

Drug interactions: a review and update

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People worldwide rely on medications to prevent, cure, or lessen an ever-expanding list of diseases. Drugs can be beneficial as well as detrimental. The goal of therapy is to maximize beneficial effects, while trying to minimize the detrimental effects. Each drug prescribed has a risk–benefit ratio. If the benefit of taking the drug outweighs the risk of adverse effects, then the drug therapy is appropriate. Taking one or more drugs that interact may change this risk–benefit ratio. What was once a safe and appropriate drug therapy may now be inappropriate due to an increased risk from a drug interaction. Studies have shown that when the number of co-administered drugs exceeds four, the risk associated with such use for the patient increases substantially (1).

As the age of an individual increases, so do the number of diseases and the number of drugs an individual may take. The patient may be taking more than one drug to treat multiple disorders or they may be taking multiple drugs to treat a single disorder. When multiple drug therapies are prescribed, drug interactions become an important consideration for the patient and the dentist (2). It is estimated that the incidence of clinical drug interactions ranges from 3 to 5% in patients taking (3) a few medications, but increases to 20% in patients receiving 10–20 drugs. In addition, they may be taking over-the-counter drugs or dietary supplements with their prescription medicines.

Information about drugs continues to increase exponentially. Not only do we have more drugs coming on the market every year, but we also have much more information about older drugs, as a result of continuing research. Our understanding of drug interactions has grown many-fold. Knowledge of the mechanisms of drug interactions has matured and ideas once held as absolute truth are being re-examined. The significance of protein-binding displacement has been called into question with new foundations for drug interactions, such as

enzyme changes or alterations in active drug transport becoming clearer (4). As with any area of complex study, the more one discovers, the more questions one may ask. A few drugs are involved in so many potentially serious drug interactions that they should be viewed as ‘red flags’. These include warfarin, cyclosporine, erythromycin, itraconazole, ketoconazole, the HIV protease inhibitors, and the HMG-CoA reductase inhibitors (statins).

It must be kept in mind that not all drug interactions are clinically significant. The significance of drug interactions can range from theoretical and no effect to life threatening. A drug interaction is considered clinically significant when it occurs between two or more co-administered agents and results in the need for a dosage adjustment of one of the agents or other medical intervention (5). The withdrawal of medications such as terfenadine, astemizole, cisapride, and mibefradil from the market due to fatal drug interactions demonstrates the relevance of drug interactions. Drugs most likely to pose interaction problems are those having (6, 7):

- a narrow therapeutic index (small difference between therapeutic dose and toxic dose);
- steep dose–response curve;
- high first-pass metabolism (the loss of drug as it passes through the liver for the first time);
- a single, inhibitable route of elimination.

Pharmacotherapy in dentistry is unique in that a drug is usually administered for a short duration. Many drug interactions occur after repeated or prolonged dosing. Most of the dental drugs have a large margin of safety and there are a limited number of agents included in a practitioner’s armamentarium.

Drug interactions occur when two or more drugs are administered at the same time. The action of one drug is altered by the presence of another drug. The power of desirable drug interactions is not always recognized.

There are many examples of desirable and successfully used drug interactions to enhance drug efficacy in the management of infection, pain, and cardiovascular disorders. Hundreds of other drug interactions are considered to be undesirable. Interaction mechanisms can be broadly divided into two groups: *pharmacodynamic interactions* and *pharmacokinetic interactions*.

A *pharmacodynamic interaction* is caused by the concurrent administration of two drugs that have the opposite effect or similar effects. In this type of interaction, there is a change in the patient's response to the drug without altering the drug's pharmacokinetics (absorption, distribution, metabolism, and excretion). That is, there is a change in drug action without altering the plasma concentration. The interaction of drugs having similar effects such as alcohol, opioids, and sedatives is considered synergistic. In this case, the resultant drug action is greater than the sum of each agent alone. Another synergistic interaction could occur in dissimilar drugs sharing a common property such as the anticholinergic effects of antidepressants, phenothiazines, and antihistamines. Synergistic drug interactions may be easier to identify than the interactions of drugs having opposite effects. An example of such an interaction with opposite effects would be where a patient with asthma is being treated with a beta-adrenergic drug such as albuterol for its bronchodilating effects, while also being given a beta-adrenergic blocking drug as an antihypertensive, which has bronchoconstricting properties. Pharmacodynamic interactions may result from one drug changing the environment necessary for the safe and effective use of a second drug. An example of this interaction is a loop diuretic that produces potassium wasting and can increase the cardiotoxic effects of digoxin.

An additional type of interaction involves a blocking agent that prevents the binding of a drug to a specific receptor. In the narcotics, the antagonist nalorphine binds to the receptor and blocks the action of the opioid agonist drugs such as morphine. The benzodiazepines such as diazepam, lorazepam, etc. also have a specific antagonist, flumazenil. An antagonist has no intrinsic activity of its own, but blocks the action of the agonist. These drugs are used in the treatment of overdoses by reversing the depression of the central nervous system and respiratory system depression associated with the agonist.

A *pharmacokinetic* (or *dispositional*) drug interaction is where one drug alters the rate or extent of any of the

four basic pharmacokinetic processes: *absorption, distribution, metabolism, or excretion* (ADME) of a second drug (Fig. 1). This type of interaction is measured by a change in one or more of the kinetic parameters, such as maximum serum concentration, half-life amount of drug excreted in the urine, area under the concentration time curve, etc. While it is easy to divide the course of drug therapy into four categories, it must be kept in mind that this process of absorption, distribution, metabolism, and excretion is a continuum, with these systems acting in concert to determine the fate of the drug.

Alterations in drug absorption

Drug absorption may be altered in numerous ways, some of which are theoretical and include:

- gut motility;
- gut pH;
- drug solubility;
- gut metabolism;
- gut flora;
- activity of protein carriers.

One mechanism involves drug *adsorption*. This occurs when a drug is adsorbed onto a binding agent and the drug is no longer easily absorbed into the blood, and may be therapeutically ineffective. Tetracycline antibiotics + polyvalent metal cations (e.g. iron, aluminum, or calcium as found in antacids) results in a decrease in serum levels of tetracycline (8). Cholestyramine, an anionic binding resin binds bile acids and many other

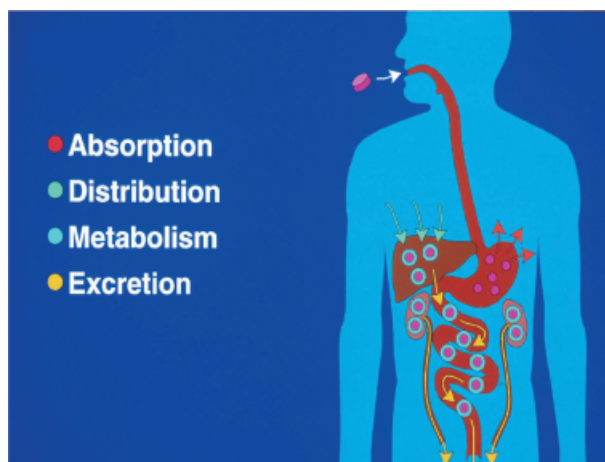


Fig. 1. Pharmacokinetics of drug fate.

substances, including the oral anticoagulant warfarin. This complex decreases the mean plasma warfarin concentration and hypoprothrombinemic effect of this drug (9).

Drug absorption may be altered by drug-induced alterations in gastrointestinal motility. Most drugs are primarily absorbed in the small intestine. Decreasing or increasing the rate at which the drug reaches this area of the gastrointestinal tract may decrease or increase the rate of drug absorption. Drugs that depress peristalsis (narcotics such as morphine and anticholinergics agents such as atropine) may prolong drug transit time in the intestine, thereby increasing the time for absorption. Drugs that are prokinetic (metoclopramide) may increase gastric emptying and thus increase the rate of drug absorption.

Changing the pH of the gastrointestinal tract can alter the absorption of some drugs. Some drugs require an acidic or basic environment in order to dissolve. Weak acids would more readily exist in a non-ionized (i.e. lipid-soluble form) in an acidic environment, thus being more readily absorbed, whereas weak bases would be more absorbable in a basic environment. Drugs that increase gastric pH such as proton pump inhibitors and antacids may reduce the absorption of drugs such as ketoconazole and itraconazole, which are absorbed best in an acidic environment (10).

Food–drug interactions can affect the bioavailability of a drug. The bioavailability and effect of most drugs are correlated. Food–drug interactions can change the bioavailability of a drug by a chemical reaction such as chelation or by a physiological response to food intake. This would include changes in gastric acidity, bile secretion, and gastrointestinal motility. Food–drug interactions that only affect the rate of drug absorption are common, but rarely of clinical importance (11).

P-glycoprotein

Another mechanism for altering drug absorption involves the activity of a membrane-bound carrier protein that is found in many tissues, especially organs responsible for drug absorption and elimination. P-glycoprotein (P-gp) is a well-described adenosine triphosphate (ATP)-dependent carrier glycoprotein in the plasma membrane responsible for the active transport of a wide variety of endogenous and exogenous substrates across various membranes in the intestines, proximal tubules of the kidneys, brain, and

testes (12–14). P-gp was discovered by Juliano and Ling (15) in multi-drug-resistant cancer cells. It was observed that mammalian cancer cells would actively extrude a wide range of cancer chemotherapeutic drugs. P-gp appears to be protective (16). P-gp acts as a pump with drugs and toxins being transported away from tissues, that is, out of the tissue. The drugs are pumped across plasma membranes and into interstitial fluid or into excretory fluids, such as bile, thereby limiting absorption (17, 18). This efflux of drugs from the cell membrane or cytoplasm is powered by the energy from the ATP hydrolysis. Because P-gps block absorption in the gut, they should be considered as part of the ‘first-pass effect’. In addition, to prevent drugs from reaching the systemic circulation, P-gp appears to remove some drugs from the systemic circulation. P-gp also appears to be the ‘gate-keeper’ for later cytochrome P-450 (CYP) actions. A drug is absorbed by passive diffusion into the enterocyte, where it may be metabolized by CYP3A and also subject to active counter-transport by P-gp back into the gut lumen. It interacts and works cooperatively with CYP (Fig. 2). The concentration of P-gp in intestinal enterocytes increases along the length of the gastrointestinal tract, reaching a maximum concentration in the colon (19). Inhibiting the function of P-gp would result in an increase in drug absorption and inducing the function of P-gp would decrease absorption. Many drugs have now been identified as substrates, inhibitors, and inducers of P-gp function. Several agents have been identified as P-gp inhibitors: erythromycin, propranolol, and amiodarone. Some examples of inducers include: dexamethasone, nefazodone, and rifampin (16).

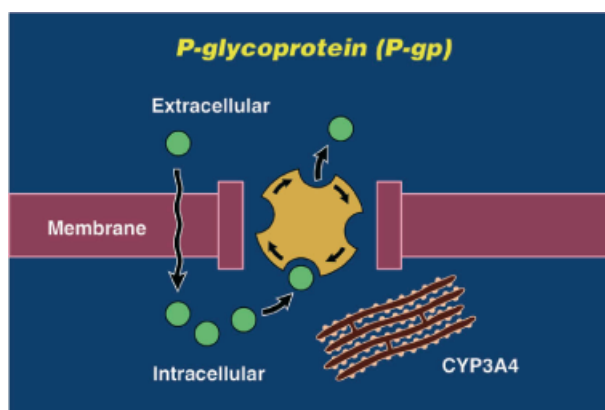


Fig. 2. P-glycoprotein carrier system.

Drug distribution

Drugs are transported to a site of action or elimination bound to serum proteins. Acidic drugs are bound to plasma albumin and basic drugs are bound to α -acid glycoprotein (20). While bound to a plasma protein, the drug does not contribute to the concentration gradient, cannot be filtered by the kidney, and in general, is pharmacologically inert. The unbound or 'free' drug is pharmacologically active. Decreasing the serum concentration of albumin could result in altered pharmacokinetics of bound drugs.

From a drug interaction standpoint, a drug with high binding affinity could displace a drug with less affinity, thereby increasing the free concentration of the drug with less affinity. However, the unbound fraction of the drug is not only more available for the site of action, but also is more available for elimination. This principle has often been applied to highly protein-bound (>90%) drugs and to drugs with a narrow therapeutic index, where small changes in free drug concentration might result in significant changes in pharmacological effect. In practice, protein-binding displacement interactions do not produce clinically important changes in drug response (21, 22), except where the displacing drug may also reduce the elimination of the substrate drug. A good example of this principle involves interactions of non-steroidal anti-inflammatory drugs (NSAIDs) and methotrexate. NSAIDs exhibit varying effects on the pharmacokinetics of methotrexate. For example, ibuprofen may decrease methotrexate clearance by 40–50% (23), possibly by reducing renal perfusion due to a decrease in renal prostaglandin synthesis (24).

Drug metabolism

The area of biotransformation, also known as metabolism, is exploding with new information. Recent studies suggest that the most clinically important drug interactions involve pathways of metabolism. Most drugs are eliminated from the body, at least in part, by being chemically altered to a less lipid-soluble product. They are not reabsorbed across a lipid membrane and are excreted by the kidney or in the bile. While metabolism takes place in numerous locations including the plasma, intestines, lungs, and skin, the majority of the metabolism occurs in the smooth endoplasmic reticulum of the hepatocyte.

Briefly, metabolism can be divided into two phases (Figs 3 and 4). Phase I metabolism involves the

oxidation, hydrolysis, or reduction of a drug. These reactions increase the water solubility of the drug and thus facilitate their elimination from the body. Phase II metabolism involves the attachment of an additional molecule to the drug in order to create an inactive compound and a more water-soluble drug. Phase II processes include glutathione conjugation, glucuronidation, sulfation, acetylation, and methylation.

The enzyme that catalyzes this reaction is known as the hepatic CYP. CYP is a complex of protein, heme, and iron. By using molecular oxygen and NADPH (a reduced form of NADP) as a source of electrons, this cytochrome system catalyzes a series of oxidation–reduction reactions, which results in the oxidized drug product (25). While there are more than 50 different families of enzymes identified, only three families CYP1, CYP2, and CYP3 are responsible for the metabolism of most compounds including steroids, prostaglandins, vitamins, other endogenous compounds, and a large number of drugs. Subfamilies

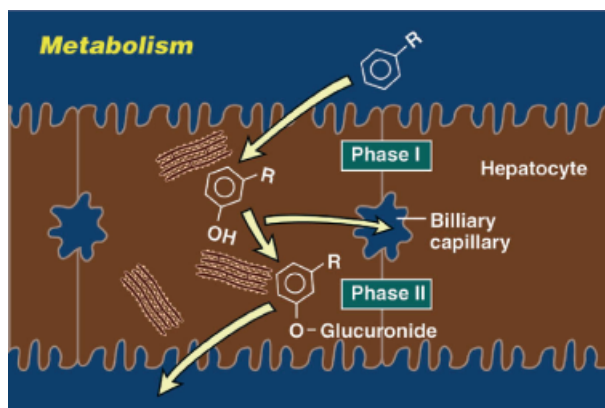


Fig. 3. Phase I and II metabolism.

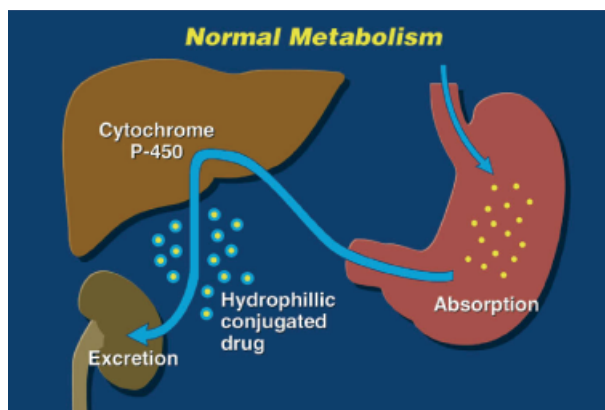


Fig. 4. Normal metabolism.

within each family are designated by a capital letter and individual enzymes are named with a final Arabic number. Thus, the individual enzymes CYP2C9 and CYP2C19 both belong to the CYP2 family and the CYP2C subfamily.

Theoretically, any two drugs that are metabolized by the same enzyme could produce a drug interaction. The two drugs would compete for the same enzyme. One drug could be metabolized and the other drug's metabolism reduced, resulting in a higher blood level of the non-metabolized drug. To anticipate a clinically significant drug interaction involving the CYP system, it is necessary to become familiar with the substrates, inhibitors, and inducers of the isoenzymes. The 'substrate' refers to that compound known to be metabolized by the isoenzyme. The term 'inhibitor' denotes a drug known to interfere or compete with the isoenzyme, and the term 'inducer' describes an agent that accelerates the metabolism of a substrate.

Drugs used in dentistry

The rate of drug metabolism may be increased or decreased based on *enzyme induction* or *enzyme inhibition*.

Induction of drug metabolism usually occurs by enhanced gene transcription following prolonged exposure to an inducing agent (Fig. 5). As a result, the consequences of enzyme induction may take considerable time to be fully exhibited. The consequences of enzyme induction are an increased rate of metabolism, enhanced oral first-pass metabolism, and a reduced bioavailability. All of this results in a decrease in the drug's plasma concentration. In contrast, in drugs that are metabolized to an active or toxic metabolite, induction may be associated with an increased effect or increased toxicity. A well-documented and classic example of enzyme induction involves the drug rifampin and oral contraceptives (OCs). Rifampin is an antibiotic used in the treatment of tuberculosis and a potent metabolic inducer of CYP. Contraceptive failure is possible due to the altered metabolism of the OC (26). Other common CYP inducers include phenytoin, carbamazepine, and the barbiturates (see Table 1) (27).

A consequence of drug-metabolizing *inhibition* is an increase in the plasma concentration of the parent drug with an exaggerated, prolonged pharmacological effect from the parent drug and a reduction in the metabolite

of that drug. This can result in the drug-induced toxicity. Unlike enzyme induction which takes a while, this interaction can be rapid and without warning. The antifungal agents ketoconazole and itraconazole, and the macrolide antibiotics, such as erythromycin and clarithromycin (but not azithromycin), are all potent inhibitors of CYP3A (6). Certain calcium channel blockers, such as diltiazem, nifedipine, and verapamil also inhibit CYP3A (28), as does a constituent of grapefruit juice (10). After ingestion, a substrate in grapefruit juice binds to the intestinal isoenzyme, impairing first-pass metabolism directly and causes a sustained decrease in CYP3A4 protein expression (29). Within 4 h of ingestion, a reduction in the effective CYP2A4 concentration occurs, with the effects lasting up to 24 h (30). The net result is the inhibition of drug metabolism in the intestine and increased oral bioavailability. Because of the prolonged response, separating the intake of the drug and the juice or whole grapefruit does not prevent interference (Table 2).

Drug excretion

Just as the liver is the primary organ involved in the metabolism of drugs, the kidney is the primary organ involved in the excretion of compounds from the body. Other sites of drug excretion include the liver, lungs, gastrointestinal tract, saliva, sweat, tears, and breast milk. Alterations in renal excretion can occur by several mechanisms, including changes in urinary pH (which can alter passive reabsorption of a drug), competition for the same transport system, changes in active tubular secretion, or changes in renal blood flow.

Acidification of the urine results in an increase in the rate of urinary excretion of weak bases. The explanation

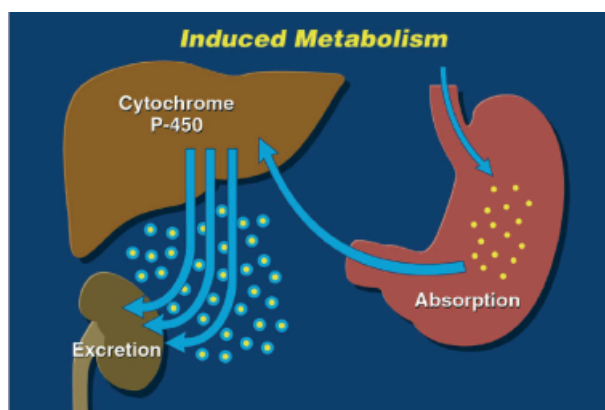


Fig. 5. Induced metabolism.

Table 1. Cytochrome P450 substrate, inhibitors, and inducers

Isozyme	Substrate	Inhibitors	Inducers
CYP1A2	<i>Acetaminophen</i> , caffeine, clozapine, <i>amitriptyline</i> , tacrine, theophylline	Cimetidine, ciprofloxacin, diltiazem, enoxacin, fluvoxamine, tacrine	Barbiturates, cigarettes, rifampin
CYP2C9	Fluvastatin, <i>ibuprofen</i> , glipizide, losartan, phenytoin, rosiglitazone, tolbutamine	Amiodarone, cimetidine, <i>fluconazole</i> , isoniazid, <i>metronidazole</i> , sulfamethoxazole	Barbiturates, phenytoin, rifampin
CYP2C19	<i>Diazepam</i> , citalopram, esomeprazole, lansoprazole, sertraline	Esomeprazole, fluconazole, fluoxetine, fluvoxamine, omeprazole	Barbiturates, phenytoin, rifampin
CYP2D6	<i>Amitriptyline</i> , <i>codeine</i> , <i>desipramine</i> , dextromethorphan, flecainide, haloperidol, imipramine, metoprolol, nortriptyline, paroxetine, propranolol, thioridazine, timolol	Amiodarone, fluoxetine, haloperidol, paroxetine, <i>propoxyphene</i> , quinidine, terbinafine, thioridazine	Rifampin
CYP3A4	Amiodarone, alprazolam, buspirone, cisapride, cyclosporin, diltiazem, <i>erythromycin</i> , felodipine, indinavir, lovastatin, midazolam, nifedipine, pioglitazone, quinidine, ritonavir, sertraline, sildenafil, simvastatin, warfarin, tacrolimus, triazolam, verapamil, zolpidem	<i>Clarithromycin</i> , troleandomycin, cyclosporin, <i>erythromycin</i> , grapefruit juice	Barbiturates, <i>carbamazepine</i> , griseofulvin, phenytoin, rifampin, St John's wort

Italics represent the drugs used in dentistry.

is that a more acidic environment favors the formation of the ionized, less lipid-soluble form of the drug, which would result in a decline in the amount that is passively reabsorbed following filtration. Conversely, renal excretion of weak acids is favored by more alkaline conditions. Alteration of urine pH does not play a major role in undesired drug interactions. However, it has been used in the detoxification process to help rid the body of a drug overdose.

Probenecid serves as a classic example of a drug that alters active tubular secretion of drugs from the plasma into the renal tubular filtrate by competing with other drugs for active transport sites in the proximal renal tubular epithelial cells. At one time, this drug interaction

was used therapeutically. Penicillin was given with probenecid to increase the plasma level of the penicillin to enhance the therapeutics of penicillin.

Selected drug interactions

NSAIDs

NSAIDs + lithium

Several NSAIDs have been shown to *increase* plasma lithium concentrations. The magnitude of the interaction varies with the NSAID and the dose. Evidence for this interaction is available for ibuprofen (31),

Table 2. Possible interactions between grapefruit juice and drugs metabolized by CYP3A4

Drug class	Drug	Possible adverse effects
Antiarrhythmic	Amiodarone	Arrhythmias
Anxiolytics	Buspirone	Decreased psychomotor performance, increased sedation
	Diazepam	
	Midazolam	
	Triazolam	
Calcium channel blockers	Amlodipine	Tachycardia, hypotension
	Felodipine	
	Nifedipine	
	Nimodipine	
HMG-CoA reductase inhibitors	Atorvastatin	Myopathy, headache, rhabdomyolysis
	Cerivastatin	
	Lovastatin	
	Pravastatin	
Immunosuppressants	Cyclosporin	Renal/hepatic dysfunction, increased immunosuppression
	Tacrolimus	
Neuropsychiatrics	Carbamazepine	Drowsiness, ataxia, nausea, respiratory depression
	Clomipramine	
Antifungal	Itraconazole	Nausea

naproxen (32), diclofenac (33), flurbiprofen, (34) ketorolac (35), and valdecoxib (36). Sulindac appears to be an exception (37). Evidence of lithium toxicity includes nausea, vomiting, diarrhea, anorexia, coarse tremor, slurred speech, vertigo, confusion, lethargy, and in extreme cases, seizure, coma, and cardiovascular collapse. While the exact mechanism is unknown, it appears that the renal clearance of lithium is decreased, possibly by the inhibition of the renal prostaglandins (Fig. 6).

NSAIDs + angiotensin-converting enzyme inhibitors

NSAIDs have been shown to diminish the antihypertensive effect of angiotensin-converting enzyme (ACE)

inhibitors (38). This is probably of most concern with long-term dosing of NSAIDs; however, blood pressure increases have been documented after a single dose of an NSAID. A recent report described an increase in blood pressure associated with the selective cyclooxygenase-2 (COX-2) inhibitor, rofecoxib (39). The mechanism of the interaction appears to be related to the ability of the prostaglandins to reduce the synthesis of the vasodilating renal prostaglandins.

NSAIDs + methotrexate

NSAIDs have been shown to decrease the clearance of methotrexate (23, 24), probably by the same mechanisms as the other agents and that is by a reduction in the vasodilating renal prostaglandins.

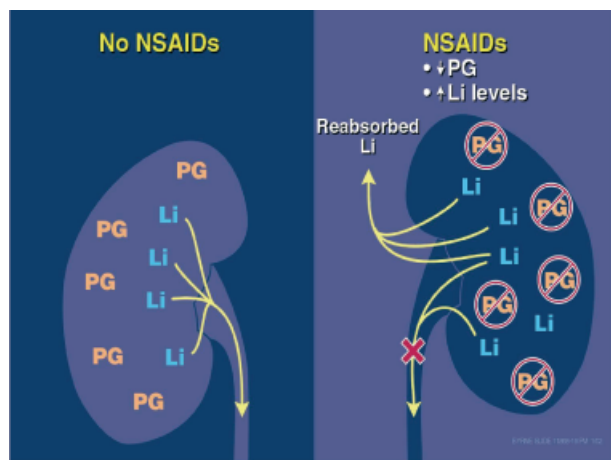


Fig. 6. Lithium+NSAIDs interaction.

NSAIDs + warfarin

Medications such as aspirin and other NSAIDs can increase the risk of warfarin-related bleeding by inhibiting platelet function. Aspirin poses the most significant risk due to its common use and irreversible prolonged effect on platelets. One proposed mechanism of the interaction has been the possibility that these drugs displace warfarin from plasma protein-binding sites. However, the transient nature of the interaction makes the significance of this mechanism questionable. Aspirin and NSAIDs also produce gastric erosions that increase the risk of serious upper gastrointestinal bleeding.

Acetaminophen + warfarin

Acetaminophen is one of the most common drugs used in the United States. Unlike other analgesics, it does not cause significant platelet inhibition or gastrointestinal bleeding. These characteristics have led to acetaminophen being the most frequently recommended analgesic for use by patients also taking warfarin.

Of all the potential interactions between warfarin and other drugs, the interaction with acetaminophen is probably the most confusing. The published data on the interaction are conflicting (40–42), but acetaminophen appears to increase the anticoagulant effect of warfarin in a dose-dependent manner (43). Approximately 30% of patients stabilized on warfarin who ingest approximately 2 g of acetaminophen daily can experience an intensification of warfarin response. The interaction between acetaminophen and warfarin

appears more likely with daily acetaminophen doses of greater than 2 g daily for a week or more. Occasional doses of acetaminophen do not appear likely to interact with warfarin. Acetaminophen is still a valuable drug to use for patients taking warfarin. Unlike aspirin and NSAIDs, acetaminophen does not inhibit platelet function, nor does it cause a significant gastric irritation, which can lead to bleeding. Faced with a choice of analgesics for anticoagulated patients, acetaminophen still possesses advantages. Coagulation parameters should be monitored more frequently, such as once or twice a week when a patient is starting or stopping chronic acetaminophen therapy (44). The mechanism of this interaction is not known; however, inhibition of CYP has been suggested (44). Regardless of the mechanism, this is a potential interaction that clinicians should be aware of and monitor closely.

Macrolide interactions

The currently available macrolide antibacterials used in dentistry include erythromycin, azithromycin, and clarithromycin. The primary mechanism by which they interact with other drugs is inhibition of hepatic microsomal metabolism. An exception is the increase in digoxin bioavailability caused by erythromycin's suppression of gut bacteria that normally degrades some digoxin prior to absorption, thus leaving greater quantities of digoxin to be absorbed (45). This interaction occurs in only about 10% of the patients receiving the combination.

The macrolides inhibit the CYP3A-mediated metabolism of a plethora of drugs. Certain macrolide antibiotics, such as erythromycin and troleandomycin are fairly potent inhibitors, while other macrolides, including clarithromycin, are less effective CYP3A inhibitors, and azithromycin and dirithromycin do not appear to cause significant clinical drug interaction (7) (Table 3).

Tetracycline interactions

The bioavailability of tetracycline is reduced by 46–57% when taken with food, by 50–65% when taken with dairy products and up to 85% when taken with iron supplements. Tetracycline chelates with polyvalent cations (e.g. iron, calcium magnesium, and aluminum in the gut preventing its absorption) resulting in treatment failures (Fig. 7).

Antibiotics + OCs

The first report of potential interactions between antibiotics and OCs appeared in 1971 when Reimers and Jezek (46) reported an increase of intermenstrual breakthrough bleeding in 38 of 51 women treated concomitantly with OCs and the antituberculosis drug rifampin. Rifampin soon became implicated in unplanned pregnancies (47). After reports of rifampin interaction appeared, possible links between the use of other antibiotics and OCs began to appear (48, 49).

Clinical studies show that rifampin significantly reduces blood levels of the OCs, resulting in ovulation. Rifampin is a potent inducer of the liver CYP enzyme system and increases the metabolism of the OC (Fig. 5).

OC failure rate with other antibiotics remains less clear. Antibiotics that do not induce CYP may reduce the plasma levels of steroids based on indirect interference with the enterohepatic circulation of the estrogen component of the OC. Briefly, the estrogen component of the OC is conjugated in the liver and excreted in the bile, where the drug would be eliminated if not for the bacteria in the gut, which is thought to deconjugate the estrogen and allow for its reabsorption. Antibiotics that kill the gut bacteria involved in the deconjugation process can inhibit this enterohepatic recirculation (50) (Figs 8 and 9). However, this mechanism has not been proven, and

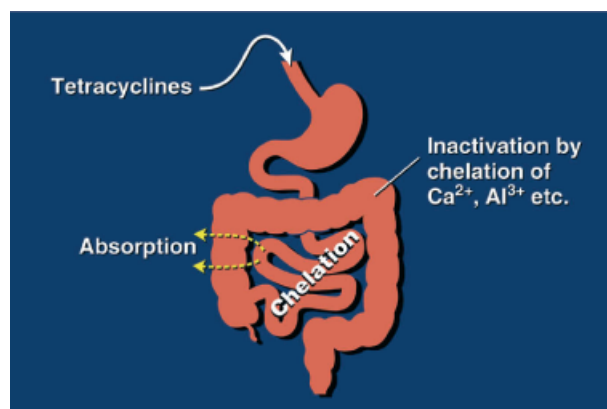


Fig. 7. Tetracycline chelation interaction.

except for rifampin, antibiotics do not significantly affect the plasma concentration of the OC. However, due to the existing retrospective case reports, it is possible that certain individuals may be at risk of this interaction. In light of this, both the American Medical Association (51) and the American Dental Association (52) have adopted policies.

(American Medical Association, June 2001)

1. Women prescribed rifampin concomitantly with OCs faced significant risk of OC failure and should be counseled about the additional use of nonhormonal contraceptive methods during the course of rifampin therapy.

Table 3. Macrolide drug interactions of potential clinical importance

Interacting drug	Comments
Carbamazepine	Two- to four-fold increase in carbamazepine concentration with marked toxicity including lethargy, weakness, ataxia, dizziness, blurred vision, nystagmus, confusion, tremor
Cyclosporin	Marked increases in plasma cyclosporin following erythromycin and clarithromycin resulting in reversible renal dysfunction, hepatotoxicity, hypertension
Digoxin	Increased serum digoxin following erythromycin in selected patients (only 10% of the population appears to be at risk)
Feldopine	Case reports suggest that erythromycin increases feldopine adverse effects including hypotension, tachycardia and edema
HMG-CoA reductase inhibitors: atorvastatin, cerivastatin, lovastatin	Rhabdomyolysis, muscle weakness and myalgias
Theophylline	Increased serum theophylline resulting in tachycardia, cardiac arrhythmias, tremor, and seizures
Warfarin	Increased INR with markedly enhanced hypoprothrombinemic response to warfarin

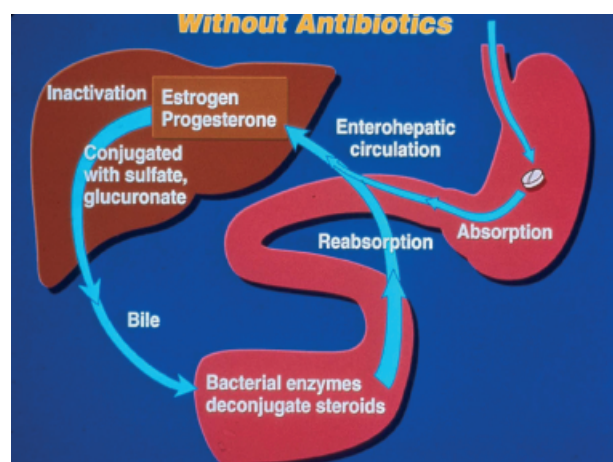


Fig. 8. OC fate without antibiotics.

- Women using combined OCs should be informed about the small risk of interactions with antibiotics and that it is not possible to identify in advance the women who may be at risk of OC failure. Women who are not comfortable with the small risk of interaction should be counseled about the additional use of non-hormonal contraceptive methods. Women who have had previous OC failures or who develop breakthrough bleeding during concomitant use of antibiotics and OCs would be counseled about the use of alternate methods of contraception if they engage in intercourse during the period of concomitant use, as they may be part of a subset of women at high risk on contraceptive failure.

(American Dental Association, July 2002)

Therefore, it is the opinion of the ADA Council of Scientific Affairs that, considering the possible con-

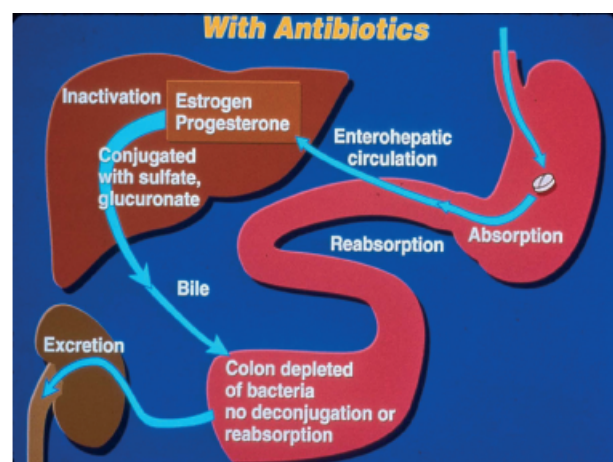


Fig. 9. OC fate with antibiotics.

sequences of an unwanted pregnancy, when prescribing antibiotics to a patient using oral contraceptives, the dentist should do the following:

- advise the patient of the potential risk of the antibiotic's reducing the effectiveness of the oral contraceptive;
- recommend that the patient discuss with her physician the use of an additional non-hormonal means of contraception;
- advise the patient to maintain compliance with oral contraceptives when concurrently using antibiotics.

Metronidazole

Metronidazole is an antibiotic used in dentistry, usually in combination with penicillin to increase its spectrum of activity. Metronidazole's chemical structure contains an imidazole ring, which is found in many other drugs known to inhibit hepatic drug metabolism (e.g. cimetidine, ketoconazole, miconazole, and omeprazole). Perhaps the most important interaction with metronidazole involves warfarin. Metronidazole inhibits the metabolism of warfarin, resulting in accumulation of warfarin and an enhanced anticoagulant effect. This combination should be avoided if possible (53).

Epinephrine interactions

Epinephrine + beta blockers

The adrenergic or sympathetic nervous system is modulated through alpha (α) and beta (β) receptors. Depending on the type and location of these receptors, they may have a stimulatory or inhibitory effect. In the myocardium, beta-receptor stimulation causes excitation that results in a positive inotropic and chronotropic effect. The sinoatrial node conduction velocity is increased, and the myocardial refractory period is decreased. The net result of beta-receptor stimulation on the heart is an increase in cardiac index, cardiac work, and oxygen consumption. This is the physiologic basis for many of the therapeutic uses of the beta-receptor antagonists better known as beta blockers. The vascular system has both alpha and beta receptors. Beta-receptor stimulation causes vasodilatation and alpha-receptor stimulation causes vasoconstriction.

Epinephrine has both alpha and beta actions (Fig. 10). Non-selective beta blockers (Table 4) block the vasodilating beta effect of epinephrine and shift the

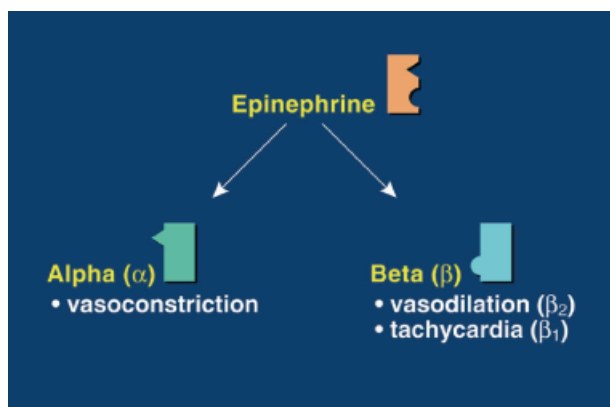


Fig. 10. Epinephrine receptor action.

response to the alpha-mediated vasoconstriction, resulting in marked hypertension followed by reflex bradycardia (Fig. 11). This interaction has been recognized for years and has been the topic of numerous case studies. The most significant report was by Foster and Aston, who cited six case studies involving plastic surgery (54). No risk appears to be associated with cardioselective beta blockers.

Epinephrine + antipsychotics

Antipsychotics such as phenothiazine may block the peripheral alpha effects of the alpha/beta agonist, leaving the beta (vasodilating) effects unopposed (55) (Fig. 11). While this interaction in theory is possible, it appears that it does not occur at normal doses and no special precautions are necessary in ambulatory patients (56).

Epinephrine + tricyclic antidepressants

Tricyclic antidepressants such as imipramine, amitriptyline, nortriptyline, desipramine, and doxepin are now

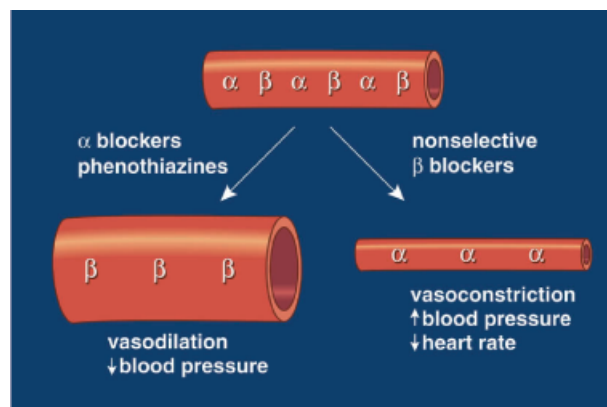


Fig. 11. Beta-blocker drug interaction.

second-line drugs for the treatment of depression after the selective serotonin uptake inhibitors. These drugs act on the central and peripheral nervous systems to block the reuptake of certain neurotransmitters, thus leaving higher concentrations in the synapse. The affected neurotransmitters are thus free to interact more effectively with their receptors. Epinephrine is subject to the same uptake process and therefore, the same potentiation. Epinephrine-impregnated gingival retraction cord is contraindicated because of the large amounts of epinephrine available for absorption. If local anesthetic is used with epinephrine, it should have no more than 1 : 100 000 epinephrine and the maximum recommended dose should be reduced by one-third (56).

Summary

Dealing with drug interactions can be challenging. New medications are continually being introduced to the market and dentists should have a fundamental knowledge of drug interactions. Medication regimens must be routinely screened for potential drug interactions. When assessing potential drug interactions, it is necessary to consider the result of such interference: whether this outcome can be adjusted for; and whether the benefit of therapy overrides the risk of such an interaction. In many situations, drug interactions are not seen clinically because the course of therapy of the potential offending agent is short (i.e. antibiotics) because of patient characteristics; or because there is a failure to identify them. New information appears quickly, especially in the area of drug metabolism. Although no one can be expected to know all drug interactions, good resources are invaluable. (e.g.

Table 4. Selectivity of beta-adrenergic receptor-blocking drugs

Cardioselective	Non-selective
Acebutolol	Carteolol
Atenolol	Nadolol
Betaxolol	Penbutolol
Metoprolol	Pindolol
	Propranolol
	Timolol

Lexi-Comp's Drug Interaction Handbook (57), Drug Interactions Facts (27) or a pharmacy/hospital drug information service)

Research is essential in the early stages of drug development to identify drug interactions, define the mechanisms of older interactions, and examine the safety of new drugs from classes that are known to cause interactions.

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