The author discusses some of the more common drug interactions that the nurse anesthetist is likely to encounter, putting emphasis on what can or should be done to minimize, prevent, and for that matter, treat a potential problem.

The subject of drug interactions is a broad one which, if covered in depth, would approach the size of a good pharmacology textbook. When one considers the vast proliferation of drugs which are available to and are being ingested by patients for one or several reasons, one acquires a great deal of respect for the possibilities and consequences of an interaction between the components of the mixture.

Consider, for example, this patient: A 57-year-old, white female diabetic, mother of four, whose past history includes a hysterectomy, hemorrhoidectomy, bilateral carotid endarterectomies, right femoro-popliteal by-pass graft, angina, paroxysmal atrial tachycardia, and hypertension. Her present drug regimen consists of digoxin, Apresoline®, Esidrix®, propranolol, Valium®, insulin, and occasionally, acetaminophen or aspirin for headache.

Suppose you are called upon to anesthetize this patient for a left-lumbar sympathectomy. What possible interactions exist between the drugs she now requires and your proposed anesthetic regimen? (1) Which drugs should be stopped and for how long? (2) When should they be restarted? (3) Which should be continued? If the answers to these routine questions are obvious, you may stop reading right here. If you are unsure about some of them, or would like a refresher on common drug interactions, then please read on.

The receptor theory, protein binding, microsomal enzyme, and sympathetic neuronal physiology have been reviewed by Mellema, et al.,¹ and a list summarizing common drug interactions with an excellent reference summary was compiled by Drain and Campman² in previous publications to which the reader is referred.

The objective of this article is to present the more common drug interactions which the anesthetist is likely to encounter, and to discuss what can or should be done to minimize, prevent, or treat a potential problem.

Not all drug interactions are undesirable, and many are used by us therapeutically. A good example of this is the reversal of non-depolarizing skeletal muscle relaxants by the use of enzyme inhibitors. To achieve the reversal of the relaxant effect involves a most interesting series of events. To begin with, the relaxation which results is attributed to an ionic bond which forms between the ionized species of the relaxant drug and an oppositely charged portion of the end plate receptor.

This electrostatic attraction allows the drug to block the cholinergic receptor of the end plate so that the effects of acetylcholine (ACH) are inhibited. ACH...
is still liberated by the nerve ending, but is unable to interact with its receptor; therefore, depolarization of the end plate is prohibited, and interruption of nerve stimuli to the muscle fiber is accomplished.

To reverse this state of affairs, we administer one of several compounds which have the property of combining reversibly with the enzyme acetylcholinesterase, which aids in the hydrolysis of ACH. In the absence of this enzyme, the destruction of ACH takes about 1,000 times longer than it usually does. As a rule, ACH is liberated and hydrolyzed by ACH. In the absence of this enzyme, inhibition effectively increases the action of acetylcholine to 2-4 seconds. This results in a rather massive buildup of acetylcholine at the end plate. Because of the law of mass action, the muscle relaxant becomes overwhelmed by ACH and is physically removed from the end plate, whereupon, transmission of nerve impulses once again takes place.

Of course, administration of cholinesterase inhibitors in therapeutic doses does not result in total enzyme inhibition, since such a situation may be rapidly fatal. For this reason, and because the enzyme inhibitors themselves have a depolarizing effect on nerve end plates, a maximum dose is recommended for each one. Also, an anticholinergic drug, such as atropine, is administered either before or concurrently with the enzyme inhibitor to prevent the muscarinic effects which are produced by increased ACH acting on post-ganglionic parasympathetics.

Interactions of muscle relaxants

While on the subject of muscle relaxants, it might be wise to discuss other interactions which may occur. Most inhalation drugs have a potentiating effect on muscle relaxants so that a lower total dose is generally required when inhalation agents are used, in contrast to what would happen if intravenous anesthetics were given.

A rather important drug interaction may be observed when curare is administered to a patient receiving magnesium sulphate. The usual situation involves an emergency Caesarean section on an eclamptic hypertensive patient who is receiving MgSO₄ to reduce cerebral edema and prevent convulsions. Most authorities suggest that a patient of this type should receive some form of regional anesthesia, such as epidural or spinal. However, if this is not possible, an endotracheal technique must be considered. In most institutions, the technique would involve a "crash intubation," wherein a small dose (3-6 mg) of curare is first administered to prevent fasciculations from the succinylcholine, which will ultimately be given to facilitate intubation.

If the patient is receiving MgSO₄, the "precurarisation" dose may produce complete neuromuscular blockade, which responds poorly, if at all, to the use of anticholinesterases.

What happens is fairly complex and poorly understood. Essentially, magnesium is an intracellular ion which functions in a manner similar to potassium. We know that excess amounts in the extracellular fluid will eventually produce unconsciousness and anesthesia. On the other hand, deficiencies produce a state much like the tetany which accompanies calcium deficiencies.

It is also well known that magnesium anesthesia can be completely reversed by the administration of an equivalent dose of calcium intravenously. It, thus, seems reasonable to conclude that a calcium/magnesium ratio must be maintained if normal neuromuscular transmission is to take place. Therefore, if you find yourself with an eclamptic patient taking MgSO₄, who becomes paralyzed by a small dose of curare, the best course of action is to administer 1 gm of calcium gluconate IV and wait for the results. As a rule, a complete reversal of the effect will follow in a few minutes.

Several drugs in the "mycin" family of antibiotics, when administered in the intraperitoneal space, have been shown to produce neuromuscular block-
ade, and to markedly potentiate the effects of non-depolarizing muscle relaxants. The “mycins” are capable of producing a type V neuromuscular block which is similar to the type produced by botulinus toxin. With this type, a marked diminution in the release of acetylcholine from nerve endings is found. It has also been demonstrated that neomycin possesses a curare-like end plate stabilizing effect of its own.

The use of intraperitoneal mycin drugs should be avoided until the patient has completely recovered from the effects of the relaxant to prevent this troublesome interaction. It has been suggested that an intraperitoneal catheter be left in place to allow instillation of the drug at a later time.

Should this unwanted interaction occur, management is first aimed at supporting ventilation. Attempts to reverse the block may be made with anticholinesterases, and calcium may be of value, since it increases the release of ACH from nerve endings.

Another potentially dangerous interaction involving muscle relaxants occurs when patients using phospholine iodide (echothiopate) eyedrops are given succinylcholine. Phospholine iodide is a cholinesterase inhibitor used in the treatment of glaucoma. It also effectively inhibits pseudocholinesterase which aids in the hydrolysis of succinylcholine. When used concurrently, a marked potentiation of effect and duration of action of succinylcholine is possible. The best course of action to take in this situation is to avoid the use of succinylcholine, bearing in mind that it may be necessary to increase the dosage of non-depolarizers in the presence of the enzyme inhibitor.

Reactions with antihypertensive drugs

One of the most common series of drugs used today are those given for the treatment of hypertension. There are many compounds used, depending on the severity of the condition. Those which we are most likely to see are: Apresoline® (hydralazine), Aldomet® (alpha methyldopa), reserpine and other rauwolfia derivatives, and Ismelin® (guanethidine). The effects of these drugs are similar, however, the mechanisms of action differ significantly. Apresoline® appears to act peripherally by directly affecting the vascular smooth muscle. Aldomet® inhibits the synthesis of catecholamines, which leads to a lowering of the serum concentration of these vaso-active substances. Reserpine and its congeners act to deplete stores of catecholamines in many organs, while Ismelin® is representative of a group of drugs that depress the function of postganglionic sympathetic nerve fibers.

Several years ago, a great deal of concern was placed on patients who were receiving antihypertensive therapy, and who later also required an anesthetic. Depending on the type of drug used in the therapy, a period of withdrawal from 2-3 weeks was recommended prior to surgery. Unfortunately, this left the patient subject to a hypertensive crisis which, more often than not, was a more severe consequence than the risk imposed by anesthesia.

Current thinking would have us continue these patients on their medication up to 6, 12, or 24 hours before surgery, basing this philosophy on the fact that controlled hypertension is preferable to uncontrolled. The great fear that these patients would develop severe hypotension and shock under anesthesia is rarely founded in fact. Nevertheless, it is still good practice to have an infusion of either Neo-synephrine® (phenylephrine) or Levophed® (norepinephrine) available to counter an unexpected hypotensive episode.

While the preceding statements and suggestions are generally true with most anti-hypertensive drugs, there is one group of compounds with which special care must be taken. The drugs in this group are known as the mono-amine oxidase (MAO) inhibitors. Although rarely used in the treatment of hypertension today, these drugs are still in fairly
common use as psychotherapeutic agents because of their anti-depressant effect.

MAO inhibitors do what one would expect them to do—inhibit mono-amine oxidase. Since this enzyme is associated with the oxidation of compounds containing amines, MAO inhibitors will reduce the rate of destruction of any compound metabolized by amine oxidation. This, in part, explains their mechanism of action as a mood elevator in the CNS.

Catecholamines are metabolized partly by oxidation of the amino group, which is part of their structure. If this metabolism is inhibited, catechols will build up centrally and produce a feeling of well being and mood elevation. Unfortunately, it has been shown, that MAO inhibitors also have a depressing action on the microsomal enzyme system which is responsible for metabolizing a great number of varied compounds including narcotics, tranquilizers, barbiturates, and general anesthetics.

Some representative drugs of the MAO inhibitor group are: Eutonyl® (pargyline), Parnate® (tranylcyproamine), Nardil® (phenelzine), and Marplan® (isocarboxazid).

These compounds are irreversible inhibitors of MAO; therefore, the only way MAO levels can be built up again is by biosynthesis, a process which takes 3-4 weeks. For this reason, patients taking these or other MAO inhibitors should be withdrawn from the drug for at least that time period before surgery. It should be borne in mind, however, that withdrawal from the drug may precipitate an acute depression which may culminate in a suicide attempt. This disadvantage must, therefore, be weighed against the possible risks of administering an anesthetic in the presence of these drugs.

If the patient cannot be withdrawn from the drug, the safest anesthetic technique is probably one which employs an inhalation drug and avoids the use of meperidine and piperidine-derived narcotics in particular. Anesthetic management may be complicated by troublesome hypotension, because of the combined cardiovascular depressing actions of the anesthetic and the MAO inhibitor.

Other interactions

A series of drugs which have central actions similar to the MAO inhibitors but appear to be far safer and present less complications to the anesthetist are the tricyclic antidepressants. These drugs are remarkably similar to the phenothiazines structurally, but do not have a profound alpha blocking effect or inhibit enzyme systems. Some of the more common drugs in use are: Tofranil® (imipramine), Elavil® (amitriptyline), and Concordin® (protriptyline). No specific contraindication exists to the use of any particular anesthetic agent; however, since these drugs have a sympatholytic effect, the possibility of troublesome hypotension does exist.

The recent discovery of L-Dopa therapy for patients with Parkinson's disease has created another potential drug-anesthetic interaction. L-Dopa crosses the blood-brain barrier, whereupon it is converted to dopamine. There is, thus, an increased amount of dopamine in the system which, at least in theory, may produce arrhythmias, hypertension, or hypotension. Most authorities feel that the drug should be discontinued from 6-12 hours before surgery, and butyrophenone-derived drugs, such as droperidol should be avoided entirely.

Inderal® (propranolol) is now a very commonly used anti-arrhythmic agent. Its beta blocking properties also make it desirable for patients with angina and hypertension. The patient presented at the beginning of this paper is more or less typical of the type of patient who has been treated with Inderal®. The potential problems created by Inderal® therapy include a decreased response to endogenous or exogenous beta stimulators, which could conceivably result in cardiac failure or hypotension.

Because of these potentially severe problems, a wide range of variance can be seen in the literature regarding withdrawal periods prior to the administra-
tion of an anesthetic. The extremes range from discontinuance 2 weeks before surgery, to not discontinuing the drug at all. If a patient is taking Inderal®, it must be assumed that he needs the drug, and we must further assume that without it, he will have some degree of cardiovascular problem. It is, therefore, probably not in the best interest of the patient to discontinue the drug as long as 2 weeks.

A more reasonable time period for discontinuance of Inderal® is probably 24 hours before surgery, with the patient being watched closely during this period. If it is not possible to interrupt therapy prior to surgery, the possibility of cardiac decompensation must be kept in mind. If cardiac failure becomes apparent and beta stimulators are indicated, larger doses than usual will be required. Response to alpha stimulators, digitalis, and glucagon is not altered in beta blocked patients.

A large group of compounds in common use have been recently noted to possess the capability of inducing the enzymes of the microsomal system, in addition to the primary action for which they are prescribed. Among this diverse group of drugs, we find the barbiturates, which are so often prescribed as sedatives or hypnotics. Certain of the general anesthetics, including halothane and methoxyflurane, have also been shown to induce their own metabolism. Since the microsomal enzyme system is non-specific, inducement by one drug can lead to increased metabolism of several other non-related drugs. For example, a patient who chronically uses phenobarbital (a potent enzyme inducer), is given halothane for general anesthesia. It is well known that halothane is metabolized by the microsomal enzyme system, and some believe that there is a link between the metabolites of halothane and hepatitis. In the presence of enzyme inducers, the amounts of halothane metabolized will be increased, thus increasing the hepatic problems—if this is the mechanism by which they are produced.

At the very least, one may notice an increased tolerance for other depressants of alarming proportions in the presence of enzyme induction.

Conclusion

I began this discussion with a hypothetical case presentation. To emphasize the importance of a thorough knowledge of pharmacologic interactions and their consequences, I shall summarize by presenting an actual case which appeared in the June, 1975, issue of the Journal of the American Medical Association.

A 33-year-old man with severe hypertension was admitted for evaluation of a suspected aortic dissection. During his 31-day hospitalization, he was treated with Arfonad®, reserpine, and Practolol® (a beta blocker), for which Aldomet® was substituted 7 days prior to surgery.

To confirm the diagnosis, an aortogram was performed under halothane-curare anesthesia. The patient was also given atropine as part of the premedication regimen.

During the procedure, blood pressure averaged 150/90-170/90 torr. At the end of anesthesia, neostigmine was given to reverse the curare effects, whereupon the blood pressure rose to greater than 260/140 torr. The patient convulsed and never regained consciousness. Necropsy failed to determine an anatomic cause and death was attributed to anesthesia on the basis of “Cannon Law,” which states that denervation of an organ or tissue will cause an exaggerated response to chemical neurotransmitters.

It was, therefore, proposed that a medical denervation had been produced as follows:

1. Practolol® had blocked the beta adrenergic receptors.
2. Atropine had blocked the muscarinic receptors.
3. Curare had blocked the nicotinic parasympathetic receptors.

When neostigmine was administered, the increase in ACH resulted in preganglionic stimulation of the sym-
pathetic fibers which produced release of catecholamines, and possibly alpha methyl norepinephrine, a potent alpha receptor stimulator which is a metabolite of Aldomet®. Since Practolol® had blocked his beta receptors and atropine had blocked his muscarinic parasympathetics, there was little or no compensatory vasodilation. The result was a hypertensive crisis, with accompanying convulsions and apnea.

We can learn much from this case. In particular, it enforces the fact that pharmacologic principles must always be adhered to at all times. Also, it proves that withdrawal of a drug, in this case Practolol® for a predetermined period, does not ensure the absence of an interaction. The fact is that the potential for a drug interaction is always present and constitutes another problem for which the anesthetist must always be prepared.

REFERENCES
(7) Wollman, H. 1974. Anesthetic Considerations for Patients on Propranolol, L-Dopa and MAO Inhibitors; Refresher Course presentation, American Society of Anesthesiologists annual meeting in Washington, D.C., October.
(9) Stephen, C. R., Personal Communication.

AUTHOR
Bernard A. Kuzava, CRNA, is a graduate of New York University Bellevue Hospital School of Nursing, New York, New York, and a graduate of Montgomery Hospital School of Nurse Anesthesia, Norristown, Pennsylvania. He is currently chairman of the Department of Nurse Anesthesia and assistant professor of anesthesiology at the Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia.

This paper was presented at the 2nd Annual Seminar of the Rush-Presbyterian-St. Lukes Medical Center in Chicago during September, 1975.