CHAPTER 32

Common Drug Interactions in Podiatric Medicine

Mickey D. Stapp, D.P.M.

INTRODUCTION

Any physician licensed to prescribe medication for a patient must be cognizant of potential drug interactions. The physician must be aware of potential interactions between medications that he might prescribe, as well as interactions between the medications the patient might be taking, regardless of the prescribing physician. A thorough history and physical, with special emphasis on current medications, is imperative before prescribing any medication. A physician might have greater success in obtaining an accurate list of medications and their appropriate dosages by contacting the patient's internist, family physician, or pharmacist. The patient should also be encouraged to bring their medications, in originally dispensed packaging, to the office on a regular basis.

Drug interactions may occur through pharmacokinetic or pharmacodynamic mechanisms, or through a combined toxicity. Pharmacokinetic mechanisms occur when one drug alters the absorption, distribution, metabolism, or excretion of another drug.

The absorption of a drug may be affected by concurrent use of another agent which binds (chelates) to the drug, or through an alteration of gastrointestinal motility. The distribution of a drug may be altered by another drug which competes for plasma binding sites and/or causes displacement from tissue binding sites.

The metabolism of a drug may be stimulated or inhibited by a variety of other agents. Stimulation of the metabolism of a drug may occur when drugs such as barbiturates, carbamezepine, phenytoin, or rifampin, induce the hepatic microsomal drug-metabolizing enzymes. Drugs which can inhibit the metabolism of other drugs by inhibiting the hepatic microsomal enzymes include allopurinol, cimetidine, isoniazid, metronidazole, propoxyphene, and sulfonamides. Renal excretion of an active drug can also be affected by drugs which alter urinary pH.

Pharmacodynamic drug interactions occur when drugs with similar effects or mechanisms of action are administered concurrently. An additive or synergistic response is usually seen. When drugs with antagonistic effects or mechanisms of action are administered concurrently, the response to one or both drugs may be reduced.

A combined toxicity drug interaction occurs when two or more drugs with toxic effects on the same organ are given together. This greatly increases the likelihood and severity of organ damage.

MEDICATION CLASSES

Certain medication classes or individual agents should raise one's index of suspicion for drug interactions. Patients taking antacids, anticoagulants, cimetidine, digoxin, lithium, nonsteroidal anti-inflammatory drugs (NSAIDs), phenytoin, diuretics, and theophylline, deserve close attention before multiple agents are prescribed or new agents are added.

Antacids can inhibit the absorption of a second drug by a variety of mechanisms. They may bind to the drug and decrease its gastrointestinal uptake, thus reducing absorption. Antacids also increase gastric emptying and reduce transit time, thus reducing absorption. Some antacids can alkalinize the urine thus altering the excretion of drugs sensitive to urinary pH.

Anticoagulants are susceptible to induction and inhibition of their metabolism by drugs such as those previously mentioned. Anticoagulants are also highly bound to plasma proteins and may be displaced easily by drugs competing for the same site.

Cimetidine has many well documented drug interactions, mainly through its inhibition of hepatic microsomal drug-metabolizing enzymes. By inhibiting the metabolism of these drugs, a longer duration of action and a greater intensity in the inhibited drugs' mechanism of action is seen.

Digoxin is susceptible to drug interactions with any agent which may induce an electrolyte imbalance. Digoxin's renal excretion is also sus-

ceptible to inhibition. Diuretics may alter the renal excretion of digoxin and other drugs, causing undesired effects. Potassium sparing diuretics can have an additive effect with other agents which increase serum potassium.

Patients taking lithium are also prone to drug interactions. Lithium has a narrow therapeutic margin and must be monitored closely with agents which may alter sodium balance. Patients taking lithium are also susceptible to drugs which may enhance central nervous system lithium toxicity.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis which may result in resistance to antihypertensive medications. NSAIDs also inhibit platelet function which may increase the likelihood of bleeding when combined with other drugs which inhibit hemostasis. Most NSAIDs are highly protein bound and can displace other highly protein bound drugs.

Phenytoin is another drug which has a narrow margin of therapeutic safety. Phenytoin must also be monitored closely when a new drug is added to the pharmacologic regimen. Phenytoin induces hepatic microsomal enzymes affecting the metabolism of other drugs. Phenytoin's metabolism can also be inhibited by other drugs which inhibit the hepatic microsomal enzymes.

Another drug with a narrow therapeutic margin is theophylline. Theophylline is metabolized in the liver by the microsomal enzyme system. Its metabolism is susceptible to both inhibition and induction by other agents with these properties. Theophylline has many documented drug interactions and careful attention should be made before additional drugs are prescribed for these patients.

While these drugs (antacids, anticoagulants, cimetidine, digoxin, lithium, NSAIDs, phenytoin, diuretics and theophylline) should raise a red flag when considering prescribing a new medication for a patient, it must be remembered that all drugs have the potential for interactions. A drug interaction table with the most commonly prescribed drugs in podiatric medicine is included. This table is not meant to be inclusive of all the possible drug interactions for each of these commonly prescribed drugs. There may be other agents prescribed in podiatric medicine which are not included. A brief explanation of the adverse effects and some comments or recommendations for these drug interactions is included in the table on the following page.

DRUG	INTERACTING DRUG	ADVERSE EFFECTS	COMMENTS
Acetaminophen	Probenecid	↑ acetaminophen toxicity	Avoid
Aspirin	ACE Inhibitors	↓ antihypertensive effect	Avoid if possible
	Anticoagulants	↑ bleeding risk	Avoid if possible Monitor PT
	Heparin	↑ bleeding risk	Avoid if possible
	NSAID	↑ toxicity of both	Avoid
	Quinidine	Bleeding	Avoid
Benzodiazepines (BZDP)	Antacids	↓ oral effect	Give 2 hrs apart
	Tricyclic anti-depressants	↑ impairment	Warn patients
	Cimetidine	↑ BZDP toxicity	Monitor
	Levodopa	↓ levodopa effect	Avoid if possible
	Probenecid	↑ BZDP toxicity	Avoid
	Ranitidine	Altered BZDP effect	Monitor
Cephalosporins	Alcohol	Disulfiram reaction	Avoid alcohol
	Aminoglycosides	↑ nephrotoxicity	Avoid in elderly & renal disease
	Anticoagulants	↑ anticoagulant effect	Avoid
	Aspirin	↑ bleeding (moxolactam)	Avoid
	Furosemide	↑ nephrotoxicity	Monitor renal fxn
	Heparin	↑ bleeding (moxolactam)	Avoid
	Vancomycin	↑ nephrotoxicity	Avoid
Corticosteroids	Antacids	↓ corticosteroids effect	Give far apart
	Furosemide	↑ potassium loss	Monitor potassium
	Ketoconazole	Possible toxicity of prednisone	Monitor steroid
	Metronidazole	↓ metronidazole effect	Monitor
	Phenytoin	↓ phenytoin effect	Monitor phenytoin
	Rifampin	↓ steroid effect	Avoid if possible
	Salicylates	↓ salicylate effect	Monitor
	Thiazide diuretics	↑ potassium loss	Monitor potassium
Erythromycins	Alcohol	↓ antibiotic effect	Avoid
	Anticoagulants	↑ anticoagulant effect	Monitor PT
	Antihistamines	Arrhythmias with terfenadine & astemizole	Use another antihistamine
	Carbamazepine	↑ carbamezepine toxicity	Avoid if possible
	Digoxin	Possible digoxin toxicity	Avoid if possible

DRUG	INTERACTING DRUG	ADVERSE EFFECTS	COMMENTS
	Disopyramide	↑ disopyramide toxicity	Avoid
	Ergot alkaloids	↑ ergot toxicity	Avoid
	Phenytoin	Possible phenytoin toxicity/↓ effect	Monitor phenytoin concentration
	Theophyllines	Possible toxicity	Monitor
	Valproate	Valproate toxicity	Monitor valproate
Fluconazole	Anticoagulant	↑ anticoagulant effect, GI bleed	Monitor PT
	Phenytoin	Phenytoin toxicity	Monitor phenytoin
	Theophyllines	Possible toxicity	Monitor
Fluoroquinolones	Antacids	↓ antibiotic effect	Avoid if possible
	Anticoagulants	↑ anticoagulant effect	Monitor PT
	Iron, oral	↓ antibiotic effect	Avoid
	Phenytoin	Altered phenytoin	Monitor phenytoin
	Theophyllines	Possible toxicity	Monitor
	Zinc, vitamins	↓ antibiotic effect	Avoid
Griseofulvin	Anticoagulants	↓ anticoagulant effect	Monitor PT
	Contraceptives,oral	↓contraceptive effect	Alternative birth control method
Itraconazole	Antihistamines	Arrhythmias with terfenadine & possibly astemizole	Use another antihistamine
	Carbamezepine	↓antifungal effect	Monitor
	Digoxin	Digoxin toxicity	Monitor digoxin
	Phenytoin	↓antifungal effect	Monitor
Ketoconazole	Alcohol	Possible disulfiram reaction	Avoid
	Antacids	↓antifungal effect	Give 2 hrs apart
	Anticoagulants	↑anticoagulant effect	Monitor PT
	Antihistamines	↑cardiac toxicity with terfenadine and astemizolde	Use another antihistamine
	Cimetidine	↓antifungal effect	Avoid
	Corticosteroids	Possible toxicity of prednisone	Monitor steroid effects
	Phenytoin	Altered effects of both drugs	Monitor phenytoin
	Ranitidine	Possible ↓ anti-fungal effect	Avoid
	Sucralfate	Possible ↓ anti-fungal effect	Give 2 hrs apart

DRUG	INTERACTING DRUG	ADVERSE EFFECTS	COMMENTS
	Theophylline	Possible ↓ anti-fungal effect	Monitor theophylline
Metoclopramide	Cimetidine	↓cimetidine effect	Give 2 hrs apart
	Digoxin, tablets	↓digoxin effect	Use digoxin caps
	Narcotics	Over-sedation	Monitor pt status
	Quinidine	Possible ↓ effect of quinidine SR	Monitor quinidine
Metronidazole	Alcohol	Disulfiram reaction	Avoid
	Antacids	↓antibiotic effect	Monitor
	Anticoagulants	↑anticoagulant effect	Monitor PT
	Barbiturates	↓antibiotic effect (phenobarbital)	Double antibiotic dose
	Cholestyramine	Possible ↓ antibiotic effect	Monitor
	Cimetidine	Possible ↑ effect of IV metronidazole	Avoid
	Corticosteroids	↓antibiotic effect	Monitor
	Disulfiram	Organic brain syn.	Avoid
	Fluorouracil	↑metronidazole toxicity	Avoid
	Lithium	Lithium toxicity	Monitor lithium
	Phenytoin	Possible phenytoin toxicity	Monitor phenytoin
Narcotics (Meperidine & congeners)	Acyclovir	Possible meperidine toxicity	Avoid if possible
	Barbiturates	↑ CNS depression	Avoid
	Cimetidine	Severe narcotic toxicity	Avoid in dialysis Use cautiously
	MAO Inhibitor	Encephalopathy	Avoid
	Phenothiazines	↑ narcotic toxicity	Monitor
	Phenytoin	↓ meperidine effect	Monitor
Narcotics (Morphine-like)	Cimetidine	Severe narcotic toxicity	Avoid in dialysis Use cautiously
	Metoclopramide	Over-sedation	Monitor
	Quinidine	Absence of codeine analgesia	Monitor, use other analgesic
	Ranitidine	↓ analgesia	Monitor
Narcotics (Pentazocine)	Tri-cyclic anti-depressants	Possible resp. depression (amitriptyline)	Monitor resp.
NSAIDs	Alcohol	↑ bleeding	Avoid excessive alcohol
	ACE Inhibitor	Impaired renal fxn ↓ hypotensive effect	Avoid

DRUG	INTERACTING DRUG	ADVERSE EFFECTS	COMMENTS
	Anticoagulants	↑ bleeding risk (diclofenac, ibuprofen, & naproxen may not ↑ hypoprothrombinemic response)	Monitor PT
	Aspirin	Possible ↑ NSAID toxicity (diclofenac may not be clinically significant)	Avoid
	Beta blockers	↓ antihypertensive effect (naproxen may not interact)	Monitor BP
	Cimetidine	Possible piroxicam toxicity	Use other NSAID
	Dipyridamole	Water retention (indomethacin)	Monitor
	Furosemide	↓ diuretic and antihypertensive effect	Monitor BP and diuresis
	Haloperidol	Severe drowsiness (indomethacin)	Avoid
	Hydralazine	↓ hypotensive effect	Monitor BP
	Hypoglycemics, sulfonylureas	Hypoglycemia (tolbutamide) (no rxn with ketoprofen or ibuprofen)	Avoid
	Lithium	↑ lithium toxicity (no rxn with sulindac)	Monitor lithium
	Methotrexate (MTX)	↑ MTX toxicity	Stop NSAID 2-3 days before MTX in elderly & ↓ renal fxn
	Nifedipine	Possible ↓ anti-hypertensive effect	Monitor BP
	Prazocin	↓ hypotensive effect	Monitor BP
	Probenecid	Possible ↑ toxicity	Monitor
	Salicylates	Possible ↑ toxicity with topical	Monitor topical concentrations
	Spironolactone	↓ diuretic effect (indomethacin)	Avoid
	Sympathomimetic amines	Severe HTN with phenylpropanolamine & indomethacin	Avoid
	Thiazide diuretics	↓ diuresis ↓ antihypertensive effect Hyponatremia	Monitor BP, diuresis, and sodium

DRUG	INTERACTING DRUG	ADVERSE EFFECTS	COMMENTS
	Triamterene	Renal failure and ↑toxicity with indomethacin or diclofenac	Avoid if possible
	Verapamil	Possible ↓ effect with diclofenac	Monitor
Penicillins	Anticoagulants	↓anticoagulant effect (nafcillin & dicloxacillin)	Monitor PT
	Beta blockers	Possible ↓ atenolol effect (ampicillin)	Monitor
	Contraceptives, po	↓contraceptive effect (pen V & oxacillin)	Low incidence Alternate method
	Fluorquinolones	Possible ciprofloxacin toxicity (azlocillin)	Monitor
	Lithium	Hypernatremia (ticarcillin)	Avoid
	Methotrexate (MTX)	Possible ↑ toxicity of MTX	Avoid
Pentoxifylline	Cimetidine	Possible ↑ toxicity	Monitor
	Theophylline	Possible toxicity of theo. with SR pentoxifylline	Monitor theophylline
Phenothiazines	Alcohol	Impaired motor fxn.	Warn patients
	Anticholinergics	↓phenothiazine effect	Monitor
	Tricyclic antidepressants (TCA)	↑ TCA toxicity	Monitor TCA conc.
	Barbiturates	↓ phenothiazine effect	Avoid
	Beta blockers	Possible toxicity of both drugs	Monitor
	Chloroquine	Possible chlorpromazine toxicity	Monitor
	Cimetidine	Excessive sedation (chlorpromazine)	Monitor
	Clonidine	Organic brain syn.	Monitor mental
	Disulfiram	↓ phenothiazine effect	Avoid
	Guanadrel	↓ antihypertensive effect	Avoid
	Guanethidine	↓ antihypertensive effect	Avoid
	Levodopa	↓ levodopa effect	Avoid if possible
	Lithium	↑ neurotoxicity	Monitor neuro status

DRUG	INTERACTING DRUG	ADVERSE EFFECTS	COMMENTS
	Narcotics: meperidine	↑ narcotic toxicity	Monitor closely
	Trazodone	Hypotension	Monitor BP
	Valproate	Possible valproate toxicity	Monitor valproate
Salicylates	Antacids	↓ salicylate effect	Monitor
	Anticoagulants	Possible ↑ bleeding	Monitor PT
	Beta blockers	↓ antihypertensive effect	Monitor BP
	Cimetidine	Possible salicylate toxicity	Monitor
	Corticosteroids	↓ salicylate effect	Monitor
	Hypoglycemics, sulfonylurea	↑ hypoglycemic effect	Monitor glucose
	Insulin	Possible ↑ hypoglycemic effect	Monitor glucose
	Lithium	Possible lithium toxicity	Monitor lithium
	Methotrexate (MTX)	Possible ↑ MTX toxicity	Avoid
	Probenecid	↓ uricosuric effect	Avoid salicylates
	Spironolactone	↓ diuretic effect	Monitor diuresis
	Valproate	Possible valproate toxicity	Use alternative
Trimethoprim-Sulfamethoxazole	Anticoagulants	↑ anticoagulant	Monitor PT effect
	Antidepressants, tricylic	Recurrence of depression	Monitor mental status
	Contraceptives, po	↓ contraceptive effect	Use alternative method
	Digoxin	Possible digoxin toxicity	Monitor for signs
	Methotrexate (MTX)	Megaloblastic anemia & pancytopenia	Avoid
	Procainamide	Possible procainamide toxicity	Monitor procainamide
	Rifampin	Possible rifampin toxicity	Monitor status
Vancomycin	Aminoglycoside	Possible↑nephrotoxicity & ototoxicity	Avoid
	Cephalosporins	↑ nephrotoxicity	Avoid
	Digoxin	Possible ↓ digoxin effect	Monitor digoxin

Adapted from *The Medical Letter Handbook of Adverse Drug Interactions*, 1993.

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