In Brief

This article focuses on common prescription drug interactions in the treatment of diabetes, dyslipidemia, hypertension, and erectile dysfunction. Mechanisms of the drug interactions and recommendations for clinical practice are highlighted. Because of concerns about potentially negative effects some prescription medications may have on glycemic control in people with diabetes, some of these drug-disease interactions are also addressed.

Common Drug Pathways and Interactions

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The Food and Drug Administration approves about 25 new drug entities each year, and new interactions are also reported for drugs already in use. Only recently have serious drug interactions been responsible for the withdrawal of drugs from the marketplace. Terfenadine (Seldane), astemizole (Hismanal), mibefradil (Posicor), and cerivastatin (Baycol) are examples. Cisaparide (Propulsid), used to treat diabetic gastroparesis, is only available through a special process involving strict criteria because of clinically significant drug interactions that resulted in patient deaths.

Knowing about every drug interaction is impractical, and not all drug interactions have adverse clinical consequences. Computer screening programs are available in pharmacies, but they do not always contain the most recent information. In addition, many screening programs are too inclusive and sometimes numb users to clinically important drug interactions. *Drug Interaction Facts*[1] and *Drug Interactions Analysis and Management: A Clinical Perspective and Analysis of Current Developments*[2] are two good resources commonly used by pharmacists for information on drug interactions.

Significant drug interactions and patient harm that results from them are common concerns in clinical practice. One study showed that although drug interactions account for only 3.8% of emergency room visits, the patients affected by them usually have to be admitted to the hospital.[3] Another study demonstrated that about one-third of all adverse drug events in hospitalized patients can be attributed to preventable drug interactions.[4] These account for half of the total costs of adverse outcomes from drug therapy.

Quite simply, a drug-drug interaction occurs when the effects of one drug are changed by the presence of another drug. Drug-drug interactions can be categorized as pharmacokinetic or pharmacodynamic. Pharmacokinetic drug interactions occur when one drug enhances or interferes with the absorption, distribution, metabolism, or excretion of another drug resulting in a change in drug concentration in the body. The ability of phenobarbital to decrease the effect of warfarin (Coumadin) by increasing its metabolism through hepatic enzyme induction is an example of a pharmacokinetic drug interaction.[1,2] Pharmacodynamic drug interactions occur when one drug enhances or decreases the effect of another drug at its site of action without altering the drug's concentration in the body. The interaction between propranolol (Inderal) and albuterol (Proventil, Ventolin) is a pharmacodynamic drug interaction in which propranolol (a β-blocker) diminishes the effect of albuterol (a β-agonist) through antagonism at the β2 receptor site in the lungs.[1,2]

Because most drugs are detoxified by the liver, the most important of the pharmacokinetic drug interactions involve drug metabolism. This is influenced by genetics, which explains why some patients suffer adverse consequences from some drug combinations and others do not.

The cytochrome P450 (CYP450) enzyme system is responsible for the oxidative-reductive metabolism of medications. These enzymes are primarily concentrated in the liver and small intestines. More than 30 human CYP450 enzymes have been identified; however, only four isoenzymes (CYP3A4, CYP2C9, CYP1A2, and CYP2D6) are responsible for the majority of drug metabolism.[5] CYP3A4 metabolizes the greatest number of medications and endogenous substances in the body, accounting for most CYP450 enzymes in the liver and small intestines (60 and 70%, respectively).[6]

Many substrates, inhibitors, and inducers of CYP450 isoenzymes have been identified. A substrate is the medication being metabolized by the enzyme system. Warfarin, statins (e.g. lovastatin [Mevacor] and simvastatin [Zocor]), and theophylline are examples of substrates. An inhibitor is a medication that decreases enzyme activity and leads to increased concentrations of the substrate. Some macrolide antibiotics (e.g., erythromycin and clarithromycin [Biaxin]), cimetidine (Tagamet), and azole antifungals (e.g., fluconazole [Diflucan], itraconazole [Sporanox], and ketoconazole [Nizoral]) are known inhibitors of CYP450. An inducer is a medication that increases the number of enzymes and leads to decreased concentrations of the substrate. Notorious enzyme inducers are rifampin (Rifadin, Rimactane), carbamazepine (Tegretol), phenytoin (Dilantin), and phenobarbital. Thus, enzyme inhibitors can predispose to drug toxicity, whereas enzyme inducers have the potential to decrease the effectiveness of a medication. Of the two processes, an interaction that leads to inhibition has a more rapid onset.

The optimal management of a drug interaction involves recognition of the interaction; decision regarding whether to prescribe, dispense, or administer the interacting combination; follow-up monitoring; and appropriate patient counseling. Once the interaction is recognized, one must consider the possible outcome before deciding whether to prescribe, dispense, or administer the interacting drugs. If the outcome were possible death, the risk would likely outweigh the benefit. If the outcome were increased drowsiness, the benefit would appear to outweigh the risk.

The availability of alternative medications and the ease of monitoring the drug interaction are secondary considerations. In today's managed care environment, drug formularies may limit alternatives or make them cost-prohibitive. This is not necessarily bad because drugs can be costly, and drug interactions are not generally regarded as contraindications unless the outcome is extremely serious.

DRUG INTERACTIONS IN DIABETES

Pharmacokinetic drug interactions among medications used to treat diabetes are not very common because antidiabetic agents are generally not substrates, inducers, or inhibitors of the major CYP450 enzymes. Repaglinide (Prandin) is an exception because it is metabolized by CYP3A4 and is therefore a substrate; however, clinically significant drug interactions with repaglinide are not common.[1,2] The more common clinically relevant drug interactions in the treatment of diabetes are drug-disease interactions.

Drug-Disease Interactions

Metformin (Glucophage)

Since its approval in 1995, metformin has been widely prescribed to treat type 2 diabetes. Although it has many beneficial effects, it is not the drug of choice for all patients because of the risk of lactic acidosis, which can occur with inappropriate use. Metformin is absolutely contraindicated in patients with renal dysfunction (defined as a serum creatinine >1.5 mg/dl for males and >1.4 mg/dl for females) and in those with congestive heart failure requiring pharmacological treatment.[7] It should not be prescribed for patients >80 years of age unless measurement of creatinine clearance shows that renal function is not reduced.[7] Patients with conditions predisposing them to lactic acidosis (e.g., dehydration, hepatic disease, sepsis) should not use metformin.[7] Additionally, metformin should be temporarily discontinued in patients undergoing procedures involving administration of intravenous iodinated contrast materials, which can decrease renal function.[7]

In a recently published retrospective chart review of 100 patients who received two or more prescriptions for metformin during a 9-month period,[8] 22 patients had either renal insufficiency or congestive heart failure. Two charts contained documentation that the prescriber had considered the contraindications to metformin. The researchers did not mention whether any of the patients developed lactic acidosis.

Corticosteroids

Corticosteroids are commonly used as anti-inflammatory and immunosuppressive agents. They are administered by oral, parenteral, topical, intra-articular, and inhaled routes. It is widely accepted that corticosteroids can increase plasma glucose levels in patients with diabetes. Hyperglycemia can occur with any route of administration.[9–14] The degree of hyperglycemia depends on the dose, route, duration, and patient-specific characteristics.

Corticosteroids affect glucose control by decreasing glucose utilization and increasing gluconeogenesis.[13] The addition of corticosteroids, especially high-dose systemic steroids, necessitates an adjustment of the dosage for diabetes medication or, in some cases, initiation of insulin. All patients on corticosteroids should routinely monitor their blood glucose levels and have instructions on what to do to address increasing glucose levels.

Niacin

Niacin, an antilipemic agent, is available as a prescription in a sustained-release form and in combination with lovastatin. Published reports discourage the use of niacin in patients with diabetes because of resultant deterioration in glycemic control.[15–17] However, these are uncontrolled studies or case reports.

The ADMIT study[18] prospectively randomized patients with and without diabetes who had peripheral arterial disease to treatment with immediate-release niacin or placebo. The patients with diabetes had glycemia well controlled at baseline. The mean glucose level was 168 mg/dl, the mean hemoglobin A1c (A1C) was 7.8%, and only 59% of patients received drug therapy for their diabetes.

There were statistically significant improvements in the lipid profiles of patients with and without diabetes. HDL cholesterol increased by 29%, LDL cholesterol decreased by 8–9%, and triglycerides decreased by 23–28%. Niacin only modestly increased glucose levels 8.7 and 6.3 mg/dl in patients with and without diabetes, respectively. A small but sta-

tistically significant increase in A1C of 0.3% occurred in niacin-treated patients with diabetes. There were no significant differences in niacin discontinuation, niacin dosage, or antidiabetic therapy in patients with diabetes assigned to niacin versus those assigned to placebo. The average dose of niacin was ~2,500 mg, and the study duration was 60 weeks. The authors concluded that niacin can be safely used in patients with diabetes and should be considered an alternative to statins or fibrates.

This trial provides evidence that niacin can be used with careful monitoring in patients with diabetes, especially those in whom glycemia is fairly well controlled. The American Diabetes Association (ADA) considers statins as first-line therapy for lowering LDL cholesterol. However, its guidelines acknowledge that niacin is the best drug for raising HDL cholesterol and that glycemic control can be maintained with adjustments in the antidiabetic regimen with niacin doses ≤3 g/day.[19]

Diuretics

Diuretics are recommended as add-on treatment for hypertension if they were not chosen as initial drug therapy because they have additive effects with other antihypertensive classes.[20] Many clinicians are hesitant to use diuretics, particularly thiazide diuretics, in patients with diabetes because of the possibility of increased glucose concentrations. Thiazide diuretics (e.g., hydrochlorothiazide [HCTZ, Hydrodiuril]) have a greater effect on blood glucose than loop diuretics (e.g., furosemide [Lasix]), and the effect is dose-related, with an increased likelihood at HCTZ doses ≥25 mg or its equivalent.[10–13] The mechanism for diuretic-induced hyperglycemia may be related to drug-induced hypokalemia leading to decreased insulin secretion; however, this has been debated.

A retrospective study suggested that patients with diabetes who received diuretics had increased cardiovascular mortality.[21] However, in the prospective, randomized SHEP trial, low-dose chlorthalidone (Hygroton) 12.5–25 mg/day, reduced the cardiovascular event rate 34% compared with placebo, and the absolute risk reduction was twice as much for patients with diabetes as for those without diabetes.[22] At 3 years, serum glucose levels were increased by 5.6 mg/dl in the placebo group and 9.2 mg/dl in the chlorthalidone group.

In summary, diuretics should be used more frequently in the management of hypertension because changes in glucose and cholesterol concentrations are minor, especially with the lower doses of diuretics prescribed today.[23] Also, cardiovascular morbidity and mortality have been reduced in patients with hypertension when diuretics are prescribed, including patients with dyslipidemia or diabetes.[23]

β-Blockers

β-Blockers are another antihypertensive drug class that many providers avoid in patients with diabetes because of concerns that β-blockers could mask symptoms of hypoglycemia, such as palpitations, tremor, and hunger and could prolong recovery from hypoglycemia. Inhibition of hypoglycemia-induced sweating is not affected because it is not under sympathetic control.

The nonselective beta-blockers (e.g., propranolol [Inderal] and nadolol [Corgard]) are more likely to blunt the counterregulatory effects of epinephrine compared to cardioselective β-blockers (e.g., atenolol [Tenormin] and metoprolol [Lopressor]).[1,2] This action inhibits glycogenolysis, especially in patients who take insulin. In this way, nonselective beta-blockers may delay recovery from hypoglycemia; however, the clinical importance of this is unknown.

The United Kingdom Prospective Diabetes Study[24] did not demonstrate an increased incidence of hypoglycemia in the group treated with beta-blockers. In addition, Shorr et al.[25] concluded that specific antihypertensives had little impact on the risk of hypoglycemia in older patients with diabetes. Angiotensin-converting enzyme (ACE) inhibitors, β-blockers (cardioselective and nonselective), thiazide diuretics, and calcium-channel blockers (CCBs) were included in the study.

β-Blockers have shown relative risk reductions in mortality of ~25% in patients with myocardial infarction.[26] Because diabetic patients with myocardial infarction have a higher mortality than nondiabetic patients with myocardial infarction, the absolute benefit of a given relative reduction may be greater in patients with diabetes.[26]

In summary, β-blockers have clear benefits in patients with diabetes and myocardial infarction. They have also been used safely and with good outcomes in the treatment of concomitant hypertension in patients with diabetes. Patients should be counseled regarding hypoglycemia unawareness, especially if they use insulin. Cardioselective β-blockers are preferred over noncardioselective β-blockers in patients with diabetes.

It is important to control blood pressure in patients with diabetes regardless of the antihypertensive chosen. In clinical trials, intensive blood pressure control decreased cardiovascular morbidity and mortality in patients with diabetes. This held true regardless of whether patients received low-dose diuretics, β-blockers, ACE inhibitors, or CCBs as initial drug therapy.[27]

Atypical Antipsychotics

Case reports, chart reviews, and results from clinical trials have shown a relationship between increased glucose levels and treatment with the atypical antipsychotics clozapine (Clozaril) and olanzapine.[28] A few cases of hyperglycemia have also been reported with risperidone (Risperdal) and quetiapine (Seroquel).[28] The hyperglycemia is not dose dependent, is reversible with drug discontinuation, and reappears with rechallenge.[28] Postulated mechanisms for the hyperglycemia include antagonism of several neurotransmitters and insulin resistance.

DRUG INTERACTIONS IN DYSLIPIDEMIA

Compared to medications used to treat diabetes or hypertension, drugs used to treat dyslipidemia are associated with more clinically significant pharmacokinetic drug interactions. Also, drug interactions may be common in clinical practice because atorvastatin (Lipitor), simvastatin, and pravastatin (Pravachol) were the No. 1, No. 17, and No. 37 most prescribed medications by sales volume in 2000, respectively.[29] Given the recent results of the Heart Protection Study,[30] sales of these medications are likely to increase further.

The management of dyslipidemia in patients with diabetes needs to be aggressive. Diabetes is considered a coronary heart disease (CHD) risk equivalent because diabetes itself poses a high risk of new CHD within 10 years.[31] Also, patients with diabetes who experience a myocardial

infarction have an unusually high death rate.[26,31] Ideally, goals should be LDL cholesterol <100 mg/dl, HDL cholesterol >40 mg/dl, and triglycerides (TGs) <150 mg/dl.[19,31] Patients with diabetes may be at increased risk for drug interactions because they often have mixed dyslipidemias and thus may require one medication to decrease LDL cholesterol and another medication to decrease TGs and increase HDL cholesterol.

Statins

Atorvastatin, lovastatin, simvastatin, pravastatin, and fluvastatin (Lescol) are the currently available statins. Cerivastatin was removed from the market because of its association with unusually high rates of rhabdomyolysis and death. As a class, the statins are the most potent drugs for reducing LDL cholesterol. However, they only modestly increase HDL cholesterol and lower TGs.

An appreciation of the metabolism of these drugs is important in predicting drug interactions. (See Case Study 1.) Lovastatin, simvastatin, and atorvastatin are primarily metabolized by CYP3A4.[5,6,32] Fluvastatin is mainly metabolized by CYP2C9, and pravastatin does not undergo substantial metabolism by CYP450 enzymes.[5,32] It makes sense that drugs that affect CYP3A4 will likely interact with lovastatin, simvastatin, and atorvastatin but not with fluvastatin or pravastatin. Inhibitors and inducers of CYP3A4 are listed in Table 1. Induction of CYP3A4 can lead to suboptimal cholesterol control, whereas inhibition of CYP3A4 can predispose susceptible patients to drug toxicity from statins.

Adverse effects on skeletal muscle are the most serious side effects of the statins. They can range from myalgia to myositis to myopathy and rarely to rhabdomyolysis.[32] In large clinical trials, the incidence of myalgia was 2–7% compared to 0.1–0.2% for myopathy in patients treated with statin monotherapy.[33]

By definition, myopathy must be muscle aches or weakness with elevations in creatine kinase (CK) levels more than 10 times the upper limit of normal. The risk of myopathy is increased by *1*) high-dose statin use; *2*) concurrent use of fibrates; *3*) concurrent use of CYP3A4 inhibitors; and *4*) acute viral infections, major trauma, surgery, hypothyroidism, and other conditions.[33]

Rhabdomyolysis is severe skeletal muscle breakdown. The leakage of myoglobulin (skeletal muscle contents) into the blood or urine can cause acute renal failure and death.

In clinical trials with patients treated with lovastatin, the risk of rhabdomyolyis was 0.15% with lovastatin monotherapy, 5% for lovastatin-gemfibrozil (Lopid) combination therapy,

Table 1. Clinically Significant Drug Interactions in the Treatment of Dyslipidemia[1,2,5,6,32,33*]

Medication	Interacting Medication	Mechanism	Effects	Recommendations**
Atorvastatin, lovastatin, or simvastatin	Macrolide antibiotics (erythromycin or clarithromycin)	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Alternative antibiotic or temporarily stop statin or change to pravastatin or fluvastatin
	Azole antifungals (fluconazole, ketoconazole, or itraconazole)	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Alternative antifungal (topical or terbinafine) or temporarily stop statin or change to pravastatin or fluvastatin
	Cyclosporine	Unknown	Myopathy or Rhabdomyolysis	Change to pravastatin or fluvastatin
	Verapamil or diltiazem	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Alternative antihypertensive or change to pravastatin or fluvastatin
	Gemfibrozil	Unknown	Myopathy or Rhabdomyolysis	Counsel patient and monitor CPK and myalgias
	Protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, amprenavir†)	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Change to pravastatin or fluvastatin
	Nefazodone	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Alternative antidepressant or counsel patient and monitor CPK and myalgias, or change to pravastatin or fluvastatin
	Niacin	Unknown	Myopathy or rhabdomyolysis	Counsel patient and monitor CPK and myalgias
Lovastatin, simvastatin, fluvastatin, gemfibrozil, or fenofibrate	Warfarin	Inhibition of warfarin metabolism	Increased INR with potential for bleeding	Counsel patient and monitor INR

*This list is not all-inclusive
**Based on literature and the author's professional opinion
†Indinavir (Crixivan); nelfinavir (Viracept); ritonavir (Norvir); saquinavir (Fortovase, Invirase); amprenavir (Agenerase)
CPK, Creatine phosphokinase
INR, International Normalized Ratio: a standardized test to monitor warfarin therapy

2% for lovastatin-niacin combination therapy, and 28% for cyclosporine (Neoral, Sandimmune)-gemfibrozil-lovastatin combination therapy.[33] Myalgia or myopathy usually precedes rhabdomyolysis.[6]

Given the propensity for drug interactions, why wouldn't providers always prescribe either pravastatin or fluvastatin when a statin is indicated? Fluvastatin is the least potent of the statins and may not produce the LDL cholesterol reductions needed to reach aggressive goals. Simvastatin and atorvastatin are both more potent than pravastatin. Lovastatin has recently become available generically and can lead to considerable cost savings in the treatment of dyslipidemia. In addition, drug interactions with statins are well documented and can be monitored. Patient education can reduce complications from the drug interaction. Patients should be advised to discontinue their statin if they develop generalized muscle aches or weakness, especially if accompanied by flu-like symptoms or tea-colored urine. A CK should be ordered if muscle breakdown is suspected.

When multiple CYP3A4 inhibitors are prescribed, it is best to choose pravastatin or fluvastatin because the risk of rhabdomyolysis is increased with other statins. When either cyclosporine or protease inhibitors are prescribed, pravastatin or fluvastatin should be the statins of choice because cyclosporine and protease inhibitors most significantly increase statin plasma concentrations.[5]

Bile Acid Sequestrants

Bile acid sequestrants (e.g., colestipol [Colestid] and cholestyramine [Questran]) are generally not used in the treatment of hypercholesterolemia in patients with diabetes because they can raise TGs that may already be above target levels. Because bile acid sequestrants reduce the absorption of many oral medications, patients should be advised to take other drugs at least 2 hours before or 6 hours after the bile acid sequestrant.[1,2] Clinically significant interactions have been reported with digoxin (Lanoxin), furosemide, hydrocortisone, HCTZ, and warfarin;[1,2] however, it is probably a good idea to separate administration times for all medications and bile acid sequestrants.

Combination Antilipemic Agents

Niacin, gemfibrozil, and fenofibrate (Tricor) can interact with statins by an unknown mechanism.[1,2] (See Table 1.) This is important because either fibrates (gemfibrozil, fenofibrate) or niacin may be prescribed with a statin to lower TGs and LDL cholesterol and increase HDL cholesterol. Mixed dyslipidemia is often seen in patients with diabetes. Statins decrease LDL cholesterol 18–55%, decrease TGs 7–30%, and increase HDL cholesterol 5–15%.[31] Niacin and fibrates have much less effect on LDL cholesterol. However, TGs are reduced by 15–35% with niacin and 20–50% with fibrates, and HDL cholesterol is increased 15–35% with niacin and 10–20% with fibrates.[31]

The same precautions should be followed for combination therapy with fibrates and statins or niacin and statins as if a CYP3A4 inhibitor were prescribed. In a retrospective analysis, ~10% of 70 patients who received lovastatin plus gemfibrozil experienced mild elevations in CK without muscle weakness or pain.[34]

Case Study 1: Statins

P.R. is a 56-year-old woman with type 2 diabetes, hypertension, and dyslipidemia. Her medications include metformin, 1 g twice daily; glyburide (Micronase), 10 mg twice daily; enteric-coated aspirin, 325 mg daily; lisinopril (Prinivil, Zestril) 20 mg daily; HCTZ, 12.5 mg daily; and lovastatin, 40 mg daily. She developed an upper respiratory infection (URI) for which she was prescribed erythromycin, 333 mg three times daily for 10 days.

Questions:

1. Identify any significant drug interactions with the patient's lovastatin.
2. What option is best to protect this patient from a clinically significant drug interaction?
   a. Counsel her regarding the drug interaction. Instruct her to stop taking lovastatin, and call her health care provider if she develops any unexplained muscle aches or weakness, especially if accompanied by fever, fatigue, or tea-colored urine.
   b. Have her hold off on the lovastatin until the course of erythromycin is finished.
   c. Consider changing her prescription to another antibiotic such as amoxicillin (Amoxil, Trimox) or azithromycin (Zithromax).
   d. Consider changing the lovastatin prescription to either pravastatin or fluvastatin.

Answers:

1. Erythromycin can increase lovastatin drug concentrations through inhibition of the CYP3A4 isoenzyme. Myopathy, myositis, and rhabdomyolysis are possible clinical outcomes.
2. Any of the four options are reasonable. However, answer c probably makes the most sense since there are many available antibiotics for URI treatment that will not interact with statins. Instructing to hold off on the lovastatin until finishing the antibiotic could give P.R. the idea that the lovastatin is not really important.

DRUG INTERACTIONS IN HYPERTENSION

As with dyslipidemia, the treatment of hypertension in patients with diabetes needs to be aggressive. Recommendations from both the ADA[19] and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[20] suggest a goal blood pressure of <130/80–85 mmHg for patients with diabetes. At least 40–55% of patients will require more than one medication to reach this goal.[27] In clinical practice, we take advantage of pharmacodynamic drug interactions in the treatment of hypertension to prescribe medications that will have additive effects to lower blood pressure.

CCBs, β-blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs) are metabolized by CYP450, and drug concentrations may be decreased when combined with enzyme inducers (rifampin, carbamazepine, phenobarbital, phenytoin) or increased when combined with enzyme inhibitors (azole antifungals, cimetidine, erythromycin).[35] Diuretics are eliminated by the kidney and, therefore, are not subject to CYP450 interactions. The same is true for the hydrophilic β-blockers nadolol and atenolol.

CCBs are classified as dihydropyridine (nifedipine [Procardia XL and Adalat CC], nicardipine [Cardene], isradipine [DynaCirc], nisoldipine [Sular], felodipine [Plendil], and amlodipine [Norvasc]) and nondihydropyridine (verapamil [Calan, Isoptin, Covera-HS, and Verelan], diltiazem [Cardizem, Dilacor, and Tiazac]). This is an important distinction not only because of different effects on heart rate (verapamil and diltiazem

decrease heart rate; others increase or have neutral effects on heart rate) but also because of different metabolic fates. Although all CCBs are substrates for CYP3A4, only diltiazem and verapamil also inhibit CYP3A4.[35] Thus, drug interactions shared by verapamil and diltiazem may not translate to the dihydropyridine CCBs. Rifampin, phenobarbital, carbamazepine, and phenytoin can induce the metabolism of all CCBs because all CCBs are substrates for CYP3A4.[35] This could lead to loss of blood pressure control. Azole antifungals (ketoconazole, fluconazole, itraconazole), macrolide antibiotics (erythromycin, clarithromycin), nefazodone (Serzone), cimetidine, and protease inhibitors can increase serum concentrations of the CCBs through inhibition of CYP3A4.[35] The net effect is the potential for increased CCB side effects and symptomatic hypotension.

β-blockers exhibit significant pharmacodynamic drug interactions with some drugs.[36] Noncardioselective beta-blockers and cardioselective beta-blockers in larger doses can antagonize the effects of β-agonists and lead to bronchoconstriction.[36] β-blockers in combination with amiodarone (Cordarone), diltiazem, digoxin, and verapamil can have increased effects on heart rate and possibly lead to significant bradycardia.[36]

Probably one of the most common and often unrecognized drug interactions in clinical practice is that between nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensives. The NSAIDs ibuprofen (Motrin) and naproxen (Naprosyn) are available by prescription as well as over-the-counter. All other NSAIDs are available by prescription only. Inhibition of renal prostaglandins and promotion of sodium and water retention by NSAIDs antagonize the actions of thiazide and loop diuretics. This interaction has also been documented for ACE inhibitors, ARBs, β-blockers, and peripheral α-blockers.[37,38] The same interaction does not appear to occur with CCBs.[37,38]

Pooled data indicate that the average NSAID-induced increase in mean arterial pressure is 10 mmHg. The effect can be transient or chronic. Significant drug interactions between NSAIDS and antihypertensive agents are estimated to occur in about 1% of patients per year.[37] Elderly patients, African Americans, and patients with low-renin states are at greatest risk.[37,38]

Indomethacin (Indocin) has been the most reported NSAID to blunt antihypertensive effects. However, given the mechanism of the interaction, most, if not all, NSAIDs are likely to interact. There is some controversy with this issue related to sulindac (Clinoril).[37,38]

With the introduction of cyclooxygenase type 2 inhibitors for the treatment of pain and inflammation, one wonders if the same interaction is possible. To date, there has been one published case report of a 59-year-old man who was successfully treated with lisinopril, 10 mg/day.[39] After staring rofecoxib (Vioxx), 25 mg/day, blood pressure control was diminished. Eventually, the patient maintained good blood pressure control with lisinopril, 20 mg/day, and rofecoxib, 25 mg/day. Although the mechanism for the interaction has not been established, it is theorized that rofecoxib-induced inhibition of renal prostaglandins is probable.[39]

Lithium is considered a narrow-therapeutic-index drug. Thiazide diuretics, ACE inhibitors, and ARBs can increase lithium concentrations by interfering with lithium's renal excretion.[1,2] In general, thiazides should be avoided in patients prescribed lithium. If a diuretic is needed, a loop diuretic such as furosemide is recommended. Patients who are on ACE inhibitors or ARBs and lithium should have lithium levels checked and should be counseled to seek medical attention for signs of lithium toxicity. These include nausea, vomiting, diarrhea, coarse tremor, slurred speech, and disorientation.

DRUG INTERACTIONS IN ERECTILE DYSFUNCTION

Approximately 50% of men with diabetes have erectile dysfunction (ED).[40] Since sildenafil (Viagra) became available in 1998, it has become the drug of choice for most men with ED.

When sildenafil is combined with nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin) severe hypotension and possible death may result.[40,41] Therefore, concomitant use of nitrates and sildenafil is absolutely contraindicated.[40–42] The American College of Cardiology in collaboration with the American Heart Association published guidelines for sildenafil use in 1999.[42] Those guidelines emphasize that all men must be warned of the danger of taking sildenafil 24 hours before or after taking a nitrate preparation. (See Case Study 2.)

In addition to the pharmacodynamic interaction with nitrates, sildenafil also has the potential for clinically significant drug interactions with inhibitors of CYP3A4 because sildenafil is primarily metabolized by CYP3A4.[41] Macrolide antibiotics,[2,41] azole antifungals,[41] protease inhibitors,[1,2,41] and cimetidine[41] can increase sildenafil concentrations and increase side effects from it.

SUMMARY

Drug interactions can be complex, especially if multiple interactions exist in an individual patient. The literature on drug interactions is always changing as new information and new drugs become available.

Case Study 2: Sildenafil

G.M. is a 55-year-old man with type 2 diabetes, dyslipidemia, coronary artery disease, hypertension, ED, and gastroesophageal reflux disease. His medications include atenolol, 50 mg daily; atorvastatin, 20 mg daily; enteric-coated aspirin, 325 mg daily; glyburide, 5 mg twice daily; lisinopril, 10 mg daily; nitroglycerin, 0.4 mg sublingual as needed; and omeprazole, 20 mg daily. He carries sublingual nitroglycerin with him but has not had to use it in the past 3 years since he had angioplasty with cardiac stent placement. He is interested in obtaining a prescription for sildenafil.

Question:
Assume a history, physical exam, and lab tests were unremarkable regarding a cause for G.M.'s ED. How would you advise him?

Answer:
Sildenafil may be an option for this patient since he is not taking nitrates on a regular basis. However, he should be counseled that if he does experience chest pain or discomfort, he cannot take a sublingual nitroglycerin if he has taken sildenafil within the past 24 hours. He should seek immediate medical attention for his chest pain/discomfort. He must also realize that sexual intercourse may increase the risk of cardiac ischemia and chest pain.

When patients are prescribed drugs known to interact, they should be monitored appropriately and counseled about signs and symptoms that should trigger a call to the health care provider.

Patients should also be advised to have all of their prescriptions filled at one pharmacy so their drug regimens can be routinely screened for drug interactions. At the very least, they should keep an updated list of their medications with them to share with all health care providers.

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