of these agents in anaesthetic literature, despite the fact that drug potentiation with MAO-inhibitors is theoretically more liable to happen to anaesthetists as a group, because the particular drugs potentiated are used more frequently by them than by most other groups in the profession, it was felt that a review such as this would serve a purpose.

An outline will be given of the brain monoamines, notably 5-hydroxytryptamine (5-HT) and noradrenaline, their origins, functions and fate and how they are integrated in the central nervous system to play their part in affecting mood and behaviour. Consideration will be given to their relationship to mental depression and how they tie up with monoamine oxidase and MAO-inhibitors. After this, the actual drugs used will be mentioned, with reference to their uses and dangers, notably that of drug potentiation, the latter being that aspect of the paper which is of greatest concern. Finally an attempt will be made to indicate how to avoid the pitfalls, and how to deal with emergencies.

BRAIN MONOAMINES

Definition

Also known as neurohormones, they are defined as either transmitter substances, released from nerve endings and activating the post-synaptic membrane, or substances enhancing or inhibiting (modulating) the action of the transmitter.[6] Their release stimulates the transmission of the appropriate emotional reactions. We have thus arrived at the stage where mood and behaviour are placed on a chemical basis. It is now known that 2 monoamines, (physiologically important amines with only 1 amine radicle) appear to play a significant role. They are 5-HT (serotonin) and noradrenaline, and they may act as transmitters or modulators in the central nervous system, affecting mood and behaviour considerably. Other monoamines which may also well be involved are tyramine, tryptamine, dopamine and adrenaline.

Storage

Both noradrenaline and 5-HT are found in high concentrations in that part of the brain concerned with emotional behaviour; in the hypothalamus, reticular activating system and limbic system, very little monoamine being present in the cerebral cortex or cerebellum. They are stored in an inactive form, and it is suggested that at the correct movement, nerve impulses release their free forms which then stimulate the transmission of emotional reaction.

Function

Anaesthetists are familiar with the physiological opposing actions of the sympathetic and parasympathetic divisions of the autonomic nervous system, but this takes no cognizance of the role these systems play in regulating emotional behaviour. To understand psychiatric colleagues, and the drugs they use, one must grasp the concept of how the autonomic nervous system is integrated into the whole of the central nervous system. This in turn, involves an understanding of Hess and Brodie's division of the subcortical systems of the central nervous system into 2 separate and antagonistic systems—ergotropic and trophotropic.

It appears that, in fact, the sympathetic and parasympathetic divisions of the autonomic nervous system are integrated into the central nervous system and play a vital part in regulating mood and behaviour, and each forms part of the ergotropic and trophotropic systems. The theory is that 5-HT and noradrenaline are involved in the functions of the trophotropic and ergotropic systems, acting as transmitters. Impulses arising from consciousness, viscera and somatic supporting structures may pass to either of the 2 coordinating systems and, by stimulating them, produce different effects through medium of either 5-HT or noradrenaline.

The ergotropic system consists of an integrated combination of sympathetic, reticular activating and somato-sensory-motor systems. Stimulation thereof will result in the release of the transmitter, noradrenaline, which then activates the system to produce patterns of arousal with psychic stimulation and heightened sympathetic activity, features which are absent in mental depression.

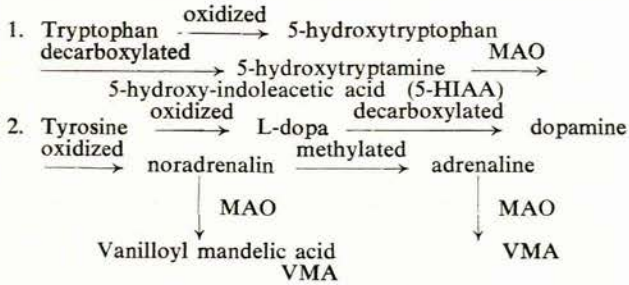
The trophotropic system on the other hand, integrates the parasympathetic system with the somato-motor-sensory

system and the limbic systems, possessing 5-HT as transmitter. Stimulation of this system results in behaviour patterns of a relaxing and subduing nature with a general decrease in psychic, and increase in parasympathetic activity; a state preparing the body for rest and sleep.

It is felt that in mental depression there is an upset in balance between these 2 systems because of a disturbance in the hormones which regulate them, notably 5-HT and noradrenaline. Which neurohormone is of the greatest importance is, as yet, uncertain, but it would seem that a deficiency of 5-HT is of considerable significance in these depressed states. A MAO-inhibitor will correct this upset balance by increasing the brain concentrations of mainly 5-HT, and to a lesser extent of noradrenaline.[4, 5]

Synthesis and Destruction

The important monoamines are derived from the amino acids tyrosine and tryptophan.



In this simplified version it will be noted that those monoamines are broken down in the presence of a most important enzyme, monoamine oxidase.

Monoamine oxidase. Noradrenaline, 5-hydroxytryptamine, adrenaline, tyramine and tryptamine are all inactivated by this enzyme monoamine oxidase, which exists in close association with these hormones, especially in the subcortical levels of the brain and in the liver. This inactivation can be prevented by the administration of a monoamine oxidase inhibitor, and, to recapitulate, it is believed that mental depression may be associated with a disturbance in the balance of free noradrenaline and 5-hydroxytryptamine. When a monoamine oxidase inhibitor is used, it abolishes the effect of monoamine oxidase and thus the mechanism for destruction of brain monoamines, with the result that concentrations of 5-hydroxytryptamines, and to a lesser extent, noradrenaline increase. This is considered to counter the disturbed balance of neurohormones and to result in increased motor and psychic activity and will decrease the retardation of thought as well as visceral dysfunction common to mental depression.

After monoamine oxidase blockade, the store of brain monoamines increases by 2 to 3 times. It is still uncertain whether the stimulating action of a MAO-inhibitor is caused by an increase in 5-HT or noradrenaline.[6] MAO-inhibitors reduce not only the activity of monoamine oxidase, but also of other enzyme systems, especially in the liver, and this may have a very important bearing on the mechanism of drug potentiation.

THE DRUGS USED

Many drugs are MAO-inhibitors *in vitro*, but only the following are used clinically for the purpose of inhibiting monoamine oxidase. A few of the drugs mentioned have been withdrawn from the market as a result of toxic reactions.

1. *Hydrazines*
   - (a) Phenelzine ('nardil')
   - (b) Iproniazid ('marsilid')
   - (c) Isocarboxazid ('marplan')
   - (d) Nialamide ('niamid')
   - (e) Etryptamine ('monase')
   - (f) Pheniprazine ('catron')
   - (g) Phenoxypropazine ('drazine')
   - (h) Mebanazine ('actomol')
   - (i) Pivhydrazine ('tersavid')
2. *Nonhydrazines*
   - (a) Tranylcypromine ('parnate')
   - (b) Tranylcypromine and Trifluoperazine ('parstelin')
   - (c) Pargyline ('eutonyl')

Pharmacological Actions[1]

Many, but certainly not all of the effects of MAO-inhibitors are based on MAO-inhibition.

1. *Effects based on MAO-inhibition*

(a) *Increase in tissue endogenous monoamines.* Increased concentrations of monoamines occur in the brain, blood, liver, heart and gut after administration of a large dose of inhibitor. The substances which are increased include 5-HT, noradrenaline, dopamine, tyramine and tryptamine, and this increase is related to the action of the MAO-inhibitor providing for a decreased breakdown of monoamines. The increase in monoamines is probably responsible for the psychic stimulation and feeling of wellbeing, the chief action of a MAO-inhibitor probably being that of excitation of the central nervous system.

(b) *The effects of exogenous monoamines and their precursors is enhanced.*

(c) *Diminution of the effects of monoamine liberators (Reserpine).* Normally reserpine releases brain monoamines and depletes that organ of its stores. This action is antagonized by MAO-blockade, following pretreatment with a MAO-inhibitor, so that reserpine now no longer has sedative and hypothermic effects—in fact the opposite may occur. This is possibly due to the fact that the monoamines are liberated and no monoamine oxidase is available for their degradation.

2. *Effects probably not Related to MAO-inhibition*

(a) *Drug potentiation.* A whole host of commonly used drugs are affected—opium alkaloids, pethidine and cogeners, adrenalin and all sympathomimetic pressor amines including ephedrine, methylamphetamine, mephentermine, phenylephrine, metaraminol, methoxamine, as well as amphetamine, barbiturates, procaine and cocaine, atropine, hypotensive agents, steroids, alcohol, imipramine (tofranil) and drugs used in the treatment of Parkinson's disease. It will be noted that many of the anaesthetist's old friends are classified here as undesirables. Though this is an impressive list, in practice most of the problems associated with drug potentiation have arisen mainly after the use of the powerful analgesics and the vasopressors.

(b) *Cardiovascular effects.* These include hypertension and hypotension. Ganglion blockade occurs in the isolated superior cervical ganglion and postural hypotension is a problem following the use of these drugs.[7] Hypertensive crises are liable to occur.

(c) *Analgesic effect.*

(d) *Reduction in the activity of other enzyme systems.* Many enzymes in the liver, other than monoamine oxidase, are also put out of action and it seems likely in many instances that the enzyme systems responsible for degrading the potentiated drugs mentioned, are interfered with. Thus drug potentiation results.

Uses

1. *As antidepressants.* They are most extensively used for this purpose and are of considerable benefit mainly in reactive depressions. Beneficial effects occur after 1 - 4 weeks.

The effects of these drugs persist for an extremely long time, even up to *3 weeks* after discontinuing them, while dramatic drug potentiation has been known to occur even after 1 day's administration.[6] Tranylcypromine is the most rapidly eliminated member of the group. They are also used to effect a reduction in the number of treatments using electro-convulsive therapy.

2. *Angina pectoris.* Symptomatic improvement does occur, possibly due to central stimulation or interference with the pain pathway.

3. *In hypertension.* Pargyline is used mainly for this purpose.

4. *Peripheral vascular disease.*

Overdose[5]

Some cases exhibit hypotension with dizziness and weakness, while others show marked cerebral excitation. In a case of severe overdose intense headaches occur, combined with profuse sweating and hypertension or alternatively hypotension. Cerebral excitation is manifest as agitation, going on to convulsions, opisthotonos and coma. This is eventually followed by circulatory collapse and ventilatory impairment. Hyperpyrexia occurs.

DRUG POTENTIATION

A true potentiating agent prolongs the duration of the action of a drug in more than additive manner and, as thus defined, a potentiator could exert its effects by decreasing the rate of metabolic transformation of the other drug (prolonging agent), or by sensitizing the body to it, (true potentiator).[9] The MAO-inhibitors seem to be prolonging agents.

1. **Powerful Analgesics**

Most of the reported cases have followed the administration of pethidine,[8, 10-17] but some have occurred after morphine and none of the opium alkaloids could be considered safe in combination with a MAO-inhibitor. Though case reports have not appeared after the use of other synthetic powerful analgesics, theoretically it is quite possible that drug potentiation would occur. It seems that aspirin and similar drugs are the only ones which could be used safely under these circumstances.

Types of clinical picture. They resemble (*a*) severe, acute pethidine poisoning, which has many of the features of atropine intoxication—here cerebral irritability is a prominent feature; (*b*) a more moderate overdose of pethidine with gradually developing coma with respiratory and cardiovascular depression; and (*c*) they resemble an overdose of MAO-inhibitor itself. This is very similar to pethidine intoxication.

Case Histories

(*a*) A not uncommon type of case is one where a patient on a MAO-inhibitor requires pethidine for a variety of reasons and within a few minutes becomes highly excitable, rigid, cyanosed, convulses, has opisthotonos, and lapses in a coma. Hyperpyrexia is common.

(*b*) Other cases have occurred where almost immediate restlessness developed, followed by coma in 20 minutes. They were flushed, sweating profusely, exhibiting Cheyne-Stokes respiration, dilated pupils and hypertension, a picture suggesting a cerebrovascular accident.

(*c*) Some cases are of more gradual onset. Slowly developing coma over a few hours has been reported, with hypotension, circulatory failure and constricted pupils. This is more the picture of pethidine poisoning without the atropine-like stimulation.

Some of the toxic effects of pethidine result from its atropine-like effects, as pethidine has some anticholinergic action. Thus, the flushing, tachycardia and hyperpyrexia with cerebral irritation and convulsions in many of these cases may be due to the atropine-like features of pethidine.

The development of untoward reactions is not inevitable after the combination of a MAO-inhibitor and a powerful analgesic—some cases have had morphine without ill-effects and I have seen 50 mg. of pethidine mistakenly given as a premedication, after which the only feature was some delayed recovery following general anaesthesia.

Theories explaining Drug Potentiation

(*a*) These drugs inhibit other enzymes in the liver as well as monoamine oxidase, and these may include those which play a part in the breakdown of pethidine[9, 18] and related drugs. Pethidine is normally demethylated and de-esterified in the liver, and in patients with severe liver disease exaggerated responses may occur after pethidine administration, including cerebral irritability and confusion. If this theory is correct, the toxic features are obviously those of an overdose of pethidine, but note that this is very similar to an overdose of a MAO-inhibitor.

(*b*) Pethidine is itself a MAO-inhibitor. Potentiation may occur *in vivo* and the toxic effects would be those of an overdose of a MAO-inhibitor.

(*c*) Pethidine and the latter drug or its degradation products form a loose chemical bond producing cerebral irritability and coma. This bond is blocked or reversed by steroids.

The first theory seems the most likely. This dangerous potentiation may occur even after the administration of a MAO-inhibitor over *one* day only, though in some cases it takes several weeks. Pethidine is potentiated 5 times in mice by these drugs.

2. **Vasopressors**

All sympathomimetic pressor amines are potentiated violently. Again, in mice this is five-fold, i.e. given one-fifth the normal toxic dose of vasopressor, and pre-treated with a MAO-inhibitor, mice die from acute poisoning from the drug used.[19] These sympathomimetic amines are normally deaminated in the liver, and they are also MAO-inhibitors *in vitro*.

Clinical picture. The disaster usually follows the administration of sympathomimetic amine[20-24] as well as the taking of cheese[25-30] or 'marmite'. It closely resembles that of a crisis associated with phaeochromocytoma, with severe headache, hypertension with arrhythmias, leading to cardiac failure, pulmonary oedema, or a cerebrovascular accident. Many cases closely resemble a subarachnoid haemorrhage and some in fact do develop this. There has been reported the twin iatrogenic catastrophe of a hypertensive headache followed by coma from the pethidine given to relieve it. Tranylcypromine[31] appears to be the drug involved in many of the reports.

Theories explaining potentiation. (*a*) Some vasopressors act by releasing tissue-stored noradrenaline and as there are already considerably increased levels of tissue noradrenaline after MAO-inhibitor administration, it is likely that an exaggerated response will be obtained. (*b*) These vasopressors are weak MAO-inhibitors *in vitro*—possibly they might potentiate these agents. (*c*) A decreased rate of degradation of sympathomimetic amine occurs in the liver owing to enzyme inhibition by MAO-inhibitor.

3. **Barbiturates**

Their action too is prolonged by MAO-inhibitors. In animals, premedication with tranylcypromine prolongs the duration of amylobarbitone narcosis 2½ times.[32] The side-chain of barbiturates is normally oxidized in the liver, and again these drugs appear to prolong the effects by interference with the rate of metabolic transformation.

4. **Local Analgesics**

(a) *Cocaine.* This has an adrenergic effect and potentiates adrenaline. It is a MAO-inhibitor in its own right. Its destruction in the liver is possibly interfered with after using a MAO-inhibitor.

Apart from one case reported involving a cocaine spray during general anaesthesia, where unfortunately the picture was complicated by the addition of a vasopressor, pethidine and adrenaline infiltration, resulting in marked hyperpnoea and hyperpyrexia,[11] no other definite information is available. It would seem prudent to avoid the combination.

(b) *Procaine and lignocaine.* Procaine is also a MAO-inhibitor *in vitro* and it has been suggested that the drug should not be combined with other inhibitors. Lignocaine is not, and so far no reports have appeared showing harmful effects as a result of its combination with MAO-inhibitors.

Dangerous Situations

Possible tight corners an anaesthetist would find himself in, could be visualized.

(*a*) A patient receiving a MAO-inhibitor is premedicated with an opiate.

(*b*) A person is acutely injured and requires a powerful analgesic and general anaesthesia.

(*c*) A large dose of thiopentone is used for the induction of anaesthesia.

(*d*) A sympathomimetic pressor amine is used to combat hypotension.

(*e*) Cocaine is used to spray the bronchial tree.

(*f*) Induced hypotension is employed.

(*g*) The surgeon is permitted to infiltrate with adrenaline.

(*h*) The anaesthetist is called to resuscitate a case of suicidal overdosage.

MANAGEMENT IN RELATION TO ANAESTHESIA

Prevention is better than cure. This is particularly applicable to these drugs, and an awareness of their use by psychiatrists, physicians and general practitioners would go a long way towards averting mishaps.

Prevention

1. *Non-emergency Procedures*

In general, patients on MAO-inhibitors, scheduled for non-urgent operations, should have them postponed for 3 weeks while they are taken off the drug. One of the most important factors influencing the decision however is whether the patient can manage without the list of potentiated drugs, and in particular, whether he will require a powerful analgesic postoperatively or not. In other words, one is more likely to anaesthetize someone having a curettage than an arthrodesis of the hip.

2. *Emergency Surgery*

If the case cannot wait, it would be wise to omit opiates and similar drugs from the premedication and to be cautious with thiopentone, if the latter is used at all. Falls in blood pressure should be avoided. If they do occur and are due to the anaesthetic agents, a test dose of one-fifth the usual dose would perhaps be prudent.[19] The manufacturers of tranylcypromine suggests that noradrenaline, administered cautiously, would probably be most suited. Should a pressor crisis arise, it would be assumed that noradrenaline is being liberated from adrenergic nerve endings, and the best course would be the administration of an adrenergic blocking agent like phentolamine. Local analgesia, when possible, might be suitable here, using lignocaine, as no adverse reactions following this combination have been reported. It is not a MAO-inhibitor, though conceivably potentiation might occur as it is also partly destroyed in the liver after hydrolysis by plasma esterase.

If a decision is made to use analgesics postoperatively, it has been suggested that a combination of chlorpromazine or promazine and codeine or dihydrocodeine would be safer than pethidine or morphine, although on theoretical grounds codeine is not entirely safe either. I have used this combination after appendicectomy without ill-effects. If it is true that pethidine is potentiated by the MAO-inhibitor and not *vice versa*, it might seem reasonable to assume interference with pethidine degradation, and satisfactory therapeutic results would be obtained with much smaller doses, as in the case of severe liver disease.[33] Assuming the potentiation to be five-fold, as it is in mice, then 20 mg. of pethidine should be sufficient. The value of other synthetic analgesics is uncertain and on theoretical grounds their advantages are dubious.

Unfortunately, the literature contributes little in the way of suggestions as to what one does under these difficult circumstances, except to make it clear that most drugs more powerful than aspirin are not entirely safe.

Treatment

1. *Pethidine and Similar Drugs*

Reactions to pethidine fall into one of 2 categories—

(*a*) Those with marked cerebral excitation.

(*b*) A later stage where coma supervenes or alternatively where coma and hypotension gradually follow the combination of pethidine and a MAO-inhibitor.

Though spontaneous recovery after severe reactions to pethidine have occurred without treatment, many deaths have also been the result. These can be averted by the correct treatment. The first group (cerebral excitation) are best managed with chlorpromazine, especially if hypertension is present, while the second type responds to hydrocortisone and supportive therapy. Intravenous barbiturates given to treat convulsions are dangerous as their effects are potentiated. Nalorphine has been suggested as an additional agent of value if the respiratory centre is depressed. The rationale involving the use of steroids is not clear, but the results are excellent. Many patients can be aroused in 10 minutes.

2. *Vasopressors*

Hypertensive crises occurring after the use of pressor agents are best handled with phentolamine or chlorpromazine. Vasopressors should not be used to combat hypotension after pethidine potentiation; the only drug one can use with safety appears to be hydrocortisone.[34]

The treatment of barbiturate potentiation is the same as for barbiturate poisoning.

Knowledge of therapy with these drugs is as important, to anaesthetists particularly, as that of steroid therapy and a plea is made that they ascertain clearly what drugs the patient is using; contacting, if necessary, the practitioner who originally prescribed them, since so many patients have no idea whatsoever of the nature of the preparation they are so innocently taking. Furthermore, these patients, like those receiving steroids, should carry a card with them to that effect.

SUMMARY

One is confronted with the unpleasant situation, where the administration of a MAO-inhibitor, (nardil, marsilid, marplan, niamid, monase, catron, drazine, actomol, tersavid, parnate, parstelin, eutonyl), probably acting by inhibiting monoamine oxidase and producing increased monoamines in the brain, thus greatly improving some forms of mental depression—which is where their key use lies, as well as being used in a variety of medical conditions—may result in violent potentiation for up to 3 weeks, of agents widely used in anaesthesia, including powerful analgesics, vasopressors, barbiturates and some local analgesics, producing fatal results in a group of patients being treated by psychiatrists, general practitioners and physicians.

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