MONOAMINE OXIDASE INHIBITORS AND ANAESTHESIA
A Review

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Iproniazid was synthesized in the early 1950s and used in the treatment of tuberculosis. Its antituberculous properties failed to meet expectations, but clinicians noted evidence of central stimulation [34]. Research into this observation attributed the central effects of iproniazid to the inhibition of monoamine oxidase (MAO). There has been recent renewal of interest in the use of monoamine oxidase inhibitors (MAOI) [14], since other forms of treatment for depression and phobias are still far from satisfactory, especially in those patients who appear to respond to treatment with MAOI. During the past three decades, there have been numerous reports of MAOI-drug interactions, often serious or fatal. Some of these relate to routine anaesthetic practice.

ACTIONS OF MAO
Two MAO subtypes have been identified [37]: type A preferentially deaminates noradrenaline and 5-hydroxytryptamine (5-HT), whilst type B deaminates phenylethylamine.

Monoamine oxidase is one of the two main enzymes involved in the inactivation of non-methylated biogenic amines (the other is catechol-o-methyl transferase (COMT)) (fig. 1). Within the adrenergic neurone, noradrenaline is stored in a stable pool (combined with adenosine triphosphate (ATP)), and in a mobile pool ready for immediate release (fig. 2). There is a constant turnover of the stable pool and MAO is the mediator. It acts to limit the size of the stored pool. Inhibition of MAO leads to a larger stable pool and, hence, a greater mobile pool.

MAO is also found in other types of neurone within the brain which use dopamine or 5-HT as transmitters. Here it serves essentially the same function. In other parts of the body, MAO is found principally in the liver and gut, where its function is to metabolize potentially hazardous amines.

MAOI act by forming a stable, irreversible complex with MAO; the main target seems to be cerebral neuronal MAO. Therefore, the size of the amine pools is no longer limited and, as a result, the amount of noradrenaline available for release in the neurone, increases. However, these effects are not confined to the brain and the concentration of noradrenaline also increases within the sympathetic nervous system. Since the majority of MAOI cause irreversible enzyme inhibition, their effects are prolonged, because the synthesis of new enzyme is a slow process.

MAOI INTERACTIONS WITH ANAESTHETIC AGENTS

Narcotic analgesics

Narcotic analgesics play an essential part in anaesthetic practice. Strong analgesics are often...
required for the relief of severe pain or as part of the anaesthetic regimen during surgery. When patients taking MAOI present in these situations, there is concern about a potentially fatal interaction on the one hand, and the inadequate relief of pain on the other. What is not appreciated is that the MAOI-narcotic interaction has two distinct forms:

First, an “excitatory” form (type I) characterized by sudden agitation, unmanageable behaviour, headache, hyper- or hypo-tension, rigidity, hyperpyrexia, convulsions and coma. It is thought to be attributable to central serotonergic overactivity.

Second, a “depressive” form (type II) consisting of respiratory depression, hypotension and coma, as a result of the inhibition of hepatic microsomal enzymes by the MAOI, leading to accumulation of free narcotic. Pethidine is the only commonly used narcotic to have elicited the excitatory response, which is, however, frequently severe and often fatal.

**Pethidine.** The first reported interaction between pethidine and MAOI concerned a 60-yr-old doctor treated for pulmonary tuberculosis with iproniazid [22]. He developed severe muscle twitching, profuse perspiration, hyperreflexia and upgoing plantar responses within 20 min of receiving pethidine 100 mg i.m. He recovered. Iproniazid also had a vogue in the treatment of intractable angina and three cases were reported of similar, sudden deterioration after the additional administration of pethidine [24, 33]. Further reports appeared of seven psychiatric patients receiving a variety of MAOI who were given pethidine for surgery, labour pains, severe headache or backache [9, 10, 12, 23, 28, 38]. Six had a sudden excitatory reaction; two of them...
died. Further cases of pethidine–MAOI interactions continue to be reported, and an animal study is presented in this issue [18].

Based on studies in animals, it has been postulated that the excitatory response is caused by an increase in the cerebral 5-HT concentration. This follows the inhibition of monoamine oxidase [30] and is potentiated by pethidine, which blocks the neuronal uptake of 5-HT [7]. This reaction occurs in about 20% of cases, probably because it is necessary to exceed a critical cerebral 5-HT concentration to trigger the response [27]. Animals pre-treated with inhibitors of 5-HT synthesis do not exhibit an increase in cerebral 5-HT concentration, or the excitatory response. However, other authors have suggested that this may be an idiosyncratic reaction [13].

Should an excitatory response occur, hypertension is treated ideally with an alpha-adrenergic receptor blocking agent, such as phentolamine or with peripheral vasodilators, such as hydralazine or sodium nitroprusside. If these are not available, parenteral chlorpromazine [7, 24] is useful as an anti-hypertensive, antipyretic and general sedative. Hydrocortisone [12] or prednisolone [33] may also be useful. Cardiac arrhythmias may be treated with beta-adrenergic blocking drugs. Acidification of the urine will increase the rate of clearance of pethidine to a small degree [17].

Morphine. In a comprehensive review of MAOI interactions, Stockley [36] wrote that "the serious pethidine–MAOI interaction also cast a shadow over morphine, resulting in the appearance of morphine in a number of lists and charts of drugs that were said to interact with the MAOI". However, another review [1] concluded that "no documentation supports the involvement of narcotic analgesics other than pethidine with the MAOIs". Two patients [23, 33] who had severe excitatory reactions to pethidine (one fatal) had previously been given morphine with no adverse effects. Brown and Waldron [6] safely gave morphine 20 mg i.m. to five patients who developed severe headache and retrosternal discomfort whilst receiving tranylcypromine.

Sargent [32] knew "of some ten cases with no side effects except a more prolonged morphine action". Thus, morphine has been recommended as the narcotic analgesic of choice in the presence of MAOI administration [1]. Morphine does not block neuronal 5-HT uptake, but its narcotic effects may be potentiated in the presence of MAOI. A single case report of a type II (depressive) reaction following morphine has been described [29]. The patient, who was receiving tranylcypromine, was given a pre-operative trial of incremental morphine i.v. After the third dose (a total of 6 mg of morphine) she became hypotensive and unconscious. Naloxone 0.4 mg i.v. restored arterial pressure to normal and the patient to full consciousness. This case illustrated the importance of careful titration of i.v. morphine against clinical response in a patient taking MAOI, when pain relief is required in an emergency. Should a depressive reaction occur, treatment is mainly supportive. Noradrenaline is the most reliable vasopressor. Indirectly-acting sympathomimetic agents (such as metaraminol) that have mixed actions also release endogenous noradrenaline and so risk provoking a hypertensive overshoot—as a result of the increase in noradrenaline concentration in the sympathetic nerve endings. Naloxone, as in the above case report, or hydrocortisone [12] may be useful.
Respiratory depression may require assisted ventilation.

Other narcotics. Dextromethorphan (Cosylan), like pethidine, blocks neuronal 5-HT uptake. Rivers and Horner [29] reported a fatal interaction. A 26-yr-old woman receiving phenelzine 15 mg 6-hourly for depression consumed 60 ml of a cough mixture containing dextromethorphan. Within 1 h she became unconscious, rigid and severely hypotensive with fixed dilated pupils. Core temperature was 42 °C. She died despite attempted resuscitation.

Phenoperidine is probably best avoided as its main metabolites are norpethidine and (to a lesser extent) pethidine. Papaveretum is a mixture of morphine and other opiate alkaloids and would appear to have no advantage over morphine. Pentazocine has been studied in animals, in which interactions with MAOI have occurred [31], but it is not clear if this occurs in man. Methadone has been given concurrently with tranylcypromine, both at 30 mg daily for 3 months without mishap, in a drug addict who developed depression while on a withdrawal programme [20]. There is anecdotal evidence to support the safety of fentanyl in the presence of MAOI. There is no information about alfentanil or meptazinol. For buprenorphine, see the paper by Mackenzie and Frank in this issue [18].

Induction agents

Studies in animals suggest that MAOI may have a non-specific inhibitory effect on hepatic microsomal enzymes. Because of this, potentiation of barbiturates may be expected. This has been found in animals [39], although there is a case report of hypotension following induction with sodium thiopentone [16]. The patient had received morphine and hyoscine as premedication. The same authors give anecdotal evidence of prolongation of the effect of thiopentone by MAOI.

Although no interactions have been reported with the use of ketamine and MAOI, theoretically, it should be avoided in patients taking MAOI because of the stimulatory response of the cardiovascular emergence phenomenon after ketamine.

Neuromuscular blocking agents

Phenelzine has been shown to decrease pseudocholinesterase concentration; accordingly, there have been case reports of a prolonged effect from suxamethonium [3, 5]. This may lead to apnoea following suxamethonium and may modify the fit during electroconvulsive therapy.

There is no information regarding interactions with non-depolarizing neuromuscular blocking drugs. However, since pancuronium bromide releases stored adrenaline, it is a theoretical hazard.

Vecuronium, atracurium or alcuronium would all appear to be suitable alternatives.

Anti-emetics

Phenothiazines. Although the combination of MAOI and phenothiazines has been recommended in patients with psychiatric conditions, three reputed fatalities have been reported with this combination [2, 19]. However, none of these cases involved the use of a phenothiazine as an anti-emetic. In fact, chlorpromazine is considered a good sedative for treatment of the hypertensive excitatory reaction induced by MAOI.

Droperidol. There is solitary report of hypotension in a patient taking MAOI, who was given a relatively large dose (20 mg) of droperidol as premedication, 4 days after ceasing his psychiatric medication [26]. There is no evidence that this was an interaction.

Anticholinergics

There is no confirmed interaction between anticholinergic drugs and MAOI. Hyperthermia has been reported in animals and, theoretically, atropine would worsen any excitatory interaction of MAOI. Sheehan, Claycomb and Kouretas [34] stated that “anticholinergics are significantly potentiated” by MAOI.

Anaesthetic gases and volatile agents

Nitrous oxide, halothane, enflurane and isoflurane are all safe in the presence of MAOI. There is a report that rats, pre-treated with MAOI, required a greater minimum alveolar concentration of cyclopropane for anaesthesia [21].

These drugs also have inhibitory actions on other enzyme systems, most notably the hydroxylation and oxidation systems in liver microsomes [35]. Therefore, theoretically, there is a chance of increased reductive metabolites of halothane being formed. Thus, although no reports of any problems exist, there is an increased possibility that halothane could cause hepatic damage.
Local anaesthetic preparations

The only known report of an interaction between a local anaesthetic drug and an MAOI was with cocaine, which was used in a patient also given pethidine and local adrenaline [9]. It has been recommended that adrenaline-containing solutions should be avoided. If a vasoconstrictor is thought to be necessary, felypressin is a suitable alternative.

Regional blockade can be utilized for postoperative analgesia.

Other associated agents used during anaesthesia

Doxapram. Based on animal studies, it has been suggested that pretreatment with MAOI potentiates the therapeutic and side effects of doxapram [36]. The manufacturers recommend caution with its use, although there are no clinical data available.

Benzodiazepines. The concurrent use of MAOI and benzodiazepines is usually considered safe. There have been, however, two reports of gross oedema which was attributed to a benzodiazepine–MAOI interaction [15, 25].

Sympathomimetic agents. Agents such as amphetamine, ephedrine and metaraminol act partially by releasing endogenous noradrenaline and adrenaline and risk provoking a fatal hypertensive crisis. During treatment with MAOI, large amounts of noradrenaline accumulate, not only in the brain, but also within sympathetic nerve endings in general. Indirectly-acting sympathomimetics will release these stores and produce an exaggeration of the normal physiological response. This is a serious and possible lethal interaction [36]. Hypertensive reactions can be treated with alpha-adrenoceptor blocking agents (such as phentolamine) or directly-acting vasodilators (such as sodium nitroprusside or nitrates) [7]. Chlorpromazine i.m. can also be used.

Directly-acting sympathomimetic agents (noradrenaline, adrenaline, isoprenaline) are the surest and most reliable pressor agents in the presence of MAOI. However, care must be taken, since it appears that their effects may be enhanced by receptor hypersensitivity. This augmentation of effect is unlikely to be clinically hazardous, except in those patients who show a marked hypotensive response to MAOI [4, 11]. These patients may show a several-fold enhancement of the pressor effects of noradrenaline.

DISCUSSION

Anaesthesia for patients taking MAOI has been a cause of concern to anaesthetists for many years. Advice that MAOI should be stopped 10–14 days before anaesthesia is unreasonable on two counts. First, MAOI are often a treatment of last resort; they are commonly used to good effect in patients who have been unresponsive to other forms of therapy; to discontinue effective treatment and compromise the patient's psychiatric status is, we believe, unreasonable. Second, MAOI form a stable complex with MAO and thus further MAO has to be synthesized; this is a long process. Adverse reactions to narcotic analgesics, have been noted even 3 weeks after discontinuing therapy.

As is seen in the history of MAOI–drug interactions, it is only with pethidine (and dextromethorphan) that the fatal excitatory reaction is seen. Reference is often made to the test dose procedure of Churchill-Davidson [8]. This involves giving small incremental doses of pethidine over a period of several hours in an attempt to demonstrate sensitivity to pethidine. This is hardly appropriate in the emergency situation where adequate analgesia is required immediately. More importantly, pethidine is the only narcotic analgesic used in anaesthesia to have elicited fatal excitatory interactions.

It would seem unnecessary to persist with pethidine in this test dose procedure, when the safety of morphine has been established.

CONCLUSION

Patients taking monoamine oxidase inhibitors should continue to do so before elective surgery. Per- and postoperative pain relief using regional blockade is a safe alternative to general anaesthesia.

If necessary, for emergency or elective surgery, morphine (in reduced dosage) is the narcotic analgesic of choice. Pethidine must never be administered to patients receiving MAOI.

When general anaesthesia is required there is a wide range of suitable anaesthetic agents. However, the dangers of sympathetic overactivity must be remembered.

REFERENCES

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