Review Article

Monoamine oxidase inhibitors revisited

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The monoamine oxidase inhibitors (MAOI'S) were developed during the late 1950's as the first effective antidepressant agents. With the development of the tricyclic antidepressants, their use was superseded by drugs which appeared to be generally more effective and lacked the dangerous side effect of hypertensive crises. Recently there has been a resurgence of interest in their use, prominently for atypical depressions but also for anxiety states, obsessive-compulsive disorders, eating disorders, chronic pain syndromes and migraine.[1,2]

Because of widespread belief among anaesthetists concerning the likelihood of life-threatening cardiovascular instability and central nervous system (CNS) dysfunction during anaesthesia and surgery when these agents are present, usual recommendations have been to withdraw them two to three weeks before surgery. A growing awareness of the relative safety of these agents has led to questioning of this policy. The true incidence of those previously reported adverse drug effects was and is unknown, but certainly they occur in a very small minority of patients.

Although firm epidemiologic data of recent years are lacking, anaesthetists may encounter increasing numbers of patients receiving MAOI's. The purpose of this review is to present the modern understanding of the MAO system, its drug inhibitors and relevant drug interactions in order that rational clinical decisions can be taken concerning these agents and the anaesthetic problems which can arise in their presence.

Key words

INTERACTIONS (DRUG): monoamine oxidase inhibitors, sympathomimetic amines, meperidine, barbiturates; PHARMACOLOGY: monamine oxidase inhibitors.

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History

Isoniazid and its close relative iproniazid were introduced for the treatment of tuberculosis in 1951.[3] Zeller *et al.*[4] demonstrated enzyme inhibition of MAO by iproniazid, and in 1957 it was first used for the treatment of depression.[5] Iproniazid was withdrawn from the United States' market in 1960 because of instances of severe and sometimes fatal hepatotoxicity.[6] Those agents in current use (tranylcypromine, phenelzine, isocarboxazid and pargyline, which in the U.S. is approved in the treatment of hypertension only) are the result of efforts to synthesise MAOI's having the benefits of ipronazid without its adverse effects. An often quoted figure is that tranylcypromine and phenelzine account for over 90 per cent of all the MAOI's currently prescribed.[1,7] Because these data were collected in the 1960's,[8,9] they may not accurately reflect contemporary usage. A host of second generation relatively type-selective MAOI's may soon be introduced.

The MAO enzyme system

MAO is a flavin-containing enzyme found principally on outer mitochondrial membranes. The active form is a dimer consisting of two subunits, each having a molecular weight of approximately 60,000 daltons. It functions via oxidative deamination to inactivate over 15 monoamines formed in the body, some of which serve important roles as synaptic neurotransmitters or neuromodulators, e.g., dopamine, 5 hydroxytryptamine (5 HT), norepinephrine and epinephrine.[10] MAO is present in most tissues of all vertebrate species.[11] Monoamine oxidase has been divided into two subtypes (MAO-A and MAO-B) on the basis of the different substrate specificities of the two forms.[12] There is now growing immunochemical evidence that the two forms are distinct isoenzymes of different molecular weight (63,000–67,000 for MAO-A vs 60,000–63,000 for MAO-B) as they yield different peptide fragments in mapping studies and have different electrophoretic behaviour.[13,14] Even more recently, a monoclonal antibody has been raised to human platelet MAO-B which cross-reacts with human liver MAO-B but not with liver or placental MAO-A.[15]

Substrates for MAO can be divided into three broad

TABLE Substrates and inhibitors of MAO

	MAO-A	*Mixed*	*MAO-B*
Substrates	epinephrine norepinephrine metanephrine serotinin (5-HT)	m,p-tyramine dopamine octopamine synephrine tryptamine N-methyltryptamine N,N-methyltryptamine	β-phenylethylamine phenylethanolamine o-tyramine benzylamine
Irreversible inhibitors	clorgyline Lilly 51641	phenelzine tranylcypromine isocarboxazid pargyline (more B)	(−)deprenyl Lilly 54781 MDL 72145 AGN 1133 AFN 1135
Reversible inhibitors	harmaline amiflamine cimoxatone moclobemide brofaramine (CGP 11305A) Ro 11-1163 MD 780515 FLA 336(+)		

categories on the basis of the affinity of the two isoenzymes for them, namely MAO-A specific, MAO-B specific and mixed substrates for which the two enzyme forms have approximately equal affinity (Table). However, it must be remembered that the substrate specificity is only relative as it is highly concentration dependent.[16,17] As the substrate concentration is increased the specificity becomes less apparent and it is now obvious that both forms of MAO are capable of metabolising all substrates if presented at an appropriate concentration.[16]

MAO inhibitors may also be divided into three categories on the basis of their specificity for the two enzyme subtypes (Table), but like the substrate specificity, the specificity of the selective inhibitors is also dose-dependent and disappears at higher doses.[18]

The picture is further complicated by differences in localisation of the MAO isoenzymes. In humans (there are considerable species differences) platelets contain exclusively MAO-B, placenta exclusively MAO-A,[14] liver has slightly more MAO-A activity than MAO-B while intestine slightly less.[19] About 60 per cent of human brain MAO activity is of the A subtype.[19] Monoaminergic neurons appear to contain mostly MAO-A, with the exception of serotonergic neurons which appear to contain a considerable amount of MAO-B.[20] Extraneuronal cells contain mostly MAO-B.[20] Although it appears likely that such a large degree of compartmentalism is likely to produce functional consequences they are far from clear at present.[20]

Monoamine oxidase has two major functions depending on the tissues considered. The target function of the use of MAO inhibitors in depression is the regulation of monoamine content within the nervous system. Here MAO metabolises neurotransmitters and transmitter synthesis byproducts both intraneurally and in combination with catechol-o-methyl transferase (COMT) extraneurally. Due to its location in the outer mitochondrial membrane,[21] MAO in neurons is only capable of deaminating substrates that are free within the cytoplasm, being unable to gain access to substrates once they are bound within storage vesicles. As a result the cytoplasmic concentration of monoamines is maintained at a very low level. MAO-A may have a higher affinity for synthesis byproducts, such as tryptamine and octopamine, than for the transmitters noradrenaline and dopamine, maintaining the purity of neurotransmitters by preventing the build-up of these compounds in the storage vesicles.[11] In addition intraneuronal MAO-A probably forms the last line of defence against circulating indirectly acting sympathomimetic amines which, without MAO, would be free to enter the cytoplasm of nerve terminals and ultimately displace the normal transmitters from their storage vesicles.

Other tissues with high MAO content include liver, kidney and lung[19] where the enzyme performs a defensive function inactivating circulating monoamines.[22] In particular, they appear to form the first line of defence against monoamines absorbed from foods, such as tyramine and β-phenyl ethanolamine, which would otherwise produce an indirect sympathomimetic response resulting in the precipitous rise in blood pressure known as the "cheese

effect." MAO is also associated with the blood-brain and gut-blood barrier where it probably performs a similar function.[22]

MAO inhibitors

Inhibition of neuronal MAO (i.e., MAO-A) produces a demonstrable increase in both the monoamine content of brain and the cytoplasmic concentration of MAO substrates within a few hours.[23] While the therapeutic action was originally believed to be due to this amine accumulation,[24] recent evidence has cast considerable doubt on this view.

There are several secondary adaptive responses to the increased amine levels. A reduction of amine synthesis by end-product inhibition of tyrosine hydroxylase has been clearly demonstrated within the noradrenergic system[25] and also for serotonergic neurons[26] after treatment with MAO inhibitors.

The increased cytoplasmic levels of synthesis byproducts, which may increase up to 30 times their normal concentration in contrast to norepinephrine and dopamine which only increase about two-fold,[23] begin to enter amine storage vesicles where they compete with norepinephrine for space. Although the rate of replacement of norepinephrine by the false transmitter octopamine is usually slow, it is accelerated by increased levels of circulating tyramine, which is converted within the nerve terminal to octopamine by dopamine β-hydroxylase.[27] Octopamine has been shown to replace almost stoichometrically the reduction of norepinephrine release normally seen after MAO inhibition.[27] There is also indirect evidence that dopamine can be stored in vesicles and released as a co-transmitter where it stimulates inhibitory pre-synaptic dopamine receptors.[27] In addition to the exocytotic release of dopamine, it is likely that some stimulation of inhibitory pre-synaptic α-adrenergic and dopaminergic receptors will result from the passive diffusion of the increased cytoplasmic amine levels into the synaptic cleft.[28]

After several weeks of treatment with MAO inhibitors effects are apparent at the receptor level. There are reductions in β-adrenoreceptor numbers, and functional activity as measured by norepinephrine stimulated cyclic-AMP formation as well as reductions in α_1- and α_2-adrenoreceptors, $5HT_1$ and $5HT_2$ receptors, but not dopamine receptors.[11] These changes closely resemble the pattern of receptor down regulation following chronic tricyclic antidepressant therapy.

A reduced neuronal firing rate has been observed in both the serotonin-containing neurons of the median raphe and the norepinephrine containing neurons of the locus ceruleus, following chronic administration of MAO inhibitors.[29,30] In addition, chronic, but not acute, clorgyline treatment attenuates the behavioural changes induced by clonidine (an α_1-adrenoreceptor agonist) in rats.[31]

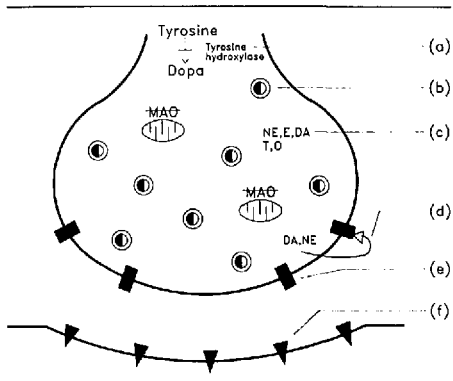

FIGURE Neuronal consequences of chronic MAO inhibition in an adrenergic neuron. NE = norepinephrine, E = epinephrine, DA = dopamine, T = tyramine, O = octopamine. (a) end-product inhibition of transmitter synthesis enzymes; (b) accumulation of false transmitters in storage vesicles; (c) increased cytoplasmic amine concentration; (d) stimulation of inhibitory pre-synaptic receptors by leakage of cytoplasmic amines; (e) down-regulation of presynaptic receptors; (f) down-regulation of post-synaptic receptors.

Systemic inhibition of MAO also produces the risk of potentiation of the effects of indirectly acting sympathomimetic drugs due to the suppression of the body's normal means of metabolising circulating monoamines. The most obvious consequence of inhibition of non-neuronal MAO is the so-called "cheese reaction" caused by ingestion of foodstuffs rich in substances such as tyramine and phenylethanolamine, or any other MAO substrates capable of displacing norepinephrine from its vesicular storage. However, the hypertensive effects of intravenous administration of indirectly acting sympathomimetic drugs may also be potentiated markedly by MAO inhibition.[32]

Overall, the recent evidence, summarised in the Figure, indicates that the major side-effects of chronic MAO inhibition will relate to a general reduction in sympathetic outflow producing a lower resting blood pressure (in fact, the only approved indication for pargyline in the U.S. is for treatment of hypertension), and a decrease in the ability of the sympathetic system to respond to stimuli resulting in such conditions as orthostatic hypotension. In addition there is the risk of a marked potentiation of indirectly acting sympathomimetic agents with a precipitous rise in blood pressure.

While the traditional MAO inhibitors (i.e., phenelzine, isocarboxazid, tranylcypromine and pargyline) are inhibitors of both MAO-A and MAO-B, there have been several

developments recently that are specific for one or other of the enzyme forms. The specificity of these agents may prove to be of some benefit in reducing the side-effects of the non-specific drugs[33] but since none of these drugs are in full-scale usage it is difficult to ascribe any definite advantages to them as yet.

Specific MAO-A inhibitors, such as clorgyline, seem likely to behave much as the non-specific inhibitors in terms of their effects on the central and sympathetic nervous systems. When used in MAO-A specific doses they should be slightly less likely to potentiate indirectly acting sympathomimetic drugs since MAO-B in the tissues responsible for metabolising circulating amines should be spared. Unfortunately, these drugs do not appear to have lived up to their promise in this regard[34,35] which may indicate that intraneuronal MAO-A is more important as a defence against this potential danger than hepatic and other extraneuronal MAO.

Specific MAO-B inhibitors such as (−)deprenyl, may be safer from the point of view of side-effects[23] but their efficacy in treating depression is as yet far from certain,[33] although this drug is currently being trialled in Europe for treatment of Parkinson's disease.[36] Since neuronal MAO-A is relatively uninhibited when this drug is used in MAO-A specific doses it seems likely that the sympathetic effects of MAO-A inhibitors will not occur,[23] nor will the cheese effect[37] although this latter property may be specific to (−)deprenyl among this group of drugs due to its tyramine uptake blocking properties.[38]

All the drugs considered up to this point are known as "suicide" inhibitors of MAO. The drugs are all substrates for MAO which converts them into highly reactive intermediates which form either irreversible or very slowly reversible covalent complexes with the enzyme to prevent its normal function.[39] In contrast to these drugs several competitive and therefore reversible inhibitors of MAO-A have been developed (Table). Although these are just as likely to produce orthostatic hypotension and other sympathetic side-effects,[33] they do appear less likely to produce an excessive hypertensive response to indirectly acting sympathomimetic amines. Because the MAO substrates are capable of displacing the inhibitor from the enzyme[40] the "cheese reaction" with these reversible agents appears to be self-limiting in animal and human studies to date.[33]

It is important to recognise that the drugs used clinically to inhibit MAO have other pharmacological effects. Tranylcypromine, phenelzine and pargyline, in decreasing order of potency, but not isocarboxazid, block the uptake of monoamine[41] as does deprenyl.[38] In addition, inhibition of the hepatic microsomal enzyme systems also seems to be a property of MAO inhibitors,[42] and has been used to explain the potentiation of the hypertensive effects of indirectly acting sympathomimetic amines that are not substrates for MAO.[43]

Finally, there are many drugs which are capable of weak to moderate MAO inhibition, including amphetamine and other α-methylated substituted amines[44] which are reversible inhibitors primarily of the A isoenzyme, as are the local anaesthetics procaine, procainamide, tetracaine, lidocaine, dibucaine and prilocaine.[45,46] Inhibition appears to be competitive and reversible in nature, with the exception of dibucaine which inhibits irreversibly.[46] The β-blockers propranolol, pindolol and oxprenolol but not atenolol also reversibly inhibit primarily MAO-A, propranolol in a competitive manner.[46]

MAO-B is inhibited to a moderate degree by a wide range of tricyclic antidepressants and antipsychotic drugs including amitryptyline, nortriptyline, doxepin, imipramine, desipramine, chlorpromazine and iprindole.[47] The clinical significance of these effects is difficult to predict but in the case of the antidepressant iprindole, which does not inhibit monoamine uptake, the inhibition of MAO may be relevant.[47]

Furazolidone and debrisoquine have also been considered to inhibit MAO. The wide range of drugs capable of inhibiting MAO indicate that the effect is not specific and may well be a property of many more, as yet unsuspected, drugs.

Drug interactions

The widespread inhibition by MAOI's of MAO enzyme and other enzyme systems indicates considerable potential for interference with the biotransformation and pharmacodynamics of other drugs. Concern has been raised in the anaesthetic literature regarding the concurrent use of MAOI's with narcotics, sympathomimetic agents and anaesthetics in general. The discontinuation of MAOI's at least two weeks before surgery has been often recommended and is a widely practised belief.[48–54] Nevertheless, there is growing appreciation, perhaps reflecting more contemporary experience, that anaesthesia can be safely administered in most patients in the presence of the chronic use of these agents.[55–60]

It is important to emphasise again that those previously reported adverse drug reactions occurred in a minority of patients. However, until we are able to identify those individual patients in whom problems are likely to arise, a cautious general approach should be followed in anaesthetising all patients who continue to receive MAOI therapy for appropriate indications and in appropriate doses. Such an attitude is vindicated by a recent clinical report detailing extreme hypertension (350 mmHg systolic) which followed induction of anaesthesia with etomidate 0.3 $mg \cdot kg^{-1}$ and atracurium 0.8 $mg \cdot kg^{-1}$ in a patient who had been maintained on tranylcypromine for the

previous two months.[61] The authors of this report were unable to attribute a specific cause for such severe hypertension. They did, however, make the point that in this patient the presence of an indwelling arterial line allowed for early detection and treatment of this problem.

Reported drug interactions of importance to the anaesthetist, classified according to the nature of the interacting agent, are summarised in the following sections.

Narcotic analgesics/MAOI interactions

Several years after the introduction of the MAOI's, isolated case reports began appearing which raised the possibility that meperidine interacted with iproniazid to produce a syndrome of coma, hyperpyrexia and hypotension.[62–64] In patients taking phenelzine, interactions with meperidine appeared to be even more severe. Perioperative death attributed to the above interaction was reported in 1960. The patient, who had been receiving phenelzine, had been uneventfully treated for pain relief with morphine, but after receiving two injections of meperidine totalling 150 mg, became restless, hyperpyrexic, cyanotic and died within several hours.[65] Taylor,[66] reporting on two phenelzine-meperidine interactions in 1962, described the case of a woman who received meperidine uneventfully on one occasion but experienced a severe hypertensive reaction with meperidine after her phenelzine dosage had been increased. Combinations of tranylcypromine and meperidine produced similar reactions.[67] About this time papaveretum (a mixture of water soluble narcotic alkaloids containing approximately 50 per cent morphine), administered as a premedicant was incriminated in a comatose, hypotensive reaction with phenelzine.[68]

By 1965 it was estimated that over 3.5 million people in the U.S. and 500,000 people in Canada had received tranylcypromine.[51] Almost certainly most patients were reacting normally to the administration of narcotics, yet there seemed to be a small group of patients in whom the combination of meperidine with MAOI's could produce severe, life-threatening reactions. For this reason Churchill-Davidson advocated the preoperative use of small test doses of analgesics,[69] in an attempt to avoid delaying anaesthesia for two weeks or using entirely non-narcotic techniques. This method has not gained widespread acceptance.

While decelerated breakdown of meperidine due to N-demethylase inhibition by MAOI's could explain the exaggerated normal response of this drug, namely hypotension and respiratory depression, it does not explain other reported effects such as hypertension and hyperpyrexia.[70] The most likely mechanism for the observed hyperpyrexia is a possible increase in cerebral 5-HT content caused by MAOI's which itself may be potentiated by meperidine because the latter blocks neuronal uptake of 5-HT.[52] Animal studies have demonstrated that a critical brain level of 5-HT, about 60 per cent above normal, is necessary before the potentiation occurs.[70] This hyperpyrexia does not occur in animals pretreated with 5-HT inhibitors. The cause of the hypertension may be excessive endogenous catecholamine release in response to narcotic-induced hypercarbia.[52] Interestingly, recent work has shown that meperidine toxicity is increased only when both MAO-A and MAO-B are inhibited.[71] Thus, these problems might be avoided by use of specific A or B MAOI's.

Reactions to morphine seem to be much less likely in patients taking MAOI's.[72,73] Brown and Waldron[74] uneventfully treated five patients with headaches believed to be due to the "cheese reaction" with morphine 20 mg. Evans-Prosser[54] administered random injections of morphine, meperidine and water to 15 patients on MAOI's. These injections were given at 45 min intervals in increasing doses. All patients reacted normally.

Experimental studies with mice pretreated with iproniazid and tranylcypromine have shown that acute toxicity of morphine, meperidine and pentazocine was increased. The dosages used were, however, enormous; namely up to $15\ mg \cdot kg^{-1}$ of tranylcypromine (normal human dose $20–50\ mg \cdot day^{-1}$).[70] Based on later similar work performed on rabbits pretreated with pargyline, claims were made for the greater safety of pentazocine.[73] Similar claims have been made concerning codeine.[50,75] Scrutiny of published data pertaining to humans, however, supports the possibility of problems only with meperidine and even then relatively infrequently.

Published series by El-Ganzouri *et al.*[57] and Wong,[60] involving a total of 22 patients (El-Ganzouri *et al.* 14 patients, Wong eight patients) who underwent general surgical procedures while maintained on MAOI's reported no unusual or unexplainable problems. Of the 14 patients anaesthetized by El-Ganzouri *et al.*, 12 received general and two regional anaesthesia. Three of the 12 patients administered general anaesthesia received intraoperative fentanyl. Postoperatively, three of the 14 patients received fentanyl and nine of the 14 patients received morphine. Intraoperative hypotension occurred in one patient following 13 ml of 0.5 per cent bupivacaine administered as a thoracic epidural, and was corrected by intravenous phenylephrine.

In Wong's group of eight patients six received a general anaesthetic (of which three received intraoperative fentanyl) and two were given a sub-arachnoid block. Both patients administered sub-arachnoid anaesthesia and one patient receiving general anaesthesia developed mild intraoperative hypotension. All were treated uneventfully with intravenous ephedrine.

Cardiac surgery has been safely performed in two patients (one coronary artery bypass grafting, one mitral valve replacement) premedicated with morphine and anaesthetised with fentanyl 75 $\mu g \cdot kg^{-1}$.[58] Braverman *et al.*[56] found no significant differences in awakening times in dogs anaesthetised with amylbarbitone 25 $mg \cdot kg^{-1}$ who were then intubated and mechanically ventilated with fentanyl (approximately 25 $\mu g \cdot kg^{-1}$), one per cent enflurane and 70 per cent nitrous oxide for three hours in the presence or absence of a three-week course of tranylcypromine.

A recent clinical report describes the use of a continuous epidural fentanyl infusion at about 60 $\mu g \cdot hr^{-1}$ to provide postoperative analgesia for four days following an abdominoperineal resection for adenocarcinoma of the rectum. This particular patient, who had received tranylcypromine daily for 12 years, experienced an uneventful postoperative course.[76] El-Ganzouri *et al.*[57] administered epidural morphine 0.2 $mg \cdot hr^{-1}$ as a continuous infusion during surgery and throughout the postoperative period in a single patient undergoing a gastrectomy. There were no problems attributable to the use of epidural morphine.

In summary, general opinion favours the use of morphine or fentanyl when the use of intra- or postoperative narcotic is required in patients receiving MAOI's. The use of meperidine is totally unsuitable in view of the number of adverse reactions reported with its use, although it must be acknowledged that most of the information relating to meperidine is in the form of anecdotal case reports. On the other hand, there is a limited amount of scientific data pertaining to animals and humans describing the safe use of fentanyl and morphine with an absence of incriminating case reports pertaining to these agents.

Sympathomimetic amines/MAOI interactions

The so-called "cheese reaction" that may follow ingestion of tyramine-containing foods is the most feared general problem associated with MAOI therapy.[50] This reaction was first recognised by a chemist who noticed his wife developing severe headaches after eating cheese.[52] Other foods implicated in this syndrome include beer, wine, pickled herring, snails, chicken liver, yeast, large quantities of coffee, citrus fruits, canned figs, broad beans (which contain dopa) and chocolate and cream or their products.[75] MAOI's prevent the inactivation of tyramine by MAO enzyme in the gastrointestinal tract and liver.[53] Tyramine therefore enters the bloodstream and releases norepinephrine from intracellular vesicles in sympathetic nerve terminals. Severity of the reaction depends upon several factors. At least 6 mg tyramine PO is required to produce a moderate rise in blood pressure, which becomes severe if over 20 mg is ingested.[9] Subarachnoid haemorrhage has been described after 50 mg oral ingestion of ephedrine-provoked hypertension in a patient receiving nialamide, an older MAOI.[77]

The hydrazine MAOI's are reported to be less likely to result in a hypertensive crisis than the nonhydrazine derivatives.[8] Hypertensive responses are five times more common with tranylcypromine than with phenelzine, and may be least problematic with isocarboxazid.[9] Nevertheless, it should be assumed that all currently marketed MAOI's are capable of producing hypertensive crises. Hypertensive reactions with a vasopressor (methylamphetamine, 3 mg IV) have been reported as long as three weeks after medication was discontinued.[78] In this instance the administration of methylamphetamine in response to anaesthetic-induced hypotension caused a rise in systolic blood pressure from 85 mmHg to 230 mmHg in a patient formerly receiving pargyline. The authors commented that this response was of the order of three times that expected with this dose of methylamphetamine.

In addition to tyramine,[9,52] hypertensive reactions have been reported with ephedrine,[79] metaraminol[80], methylamphetamine,[78,81] phenylpropranolamine,[81] phenylephrine,[51,83,84] levodopa[85] and dopamine.[86]

There are no controlled studies attributing development of such severe hypertensive episodes to concurrent use of directly acting sympathomimetic amines (e.g., epinephrine, norepinephrine, isoproterenol and methoxamine) and chronically administered MAOI's. That the intravenous administration of directly acting sympathomimetic amines failed to provoke hypertension was demonstrated some 20 years ago.[84] The reason for this may be that exogenous, directly acting sympathomimetic amines are primarily removed from the vicinity of the receptors by neuronal uptake. They are also in part degraded by an extracellular enzyme, namely catechol-o-methyl transferase (COMT).[87] They do not flood the intracellular sites of action of MAOI's with monoamines. There is no experimental evidence to support the former widespread claim of avoiding all vasoactive amines in the presence of monoamine oxidase inhibitors.[7,50,51,88] Boakes *et al.*[89] infused catecholamines to healthy human volunteers given a five- to seven-day course of phenelzine or tranylcypromine. They found a 2–2.5-fold potentiation of the pressor effect of phenylephrine but no clinically significant potentiation of the cardiovascular effects of norepinephrine, epinephrine or isoproterenol. Wong *et al.*[55] demonstrated no difference in epinephrine-induced arrythmias in pargyline-treated dogs versus control animals. Using dogs anaesthetised with amylbarbitone, fentanyl (approximately 25 $\mu g \cdot kg^{-1}$), 70 per cent nitrous oxide and one per cent enflurane, Braverman *et al.*[56] showed the mean blood pressure increases to norepinephrine and ephedrine were not significantly different

before or after three weeks of treatment with tranylcypromine, although the baseline blood pressure remained elevated after each dose of ephedrine. El-Ganzouri *et al.*[57] described one patient administered a thoracic epidural anaesthetic who developed a brief period of hypotension that responded to treatment with Ringer's lactate and three 100 μg divided doses of phenylephrine. Wong[60] retrospectively described three of eight patients anaesthetised for surgical procedures who developed mild intraoperative hypotension. In two of these spinal anaesthesia had been used. All were successfully treated with ephedrine.

To date the most consistent theme with sympathomimetic amine/MAOI interactions is that significant cardiovascular problems have not been reported in either humans or animals with directly acting agents. There is an unknown but seemingly very low incidence of hypertensive episodes in the presence of indirectly acting compounds. Ideally, the use of vasoactive compounds in the treatment of anaesthetic induced hypotension should be kept to a minimum. If needed, the use of a directly acting compound (e.g., methoxamine) is preferable to that of an indirectly acting one. Certainly vasoactive drugs should be initially administered in very small doses, about one-third of normal, with additional titration of doses against cardiovascular responses.

Barbiturate/MAOI interactions

As with the narcotics and sympathomimetic amines, the dangers of barbiturate use in patients on MAOI's seem to have been exaggerated. While several oft-quoted animal studies indicated prolonged sleeping times[42,90,91] and numerous authors have advocated reduced doses of barbiturates,[87,88,92] there seem to be only two cases which suggest potential risk to humans of a barbiturate-MAOI combination. A 1962 report describes barbiturate intoxication in a psychiatric patient, maintained on tranylcypromine, who received amobarbital 250 mg orally.[93] This case may have been complicated or indeed even attributable to an underlying concussion. Jenkins and Graves[51] reported a 52-year-old male taking tranylcypromine whose blood pressure fell precipitously during induction with thiopentone. On the other hand, Brown and Cass[52] noted the safety of thiopentone when used frequently in patients on MAOI's. El-Ganzouri *et al.*[57] administered 1–3 $mg \cdot kg^{-1}$ thiopentone to all of 13 patients receiving electroconvulsive therapy (ECT) and eight of 14 patients undergoing general surgery. Three general surgical patients were induced with etomidate (0.3–0.6 $mg \cdot kg^{-1}$). Hypotension documented in one patient could be readily attributed as previously described to the presence of an accompanying thoracic epidural. No other adverse effects were reported.

Neuromuscular blocker/MAOI interactions

There is one documented case of prolonged apnoea as a result of the administration of succinylcholine in a patient receiving phenelzine.[94] These authors demonstrated low pseudocholinesterase levels in four of ten patients receiving phenelzine but in none of 12 patients receiving other MAOI's. Problems have not been reported with the use of nondepolarising relaxants. It therefore appears that monitoring of neuromuscular function should be undertaken if succinylcholine is used in patients maintained on phenelzine.

Anaesthetic guidelines

There have been and may continue to be significant drug interactions occurring in some patients receiving MAOI's who undergo anaesthesia and surgery. However, the current dictum advocating their discontinuation some two to three weeks prior to surgery places all patients in danger of developing potentially severe psychiatric problems. This policy of drug withdrawal seems based more on anecdotes and isolated responses than on controlled scientific studies.

As previously indicated, significant adverse drug responses reported to date have usually occurred with meperidine and some indirectly acting sympathomimetic amines. Anaesthetists with a good understanding of the pharmacology of MAOI's may wish to conduct their anaesthetic management of patients taking appropriate does of these agents for appropriate conditions within the following guidelines.

1 *Preoperative evaluation*

The overall status of the patient combined with the anticipated nature of surgery will dictate the extent of the preoperative workup. Patients should probably have documentation of preoperative liver function, in view of the possibility of drug-induced abnormalities and interactions. For elective procedures, consultation between anaesthetist, surgeon and psychiatrist is indicated in order that an overall assessment of the potential, albeit uncommon, risks of anaesthesia are balanced against the psychiatric complications of drug withdrawal, in particular the potential for suicide.

2 *Premedication*

Prior to elective surgery, premedication should be administered in sufficient dosage to alleviate anxiety and its accompanying sympathetic discharge. Use of benzodiazepines would seem appropriate. Unless specifically indicated, the use of anticholinergic agents as part of premedication would seem inadvisable.[95]

3 *Monitoring*

The nature and extent of surgery will dictate the type of

monitoring required. Wong[60] believes that beat-to-beat monitoring of heart rate and blood pressure via an arterial cannula should be considered in all patients.

4 *Anaesthetic technique*

The anaesthetic technique chosen should avoid sympathetic stimulation, either directly or indirectly, as a response to decreases in blood pressure. Reasonable control of blood pressure within those limits defined preoperatively as normal makes sense here. Close attention should be paid to control of blood volume. Never could the often-ridiculed statement of "avoid hypoxia, hypercarbia and hypotension" be more appropriate, in view of the possibility of exaggerated sympathetic responses to these abnormalities.

Meperidine should certainly be avoided. Fentanyl or morphine is suitable.[56–58] Enflurane or isoflurane should probably be employed in preference to halothane, to decrease the potential for arrythmogenic effects in concert with catecholamines.[96] While spinal and epidural anaesthesia have been successfully utilised,[57,60] their potential for hypotension and consequent need for vasopressors may mitigate in favour of general anaesthesia. If intraoperative hypotension does occur it should be treated with restoration of fluid volume and then, if necessary, with small doses of directly acting sympathomimetic amines (e.g., methoxamine). Any vasoactive drug administered must be titrated in small doses against cardiovascular response. If regional anesthesia is to be performed, a cautious approach would argue in favour of the use of local anaesthetic agents without epinephrine although problems have not been reported with epinephrine in the standard 1:200,000 dilution. Cocaine, which blocks re-uptake of monoamines into adrenergic nerve terminals, and therefore may potentiate the action of indirectly acting sympathomimetic amines, should probably be avoided. Should bronchospasm occur, its treatment by volatile anaesthetic agents and theophylline is indicated.[50]

Conclusion

Until recently, traditional teaching has been to discontinue MAOI therapy two to three weeks before surgery. The literature and texts relating to the concurrent use of MAOI's with anaesthesia are confusing, outdated and often contradictory. Significant adverse drug reactions can and have occurred in a minority of patients receiving MAOI's. The true incidence of such reactions is unknown.

While there are several recent clinical reports indicating the safety of these agents in combination with anaesthesia, only small numbers of patients are described in each series. Until it is possible to define those individual patients in whom adverse reactions are likely to occur, all patients must be assumed to be at some level of potential risk.

However, assuming administration in appropriate doses and for appropriate indications, patients can and likely should continue to receive MAOI therapy. A final decision on the administration of anaesthesia in the presence of MAOI therapy can only be made by an anaesthetist familiar with the pharmacology of the MAO system and its inhibitors.

References

1 *Zisook S.* Side effects of isocarboxazid. J Clin. Psych 1984; 45: 53–8.

2 *Anthony M, Lance JW.* Monoamine oxidase inhibition in the treatment of migraine. Arch Neurol 1969; 21: 263–8.

3 *Selikoff IJ, Robitzek EH.* Tuberculosis chemotherapy with hydrazine derivatives of isonicotinic acid. Dis Chest 1952; 21: 3.

4 *Zeller EA, Barsky J, Fouts JR, Kircheimer WF, Van Orden LS.* Influence of isonicotinic and hydrazine (INH) and 1-isonicotinyl-2-isopropyl hydrazide (IIH) on bacterial and mammalian enzymes. Experentia (Basel) 1952; 8: 349–50.

5 *Kline NS.* Clinical experience with iproniazid (marsilid). J Clin Exp Psychopathol 1958; 19: 72–8.

6 *Goldberg LI.* Monoamine oxidase inhibitors: adverse reactions and possible mechanisms. JAMA 1964; 190: 132–8.

7 *Sheehan DV, Claycomb JB.* The use of MAO inhibitors in clinical practice. *In*: Psychiatric Medicine Update, Manschreck TC, Murray GB (Eds). Massachusetts General Hospital reviews for physicians, New York, Elsevier 1984; 143–62.

8 *Biel H.* Monoamine oxidase inhibitor antidepressants. Structure activity relationships. *In*: Principles of Psychopharmacology, Clark WG, Del Guidice J (Eds). New York, Academic Press 1970; 269–78.

9 *Blackwell B, Marley E, Price J, Taylor D.* Hypertensive interactions between MAO inhibitors and foodstuffs. Br J Psychiatry 1967; 113: 349–65.

10 *Singer TP, Van Korff RW, Murphy DL.* Monoamine oxidase: structure, function and altered functions. New York, Academic Press 1979; 477–96.

11 *Murphy DL, Garrick NA, Aulakh CS, Cohen RM.* New contributions from basic science to understanding the effects of monoamine oxidase inhibiting antidepressants. J Clin Psych 1984; 45: 37–43.

12 *Johnston JP.* Some observations upon a new monoamine oxidase in brain tissue. Biochem Pharmacol 17: 1285–97.

13 *Cantham RM, Pintar JE, Haseltine FP et al.* Differences in the structure of A and B forms of human monoamine oxidase. J Neurochem 1981; 37: 363–72.

14 *Brown GK, Powell JF, Craig IW.* Molecular weight

differences between human platelet and placental monoamine oxidase. Biochem Pharmacol. 1980; 29: 2595–603.

15 *Denny RM, Fritz RR, Patel NT et al.* Human liver MAO-A and MAO-B separated by immunoaffinity chromatography with MAO-B-specific monoclonal antibody. Science 1982 215: 1400–3.

16 *Tipton KF, Fowler CJ, Houslay MD.* Specificities of the two forms of monoamine oxidase. *In*: Monoamine Oxidase: Basic and Clinical Frontiers. Kamijo E, Uskin E, Nagatsu T (Eds). 1982; 87–99.

17 *Suzuki O, Katsumata Y, Oya H.* Substrate specificity of type A and type B monoamine oxidase. *In*: Monoamine Oxidase: Basic and Clinical Frontiers. Kamijo E, Usdin E, Nagatsu T (Eds). 1982; 74–86.

18 *Fowler CJ, Ross SB.* Selective inhibitors of monoamine oxidase A and B; biochemical, pharmacological and clinical properties. Med Res Reviews 1984; 4: 323–58.

19 *Lewinsohn R, Glover V, Sandler M.* Development of benzylamine oxidase and monoamine oxidase A and B in man. Biochem Pharmacol 1980; 29: 1221–30.

20 *Glover V, Sandler M.* Clinical chemistry of monoamine oxidase. Cell Biochem. Funct 1986; 4: 89–97.

21 *Schnaitman C, Erwin VG, Greenawalt JW.*The submitochondrial localisation of monoamine oxidase. J Cell Biol 1967; 32: 719–35.

22 *Blaschko H.* The natural history of amine oxidases. Physiol Biochem Pharmacol 1974; 70: 83–148.

23 *Glover V, Sandler M.* Clinical chemistry of monoamine oxidase. Cell Biochem. Funct 1986; 4: 89–97.

24 *Schildkrant JI.* The catecholamine hypothesis of affective disorders. A review of the supporting evidence. Am J Psychiatry 1963; 122: 509–22.

25 *Neff NH, Costa E.* The influence of monoamine oxidase inhibition on catecholamine synthesis. Life Sciences 1966; 5: 951–8.

26 *Lin RC, Neff NH, Nga SH et al.* Turnover rates of serotonin and norepinephrine in brain of normal and pargyline-treated rats. Life Sciences 1969; 8: 1077–84.

27 *Kapin IJ.* False transmitters revisited: their role in the hypotensive action of MAO inhibitors. *In*: Monoamine Oxidase: Basic and Clinical Frontiers. Kamijo E, Uskin E, Nagatsu T (Eds). 1982.

28 *Finberg JPM.* Effects of selective inhibition of MAO types A and B on peripheral sympathetic function. *In*: Monoamine Oxidase: Basic and Clinical Frontiers. Kamijo E, Uskin E, Nagatsu T (Eds). 1982.

29 *Aghajanian GK.* Influence of drugs on the firing of serotonin-containing neurons in brain. Fed Proc Am Soc Exp Biol 1972; 31: 91–6.

30 *Campbell IC, Murphy DL, Gallager DW et al.* Neurotransmitter related adaption in the central nervous system following chronic monoamine oxidase inhibition. *In*: Monoamine oxidase: structure, function and altered functions. Singer TP, Von Korff RW, Murphy DL (Eds). New York, Academic Press 1979.

31 *Cohen RM, Anlakh CS, Campbell K et al.* Functional subsensitivity of α-adrenoreceptors accompanies reductions in yohimbine binding after clorgyline treatment. Eur J Pharmacol 1982; 81: 145–8.

32 *Simpson GM, White K.* Tyramine studies and the safety of MAOI drugs. J Clin Psychiatry 1984; 45: 59–61.

33 *Mann JJ, Aarons SF, Frances AJ, Brown RD.* Studies of selective and reversible monoamine oxidase inhibitors. J Clin Psychiatry 1984; 45: 62–6.

34 *Lader MH, Sakalis G, Tansella M.* Interaction between sympathetic amines and a new monoamine oxidase inhibitor. Psychopharmacologia 1972; 18: 118–23.

35 *Pare CMB.* The present status of monoamine oxidase inhibitors. Brit J Psychiatry 1985; 146: 576–84.

36 *Birkmayer W, Riederer P, Yondim MBH.* (–)deprenyl in the treatment of Parkinson's disease. Clin Neuropharmac 1982; 5: 195–230.

37 *Elsworth JD, Glover V, Reynolds GP et al.* Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the "cheese effect." Psychopharmacology 1978; 57: 33–8.

38 *Knoll J.* The possible mechanisms of action of (–)deprenyl in Parkinson's disease. J Neural Transmission 1978; 43: 177–98.

39 *Richards LE, Burger A.* Mechanism-based inhibitors of monoamine oxidase. Prog Drug Res 1987; 30: 205–19.

40 *Benedetti MS, Boucher T, Carlsson A, Fowler CJ.* Intestinal metabolism of tyramine by both forms of monoamine oxidase in the rat. Biochem Pharmacol 1983; 32: 47–52.

41 *Hedley ED, Snyder SH.* Relationship between the action of monoamine oxidase inhibition on the noradrenaline uptake system and their antidepressant efficacy. Nature 1968; 220: 1330–1.

42 *LaRoche MJ, Brodie BB.* Lack of relationship between inhibition of monoamine oxidase and potentiation of hexobarbital hypnosis. J Pharmacol Exp Ther 1960; 130: 134–7.

43 *Bowman WC, Rand MJ.* A Textbook of Pharmacology (2nd ed). Blackwell Scientific Publications, Oxford 1980; 11.7–11.11.

44 *Mantle TJ, Tipton KF, Garrett NJ.* Inhibition of monoamine oxidase by amphetamine and related compounds. Biochem Pharmacol 1976; 25: 2073–7.

45 *Fowler CJ, Callingham BA, Mantle TJ, Tipton KF.* The effect of lipophilic compounds upon the activity of rat liver mitochondrial monoamine oxidase -A and -B. Biochemical Pharmacol 1980; 29: 1177–83.

46 *Yasuhara, H, Wada I, Sakamoto K.* Inhibitory effects of β-blockers and local anaesthetics on monoamine oxidase and their membrane effects. *In*: Monoamine oxidase: basic

and clinical frontiers. Kamija K, Usdin E, Nagatsu T (Eds). Excerpta Medica, Amsterdam 1982; 251–61.
47 *Roth JA.* Inhibition of human brain type B monoamine oxidase by tricyclic psychoactive drugs. Mol Pharmacol 1978; 14: 164–71.
48 *Roizen MF.* Anesthetic implications of concurrent disease. *In*: Miller RD (Ed). Anesthesia. 2nd ed. New York: Churchill Livingstone, 1986; 331–2.
49 *Perks ER.* Monoamine oxidase inhibitors. Anaesthesia 1964; 19: 376–86.
50 *Davidson J, Zung WW, Walker JI.* Practical aspects of MAI inhibitor therapy. J Clin Psychiatry 1984; 45 (sec. 2): 81–4.
51 *Jenkins LC, Graves HB.* Potential hazards of psychoactive drugs in association with anaesthesia. Can Anaesth Soc J 1965; 12: 121–8.
52 *Brown TCK, Cass NM.* Beware – the use of MAO inhibitors is increasing again. Anaesth Intensive Care 1979; 7: 65–8.
53 *Sheean DV, Claycomb JB, Kouretas N.* Monoamine oxidase inhibitors: prescription and patient management. Int J Psych Med 1980–1981; 10(2): 99–121.
54 *Evans-Prosser CDG.* The use of pethidine and morphine in the presence of monoamine oxidase inhibitors. Br J Anaesth 1968; 40: 279–82.
55 *Wong KC, Puerto AX, Puerto BA, Blatnick RA.* Influence of imipramine and pargyline on the arrythmogenicity of epinephrine during halothane, enflurane or methoxyflurane anaesthesia in dogs. Life Sciences 1980; 27: 2675–8.
56 *Braverman B, Ivankovich AD, McCarthy R.* The effects of fentanyl and vasopressors on anaesthetized dogs receiving MAO inhibitors. Anesth Analg 1984; 63: 192 (Abs).
57 *El-Ganzouri AR, Ivankovich AD, Braverman B, McCarthy R.* Monoamine oxidase inhibitors: should they be discontinued preoperatively? Anesth Analg 1985; 64: 592–6.
58 *Michaels I, Serrings M, Shier N, Barash PG.* Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors. Anesth Analg 1984; 63: 1041–4.
59 *Ayd F.* Should monoamine oxidase inhibitors be discontinued preoperatively? Int. Drug Therapy Newsletter 1986; 21(6): 24.
60 *Wong KC.* Preoperative discontinuation of monoamine oxidase inhibitor therapy: an old wives tale? Sem Anes 1986; 5: 145–8.
61 *Sides CA.* Hypertension during anaesthesia with monoamine oxidase inhibitors. Anaesthesia 1987; 42: 633–5.
62 *Mitchell RS.* Fatal toxic encephalitis occurring during iproniazid therapy in pulmonary tuberculosis. Ann Int Med 1955; 42: 417–24.
63 *Papp C, Benaim S.* Toxic effects of iproniazid in a patient with angina. Br Med J 1958; 2: 1070–2.
64 *Shee JC.* Dangerous potentiation of pethidine by iproniazid and its treatment. Br Med J 1960; 2: 507–9.
65 *Palmer H.* Potentiation of pethidine. Br Med J 1960; 2: 944.
66 *Taylor DC.* Alarming reaction to pethidine in patients on phenelzine. Lancet 1962; 2: 401–2.
67 *Denton PH, Borell VM, Edwards NV.* Dangers of monoamine oxidase inhibitors. Br Med J 1962; 2: 1752.
68 *Spencer GT, Smith SE.* Dangers of monoamine oxidase inhibitors. Br Med J 1963; 1: 750.
69 *Churchill-Davidson HC.* Anaesthesia and monoamine-oxidase inhibitors. Br Med J 1965; 1: 520.
70 *Rogers KJ, Thornton JA.* The interaction between monoamine oxidase inhibitors and narcotic analgesics in mice. Br J Pharmacol 1969; 36: 470–80.
71 *Dostert P.* Myth and reality of the classical MAO inhibitors. Reasons for seeking a new generation. *In*: Tipton KF, Dostert P, Benedeth MS (Eds). Monoamine oxidase and disease. Prospects for therapy with reversible inhibitors. London: Academic Press, 1984: 9–25.
72 *Vickers MD.* Anaesthesia and MAO inhibitors. Br Med J 1965; 1: 1126.
73 *Penn RG, Rogers KJ.* Comparison of the effects of morphine, pethidine and pentazocine in rabbits pretreated with an MAO. Br J Pharmacol 1971; 42: 485.
74 *Brown DD, Waldron DH.* An unusual reaction to tranylcypromine. Practitioner 1962; 189: 83–5.
75 *Baldessarini RJ.* Drugs and the treatment of psychiatric disorders. *In*: Gillman AC, Goodman LS, Gilman A (Eds). The pharmacological basis of therapeutics. 6th ed. New York: Macmillan, 1980: 427–30.
76 *Youssef MS, Wilkinson PA.* Epidural fentanyl and monoamine oxidase inhibitors. Anaesthesia 1988; 43: 210–2.
77 *Hirsch MS, Walter RM, Hasterlik RJ.* Subarachnoid hemorrhage following ephedrine and MAO inhibitor. JAMA 1965; 194: 1259.
78 *Cousins MJ, Maltby JR.* Delayed recovery of sympathetic transmission following ten years MAO inhibition. Br J Anaesth 1971; 43: 803–6.
79 *Hirsch MS, Walter RM, Hauterlik RJ.* Subarachnoid hemorrhage following ephedrine and MAO inhibitors. JAMA 1965; 194: 1259.
80 *Horler AR, Wayne NA.* Hypertensive crises due to pargyline and metaraminol. Br Med J 1965; 2: 460–1.
81 *Mason A.* Fatal reaction associated with tranylcypromine and methylamphetamine. Lancet 1962; 1: 173–7.
82 *Cuthbert MF, Greenberg MP, Morley SW.* Cough and cold remedies: a potential danger to patients on monoamine oxidase inhibitors. Br Med J 1969; 1: 404–6.
83 *Blackwell B.* Hypertensive crisis due to MAO inhibitors. Lancet 1963; 2: 849–51.
84 *Elis J, Laurence Dr, Mattie H, Prichard BNC.* Modification by monoamine oxidase inhibitors of the effect of some sympathomimetics on the blood pressure. Br Med J 1967; 2: 75–8.

85 *Hunter KR, Boakes AJ, Laurence Dr, Sterne GM.* Monoamine oxidase inhibitors and L-dopa. Br Med J 1970; 3: 338.

86 *Horwitz D, Goldberg LI, Sjoerdsma A.* Increased blood pressure responses to dopamine and norepinephrine produced by monoamine oxidase inhibitor in man. J Lab Clin Med 1960; 56: 747–53.

87 *Janowsky EC, Risch SC. Janowsky DS.* Psychotropic agents. *In*: Smith TY, Miller RD, Corbascio AN (Eds). Drug Interactions in Anesthesia. Philadelphia: Lea and Febinger, 1981: 177–95.

88 *Jacobson J.* A review of the danger of monoamine oxidase inhibitors, with special reference to anesthesia. S Afr Med J 1965; 39: 10–4.

89 *Boakes AJ, Teoh PC, Barar FKS, Benedikter LT, Prichard BNC.* Interaction between sympathomimetic amines and antidepressant agents in man. B Med J 1973; 1: 311–5.

90 *Wulfsohn NL, Politzer WM.* 5-Hydroxytryptamine in anaesthesia. Anaesthesia 1962; 17: 64–8.

91 *Fouts JR, Brodie BB.* On the mechanism of drug potentiation by iproniazid. J Pharmacol Exp Ther 1956; 116–480–5.

92 *Gaines GY, Ress DI.* Electroconvulsive therapy and anesthetic considerations. Anesth Analg 1986; 65: 1345–56.

93 *Domino EF, Sullivan TS, Buby ED.* Barbiturate intoxication in a patient treated with a MAO inhibitor. Am J Psych 1962; 118: 941–3.

94 *Bodley PO, Halwax K, Potts L.* Low serum pseudocholinesterase levels complicating treatment with phenelzine. Br Med J 1969; 3: 510–2.

95 *Sjoquist F.* Psychotropic. (2) Interaction between monoamine oxidase (MAOI) inhibitors and other substances. Proc R Soc Med 1965; 58: 967.

96 *Johnston RR, Eger EI, Wildon C.* A comparative interaction of epinephrine with enflurane, isoflurane and halothane in man. Anesth Analg 1976; 55: 709–12.