Anesthetic concerns for patients on psychotropic agents

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This paper offers a review of some of the important considerations in the anesthetic management of the surgical patient taking psychotropic drugs. Special attention is given to possible interactions that can occur between psychotropic drugs and those drugs used during anesthesia.

The incidence and prevalence of mental illness is expected to increase substantially in the next twenty years. There are two reasons for this increase: (1) the declining mortality rate of mentally ill individuals and (2) the increasing life span of persons with chronic illnesses and disabilities that are associated with psychological problems.¹

Many of these people are now seen in the operating room for a variety of procedures. Data reveals that at least 50% of emotionally and mentally disturbed individuals have a physical illness.² Not only must the anesthetist be able to deal with the patient’s emotional state but he must also have knowledge about possible interactions between the psychoactive drugs and those drugs used in anesthesia.

For any patient the possibility of surgery can be a frightening experience. The psychiatric patient may not be able to cope with his anxiety as well as other patients can. It is important to make these patients as comfortable and secure as possible in their new environment. A proper preoperative visit may be all that is necessary to help alleviate undue anxiety. If a preoperative medication is necessary, the anesthetist should know what type of condition the patient is being treated for and what medications the patient is receiving.

Plans for the treatment of possible drug reactions, interactions and toxicity should always be established before the initiation of any kind of therapy. Psychotropic drugs in general profoundly affect central and peripheral neurotransmitter and ionic mechanisms. Hence, prior intake of these drugs is an important consideration in the management of the surgical patient.

These patients frequently are taking phenothiazines, tricyclic antidepressants, monoamine oxidase (MAO) inhibitors or a combination of all three. In 1977, 20% of all prescriptions were for mood-altering drugs.³ Many of these people are not institutionalized, but live in the community and may not wish to talk about their medical history or the drugs that they are taking. It is especially important to establish a good rapport with these patients and to emphasize the confidentiality of the preoperative interview.

Psychoactive drugs and their interactions with anesthetic agents

One of the drugs that the patient may be receiving may be an MAO inhibitor. Before tricyclic antidepressants became popular, a variety of MAO
Inhibitors were developed and were found to be effective as antidepressant agents. MAO inhibitors include isocarboxazid (Marplan®), pargyline (Eutonyl®), tranylcypromine (Parnate®), and phenelzine (Nardil®).

Currently, in the United States only one MAO inhibitor — tranylcypromine — is approved for the treatment of depression. Another, pargyline, is approved as an antihypertensive agent. However, other MAO inhibitors are used outside the United States. These drugs were more popular in the past. Their potential toxic effects are such that there is now a tendency to employ them in cases which fail to respond to other drugs or electroconvulsive therapy. They are, however, of value in the treatment of reactive (nonendogenous) depression, particularly when there are phobic symptoms and anxiety, which are often made worse by tricyclic antidepressants.

MAO inhibitors inhibit the oxidative deamination of dopamine, norepinephrine and serotonin. Normally after catecholamines are synthesized from L-tyrosine, they are stored in cytoplasmic vesicles of the sympathetic nerve terminals where they are available for release upon the arrival of an electrical nerve impulse. The release of norepinephrine or dopamine is followed by the receptor-neurotransmitter interaction.

This action is terminated by either metabolism of the neurotransmitter by catechol-O-methyl transferase, or re-uptake of the catecholamine into the presynaptic nerve terminal, where it may be metabolized by the mitochondrially bound monoamine oxidase. MAO inhibitors cause irreversible inactivation of the enzyme, and although the drug is excreted in the urine in 24 hours, the inactivation persists until new MAO is produced. This may take as long as two weeks.

Because of the unpredictable toxic effects which occur, surgical operations should, whenever possible, be postponed until the effects of these drugs have been eliminated. This depends again upon the generation of fresh enzyme and takes at least 10 to 14 days. During this time, if necessary, the patient may be transferred to another type of antidepressant. If, however, the operation cannot be postponed, the drugs which must be avoided are pethidine (Meperidine®) and the sympathomimetic amines, particularly those which release transmitters or which are normally metabolized by monoamine oxidase.

Inhibition of hepatic microsomal enzymes by MAO inhibitors delays the elimination of drugs such as barbiturates and narcotics, thus prolonging and potentiating their effects. Pethidine’s action seems to have a greater effect than other narcotics. Pethidine may cause hypotension, respiratory depression and coma, or a severe hypertensive crisis. The mechanism of this action is not entirely clear. However, it is of interest that in normal individuals, in the absence of circulatory depressant drugs, IV pethidine usually produces an initial rise in blood pressure before a comparable fall, and this toxic response may be, therefore, an idiosyncratic exaggeration of a normal response.

However, based on animal experiments, several authors postulate that the response is caused by the elevation of serotonin levels in the brain following MAO inhibitors in the presence of pethidine. Although prevention is the best treatment of a narcotic-MAO inhibitor interaction of this type, various sources recommend administration of prednisolone hemisuccinate 25 mg IV, as well as other supportive measures as indicated, and control of the patient’s blood pressure if arterial pressure reaches excessive levels. Treatment which is primarily supportive may include the narcotic antagonist naloxone.

In addition, prompt acidification of the urine using lysine or arginine hydrochloride or sodium biphosphate intravenously, and the production of a large volume of urine has been used to hasten pethidine excretion. If vasoactive drugs are required for the treatment of hypertension or hypotension, they should be direct-acting agents that do not depend on the release of endogenous catecholamines for their action. This would allow for a more precise titration of drug effect. Drugs that conform to these requirements include chlorpromazine (Thorazine®), trimethaphan, pentolinium, and sodium nitroprusside. For hypotension, norepinephrine, epinephrine and isoproterenol may be used with caution.

Similarly, indirect-acting vaspressors, including tyramine, mephentermine, metaraminol, ephe drine and phenylpropanolamine, all of which release norepinephrine and dopamine from bound intracellular neuronal stores, can interact with MAO inhibitors and cause hypertensive crisis. The hypertensive crisis may consist of precipitous hypertension, hyperpyrexia, sweating, tachycardia, throbbing occipital headache and intracranial bleeding. It appears to be caused by a “sympathetic storm,” and is similar to the effects of an overdose of amphetamines.

Drugs such as MAO inhibitors increase central catecholamine levels and hence increase minimum alveolar anesthetic concentration.
inhibitors have been reported to augment barbiturate and sedative hypnotic effects in animals and in man. This is probably due to MAO inhibitors' inhibition of liver microsomal enzymes necessary for barbiturate detoxification. A combination of MAO inhibitor and a barbiturate has been shown in experiments to increase sleep time and duration of anesthesia in animals. Similar effects have been noted in man; thus, a patient on MAO inhibitor medication should receive lower doses of barbiturates during surgery.

Investigation of plasma cholinesterase levels revealed depressed enzyme activity in 40% of patients taking phentolamine and normal levels in patients receiving other MAO inhibitors. One animal study dealing with the effect of d-tubocurarine on long term MAO inhibitor therapy has found that the relaxant effect is not prolonged. In the absence of clinical reports on this interaction, it is probably safe to use this non-depolarizing agent in patients on MAO inhibitors.

Tricyclic antidepressants. Monoamine oxidase inhibitors are being used with decreasing frequency, but the use of tricyclic antidepressants is increasing. While their primary indication is the treatment of severe depression, they are also commonly being prescribed for mild to moderate depression and nonpsychiatric problems such as enuresis in pediatric patients.

Tricyclics represent structural modifications of phenothiazine drugs with which they share some common actions and effects. The commonly used agents are: imipramine (Tofranil®), desipramine (Pertrofrane®), amitriptyline (Elavil®), nortriptyline (Aventyl®) and doxepin (Sinequan®).

Tricyclic antidepressants work by blocking the uptake of norepinephrine and/or serotonin or dopamine into the presynaptic nerve ending, thereby increasing central and peripheral adrenergic tone. This effect has been linked to their antidepressant activity. The majority of tricyclic antidepressants also possess moderate anticholinergic effects, which may also alleviate depression. The anticholinergic and catecholamine uptake blocking properties of the tricyclic antidepressants seem to cause their most significant clinical interactions with anesthetic agents.

The peripheral anticholinergic actions lead to side effects such as dryness of the mouth, blurring of vision, constipation, delirium, cardiac dysrhythmias (including severe tachycardia), prolongation of the QRS complex, development of left bundle branch block and development of sinoatrial block. More recently it has been noted that the side effects have been partially or completely reversed by physostigmine. Sleep time may be prolonged as a result of central anticholinergic effects; and again, physostigmine given intravenously may treat this side effect.

Elderly hypertensive patients with preexisting cardiac diseases are especially prone to development of serious complications from the use of tricyclics. The combination of chronic imipramine therapy with halothane and pancuronium has been found to predispose patients to dysrhythmias. In experiments using dogs, no such dysrhythmias were noted when using enflurane. Accordingly, the combination of tricyclic antidepressants, halothane and pancuronium seems to be very dangerous and should be avoided.

Patients on tricyclics may show an exaggerated response to vasopressors. According to Guerra and Usubiago, the use of direct-acting agents probably allows better control over blood pressure than does the use of agents causing the release of catecholamines. The belief is that, as with MAO inhibitors, the effects of direct-acting antihypertensive agents are more predictable than those of indirect agents. Janowsky, Risch, and Janowsky, on the other hand feel that direct-acting sympathicotropic amines, including norepinephrine, epinephrine and phenylephrine, under controlled conditions elicited responses which resulted in hyperthermia, sweating, hypertensive crisis, severe headache, rupture of cerebral blood vessels and death. In view of this potential hazard these sources advise stopping all tricyclics two weeks prior to an operation. If this is not possible because of the patient's psychiatric condition, and if a surgical procedure must be performed while tricyclic antidepressants are present, avoidance of direct-acting sympathetic pressor amines is suggested.

Treatment of hypertensive crisis, if it develops, consists of the administration of chlorpromazine or of an alpha-adrenergic blocking agent such as phentolamine, or of the vasodilator, sodium nitroprusside. Cooling measures should be instituted if the patient is hyperpyrexic. Octapressin is a synthetic vasoconstrictor that does not interact adversely with tricyclics, but it is not currently available in the United States.

Although little data exists to support the contention that tricyclic antidepressants augment the analgesic and other effects of narcotic analgesics in human beings, imipramine and amitriptyline potentiate morphine analgesia in mice and increase pethidine-induced respiratory depression. These effects are theoretically important and sup-
port the administration of lower doses of narcotics in patients taking tricyclic antidepressants. Some animal experiments suggest that tricyclic antidepressants increase sedative and hypnotic effects of barbiturates. Imipramine has been known to prolong hexobarbital narcosis, possibly by means of enzyme inhibition, and to prolong apnea following thiopental administration in humans. This potential interaction may be reason to administer lower doses of barbiturates in patients receiving tricyclic antidepressants.

Antipsychotic drugs. Phenothiazines and butyrophenones are widely used to treat psychotic symptoms in patients affected with schizophrenia, mania and organic brain syndromes associated with psychosis. All antipsychotic drugs elevate serum prolactin and block dopaminergic receptors. The most popular current psychobiologic theory attributes the effect of antipsychotic drugs to their dopamine blocking properties. In fact, phenothiazines and butyrophenones effectively block dopamine receptors, a characteristic not found in related compounds devoid of antipsychotic properties. However, antipsychotic drugs differ from one another in their central and peripheral anticholinergic and anticholinergic properties and thus in their side effects.

The phenothiazines were first introduced into clinical use for the treatment of schizophrenia in the United States in 1954. The most common preparations today are triflupromazine (Vesprin®), thioridazine (Mellaril®), trifluoperazine (Stelazine®), and chlorpromazine. Phenothiazines act primarily on the central nervous system with actions that are primarily antidiadrenergic, and anticholinergic to a degree. Antidopaminergic effects, such as extrapyramidal symptoms, occur less frequently.

The most frequently seen side effects are oversedation, dystonia, pseudoparkinsonism, akathisia and tardive dyskinesia. The movement disorders result from the side effects of the drugs as blockers of dopaminergic pathways in the gray matter portion of the corpus striatum or from an increase in the sensitivity of their pathways to dopamine (as in the case of tardive dyskinesia). Other side effects associated with phenothiazines include orthostatic hypotension (partly due to alpha blockade), and a hypothermia effect (due to a depressant action on the hypothalamus that modifies temperature regulation so that heat production is diminished while heat loss is enhanced; thus body temperature is lowered and the body tends to take on the environmental temperature.)

The effects of greatest concern to the anesthesiologist are the central nervous system, autonomic and cardiac effects. Electrocardiographic abnormalities include prolongation of QT or PR interval, blunting of T waves, ST segment depression and rarely PVC's. Respiratory depression from narcotics is generally increased and central nervous system seizure threshold is lowered by phenothiazines. Patients who are on antipsychotic doses of chlorpromazine (200-1000 mg or more per day) may be unable to respond to the result of blood loss or myocardial depression with enough vasoconstriction to raise blood pressure. Evaluation of some commonly used vasopressors in standard doses revealed them to be relatively ineffective in the chlorpromazine treated patient. Thus neither epinephrine (action on the heart) nor desoxynephedrine (central cerebral action) provided a desirable pressor response. Methoxamine (Vasoxyl®) which acts peripherally, however, seems to be somewhat more potent.

The anesthetist should be aware that antipsychotic agents usually block the pressor effects of norepinephrine and related alpha-adrenergic stimulating drugs. Conversely, antipsychotic drugs, especially chlorpromazine, can intensify the effects of other drugs on beta-adrenergic receptors. This selective blockade of alpha-adrenergic receptors can lead to a beta-adrenergic preponderance of such agents as epinephrine that usually exert both alpha and beta adrenergic effects, causing vasodilation and subsequent hypotension If paradoxical beta-adrenergic activation occurs in individuals receiving antipsychotic drugs, treatment with the beta-adrenergic blocking agent propranolol is indicated.

In addition to the interaction already discussed, the halogenated anesthetic enflurane and isoflurane, given in combination with antipsychotic agents, including chlorpromazine, may cause hypotensive episodes. Because this type of hypotension is often associated with hypovolemia, the replacement of fluids and/or blood is indicated along with alpha-adrenergic vasopressors such as phenylephrine or methoxamine.

In animal experiments, antipsychotic drugs have been shown to increase barbiturate and sedative-hypnotic induced sleep time and deepen barbiturate coma. In one study of 50 patients, chlorpromazine prolonged thiopental sleep time and reduced the thiopental requirement by 60%. Thus lower doses of sedative-hypnotics or barbiturates are indicated when a patient has received antipsychotic medications. Chlorpromazine potentiates the action of depolarizing muscle relaxants.
such as succinylcholine. It is probable that a similar situation exists with the other phenothiazines. There is no evidence that discontinuing phenothiazines for two or three days prior to surgery is any safer than continuing them.

Butyrophenones, most specifically haloperidol, are used in the treatment of psychosis. Anesthetists are familiar with this class of compounds because of their use of droperidol perioperatively. As with phenothiazines, haloperidol use may be associated with a multiplicity of side effects, which include dystonia, pseudoparkinsonism, and akathisia. Over-sedation, blood dyscrasias, and liver toxicity also occur with lower incidence. Butyrophenones can cause hypotension because of both central and peripheral adrenergic blocking actions and the cerebral depressant actions added to those of hypnotics, narcotics, analgesics and other tranquilizers. For general anesthesia, therefore, requirements of all drugs are greatly reduced but, as with phenothiazines, recovery may be very slow.

Minor tranquilizers. Also known as antianxiety drugs, minor tranquilizers have been recommended for the treatment of symptoms associated with psychoneurotic and psychosomatic conditions. The antianxiety agents share similar central depressant action, but their secondary central and peripheral effects vary. Chemically they can be divided according to the following subgroups: (1) diphenylmethanes, which include hydroxyzine hydrochloride (Atarax®) and hydroxyzine pamoate (Vistaril®); (2) benzodiazepines, which include chlordiazepoxide (Librium®) and diazepam (Valium®); and (3) propanedols, which include meprobamate (Equanil® and Miltown®).

Meprobamate has not been found to influence greatly the effects of anesthesia. However, patients who have been on large doses experience an exaggerated depressant effect when sedatives, narcotics, and anesthesia are used. Hypotension is not infrequent and seems to be pronounced in the post-operative period. Vaspressors such as metaraminol (Aramine®) and methoxamine give a better therapeutic response than phentylephrine (Neo-synephrine®). Diazepam's effect seems to reduce maximum alveolar concentration (MAC) for halothane by 35%. Hypotension and bradycardia have been reported after administration of chlordiazepoxide or diazepam in anesthetized animals, but have not yet been reported in human subjects dependent on benzodiazepines.

Lithium carbonate. Lithium carbonate has been used in the treatment of manic-depressive illness in the United States since 1969. Lithium affects the sympathetic nervous system by inhibiting the release of norepinephrine and serotonin by increasing the re-uptake of norepinephrine from the synaptic cleft and by possibly increasing the turnover rate of serotonin, while having little effect on the dopaminergic system. The end result is a decrease in the amount of catecholamines at receptor sites.

Lithium interacts with muscle relaxants by causing a potentiation of pancuronium, succinylcholine, and decamethonium. Reversal time of pancuronium is also prolonged. This may be due to a decrease in the synthesis or release of acetylcholine, or to its effects on the distribution of sodium and potassium across the muscle cell membrane. No such effect on blockade has been produced by gallamine or d-tubocurarine. Patients on lithium may be more sensitive than others to any of the possible causes of hypotension, including hypovolemia and myocardial depression due to anesthesia.

A nephrogenic form of diabetes insipidus as well as inhibition of antidiuretic hormone, resulting in a significant diuresis in some patients, have been reported in some patients taking lithium. Results of testing by Gerner, Psarras and Kirschbaum suggest that noninvasive testing of patients taking lithium does not reveal consistent abnormalities suggestive of seriously impaired renal function.

Lithium does cause T-wave flattening on the ECG, but cardiotoxicity has not been a major problem with the drug. It may also decrease the heart rate response to surgical stimulation. There is prolonged sleep time following thiopental, methohexital and diazepam after short term treatment with lithium, but no significant effects after prolonged treatment. There have been no reports to date of interactions between lithium and either inhalation anesthetics or local anesthetics.

The Physicians Desk Reference warns of a drug interaction between lithium and haloperidol causing an encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes BUN and FBS) followed by irreversible brain damage. Although haloperidol and droperidol are pharmacologically similar, no data appears to be available on the lithium-droperidol interaction. Janssen Pharmaceutical states that they know of no known drug interactions between lithium and droperidol. Even though no interactions have been reported, it
would still seem a responsible caution to avoid droperidol use when lithium interaction is possible.

Conclusion

Knowledge of psychotropic drugs and their effects and side effects is very important for a safe and smooth anesthesia course. As new drugs are developed, some of the dangers inherent in the older drugs may be avoided, but new dangers may appear. Thus, the anesthetist must continually seek information in this area.

REFERENCES

(13) Personal communication with Janssen Pharmaceuticals.

ADDITIONAL READINGS


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