Adverse Drug Interactions in Anesthesia

James G. Bovill, MD, PhD, FFARCSI*

Department of Anaesthesiology, University Hospital Leiden, Leiden, Netherlands.

Anesthesia often involves the administration of several drugs belonging to different classes. In addition, many patients will be taking a number of drugs related to their surgical condition or for other medical diseases. Thus, there is a considerable potential for drug interactions in the perioperative period, some of which may be potentially harmful to patients. The most common interactions involve changes in the pharmacokinetics or pharmacodynamics of one drug caused by induction or inhibition of the cytochrome P450 enzyme system by another drug. Other important interactions involve monoamine oxidase inhibitors, some antibiotics, and the tricyclic and tetracyclic antidepressants. These adverse interactions are the subject of this review. © 1997 by Elsevier Science Inc.

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Introduction

Anesthesia for anything but the most minor procedures may involve the administration of up to ten or more drugs. In addition, many patients will be taking a number of drugs related to their surgical condition or for other medical diseases. Because the probability of an adverse drug interaction increases exponentially with the number of drugs a patient receives,1 there is considerable potential for such reactions in the perioperative period. Indeed, the potential for drug interactions is probably greater in anesthesia than in other areas of medicine. Drug interactions result when the effect of one drug is altered by the concurrent administration of another. In some cases the interactions may be beneficial, for example, the synergistic interactions between many hypnotics and opioids. Unfortunately, many drug interactions are potentially harmful to patients. These adverse interactions are the subject of this review. The mechanisms involved in drug interactions may be one of three types: pharmaceutical, pharmacokinetic, or pharmacodynamic.

Pharmaceutical Interactions

Pharmaceutical interactions refer to direct chemical combinations between drugs or their absorption into the material of their containers. A common example of a direct chemical interaction is the precipitation that occurs when a solution of thiopental (highly alkaline) is mixed with acidic solutions such as succinylcholine or adrenaline. When thiopental and vecuronium are administered consecutively, a white precipitate of thiopental acid forms, which is insoluble in plasma and which may occlude intravenous (IV) tubing.2 Aminoglycosides and penicillin should never be mixed in the same container because the penicillin inactivates the aminoglycoside to a significant degree. Glycerol trinitrate is inactivated by binding to polyvinyl chloride, and insulin can adhere to the surface of glass or plastic syringes. The net result is that the patient receives a lower than expected dose of the drug, with a reduction in clinical effect. The antagonism of the anticoagulant effects of heparin by protamine results from...
the formation of an inactive chemical complex between the two substances. This is a therapeutic pharmaceutical interaction. In general, however, pharmaceutical interactions are seldom a problem in anesthesia if sensible precautions are taken. Problems are more likely to arise in the intensive care unit (ICU).

**Pharmacokinetic Interactions**

Pharmacokinetic-related drug interactions are a much more common source of adverse reactions associated with anesthesia. Pharmacokinetic interactions occur when the administration of one drug alters the disposition of another drug, changing the pharmacodynamics of the second drug. Pharmacokinetic interactions may arise because of alterations in drug absorption, distribution, metabolism, elimination, or excretion. Of these, interactions affecting distribution and metabolism are the most important for anesthesiologists.

**Absorption**

The absorption of an orally administered drug from the gastrointestinal tract may be influenced by gastric and intestinal pH, speed of gastric emptying, the pKa of the drug, its lipid solubility, and the particular pharmaceutical formulation. An example of a drug absorbed from the stomach is salicylic acid, and absorption is much greater at low than at high pH. Most drugs, however, are absorbed from the upper small intestine, and their absorption will be more influenced by gastric and intestinal motility. Premedication with opioids and anticholinergics will delay gastric emptying and drug absorption, while metoclopramide, which increases the rate of gastric emptying, may increase the rate of diazepam absorption.5 This could be relevant where these drugs are combined with oral drugs for premedication such as benzodiazepines. Within the gut, interaction between drugs can have important effects on absorption. For example, the tetracycline antibiotics can chelate with a number of divalent and trivalent metallic ions such as the calcium, aluminium, and bismuth present in dairy products and antacids to form complexes that are not only poorly absorbed but have reduced antibacterial effect.

**Distribution**

The extent of the distribution of a drug within the body depends on several factors, including tissue blood flow, lipid solubility, and protein binding. Inhatalional and IV anesthetics often produce significant hemodynamic changes that may profoundly affect peripheral blood flow and perfusion. In addition to changes in distribution, a reduction in liver and renal blood flow will also affect the clearance of most drugs.

**Metabolism and Elimination**

Drugs are eliminated from the body by several processes, of which by far the most important for IV drugs is biotransformation in the liver. Phase I biotransformations are oxidation, hydrolysis, or reduction processes. Oxidation is usually catalyzed by one or more of the cytochrome P450 enzymes. More than 60 isoforms of this hemoprotein enzyme have been described, and each individual isoform possesses a unique cytochrome system whose characteristics reflect genetic makeup and environmental and drug exposure. P450 enzymes have been grouped into three families, CYP 1, CYP 2, and CYP 3, on the basis of the degree of similarity of their amino acid sequences. Each of these families is divided into subfamilies, denoted by a capital letter. Within each subfamily specific enzymes are denoted by an Arabic numeral. CYP 3A4 is probably the most important cytochrome P450 isoform for drug metabolism. It has a very wide substrate specificity and mediates the metabolism of approximately 65 different drugs. It is the isoform with highest expression in the human liver, and it is also present in high concentrations in the intestine.4,5 CYP 3A4 is involved in the metabolism of midazolam6 and alfentanil.7 A wide range of chemical compounds, including many drugs, can interact with the cytochrome P450 system, causing either an increased activity (enzyme induction) or enzyme inhibition (Table 1). Both enzyme inhibition and induction can be responsible for adverse drug interactions. Phase II reactions involve conjugation of the metabolites or the parent drug with a water-soluble ligand such as glucuronide or sulphate. These conjugates are more polar and thus more readily excreted in the bile and urine. Phase II metabolism is not mediated by P450 enzymes and is less commonly involved in drug interactions.

**Enzyme Induction**

Enzyme induction is an adaptive response that involves the accumulation of specific mRNAs and increased expression of the associated enzymes. It may be a regulatory mechanism that has evolved to protect against the accumulation of foreign compounds to levels that may cause toxic
enzymes both in the liver and the intestine. Halothane opioids is also increased. This would result in a need for reasonable that the metabolism of fentanyl or other between rifampicin and other opioids, but it would seem that this may be even more important in this interaction than hepatic enzyme induction. Substantial concentrations of CYP 3A4 are found in the wall of the proximal small intestine. The pharmacodynamic effects of midazolam were significantly less following pretreatment with rifampicin, consistent with the reduced bioavailability (Figure 2). It is likely that other potent inducers of CYP 3A4 will cause a similar interaction. The almost total loss of the pharmacodynamic effect of midazolam in the presence of enzyme induction has obvious clinical implications for the use of benzodiazepines in patients taking enzyme inducers.

Phenobarbital was one of the earliest drugs to be recognized as an enzyme inducer. Other drugs used for the treatment of epilepsy, especially carbamazepine and phenytoin, also have this property. Both are commonly prescribed antiepileptic drugs, and carbamazepine is also used in the treatment of trigeminal neuralgia and, in psychiatry, for the treatment of depression. Carbamazepine and phenytoin are potent inducers of cytochrome P450 enzymes, in particular the CYP 3A isoforms, although carbamazepine also induces other isoforms, as well as glucuronyl-transferases. The oxidation of cyclosporin A, which is catalyzed by CYP 3A enzymes, is increased by

Figure 1. Plasma concentrations (means ± SEM) of midazolam after a 15 mg oral dose following pretreatment with placebo or 600 mg rifampicin once daily for 5 days in 10 healthy subjects. Open circles = after placebo; closed circles = after rifampicin. From Backman et al. with permission.
phenytoin\textsuperscript{24} and carbamazepine.\textsuperscript{25} These interactions result in lowered plasma concentrations of the immunosuppressant, with the attendant risk of transplant rejection. Carbamazepine and other antiepileptic drugs accelerate the metabolism of warfarin\textsuperscript{26} and dicoumarol,\textsuperscript{27} thereby reducing the anticoagulant effect. These drugs also stimulate the biotransformation of benzodiazepines, including diazepam\textsuperscript{28} and midazolam.\textsuperscript{29} In the case of diazepam, the interaction with carbamazepine is associated with increased plasma concentrations of the pharmacologically active metabolite nordiazepam\textsuperscript{28} so that there may not necessarily be a decrease in therapeutic efficacy. Because midazolam does not have active metabolites, enzyme induction will result in a decrease in pharmacologic effect. Backman \textit{et al.}\textsuperscript{29} studied the pharmacokinetics and pharmacodynamics of a single dose of oral midazolam 15 mg in six patients with epilepsy taking either carbamazepine or phenytoin, or a combination of both drugs. The control group consisted of volunteers matched by age and gender. In the patients, the AUC of midazolam was only 5.7\%, and the peak midazolam concentration was 7.4\% (5.2 ng/ml vs. 70.4 ng/ml) of the values in the control subjects. The elimination half-life of midazolam in the patients was 42\% of that in the controls. Most patients had no sedative effects after oral midazolam, whereas there was a clear sedative effect lasting 2 to 4 hours in each of the control subjects. These differences were confirmed by a variety of tests of the pharmacodynamic responses to midazolam. Carbamazepine, phenytoin, and the barbiturates also enhance the metabolism of opioids that rely on hepatic metabolism. Obviously, these pharmacokinetic and pharmacodynamic changes need to be taken into account when administering drugs metabolized by P450 enzymes to patients on chronic antiepileptic therapy.

### Inhibition of Drug Metabolism

Because many of the drugs used in anesthesia are metabolized by hepatic cytochrome P450 isoenzymes, any inhibition of these enzymes can have important consequences. Although the number of compounds that inhibit enzyme activity is less than that producing enzyme induction, their potential for causing serious adverse reactions related to anesthesia is probably much greater.

#### Antibiotics

A number of antibiotics, most notably the macrolides and azole antifungal drugs, have been implicated in significant enzyme inhibition resulting in adverse interactions with anesthetic-related drugs. Nearly all interactions with macrolide antibiotics appear to result from a dose-dependent inhibition of the cytochrome P450 isoform CYP 3A4. CYP 3A4-mediated metabolism of these drugs results in the formation of a stable complex with the haem of the enzyme, rendering it inactive.\textsuperscript{30} Troleandomycin and erythromycin both bind to P450 to form inactive complexes, although the degree of complex formation is lower with erythromycin.\textsuperscript{31} Coadministration of erythromycin with midazolam or alfentanil, which are also metabolized by CYP 3A,\textsuperscript{6,7,32,33} has resulted in delayed excretion and prolonged effects. The elimination half-life of alfentanil increased from 84 ± 8.2 minutes to 131 ± 43 minutes, and clearance decreased from 3.9 ± 0.8 ml/kg to 2.9 ± 1.2 ml/kg, in six subjects after a 7-day course of erythromycin (Figure 3).\textsuperscript{34} There are a number of case reports describing prolonged respiratory depression following alfentanil in patients treated with erythromycin.\textsuperscript{34,35} Erythromycin does not appear to inhibit the metabolism of sufentanil,\textsuperscript{36} when studied in subjects who had participated in a previous study with alfentanil.\textsuperscript{34} This finding is at first difficult to explain, because the enzyme CYP 3A4 responsible for the N-dealkylation of sufentanil (and fentanyl) is the same as that which metabolizes alfentanil and erythromycin.\textsuperscript{33,37} A possible explanation may be the differences in hepatic clearance between alfentanil and sufentanil. Sufentanil has a much greater intrinsic hepatic clearance than alfentanil\textsuperscript{38,39} and therefore will be more dependent on changes in hepatic blood flow than hepatic metabolism, so that it is less likely to be affected by enzyme inhibition than alfentanil.

The biotransformation of midazolam is mediated by at least three P450 isoenzymes, CYP 3A3, CYP 3A4, and CYP 3A5,\textsuperscript{4} and erythromycin inhibits midazolam metabolism in animals and humans.\textsuperscript{40–44} Hiller \textit{et al.}\textsuperscript{40} reported deep unconsciousness and exceptionally high midazolam con-
centrations in a child being treated with IV erythromycin
given oral midazolam as premedication. In a 61-year-old
man receiving erythromycin for suspected Legionnaires’
disease, midazolam 300 mg IV given over 14 hours in-
duced sleep lasting 6 days.43 The measured half-life of
midazolam in this patient was 24.8 hours (normally 1.5 to
2.5 hours). In a controlled study in volunteers, pretreat-
ment with erythromycin 500 mg three times daily for one
week resulted in an almost threefold increase in the Cmax
of midazolam and more than a four-fold increase in AUC
values for oral midazolam.41 These changes, caused by an
increase in oral bioavailability and a decrease in plasma
clearance of midazolam, were accompanied by excessively
long-lasting hypnotic and amnesic effects. The pharmaco-

kinetic effects of erythromycin were much less following
IV than orally administered midazolam. Both erythromy-
cin and troleandomycin reduce the metabolic clearance of
triazolam, which, like midazolam, is metabolized by CYP
3A4.43,45 In volunteers, erythromycin increased peak
plasma triazolam concentrations by 100% and prolonged
its half-life.30,46

Antifungal Drugs
The common mechanism of action of the azole antifungal
drugs is inhibition of a fungal cytochrome P450. However,
these drugs are not selective and they also inhibit human
microsomal enzymes from all three P450 enzyme fami-
lies.30 Inhibitory activity is greatest against CYP 3A4, fol-
lowed by CYP 1A2, and weakest for CYP 2C and CYP 2D.
Ketoconazole is the most potent inhibitor, followed by
itraconazole (10 times less potent) and then fluconazole
(500 times less potent).47 The best documented interac-
tion is the inhibition of cyclosporin metabolism by keto-
conazole, both in vitro and in animals and humans.49
Indeed, it has been suggested that concomitant adminis-
tration of ketoconazole could be used to reduce the dose,
and thus the cost, of cyclosporin treatment.50

In vitro, ketoconazole and itraconazole are potent
inhibitors of midazolam hydroxylation.43 Pretreatment of
volunteers with these antimycotics for 4 days increased the
AUC after oral triazolam 22- to 27-fold and the elimination
half-life 6- to 7-fold.51 The higher concentrations of tria-
zolam during treatment with antimycotics was associated
with profound pharmacodynamic effects, measured using
a battery of psychomotor tests. The same group also found
similar interactions with oral midazolam. Both ketocon-
azole and itraconazole increased the AUC following oral
midazolam 7.5 mg from 10- to 15-fold and the mean peak
plasma midazolam concentration three to four times
compared with a placebo.52 Psychomotor tests were signif-
cicantly disturbed until at least 6 hours after the ingestion
of midazolam.

Calcium Channel-Blockers
The calcium channel-blockers diltiazem and verapamil
interact with a variety of drugs including propanolol,
carbamazepine, cyclosporine, and benzodiazepines.53–55
Diltiazem and probably also verapamil are metabolized by
CYP 34A,56 and both drugs are potent inhibitors of this
enzyme.45,57 They significantly increased the bioavailability
of midazolam and triazolam and prolonged the elimi-
nation half-life.55,58 These changes in the pharmacokinet-
ics were associated with profound and prolonged sedative
effects.

Grapefruit Juice
Grapefruit juice is not a substance usually associated with
anesthesia. However, in recent years it has been the object
of considerable pharmacologic interest because of its
ability to increase the bioavailability of a number of drugs,
especially the dihydropyridine calcium channel-block-

Figure 3. Plasma alfentanil concentrations in a subject who
had taken no drugs (control) and after erythromycin 500 mg
for 1 or 7 days. From Bartkowski et al.34 with permission.
cantly decreased the mean clearance and increased the tine.64 All of these compounds are metabolized by cyto-
clearance of propranolol,68 which is a P450 substrate, and propofol impaired the intrinsic clearance of propranolol,68 which is a P450 substrate, and sufentanil is metabolized by isolated human and pig liver microsomes in vitro.69 The mechanism for this latter interaction is un-
clear. Whereas alfentanil and sufentanil are metabolized by cytochrome P450 CYP 3A enzymes, current evidence suggests that the P450 isoforms responsible for the bio-
Propanolol,68 and pantoprazole are used for the treatment of peptic ulcers and other hypersecretory conditions. They undergo oxidative metabolism in the liver by cytochrome P450 enzymes. As such, it has the potential to interact with other drugs metabolized by this enzyme system. Propofol impaired the intrinsic clearance of propranolol,68 which is a P450 substrate, and inhibited the enzymatic degradation of alfentanil and sufentanil by isolated human and pig liver microsomes in vitro.69 The mechanism for this latter interaction is unclear. Whereas alfentanil and sufentanil are metabolized by cytochrome P450 CYP 3A enzymes, current evidence suggests that the P450 isoforms responsible for the bio-
formation of propofol are primarily CYP 2A1 and CYP 2B1.68,70

Propofol
Propofol, which is widely used in anesthesia and for sedation of patients in ICUs, undergoes oxidative metabol-
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formation of propofol are primarily CYP 2A1 and CYP 2B1.68,70

Proton Pump Inhibitors
The proton pump inhibitors omeprazole, lansoprazole, and pantoprazole are used for the treatment of peptic ulcers and other hypersecretory conditions. They undergo extensive metabolism in the liver, mediated by the polymorphically expressed enzyme CYP 2C19,71 and this accounts for a pronounced interindividual variability in their pharmacokinetics. Other substrates for CYP 2C19 include S-mephentoin, propranolol, diazepam, and a number of tricyclic antidepressants. Population studies on CYP 2C19 polymorphism indicate that 2% to 6% of white Europeans and Americans are poor metabolizers of S-mephentoin, the prototype substrate for CYP 2C19, whereas in Asian populations the proportion of poor metabolizers is signif-
antly higher, from 12% to 20%.72 In poor metabolizers of S-mephentoin, diazepam is more slowly metabolized than in subjects who are extensive metabolizers.73,74 Ome-
prazole had no effect on the pharmacokinetics of diaze-
pam in the poor metabolizers, because these individuals are deficient in CYP 2C19,75 and the conditions for an interaction therefore do not exist.74,76 However, it signifi-
cantly decreased the mean clearance and increased the half-life and mean residence time in the extensive metabo-
lizers.76,77 It is worth noting that diazepam is subject to dual routes of metabolism, with approximately 40% to 50% of N-demethylation being mediated by CYP 2C19 and the remainder probably mediated by CYP 3A.78 Whether this interaction between omeprazole and diazepam has clinical relevance remains to be established. However, in view of the wide therapeutic safety index of diazepam, the changes produced are unlikely to cause serious adverse effects. Surprisingly, lansoprazole did not affect the plasma concentrations of diazepam,79 perhaps because the affinity of lansoprazole for CYP 2C19 is low in compari-
to that of diazepam.71 Pantoprazole also does not seem to have a major affect on diazepam metabolism.80

H2-receptor Antagonists
The H2-receptor antagonist cimetidine binds to the cyto-

Monoamine oxidase (MAO) is an enzyme that catalyzes the oxidative deamination of over 15 monoamines in the body, including important neurotransmitters or neuro-
modulators such as adrenaline, noradrenaline, dopamine, and serotonin (5-HT). There are two subtypes of MAO, MAO-A and MAO-B, which differ in substrate preference, inhibitor specificity, and tissue distribution.84 MAO-A prefer-
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Interactions with Monoamine Oxidase Inhibitors
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line, whereas MAO-B preferentially deaminates nonpolar aromatic amines such as 2-phenyl-ethylamines and benzyl amine. Tyramine and dopamine are substrates for both. The monoamine oxidase inhibitors (MAOIs), developed in the 1950s as the first effective antidepressant drugs, bind irreversibly with MAO-A and MAO-B by the formation of covalent bonds. Because the generation of fresh MAO is a slow process, the potential for drug interactions with these drugs persists for up to 2 weeks after stopping the drug. The newer generation of MAOIs, in contrast, are competitive inhibitors of MAO and produce a reversible inhibition of MAO-A (RIMAs). Specific MAO-B inhibitors such as selegiline (1-diprenyl) have been developed, but are less efficient than MAO-A inhibitors as antidepressants. Selegiline is marketed for the treatment of Parkinson’s disease. Because of the widespread inhibition of MAO and other enzyme systems by MAOIs, there is considerable potential for adverse interactions with other drugs as well as other substances, including certain foods such as cheese and yeast extracts that contain tyramine. Of most concern to anesthetists has been interactions with sympathomimetic drugs and opioids.

Indirectly acting sympathomimetic drugs such as amphetamine, ephedrine, and metaraminol act partly by stimulating the release of endogenous noradrenaline from sympathetic nerve terminals. Within these terminals, noradrenaline is stored in a stable pool, and in a mobile pool ready for immediate release. Following reuptake of noradrenaline into the nerve terminal, it is metabolized by the enzymes MAO and catechol-o-methyl transferase (COMT) (Figure 4). MAO acts to limit the size of the stable pool by mediating a constant turnover of noradrenaline. During treatment with MAOIs, large amounts of noradrenaline accumulate in the brain and in the sympathetic terminals, and administration of an indirectly-acting sympathomimetic will cause an exaggerated release of noradrenaline and a potentially fatal hypertensive response. Thus, in patients treated with MAOIs, the use of indirectly acting sympathomimetic drugs should be avoided. Directly-acting drugs (eg, adrenaline, isoprenaline, methoxamine, or phenylephrine) are safe to use in these patients.

Pethidine (meperidine) is the opioid most commonly associated with an adverse reaction with MAOIs. Although only a proportion of patients taking MAOIs will react adversely to pethidine, there is no sure way of predicting the small group in whom the combination could produce severe, life-threatening reactions. These reactions can present in two distinct forms. The excitatory form is characterized by sudden agitation, delirium, headache, hypotension or hypertension, rigidity, hyperpyrexia, convulsions, and coma. It is thought to be caused by an increase in cerebral 5-HT concentrations as a result of inhibition of MAO. This is potentiated by pethidine, which blocks neuronal uptake of 5-HT. The depressive form, which is frequently severe and fatal, presents as respiratory and cardiovascular depression and coma. It is the result of a reduced breakdown of pethidine due to the inhibition of hepatic N-demethylase by MAOIs, leading to accumulation of pethidine. There is evidence that the risk of adverse reactions to pethidine is more likely with drugs that inhibit both MAO-A and MAO-B, and the risk may be less with newer, specific MAO-A inhibitors. Interactions with other opioids such as morphine and pentazocine have been reported, but they are much less common. Other opioids appear to be safe in combination with MAOIs, with the possible exception of phenopiperidine, which is metabolized to pethidine, norpethidine, and pethidinic acid.

Prolongation of the action of succinylcholine has been reported with phenelzine. This seems to be a specific interaction with phenelzine, which decreases pseudocholinesterase concentration. The use of nondepolarizing muscle relaxants is not contraindicated in the presence of MAOIs, although pancuronium should be used with care because of its ability to release noradrenaline.

**Pharmacodynamic Interactions**

Pharmacodynamic interactions are those in which the effects of one drug are altered by the presence of another drug at its site of action, or where the concentration of one drug is changed by, for example, displacement from binding sites on plasma or tissue proteins by a second drug. The possibilities for this type of interaction is more limited than for pharmaceutical or pharmacokinetic interactions.

Adverse drug interactions can occur when two drugs acting at the same or a related receptor are given concomitantly. For example, β-adrenoceptor antagonists diminish the effectiveness of β-agonists such as salbutamol or terbutaline. On other occasions interactions involve drugs with quite different mechanisms. For example, the inhibition of prostaglandin production by nonsteroidal anti-inflammatory drugs (NSAIDs) can sometimes cause marked

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**Figure 4.** Metabolic pathways in the biotransformation of noradrenaline involve the enzyme monoamine oxidase (MAO). Inhibition of MAO by the class of antidepressant drugs known as MAO inhibitors can lead to important and potentially life-threatening adverse drug interactions. CNS = central nervous system; COMT = catechol-o-methyl transferase; HMMA = 4-hydroxy 3-methoxy mandelic acid; MHPG = methoxy-hydroxy phenyl ethelene glycol.
loss of antihypertensive control in patients receiving treatment with β-adrenergic receptor antagonists, diuretics, or angiotensin-converting enzyme (ACE) inhibitors.91

Antidepressants
The tricyclic and tetracyclic antidepressants act by specifically blocking the reuptake of endogenous catecholamines and serotonin into nerve terminals, by competing for the active transport mechanism. In patients receiving these drugs, the circulatory effects of adrenaline are potentiated two to three times, and that of noradrenaline by up to nine times.92 A marked increase in hypertensive effect will also occur with other directly acting sympathomimetics. Pancuronium and ketamine also inhibit the neuronal reuptake of catecholamines and should be used with caution in patients taking these drugs. Indirectly acting vasoconstrictors such as ephedrine act by causing the release of noradrenaline from adrenergic nerve terminals. In the presence of tricyclic and tetracyclic antidepressants, the uptake of these drugs into the neurons is partially or completely prevented, so the release of noradrenaline is inhibited leading to a diminished effect.

Electrolyte Disturbances
Electrolyte disturbances caused by diuretics, for example, can result in important pharmacodynamic interactions. The incidence of toxic effects of the cardiac glycosides is increased by potassium depletion brought about by potassium-depleting diuretics. Hypokalemia caused by diuretics may potentiate the activity of nondepolarizing muscle relaxants leading to prolonged paralysis. The elimination of lithium occurs almost entirely by the kidney, and lithium clearance is reduced by thiazide diuretics so that plasma lithium concentrations can rise to toxic levels. Diuretic-induced sodium depletion also may result in lithium toxicity due to compensatory increases in proximal tubular reabsorption of lithium. Clinically important increases in lithium levels have been reported in patients taking ACE inhibitors. The mechanism is unclear but may involve altered sodium reabsorption.93 Lithium toxicity also has been associated with calcium entry blockers, NSAIDs, tricyclic antidepressants, and a wide variety of antipsychotic drugs such as haloperidol, phenothiazines, and clozapine. Interactions with antipsychotics usually involve some form of neurotoxic reaction ranging from extrapyramidal symptoms to the neuroleptic malignant syndrome.

Protein Binding and Pharmacodynamics
Changes in protein binding are generally only clinically important for highly bound drugs. A reduction in binding from 95% to 90% represents a 100% increase in unbound (free) fraction of drug, whereas a reduction from 35% to 30% corresponds to only a 7.7% increase in free fraction. It is the free fraction of a drug that is responsible for the pharmacologic effect. The effects of altered protein binding are complex and often involve changes in clearance and volume of distribution that may mitigate the expected increase in free drug concentration. Concomitantly administered drugs can compete with one another for binding sites on plasma proteins, resulting in displacement interactions that may lead to increased pharmacologic effect and the possibility of toxicity. Drugs likely to be involved in displacement interactions are those that are highly protein bound, have a small volume of distribution, a high clearance, and a narrow therapeutic range of concentrations.94 One of the best documented examples is the displacement of warfarin and other anticoagulants that are highly bound to albumin, by acidic drugs such as chloral hydrate, phenylbutazone, mephenytoin, and sulphinpyrazole.95–97 However, although such displacement can result in increased anticoagulation, the effect is usually transient. Other mechanisms probably are equally important, inhibition of metabolism, in particular.

The pharmacodynamics of the coumarin anticoagulants also is increased by some antibiotics such as the aminoglycosides and cephalosporins. The mechanism is not well understood, but one possibility is that the reduction in bacteria in the gut responsible for producing vitamin K reduces production of the vitamin. However, this is normally not an essential source of vitamin K, and a more likely explanation is that vitamin K absorption is reduced by the antibiotics as part of a general antibiotic-induced malabsorption syndrome.

Interactions with Muscle Relaxants
Several classes of antibiotics possess neuromuscular blocking actions, including the aminoglycosides, tetracyclines, polymixins, and lincomycins. Most of the aminoglycosides are comparatively potent in their ability to potentiate muscle relaxants. Gentamicin, neomycin, and streptomycin, but not tobramycin, are capable of producing a dose-dependent neuromuscular block alone in the rat isolated phrenic nerve-diaphragm preparation.98 Potentiation of neuromuscular block by the aminoglycosides can occur with relatively small doses of the drugs, and enough can be absorbed from irrigation of the intraperitoneal space, peritoneal cavity, or even a wound to give rise to clinical problems. The only aminoglycoside that has not been implicated in this type of interaction is netilmicin, which does not seem to have any neuromuscular action.99 Aminoglycosides inhibit neuromuscular transmission by preventing the presynaptic release of acetylcholine; tetracyclines inhibit this transmission by chelating extraneuronal calcium. These drugs can prolong the recovery of nondepolarizing muscle relaxants, with the possible exception of atracurium.100 Aminoglycoside-induced block may be overcome by calcium salts and 4-aminopyridine, but the block caused by the other groups cannot reliably be reversed by pharmacologic means.

Chronic therapy with antiepileptic drugs, phenytoin, carbamazepine, or sodium valproate has been associated with resistance to the nondepolarizing muscle relaxants.100–103 There is an increase in the dose of muscle relaxant required to achieve a given degree of block and a reduction in the duration of action. There is potentiation
of neuromuscular block when phenytoin is acutely administered as an IV bolus, although this action is unlikely to be of clinical significance. The mechanisms of these effects may be a decrease in the sensitivity of the postjunctional membrane to acetylcholine.

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