POTENTIAL HAZARDS OF PSYCHOACTIVE DRUGS IN ASSOCIATION WITH ANAESTHESIA*

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Behind every crooked thought there lies a crooked molecule

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The fact that we have effective drugs will not stop the production of better ones

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I THE PSYCHOACTIVE DRUGS

IN RECENT YEARS, a group of drugs variously referred to as the psychoactives, psychic energizers, antidepressants, psychostimulants, psychoanaleptics, or mood elevators has been introduced into medicine in an attempt to counteract depression states pharmacologically

A *Uses of Psychoactive Drugs*

The uses of psychoactive drugs are listed in Table I The use of these drugs in clinical medicine is becoming more prevalent It is estimated that in Canada alone

TABLE I

USES OF PSYCHOACTIVE DRUGS

Psychotic depression
Psychoneurotic depression
Hypertension
Angina pectoris
Rheumatoid arthritis

over 500,000 patients have received the antidepressant tranylcypromine (Parnate) and that over 3½ million people in the U S A have taken this preparation [1] Not only are the psychoanaleptics used by psychiatrists in the management of psychotic depression, so that patients presenting for thiopentone-succinylcholine anaesthesia for electroconvulsant therapy must be suspect, but the use of these drugs has also become widespread in general practice medication of mild psychoneurotic depression They are used in the treatment of angina pectoris, hypertension, and rheumatoid arthritis as well The anaesthetist may be called upon to provide resuscitative management of a patient suffering from an overdose of these drugs

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Disturbing side-reactions to a wide variety of pharmacological agents have occurred in patients receiving antidepressants. A knowledge of the nature and actions of the psychoactive drugs is mandatory if one is to understand the problems which these drugs may present in relation to anaesthesia

B *Classification of Psychoactive Drugs*

Pharmacologically, the antidepressants may be classified into two main groups, as outlined in Table II (1) compounds which inhibit the enzyme monoamine-oxidase, (2) compounds which do *not* inhibit the enzyme monoamine-oxidase.

TABLE II

CLASSIFICATION OF PSYCHOACTIVE DRUGS (ANTIDEPRESSANTS)

A	Monoamine-oxidase (MAO) inhibitors
B	Antidepressants which are *not* monoamine-oxidase inhibitors

The monoamine-oxidase inhibitors in current use are listed in Table III under their generic and trade names

TABLE III

PSYCHOACTIVE DRUGS—MONOAMINE-OXIDASE INHIBITORS

Iproniazid (Marsilid)
Isocarboxazid (Marplan)
Phenelzine (Nardil)
Tranylcypromine (Parnate, Parstelin, Parstelin S-2)
Nialamide (Niamid)
Pargyline (Eutonyl)

1 *Monoamine-oxidase Inhibitors*

Iproniazid (Marsilid) was the first compound used, but it was too toxic, with fatal liver damage occurring

Phenelzine (Nardil) is a hydrazine It is chemically related to iproniazid

Tranylcypromine (Parnate) is not a hydrazine It closely resembles the amphetamines chemically As of March 1964 it was suggested by the manufacturer and by the Food and Drug Directorate of the Department of National Health and Welfare that this drug be restricted to in-patient use

Nialamide (Niamid) is less potent and slower acting than other MAO inhibitors This drug has been used to elevate the mood of patients with psychosomatic complaints accompanied by depression and in patients with angina pectoris who are depressed

Pargyline (Eutonyl) is a non-hydrazine compound introduced as an anti-hypertensive drug Although eutonyl inhibits the enzyme monoamine-oxidase, paradoxically, the increase in catecholamines has not been reconciled with the anti-hypertensive action of the drug It has mild antidepressant effects

2 *Antidepressants Which are Not Monoamine-oxidase Inhibitors*

The more commonly used of these drugs are outlined in Table IV

Imipramine (Tofranil) and *amitriptyline (Elavil)* are modified phenothiazines

TABLE IV

PSYCHOACTIVE DRUGS—NOT MONOAMINE-OXIDASE INHIBITORS

Imipramine (Tofranil)
Amitriptyline (Elavil)
Dimethylaminoethanol (Deanor)
Dextroamphetamine (Dexedrine)
Methamphetamine (Desoxyn)

Dimethylaminoethanol (Deanor) is an amine analogue of choline It is believed to be a precursor of acetylcholine It possesses only mild antidepressant action

II PHARMACOLOGY

A *Monoamine-oxidase Inhibitors*

(*a*) *Mode of Action*

The majority of the psychoactive drugs in current use are monoamine-oxidase inhibitors Increasing evidence lends support to the hypothesis that the antidepressant effects of these compounds are related to their ability to inhibit brain monoamine-oxidase, and to the resultant increase in the level of brain serotonin and/or norepinephrine [2]

(*b*) *Site of Action*

Increments in amine levels demonstrated to occur in diencephalic areas of the brains of animals have been associated with behavioural signs of increased activity It is believed that portions of these adrenergic areas (the mesencephalic reticular activating system and hypothalamic diencephalic area) serve as central headquarters for the sympathetic nervous system The activation of these areas has been suggested as at least one of the modes of action of the mono-amine-oxidase (MAO) inhibitors [3] This mesencephalic RAS and the hypothalamic diencephalic area are linked together by the limbic system [4] These three areas taken together constitute the so-called anatomy of the emotions, according to current concepts [5] It is also currently held that the emotions, to a great extent, are controlled by all three of these sites, anatomically connected with each other and with the cerebral cortex via the cingulate gyrus by means of the limbic system This great system—the Papez circuit[6]—connects the "emotion" areas of the brain with the cerebral cortex It is the anatomic pathway for emotional expression and behaviour Functionally it correlates the emotional and intellectual aspects of consciousness There is evidence to suggest that MAO inhibitors may activate this system at the amygdala and hippocampal areas

It might be speculated that as a centre for emotional expression, the Papez circuit functions at a higher integrative level than either the hypothalamus or the RAS what a person feels is a function of the "visceral brain", what he thinks is a function of the cortex

Preliminary experiments in some preparations in which gross unilateral lesions have been made in the mesencephalic tegmentum suggest that this subcortical

area may be a possible site for the arousal effect observed following the administration of MAO inhibitors

B *Antidepressants Which are Not Monoamine-oxidase Inhibitors*

(*a*) *Mode of Action*

Some drugs of this group of antidepressants, such as the older analeptics and amphetamines, appear to have a direct excitatory effect on neuronal cells,[3] although the amphetamines (dextroamphetamine—Dexedrine) and methamphetamine (Desoxyn) possess mild monoamine-oxidase inhibitory actions as well[4] Some are thought to increase central nervous system activity by increasing the amount of cholinergic neurohumoral transmitter substance available In fact, dimethylaminoethanol (Deaner, Deanal) is thought by some to be a precursor of acetylcholine, thus theoretically reinforcing central cholinergic excitation[3] This concept of action, however, is not entirely accepted[4]

Other antidepressants have a beneficial effect in depression because of their suppressant properties[3] Imipramine (Tofranil) is a modified phenothiazine agent which apparently acts to relieve the agitation and anxiety that contribute to certain depressions Imipramine, while possessing suppressant properties, may also sensitize hypothalamic adrenergic receptors to noradrenaline in much the same way as cocaine sensitizes receptors to the action of adrenaline[3]

III Hazards in Association with Anaesthesia

A review of four clinical presentations will serve to illustrate some of the hazards that these drugs may create in anaesthesia A summary of the salient features of these illustrative patients is outlined in Table V

TABLE V

Clinical Summary of Patients on Psychoactive Drugs with Hazards to Anaesthesia

	Patient 1 (R H T)	Patient 2 (R P N)	Patient 3 (S N L)	Patient 4 (J E P)
Age	52	48	26	36
Sex	M	F	F	F
Diagnosis	Depression	Hypertension and depression	Hypertension and psychoneurotic	Overdose (suicidal attempt)
Operation	Ventral hernia repair	Cystocoele, rectocoele, repair	D and C	—
Psychoactive drug	Tranylcypromine	Pargyline	Pargyline	Tranylcypromine, imipramine
Anaesthetic agent	Thiopentone	Meperidine	Phenylpropanolamine (nasal decongestant)	—
Reaction	Hypotension and hypertension	Hypotension	Hypertensive crisis	Coma and hyperthermia

Patient 1 (R H T)

A 52-year-old 175-lb white male presented for repair of a ventral hernia Unknown to the anaesthetist he had been taking tranylcypromine (Parnate) for a psychoneurotic

depression On the evening before surgery his blood pressure was recorded at 140/90 mm Hg, following morphine gr 1/8 and hyoscine gr. 1/150 pre-anaesthetic medication, it was 90/60 mm Hg Anaesthesia was induced with thiopentone 375 mg, and succinylcholine 50 mg was given for endotracheal intubation The patient was ventilated with oxygen Immediately his colour appeared poor The pulse was weak The blood pressure was 30/0 The patient was positioned head down The blood pressure remained low at 40/0 An intravenous infusion containing 4 mg of phenylephrine in 500 c c of 5 per cent glucose in distilled water was begun The blood pressure promptly rose to 250/140 mm Hg almost immediately after the phenylephrine infusion was begun When the vasopressor was discontinued, the blood pressure gradually fell to 40–50/10 This cardiovascular instability continued for a further 30 minutes, when the blood pressure gradually returned to 100/70 without vasopressor The surgical procedure was cancelled when careful questioning of the attending physician revealed that the patient had been on a MAO inhibitor for the previous three months Subsequently the drug was discontinued Three weeks later the patient had an uneventful repair of his ventral hernia with identical pre-anaesthetic medication and induction

Patient 2 (R P N)

A 48-year-old 135-lb female with mild hypertensive and depressive problems presented for repair of cystocoele and rectocoele She was given meperidine 100 mg and hyoscine 0 6 mg 1 hour preoperatively as the pre-anaesthetic medication On arriving in the anaesthetic room her blood pressure was 50/30 whereas the evening before it had been recorded at 130/85 mm Hg This patient was placed in the head-down position Oxygen was given Over the following three hours her blood pressure gradually returned to 90/60 Twenty-four hours later it was 130/80 There were no resulting untoward effects Enquiry elicited information that she had been taking a "new antihypertensive, antidepressive" drug It was later found to have been pargyline (Eutonyl), an MAO inhibitor

Two months later, the pargyline (Eutonyl) having been discontinued for one month, she again received pre-anaesthetic medication of meperidine 100 mg and hyoscine 0 4 mg with no significant alteration in her blood pressure She had an uneventful course during surgery and anaesthesia

Patient 3 (S N L)

A 26-year-old psychoneurotic hypertensive female presented for dilatation and curettage of the uterus was given a nasal decongestant containing phenylpropanalamine for a slight nasal congestion on the eve of her surgery She promptly developed a hypertensive syndrome with her blood pressure rising from 130/80 to 220/160 mm Hg She complained of occipital headache, later generalized, and nausea She vomited She had palpitations, complained of photophobia There was sweating Phentolamine (Rogitine) 5 mg intravenously on two separate injections appeared to make her more comfortable but her blood pressure remained at 180–190/100 mm Hg This episode lasted for one hour It was later found that she had been taking pargyline (Eutonyl) from her own supplies

Patient 4 (J E P)

A 36-year-old female with a history of psychotic depression was admitted to Emergency unconscious Her cardiovascular and respiratory status were depressed but adequate Her temperature by rectum was 107° F There was no apparent pathological cause for her elevated temperature With rapid application of ice packs and hypothermic blankets, her temperature was reduced and maintained with difficulty at 98–99° F It was learned that she had ingested an unknown quantity of tranylcypromine (Parnate) and imipramine (Tofranil) She remained comatose and semi-comatose for 48 hours, then she gradually regained consciousness and her temperature stabilized at 100° F , without cooling, over the next three days

With these case reviews in mind, Table VI lists the salient hazards to anaesthesia presented by psychoactive drugs, and particularly by monoamine-oxidase inhibitors

TABLE VI

HAZARDS OF PSYCHOACTIVE DRUGS TO ANAESTHESIA

Hypotension
Hypertensive crisis
Prolonged barbiturate sleep
Prolonged respiratory depression
Hyperthermia
Convulsions
Coma
Potentiation of atropine, corticosteroids, Arfonad

Thus, apart from the antidepressant action of these drugs on the central nervous system, there are widespread profound pharmacological effects on vital mechanisms of importance to the stability of a patient when the additional factor of anaesthesia is introduced By their action of inhibition of monoamine-oxidase enzyme systems, the normal metabolic sequence of several endogenous biologically active amines, such as epinephrine, norepinephrine, isoproterenol, histamine, and serotonin, may be interfered with in the central nervous system This results in an increased level in the brain of some of these biologically active amines, mainly norepinephrine and/or serotonin, with resultant psychoactive effects. But concentrations of these substances not only appear to be increased at central sites but may also be increased at peripheral autonomic synaptic and effector areas[7] (although there is no evidence at present of any increase in urinary catecholamines) which may provide a hazardous setting for a subsequently administered anaesthetic

As a result, patients who are taking these drugs or who have taken these drugs within the 21 days prior to anaesthesia are subject to special risks Their cardiovascular system is unstable during induction and maintenance of general anaesthesia with thiopentone or inhalation agents They may develop hypotension, in which treatment with vasopressors may be troublesome or even disastrous and should be administered with caution Uncontrollable episodes of severe hypertension may occur Phentolamine (Rogitine) has been advocated to combat severe hypertensive syndromes[8] Amusingly, as an aside, hypertensive crises in the conscious subject on these drugs may be precipitated by the intake of non-pasteurized beer and rough wines of the Chianti variety, as pressor amines of the tyramine type have been detected in these products, as well as in certain cheeses This has led to the medically well-documented "cheese reactions"[7–10] Exogenous epinephrine or other vasopressors introduced with local anaesthetics, in these patients, may precipitate a hypertensive crisis, resulting in cerebral haemorrhage or cardiac arrest from ventricular fibrillation Prolonged respiratory depression has occurred following anaesthesia in patients who are on these drugs[11] Prolongation of pentobarbital and thiopentone sleeping time has been reported[11] Any central nervous system depressant, particularly the tranquillizing phenothiazines, when given to these patients either when on MAO inhibitors or within 3 to 21 days of their withdrawal, may precipitate prolonged coma and marked hyperthermia

(case 4), for which no specific antidote is at present available The clinical effects of numerous unrelated compounds, for instance the corticosteroids, are also potentiated by amine-oxidase inhibitors

If the operation cannot be postponed 3 weeks, or if the patient cannot be off antidepressant medication for such a period, or if an emergency operation is required, then it is suggested that one-quarter to one-fifth of the usual dose of any C N S depressant that must be used should be given [8]

The anaesthetist must develop a high index of awareness for the hazards that these drugs present to the conduct of safe, stable anaesthesia He must ascertain whether patients coming to surgery are receiving these drugs, or have been on these drugs recently

IV Summary

In recent years psychoactive (antidepressant) drugs have been found useful in the treatment of both psychotic and psychoneurotic depression The use of these drugs appears to be increasing, for they have been advocated in the treatment of angina pectoris, hypertension, and rheumatoid arthritis as well Thus, not only the psychotic patient on these drugs receiving thiopentone and succinylcholine for E C T presents to the anaesthetist, but also a wide variety of surgical patients may have been exposed to these drugs

Pharmacologically, the antidepressants may be classified into two main groups (1) compounds which inhibit the enzyme monoamine-oxidase (2) compounds which do *not* inhibit the enzyme monoamine-oxidase

The majority of the psychoanaleptics in current use are monoamine-oxidase inhibitors By virtue of their ability to inhibit monoamine-oxidase, there are increased levels of brain serotonin and/or norepinephrine, with resultant psychoactive effects But the concentration of these biologically active amines not only appears to be increased at central sites but may also be elevated at peripheral autonomic synaptic and effector areas, providing a hazardous setting for subsequently administered anaesthetics Four representative patients illustrate that hypotension, hypertensive crises, hyperthermia, convulsions, coma, and potentiation of atropine, corticosteroids, and Arfonad have all been observed as untoward reactions when anaesthesia or anaesthetic agents are given to patients on psychoactive drugs

Management of these reactions is primarily supportive Caution must be used in the administration of vasopressors (norepinephrine) or adrenergic blockers (phentolamine) in the treatment of hypotensive or hypertensive reactions, respectively Avoidance of these reactions is desirable Therefore a high index of awareness of the hazards that these drugs present in association with anaesthesia and care to ascertain whether the patient is or has been taking these drugs during the 21 days prior to anaesthesia seem imperative

Résumé

Au cours des dernières années, on a trouvé que les médicaments psychoactifs (les antidépresseurs) étaient utiles dans le traitement de la dépression psychique

et psychonévrotique De plus en plus, on utilise ces substances, car elles ont été préconisées dans le traitement de l'angine de poitrine, de l'hypertension et de l'arthrite rhumatoide Ainsi se présente à l'anesthésiste non seulement le malade mental traité par ces médicaments et qui reçoit un E C sous pentothal-succinylcholine, mais aussi un bon nombre d'opérés qui peuvent avoir pris ces mêmes médicaments

Pharmacologiquement, les substances antidépressives peuvent être partagées en deux groupes (1) les composés qui inhibent l'enzyme mono-amine-oxydase, (2) les composés qui ne l'inhibent pas

La plupart des psychoanaleptiques d'usage courant sont des inhibiteurs de la mono-amine-oxydase Du fait de leur pouvoir d'inhiber la mono-amine-oxydase, ils augmentent le taux de sérotonine et/ou de norépinéphrine dans le cerveau, ce qui produit des effets psychoactifs Mais le taux de ces amines biologiquement actives semble être augmenté non seulement au niveau central mais également aux synapses autonomes périphériques et aux zones effectrices, créant ainsi une situation délicate pour l'administration subséquente d'agents anesthésiques Quatre cas typiques démontrent qu'on a observé de l'hypotension, des crises hypertensives de l'hyperthermie, des convulsions, du coma de la potentialisation de l'atropine, des corticoides et de l'Arfonad, comme réactions indésirables lorsque l'anesthésie et des agents anesthésiques ont été administrés à des malades recevant des substances psychoactives

Le traitement de ces réactions consiste en une médication de support Il faut faire attention à l'usage des vasopresseurs (norepinéphrine) ou des bloqueurs adrénergiques (phentolamine) dans le traitement de l'hypotension ou des réactions hypertensives respectivement Il est souhaitable d'éviter de telles réactions En conséquence, il devient impérieux de créer un état d'alerte sur les risques que ces substances présentent au cours de l'anesthésie et sur la nécessité de vérifier si le malade prend ou a pris de telles substances au cours des trois dernières semaines

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