# Drug Interactions for the Anesthesiologist.

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## Introduction

Drug interactions are important to anesthesiologists for several reasons. Patients are increasingly presenting for surgery while taking numerous medications. There may be drug interactions between the preoperative medications themselves, between the preoperative medications and intra- or post-operative medications or between the drugs and agents administered only by the anesthesiologist.

Drug interactions can be classified as pharmacodynamic, pharmacokinetic, or pharmaceutical. A pharmacodynamic drug interaction manifests as a decrease or increase in the effects of medications given in an additive or synergistic fashion. A pharmacokinetic interaction occurs when one drug affects the absorption, distribution, metabolism or elimination of another. A pharmaceutical interaction occurs when drugs have a chemical reaction with each other before or during their administration or with the vessel in which they are stored on administered. Finally, as in the case of giving meperidine to a patient on a monoamine oxidase inhibitor (MAOI), drug combinations can lead to difficult-to-predict but devastating interactions. Fortunately, these types of interactions are the exception rather than the rule.

## Pharmacodynamic Interactions

Pharmacodynamic interactions can be additive or supraadditive (i.e. synergistic). Additive interactions usually occur when two drugs of the same class act on the same receptor or have the same mechanism of action. Combining two volatile anesthetics or two benzodiazepines would be expected to produce an additive interaction. Synergistic interactions usually occur when two drugs are administered that produce the same effect through different mechanisms of action or via different receptors. An example of a synergistic interaction is the hypnosis produced with a combination of a small dose of an opiate and a benzodiazepine.

Antagonistic interactions are regularly utilized by anesthesiologists to reverse neuromuscular blockers, opiates or benzodiazepines. Unintended antagonistic interactions that are not due to changes in kinetics are relatively rare (1).

## Pharmacokinetic Interactions

Because anesthesiologists administer most medications parenterally, we usually do not think of pharmacokinetic drug interactions that affect drug absorption. However, we frequently administer agents which alter gastric emptying (opiates and anticholinergics slow down gastric emptying while metoclopramide will speed the transit of gastric contents into the small intestine). As little as 0.05mg/kg morphine will significantly delay gastric emptying (2). This may be relevant if a patient is given an oral medication that is absorbed in the small bowel (such as an antibiotic or benzodiazepine) in conjunction with a drug that affects gastric emptying.

Nearly all medications administered by anesthesiologists are ultimately eliminated by the kidney or lung. Toxicologists will raise or lower urine pH in attempts to enhance renal elimination of toxic substances that are weak acids (e.g. aspirin) or weak bases, (e.g. amphetamines or phencyclidine (aka PCP)) respectively. Activated charcoal and cholestyramine resins will bind drugs in the intestine and will reduce re-absorption of drugs that are eliminated in bile salts. Lithium is excreted by the kidneys. Its elimination is slowed by loop or thiazide diuretics and enhanced by osmotic diuretics or administration of sodium-containing intravenous solutions.

**Pharmaceutical Interactions**
Some pharmaceutical interactions are obvious to the naked eye. When the very alkaline drug, thiopental, is mixed with an acidic solution such as many muscle relaxants, a visible inactive precipitate is formed. Some other pharmacologic interactions are not visible to the eye and thus are potentially more hazardous. For example, penicillin inactivates aminoglycoside antibiotics. Insulin and nitroglycerin will bind to the polyvinyl chloride used for standard intravenous tubing, resulting in the patient receiving less drug than intended. A pharmaceutical interaction that occurs inside the body is the formation of inactive chemical complexes when the polycationic drug protamine is given to a patient who has circulating heparin. The formation of protamine-heparin complexes allow the patient to resume normal coagulation long before heparin would wear off by itself.

The previous examples exemplify the variety of drug interactions facing the anesthesiologist in daily practice. The purpose of this lecture is to present the prevalence and impact of drug interactions for the anesthesiologist and to examine the mechanisms by which these interactions occur. Several drug interactions that are relevant for the anesthesiologist will be reviewed.

**Prevalence of Polypharmacy**
A recent prospective study of 1025 consecutive surgical patients admitted to a university teaching hospital in New Zealand found that 49% of patients were taking medications unrelated to their surgical condition at the time of hospital admission. There were 286 different medications administered to this cohort and the average number of medications administered per admission was 9.38 with a range from 1 to 47. The potential for drug interactions is quite high when such a large number of agents are administered (3). An ASA abstract published in 2001 reported that 12% of patients presenting for a pre-admission interview at an ambulatory surgery center had potential drug interactions identified by the ePocates computing program (see below for more electronic resources). (4)

**Justification for Studying Mechanisms of Drug Interactions**
A recent search in the Pubmed database from 1970 to present (www.pubmed.com) under phrase “drug interactions” revealed 52,007 references. When this search was limited to “drug interactions AND anesthesia,” 1,921 references were produced. Clearly, it would be impossible to mentally catalog these interactions, so a framework of understanding needs to be constructed. By appreciating the mechanisms by which theses interactions occur, we will be better equipped to predict and remember potential drug interactions.

**Effects on Drug Elimination or Inactivation**
Most drugs undergo metabolism in the liver. They can undergo biotransformation through oxidation, reduction or hydrolysis in processes known as phase 1 reactions. Phase 2 reactions involve conjugation of a hydrophobic drug with a water soluble ligand such as glucuronic acid, glycine or sulfate. Phase 2 and usually phase 1 reactions form compounds that are more hydrophilic and thus, more easily eliminated in the urine or bile.

The oxidative and reductive phase I reactions are catalyzed by the cytochrome P-450 enzymes. Over 150 P-450 enzymes have been characterized in animals. A large number of drugs and agents can induce or inhibit the activity of P-450 enzymes. Enzyme inducers tend to be are lipophilic drugs that induce the activity of the enzyme(s) responsible for their biotransformation.

There is a nomenclature of P-450 enzymes which allows each enzyme to be assigned a unique name in an orderly fashion. First, the enzymes are divided into 3 families, CYP 1, 2 and 3. These families are further divided into subfamiles designated by a capital letter. Finally, each enzyme is assigned a unique number. For

example, CYP 3A4 accounts for 40-60% of the P-450 enzyme activity in humans. The CYP 3A family metabolizes large planar molecules such as lidocaine and midazolam. CYP 2D6 accounts for only 2-5% of total hepatic P450 isoenzymes but accounts for 25% of drugs metabolized, including many opiates, antiarrhythmics, beta-blockers and antihypertensives. This enzyme is easily saturated leading to non-linear kinetics. It is inhibited by a large number of drugs including ketoconazole, many selective serotonin reuptake inhibitors (SSRIs), diphenhydramine, haloperidol and propoxyphene (Darvon, Eli Lilly and Co., Indianapolis, IN). In contrast to CYP 3A4, CYP 2D6 activity is not induced by medications (5).

Enzyme induction can have significant effects on the kinetics and metabolism of anesthetic agents. Enzyme induction with rifampin has been implicated in a near-fatal case of halothane hepatotoxicity (6). Chronic isoniazid therapy induces isoflurane and enflurane metabolism, markedly increasing peak fluoride concentrations (7, 8). Rifampin can induce methadone metabolism, reducing plasma concentrations by up to 68% (9). Oral midazolam is used as for preoperative sedation in children and as a sleep aid in Europe. It undergoes significant first pass metabolism, rendering an oral availability of 30 to 70%. A five-day course of rifampin given to healthy volunteers reduced the area under the concentration-time curve (AUC) for subsequent doses of oral midazolam by 96% (10).

| **Table 1: Drugs that Inhibit P450 Enzymes** |
|---|
| Antibiotics |
| -Erythromycin |
| -Flouroquinolones |
| -Isoniazid |
| "-navir" Antiretrovirals: indina-, saquina, ritonavir |
| "-azole" Antifungals: clortrima-, Itracona-, micona- and ketoconazole, |
| SSRIs: Selective Serotonin Reuptake Inhibitors |
| Calcium channel blockers: diltiazem, verapamil |
| H2 blockers: cimetidine, omeprazole |
| Grapefruit juice |
| Propofol |

| **Table 2: Drugs That Induce P450 Enzymes** |
|---|
| Barbiturates |
| Anticonvulsants |
| Phenytoin |
| Carbamazepine |
| Primidone |
| Rifampin |
| St. John's Wort |
| Ethanol |
| Tobacco Smoke |
| Steroids especially glucocorticoids |

Changes in hepatic enzyme activity will affect the ability of the liver to transform drugs as they flow through the liver. The rate of total hepatic metabolism, or hepatic clearance, is proportional to the hepatic blood flow times the hepatic extraction ratio. The hepatic extraction ratio refers to the percent of drug that is modified or eliminated as blood flows from the hepatic artery to the hepatic vein through the liver. Changes in hepatic clearance can occur during anesthesia due to reductions in hepatic blood flow that are common during anesthesia, or modification of enzymatic processes.

**Anesthetic Drug Interactions**

Anesthesiologists intuitively use drug interactions in our daily practice. For example, we know that midazolam will synergistically reduce the amount of intravenous induction agent required to achieve unconsciousness (11). We process this information at a conscious or subconscious level to guide us when dosing these medications. In fact, the concept of the "balanced anesthetic" is based on the premise that we may minimize the undesirable side effects of some of our medications if we take advantage of the interactions between several drugs.

This review will not reiterate the anesthetic agent interactions commonly exploited by anesthesiologists, but will focus on important interactions within the category of nonanesthetic agents and between the category of nonanesthetic and anesthetic agents.

**Cardiovascular Agents**
Calcium channel blockers can produce variable degrees of hypotension due to decreased systemic vascular resistance and decreased myocardial contractility. A-V node conduction may also be impaired, especially by verapamil and diltiazem. Calcium channel blockers can decrease the MAC of volatile anesthetic agents and increase the cardiovascular toxicity of local anesthetics.

Angiotensin converting enzyme inhibitors (ACE inhibitors) are popular antihypertensives. They have been associated with intraoperative hypotension during neuraxial and general anesthesia. There is currently no consensus regarding perioperative administration of these medications. It may be reasonable to discontinue the drugs prior to surgery when the risks associated with hypotension are greater than those of hypertension, e.g. carotid stenosis or coronary artery disease. Many anesthesiologists would instruct patients to omit ACE inhibitors on the day of surgery if major blood loss or large fluid shifts are anticipated.

**Type A Monoamine Oxidase Inhibitors**
Monoamine oxidase inhibitors (MAOIs) constitute a class of medications that prevent the deamination of monoamines. The MAOIs that have enjoyed the longest use are antidepressants that irreversibly inhibit MAO type A and B enzymes that deaminate tyramine, dopamine, norepinephrine and serotonin. The three most common irreversible inhibitors are phenylzine (Nardil, Parke-Davis) tranylcypromine (Parnate, Smith Kline Beecham) and isocarboxazid (Marplan, Oxford Pharmaceuticals). Patients taking these type A MAOI medications are at risk of developing severe hypertension, fever, and diaphoresis if they are given sympathomimetic drugs (especially agents with indirect action such as ephedrine) or if they ingest foods with high tyramine content, such as beer and smoked or aged foods. Patients on MAO type A inhibitors may be very sensitive to the depressant effects of opiates, leading to excessive sedation, coma and respiratory depression. A rare and potentially lethal "excitatory" interaction has been described in patients taking MAOI-A drugs and meperidine. This reaction is characterized by agitation, hemodynamic instability, seizures, coma and death.

Due to the multitude of problems that can occur in patients taking these medications, the traditional teaching has been to discontinue MAOIs for 2 weeks before elective surgery. However, this is not always practical. The patient may require an urgent or emergent procedure. Patients who take an MAOI for depression usually have severe or refractory psychiatric disease. Stopping an MAOI for two weeks may precipitate an episode of severe depression in a patient who is already under increased emotional stress from their surgical condition. The decision to continue or stop an MAO inhibitor prior to surgery is a serious one. The anesthesiologist should consider soliciting input from the patient and the physician prescribing the medication when developing a plan for the perioperative medication management.

Some authors advocate an "MAOI-safe" anesthetic. The goals of this technique are to avoid indirect acting pressors, and serotonin agonists or antagonists. Opioids should be administered cautiously given that patients may be exquisitely sensitive to these drugs. The opioids meperidine, pentazocine and tramadol should be avoided altogether. If hypotension is encountered, the patient should be given intravenous fluid and a direct-acting pressor. Newer drugs which inhibit MAO-A in a reversible fashion (RIMAs) may allow safe anesthetic

delivery with a period of discontinuation shorter than 2 weeks. Currently no RIMAs are approved by the FDA, but the drug moclobemide is used outside the United States (12).

**Type B Monoamine Oxidase Inhibitors**
The MAO-B specific inhibitor, selegiline (Eldepryl, Somerset pharmaceuticals) is used to treat Parkinson's disease. Because MAO-B is not responsible for the breakdown of epinephrine, norepinephrine, metanephrine or serotonin, it appears that patients taking selegiline perioperatively are not as prone to perioperative complications as those taking MAO-A inhibitors (13, 14). However, it may be prudent to avoid administering meperidine to a patient taking selegiline.

**Other Antidepressants**
Tricyclic antidepressants (TCAs) inhibit the reuptake of norepinephrine into presynaptic terminals. There is conflicting evidence supporting an enhanced and reduced response to catecholamines and sympathomimetics in patients taking TCAs (15, 16). This may be due to the timing of drug administration. Acute drug administration will increase the amount of norepinephrine in sympathetic postganglionic synapses. With chronic administration, the number of postsynaptic receptors decreases which may account for the decreased sensitivity to sympathomimetics exhibited by some patients. When treating the hypotensive patient who is taking a TCA, it is probably prudent to start with smaller doses of sympathomimetics and titrate to effect. The current American Heart Association guidelines for Emergency Cardiovascular Care suggest that systemic alkalinization with sodium bicarbonate is indicated in cases of hemodynamic complications from TCA overdose. These guidelines also state that procainamide is contraindicated in this setting.

Selective Serotonin Reuptake Inhibitors (SSRIs) are among the most commonly prescribed medications for mood disorders. They generally appear to be safe in the perioperative period. They can however inhibit the P450 3A enzymes with the order of inhibition being: nefazone > fluvoxamine > sertaline > paroxetine > venlafaxine. (Serzone > Luvox > Zoloft > Paxil > Effexor). [Serzone, Bristol-Myer Squibb; Luvox, Solvay Pharm; Zoloft, Pfizer Pharm.; Paxil, Glaxo Smith Kline; Effexor, Wyeth-Ayerst Labs] (17).

**Antibiotics**
Several antibiotics can produce neuromuscular blockade by themselves and may have significant synergism with commonly used neuromuscular blockers (18). The most relevant drugs that enhance neuromuscular blockers are the aminoglycosides, clindamycin the polymyxins, and possibly bacitracin. It appears that the cephalosporins have no significant effect on neuromuscular transmission.

Many antibiotics, in particular the macrolides and antifungals cause significant enzyme inhibition. There have been case reports of prolonged respiratory depression in patients treated with erythromycin who subsequently receive alfentanil (19). Erythromycin has been implicated in prolonged unconsciousness in patients given midazolam and has quadrupled the AUC values for volunteers given oral midazolam (20, 21).

**Muscle Relaxants**
Of all the agents administered by anesthesiologists, muscle relaxants appear to be most susceptible drug interactions. In fact, we regularly employ the antagonistic interaction of the cholinesterase inhibitors neostigmine and edrophonium to reverse the paralytic effect of muscle relaxants. We do this so routinely, many anesthesiologists wouldn't even list the effect of these drugs as a "drug interaction." In addition to the obvious

effect of slowing the degradation of acetylcholine in the neuromuscular junction, neostigmine and edrophonium will slow the degredation of mivacurium and cause a transient *increase* in plazma mivacurium concentration (22). The net effect of giving a cholinesterase inhibitor to a patient paralyzed with mivacurium is to improve neuromuscular transmission, but the benefit is small due to a number of pharmacokinetic and perhaps pharmacodynamic interactions.

As mentioned above, several antibiotics potentiate neuromuscular blockade. It appears that intravenous calcium and 4-aminopyridine will at least partially overcome the interaction with aminoglycosides but not other antibiotics.

**Miscellaneous**
Metformin (glucophage, Bristol Myers Squibb) is associated with life-threatening lactic acidosis in surgical paitents who develop prolonged hypoperfusion states or renal insufficiency (23). The current practice in our institution is to have patients omit their metformin dose on the evening before and the morning of surgery. The package insert states that metformin should be temporarily discontinued in patients having all but the most minor surgical procedures (i.e. procedures performed without anesthesia or sedation).

**Herbal Medications**
Use of herbal medications is increasing in the United States. An excellent review of the important perioperative implications of herbal medications by Ang-Lee *et. al*. stated that 22-32% of presurgical patients were taking herbal medications and that the majority of patients did not disclose their use (24). Ephedra (ma huang) grows as a shrub that contains alkaloids including ephedrine and pseudoephedrine. Patients taking this herbal preparation will exhibit increased sympathetic activity and will be prone to arrhythmias, myocardial ischemia and hypertensive complications. Garlic inhibits platelet function and will potentiate the effect of other platelet inhibitors including prostacyclin, indomethacin and dipyridamole. Ginkgo biloba has been associated with spontaneous and perioperative bleeding complications. Given that garlic and ginkgo may increase bleeding, preoperative discontinuation maybe prudent. Garlic affects platelets, so a 7-day abstinence may be appropriate. The half-life of some of the terpinoids in ginkgo is as long as 10 hours, so it would be rational to discontinue ginkgo 36 hours prior to surgery.

Saint John's Wort is used for depression. Its mechanism of action is not clear, but it has been implicated in causing the syndrome of central serotonin excess. Its *in vivo* monoamine oxidase inhibition is insignificant. St. John's Wort does induces P-450 3A4, approximately doubling its metabolic activity and may also induce the CYP 2C9 isoform. Ang-Lee, *et. al*. recommend stopping St. John's Wort for 5 days prior to surgery.

Valerian has sedative properties, enhancing barbiturate sleep time in animals. An acute withdrawal syndrome similar to benzodiazepine withdrawal has been described. Kava is used as an anxiolytic and sedative. In an animal model it increases barbiturate sleep time and has been attributed to induction of a coma in a patient taking alprazolam (25, 26). It would be expected that valerian may interact additively or synergistically with other sedatives or hypnotics. Kava should be discontinued for 24 hours prior to surgery. Because of the acute withdrawal syndrome, it may be reasonable to continue valerian in the perioperative period, while being vigilant for possible increased sedation. Anesthesiologists will increasingly encounter patients taking herbal medications. It is important to query patients specifically about herbal medication use and to understand their perioperative implications.

**Resources for the Anesthesiologist.**

New medications are being introduced to the U.S. drug market at an accelerating rate. It is challenging to keep abreast of advances in drug treatment and to understand the perioperative implications of new therapies. There are a number of on-line resources that may be available to you as an individual subscriber or through your hospital. [Table 3] I have found the epocrates qRx application (www.epocrates.com) for personal digital assistants to be especially helpful in the preoperative clinic and the operating room. The It is frequently updated and it allows you to run a check for potential drug interactions between multiple medications.

Drug interactions confront the anesthesiologist on a regular basis. By understanding the principles of pharmacology and applying our knowledge of individual medications we can take advantage of desirable drug interactions and avoid or compensate for the undesirable ones. On-line and electronic resources will increasingly assist us in the safe delivery of anesthesia.

**Electronic Resources**

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| Epocrates | www.epocrates.com | Mdconsult | www.mdconsult.com |
| PDR online | www.pdrel.com | RxList | www.rxlist.com |
| Micromedex | www.micromedex.com | U.S. Food and Drug Admin. | www.fda.gov |

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