Drug Interactions: A Primer for the Gastroenterologist

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Abstract: One of the most clinically significant complications related to the use of pharmacotherapy is the potential for drug-drug or drug-disease interactions. The gastrointestinal system plays a large role in the pharmacokinetic profile of most medications, and many medications utilized in gastroenterology have clinically significant drug interactions. This review will discuss the impact of alterations of intestinal pH, interactions mediated by phase I hepatic metabolism enzymes and P-glycoprotein, the impact of liver disease on drug metabolism, and interactions seen with commonly utilized gastrointestinal medications.

One of the most clinically significant complications related to the use of pharmacotherapy is the potential for drug-drug or drug-disease interactions. Globally, drug interactions can be divided into 2 major categories: pharmacodynamic interactions and pharmacokinetic interactions. Pharmacodynamic interactions, or "what the drug does to the body," occur when various distinct mechanisms produce similar effects, which may or may not be desired. For example, an undesired pharmacodynamic interaction may occur when 2 medications that share a common adverse effect are used concomitantly, such as simultaneous use of lactulose and mycophenolate mofetil, which potentially leads to an overall increase in the incidence of diarrhea. On the other hand, desired pharmacodynamic interactions are sometimes seen, as when a combination of antibiotics with various mechanisms of action are utilized to optimize treatment for *Helicobacter pylori* infection.[1]

The basis of pharmacokinetic drug interactions are the principles of absorption, distribution, metabolism, and elimination. Drugs have the potential to alter any of these 4 criteria, which can result in alterations in the pharmacologic activity of other concomitant drugs. Absorption is the ability of drugs to get into the body, which depends on various factors, including solubility, bioavailability, disintegration, stability, gastrointestinal flow, gastric

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emptying time, and route of administration. Absorption of drugs can be affected by conditions such as cystic fibrosis or procedures such as gastric bypass surgery, which result in decreased drug exposure; factors that affect drug absorption have been reviewed in depth previously.[2-4] Drug bioavailability can be characterized by the peak drug concentration (C_{max}), time to achieve the maximum concentration (T_{max}), and area under the curve (AUC).

Distribution allows the drug to be delivered to the target tissue and can be affected by the volume of distribution, membrane permeability, and lipophilicity of the drug.

Metabolism, or "what the body does to the drug," can occur at various sites in the body; in the liver, hepatic metabolism is generally divided into 3 phases. Phase I reactions include hydrolysis, oxidation, reduction, and methylation. Phase II reactions include glucuronidation and sulfate conjugation, and phase III reactions include adenosine triphosphate (ATP)-binding drug transporters, which function in excretion.[1]

Pharmacokinetic interactions, the focus of this review, are of particular importance to gastroenterologists and hepatologists, as the gastrointestinal tract and liver together play arguably the largest role of any organ system in the absorption, metabolism, and excretion of almost all medications.[1]

Cytochrome P450 and P-Glycoprotein

Likely the most recognized pharmacokinetic drug interaction pathways are those associated with drug metabolizing enzymes, namely the cytochrome (CYP) P450 family of isoenzymes, and the drug transporter P-glycoprotein (Pgp). The primary mechanisms of CYP interactions occur through enzyme/transporter inhibition or enzyme induction. There are 6 predominant CYP P450 isoenzymes responsible for most drug metabolism: CYP3A4/3A5, 1A2, 2C9, 2C19, 2D6, and 2E1. CYP3A4 makes up 40% of the isoenzyme content of the liver and is instrumental in the metabolism of over 60% of currently available medications.[5] While the primary site of CYP3A4 expression is the liver, intestinal expression of CYP3A4 contributes significantly to oral drug metabolism, as enterocytes of the duodenal and jejunal mucosa also express large quantities of this crucial enzyme.[6]

In contrast, the expression of other isoenzymes is primarily limited to hepatic tissues. These enzymes are also expressed to a much lesser extent than CYP3A4. For example, CYP1A2, 2E1, and 2D6 have 13%, 7%, and 2% expression in hepatic tissue, respectively.[7] CYP1A2 is responsible for metabolizing caffeine, theophylline, and R-warfarin. The CYP2 family makes up one of the larger isoenzyme groups and is responsible for metabolizing many classes of drugs, including (but not limited to) analgesics, beta blockers, serotonin reuptake inhibitors, and benzodiazepines.[8]

Pgp is located in various tissues, including enterocytes, hepatocytes, and endothelial cells of the brain and kidney. Pgp is an ATP-powered pump that works to influx and efflux substances and restricts the uptake of drugs from the intestine. There is a large overlap in substrate specificity between CYP3A4 and Pgp, which allows increased CYP3A4 exposure to drug substrates due to their reabsorption into enterocytes by Pgp.[6,9] These functional interactions between Pgp and CYP3A4 work synergistically to mediate drug interactions, which may cause either decreased therapeutic effects of medications or increased risks of toxicities and side effects. The unique CYP3A4/Pgp interplay was demonstrated in a study by Ding and coauthors, which evaluated digoxin and ritonavir and showed an 86% increase in digoxin levels and a decrease in renal and nonrenal clearance due to the inhibition of Pgp.[10]

Mechanisms of Drug-Drug Interactions

Induction

Induction of various hepatic enzymes occurs primarily via increased hepatic extraction and, to a lesser extent, by increased functional hepatic blood flow. This increased hepatic extraction occurs as a result of increased enzymatic activity, increased enzymatic volume, or decreased degradation of enzymes. The time course of enzyme induction will generally be a "slow-on, slow-off" process; however, it can be highly variable, depending on the half-life of the inducing agent as well as the typical turnover of the inhibited enzyme. For example, phenobarbital's effect on warfarin does not occur until 14–21 days after administration, while rifampin produces detectable changes within 2 days, with full induction reached at approximately 1 week.[11,12] Not all CYP enzymes are susceptible to induction. In fact, CYP2D6 has not been shown to be inducible; however, it is subject to significant intrapatient variability in genetic expression.[13]

The main clinical consequence when an inducing agent is added to a patient's medication regimen is loss of medication efficacy, which can be corrected by using a higher dose of the induced medication. A more serious clinical consequence arises when the inducing medication is discontinued, as toxicity can occur if the clinician fails to reduce the dose of the induced medication to preinduction doses.[14,15] Table 1 includes the most common isoenzymes and their respective inducers and substrates; management of these interactions involves determining the expected timing of induction and making dose adjustments based on the expected intensity of the interaction.[16,17] Therapeutic drug monitoring, when

Table 1. Common and/or Clinically Important Enzyme Inducers

Isoenzyme	Inducer(s)	Substrates
1A2	Cigarette smoke, omeprazole, phenobarbital, phenytoin, rifampin	Acetaminophen, amitriptyline, cyclobenzaprine, desipramine, diazepam, erythromycin, estradiol, naproxen, theophylline, warfarin
2C9	Rifampin	Celecoxib, diclofenac, losartan, naproxen, phenobarbital, phenytoin, piroxicam, torsemide, warfarin
2C19	Rifampin	Amitriptyline, citalopram, diazepam, lansoprazole, omeprazole, phenobarbital, propranolol, topiramate
2E1	Chronic ethanol ingestion, isoniazid	Acetaminophen, alcohols, dapsone, halogenated alkanes, isoflurane, theophylline
3A4/5	Carbamazepine, dexamethasone, ethosuximide, phenobarbital, phenytoin, rifampin/rifabutin, St. John's wort	Acetaminophen, alprazolam, amiodarone, amitriptyline, amlodipine, azole antifungals, budesonide, calcineurin inhibitors, carbamazepine, celecoxib, cisapride, clarithromycin, clindamycin, codeine, cortisol, dapsone, diazepam, digoxin, diltiazem, donepezil, ethinylestradiol, fentanyl, fexofenadine, HMG-CoA reductase inhibitors, lansoprazole, loratadine, losartan, macrolides, methadone, omeprazole, propafenone, sertraline, tamoxifen, theophylline, verapamil, warfarin

HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A.

available, should be utilized to guide dose adjustments of narrow–therapeutic index medications.

Inhibition

Drug interactions secondary to inhibition of the CYP 450 enzyme system are likely the most well known of all drug interactions, and they occur more frequently than enzyme induction.[18] Enzyme inhibition, while quite common, can represent a diverse set of interactions: Medications may be classified as reversible or irreversible inhibitors. Reversible inhibition is both transient and dose-dependent; these characteristics lead to a "quick-on, quick-off" drug interaction profile and allow for increased ease in management compared to irreversible inhibition, which typically produces a "quick-on, slow-off" profile. Reversible inhibition is the most common type of inhibition and can be further defined as being competitive, noncompetitive, or uncompetitive, with the inhibiting medication acting either at the site of enzymatic activity (competitive inhibition) or at alternative sites that inactivate the enzyme (noncompetitive and uncompetitive inhibition).[19,20]

The clinical consequences of inhibition include toxicity of the inhibited medication, as in the case of increased myopathies with statin therapy or QT prolongation with azole antifungals; reduced efficacy, as when prodrugs must be activated to their functioning metabolites; enhanced efficacy, as with ritonavir-boosted HIV regimens; and, finally, utilization of inhibition to allow for economic savings with high-cost medications, as with cyclosporine and diltiazem.[21-25] Table 2 includes the most common isoenzymes and their respective inhibitors and substrates; management of these interactions is discussed in detail later in this review.[16,17]

Effects of Cirrhosis on Drug Metabolism

The integrity of the hepatic disposition of medications in the setting of mild liver dysfunction is well conserved; however, pronounced changes are noted once patients begin to develop cirrhosis. Cirrhosis can affect drug metabolism via a multitude of mechanisms. Specifically, liver disease can decrease absorption as a result of increased gastrointestinal edema from ascites, alter metabolism via decreased blood flow or alteration of enzymatic activity, or disrupt protein binding because of decreased albumin production. The effects of liver dysfunction on enzymatic activity have been of particular interest, especially as patients progress from mild to moderate cirrhosis.

Phase I drug metabolizing enzymes, CYP 450 enzymes, are the most susceptible to changes in the setting of liver disease, although to varying degrees, with cholestatic versus noncholestatic cirrhosis also playing a role. CYP isoenzymes 1A2, 2C19, and 3A4/5 all show decreased functionality with increasing severity of cirrhosis, as determined by Child-Pugh classification, while CYP isoenzymes 2C9 and 2D6 show little-to-no change in functionality (Table 3).[26,27] George and colleagues demonstrated that CYP3A4/5 activity decreased proportionally with worsening Child-Pugh classification, with reductions in clearance ranging from 30% to 50%.[28] Following up these results, these authors examined the livers of 50 cirrhotic patients who had undergone liver transplantation and were able to demonstrate a significant decrease in expression of CYP3A4/5, indicating a loss of enzymatic expression rather than decreased functionality of the isoenzymes.[28,29] Not only was hepatic expression of CYP3A4

Table 2. Common and/or Clinically Important Enzyme Inhibitors

Isoenzyme	Inhibitors	Substrates
1A2	Cimetidine, ciprofloxacin, isoniazid, macrolide antibiotics, paroxetine	Acetaminophen, amitriptyline, cyclobenzaprine, desipramine, diazepam, erythromycin, estradiol, naproxen, theophylline, warfarin
2C9	Amiodarone, chloramphenicol, cimetidine, fluvoxamine, zafirlukast	Celecoxib, diclofenac, losartan, naproxen, phenobarbital, phenytoin, piroxicam, torsemide, warfarin
2C19	Azole antifungals, fluvoxamine, omeprazole, topiramate	Amitriptyline, citalopram, diazepam, lansoprazole, omeprazole, phenobarbital, propranolol, topiramate
2E1	Acute ethanol ingestion, disulfiram	Acetaminophen, alcohols, dapsone, halogenated alkanes, isoflurane, theophylline
3A4/5	Amiodarone, azole antifungals, cimetidine, cyclosporine, fluoxetine, macrolide antibiotics, metronidazole, nicardipine, propofol, protease inhibitors, quinine, sertraline, verapamil	Acetaminophen, alprazolam, amiodarone, amitriptyline, amlodipine, azole antifungals, budesonide, calcineurin inhibitors, carbamazepine, celecoxib, cisapride, clindamycin, codeine, cortisol, dapsone, diazepam, digoxin, diltiazem, donepezil, ethinylestradiol, fentanyl, fexofenadine, HMG-CoA reductase inhibitors, lansoprazole, loratadine, losartan, macrolides, methadone, omeprazole, propafenone, sertraline, tamoxifen, theophylline, verapamil, warfarin

HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A.

Table 3. Effect of Cirrhosis on Cytochrome P450 Activity

Study population	CYP 450 enzyme	Child-Pugh scores	Change in activity
50 explanted cirrhotic livers[28]	CYP1A2	B/C	Reduced activity at Child-Pugh class C
Controls and liver failure patients[53]	CYP1A2	A/B/C	Reduced activity at Child-Pugh class C
50 explanted cirrhotic livers[28]	CYP2C9	B/C	Reduced activity at Child-Pugh class C
Controls and liver failure patients[53]	CYP2C19	A/B/C	Reduced activity at Child-Pugh class A, B, and C
Controls and liver failure patients[53]	CYP2D6	A/B/C	Reduced activity at Child-Pugh class B and C
In vitro liver tissue[50]	CYP3A	Noncholestatic cirrhosis	Reduced activity at Child-Pugh class B and C
		Cholestatic cirrhosis	No difference at any Child-Pugh class

altered, intestinal expression was also reduced by as much as 47% in patients with cirrhosis.[30]

These changes in isoenzyme expression are thought to be related to the chronic inflammatory state induced by cirrhosis. Inflammation has been shown to affect CYP 450 activity via decreased messenger RNA and protein levels, cytokine-mediated inhibition of CYP activity, and possible interferon-mediated degradation of existing CYP proteins.[27,31,32] Alterations in blood flow to the liver, whether due to physiologic shunting or an implanted shunt, have also been shown to affect CYP isoenzyme activity. Chalasani and colleagues demonstrated a significant decrease in both hepatic and intestinal CYP3A4/5 activity in patients following insertion of transjugular intrahepatic portosystemic shunts.[33]

Unfortunately, while much in vitro data exist describing the reduction in CYP isoenzyme activity as hepatic dysfunction progresses, little rigorous data exist to describe the clinical impact of these changes on drug disposition, nor are recommended management strategies available. Clinical management of drug therapy in cirrhosis has been well described previously and should include careful selection of agents that require little-to-no hepatic clearance and avoidance of agents that require significant hepatic metabolism.[34] Additional management strategies should include therapeutic drug monitoring for narrow–therapeutic index agents, potential empiric dose reductions when hepatically cleared medications are used, and frequent monitoring and follow-up when new medications are initiated.

Alternatively, phase II conjugation reactions, including glucuronidation, appear to be well preserved in patients with liver dysfunction, as evidenced by normal oxazepam, lorazepam, and temazepam clearance in multiple models.[35-38] In patients with severe cirrhosis, however, glucuronidation is also compromised.[39]

Common Medications Used in Gastroenterology

Proton Pump Inhibitors and H_2-Receptor Antagonists

The treatment of acid-related diseases, including gastroesophageal reflux disease (GERD) and peptic ulcer disease, has been revolutionized by the addition of proton pump inhibitors (PPIs). Currently, there are 7 PPI formulations (esomeprazole, omeprazole, omeprazole plus sodium bicarbonate, pantoprazole, lansoprazole, dexlansoprazole [Dexilant, Takeda Pharmaceuticals], and rabeprazole), many of which are available as over-the-counter preparations. The adverse effects of PPIs are relatively benign, which commonly lead to their overuse. In the age of polypharmacy, however, PPIs have the potential to cause drug-drug interactions. The 2 primary mechanisms of interaction are the modulation of gastric pH and CYP P450 metabolic interactions. PPIs undergo CYP3A4 and 2C19 metabolism; however, variations in metabolism among the various agents result in unique drug interaction profiles for each PPI.

Omeprazole and pantoprazole are the 2 agents whose drug interactions have been most studied. Omeprazole is almost completely metabolized via a phase I metabolic pathway, leaving essentially no unchanged drug to be excreted, whereas pantoprazole undergoes both phase I metabolism of the parent compound and phase II conjugation of the active metabolite. This difference explains the propensity of pantoprazole to produce fewer drug interactions than omeprazole.[40] Competitive inhibition has been shown with the use of diazepam and omeprazole, resulting in a 20–25% reduction in diazepam clearance.[41]

The use of clopidogrel and PPIs has been a topic of much debate, as PPIs decrease the activation of clopidogrel, a prodrug, to its active metabolite via competitive inhibition of CYP2C19. This interaction carries the concerning theoretical risk of increased cardiovascular events if exposure to activated clopidogrel is decreased. Fortunately, an analysis of the cardiovascular events associated with omeprazole (at a dose of 20 mg) versus placebo in a prospective, randomized, controlled trial showed no significant difference in cardiovascular events; however, this analysis did show a statistically significant difference in gastrointestinal events.[42]

Gastric pH is increased with the chronic use of PPIs, which decreases the absorption of acid-labile drugs such as ketoconazole, itraconazole capsules, posaconazole (Noxafil, Schering), and indinavir (Crixivan, Merck).[43] Alternatively, higher exposure is expected with weak acids such as aspirin, furosemide, and diazepam, as these drugs exhibit increased absorption with increased intragastric pH.

H_2-receptor antagonists are also commonly used for the treatment of gastric conditions. The H_2-receptor antagonists that are currently available include cimetidine, ranitidine, and famotidine. Cimetidine is the best studied of these drugs, and it has been shown to inhibit multiple CYP enzymes, including CYP1A2, CP2C, 2D6, and 3A4. Ranitidine has lower affinity for the CYP enzymes, and famotidine has essentially no effect on the isoenzymes. Cimetidine has been shown to have significant clinical effects when coadministered with phenytoin, theophylline, quinidine, lidocaine, or nifedipine.[40] Management of gastric disease for patients on multiple medications should include consideration of PPIs and/or H_2-receptor antagonists that demonstrate the least potential for drug interactions, such as pantoprazole or famotidine.

Gastrokinetic Agents

Another class of medications commonly prescribed in gastroenterology are gastrointestinal motility agents such as metoclopramide, cisapride (Propulsid), domperidone, and erythromycin. By altering gastrointestinal motility, these drugs may affect absorption of concomitant medications. Cisapride was removed from the market in July 2000 due to its potential to cause serious cardiac arrhythmias, and domperidone is currently available in Canadian pharmacies but not in the United States. Due to the limited availability of cisapride and domperidone, the use of metoclopramide has increased.

Metoclopramide is frequently prescribed for GERD, dyspepsia, emesis, and gastroparesis, and this drug works as a dopamine antagonist both centrally and peripherally. With an increase in gastrointestinal motility, the pharmacokinetic properties of concomitant medications—such as C_{max} and T_{max}—are altered when used with metoclopramide. One study showed a significant increase in diazepam concentrations and a statistically earlier T_{max} when diazepam was coadministered with metoclopramide compared to placebo.[44] Similarly, cyclosporine, an immunosuppressant used in the setting of solid organ transplantation, has a mean increase in AUC of 29% when coadministered with metoclopramide due to overall increased bioavailability of cyclosporine secondary to rapid gastric emptying.[45]

Metoclopramide is metabolized by CYP2D6, and coadministration of metoclopramide with potent 2D6 inhibitors may result in increased central nervous system adverse effects, which may be irreversible, and the need for additional monitoring, dose reduction, or avoidance (if possible), as long-term use increases these risks. This interaction was demonstrated in a study by Vlase and coauthors

in which coadministration of fluoxetine, a potent CYP2D6 inhibitor, with metoclopramide produced significant increases in metoclopramide's C_{max} and AUC.[46]

Although domperidone and cisapride are not readily available in the United States, their potential drug interactions are significant and thus warrant discussion. The primary metabolic pathway of domperidone is via CYP3A4; metabolism of this drug therefore results in a multitude of drug reactions through either inhibition or induction. Cisapride increases gastrointestinal motility by increasing activation of serotonin 5-HT_4 receptors and by releasing acetylcholine from postganglionic nerve endings. Although cisapride has no central nervous system adverse effects, it has been withdrawn from the US market due to arrhythmias but remains available in Europe. Similar to domperidone, cisapride is metabolized through the CYP3A4 metabolic pathway and interacts with major inhibitors such as macrolides, azole antifungals, antidepressants, antiretrovirals, and cimetidine. Coadministration of either cisapride or domperidone with these potent inhibitors should be avoided due to the increased risk of QT prolongation.

The concomitant use of erythromycin and cisapride appears to be an intuitive combination due to the prokinetic activity of both agents; however, coadministration of these 2 drugs has been reported to cause a 20–30% increase in QTc prolongation. The prescribing information for cisapride contraindicates the concomitant use of cisapride with erythromycin due to this increased risk of cardiac arrhythmias. Clinicians should wait approximately 2 days after discontinuation of cisapride before initiation of macrolide therapy due to the prolonged half-life of cisapride.[47]

Macrolide Antibiotics

Macrolide antibiotics are utilized widely by gastroenterologists not only as antibiotics but also as promotility agents for the treatment of a variety of gastrointestinal disorders; however, the development of tachyphylaxis limits the drug's long-term utility. The macrolide antibiotic family includes erythromycin, azithromycin, clarithromycin, and telithromycin (Ketek, Sanofi Aventis). While the macrolide class in general produces potent inhibition of CYP3A4, each agent has variable inhibitory effects. Erythromycin is one of the most potent prokinetic agents and exerts its effect at the motilin receptor; as a result, erythromycin inhibits the metabolism of many drugs, including azole antifungals, calcineurin inhibitors, and conivaptan (Vaprisol, Astellas). However, use of erythromycin is limited by its potential for major interactions, as well as the potential for induction of resistant strains of bacteria with prolonged use. One of the most concerning adverse effects that can result from these interactions is QT prolongation and the risk of torsades de pointes. Empiric dose adjustments of inhibited compounds should be considered when erythromycin therapy is indicated, and cardiac monitoring should be performed when multiple QT prolonging agents are used concomitantly. Erythromycin also appears to affect Pgp transport, as evidenced by cases of erythromycin-digoxin interactions resulting in digoxin toxicity. A pharmacokinetic study by Hughes and coworkers showed that erythromycin had little effect on the parent digoxin compound; however, erythromycin decreased the efflux of 2 active metabolites (dihydrodigoxin and digoxigenin) by 34% and 43%, respectively, via Pgp inhibition.[48]

The inhibitory effect of clarithromycin on CYP3A4 is less than the inhibitory effect of erythromycin; however, it is still potent enough to warrant empiric dose reduction of compounds highly dependent on CYP3A4 elimination. Azithromycin has a significantly less pronounced effect on CYP3A4 activity, and dose reductions are often not needed in clinical practice. Unfortunately, the efficacy of clarithromycin and azithromycin in the treatment of dysmotility disorders is not as strongly established as the benefit of erythromycin.

Protease Inhibitors

Some of the newest drug interactions to impact the gastroenterology world are those seen with the novel protease inhibitors, telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck), which are used for the treatment of hepatitis C virus (HCV) infection. These agents produce potent, reversible inhibition of the CYP3A4/5 enzyme families, which are also responsible for metabolism of these drugs. While the expectation was that these new agents would produce drug interactions similar to those seen with the currently available protease inhibitors utilized for HIV treatment, the extent to which this interaction occurs is much greater than expected.[49]

There are 2 major considerations in the management of telaprevir and boceprevir drug-drug interactions: First, any medication that is highly dependent on the CYP3A system for metabolism should be administered with extreme caution (or avoided, if possible), since telaprevir or boceprevir coadministration will likely produce supratherapeutic exposure and put the patient at risk for potential toxicities. Second, any medication that will induce the CYP3A system and therefore reduce the overall exposure to telaprevir or boceprevir should be completely avoided to reduce the risk of antiviral resistance and therapeutic failure of the protease inhibitor.[50,51]

Several medications are specifically contraindicated for these reasons. They include alfuzosin (Uroxatral, Sanofi Aventis), ergot alkaloids, cisapride, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, phosphodiesterase inhibitors (eg, sildenafil and tadalafil),

and benzodiazepines, as coadministration with telaprevir or boceprevir is expected to produce toxicities. On the other hand, rifampin, rifabutin (Mycobutin, Pfizer), and St. John's wort would be expected to decrease protease inhibitor exposure via metabolic induction, resulting in increased risk for HCV treatment failure.

Clinically, significant drug interactions are numerous and diverse, and they can be caused by a range of drugs, including antiarrhythmics, macrolide antibiotics, anticonvulsants, antifungals, colchicine, calcium channel blockers, corticosteroids, HIV antiretrovirals, hormonal contraceptives, and immunosuppressants prescribed for the prevention of rejection following solid organ transplantation. Management of drug interactions should include avoidance, if possible, and conversion of interacting medications to those that are less likely to cause interactions prior to initiation of protease inhibitor therapy. When coadministration cannot be avoided, therapeutic drug monitoring of those agents with commercially available assays should be conducted, as is the case with calcineurin inhibitors, anticonvulsants, and antiarrhythmics. When therapeutic drug monitoring is not available, conservative management includes empiric dose reduction of 25–75%, depending on the medication and the severity of potential adverse effects. Clinical monitoring should also be performed to identify and resolve other drug-drug interactions.

Of particular interest are the significant drug interactions between protease inhibitors and immunosuppressants, as this combination will be unavoidable in the treatment of recurrent HCV infection after liver transplantation. In a pharmacokinetic study involving 10 healthy volunteers, single-dose cyclosporine and tacrolimus AUCs increased 4.6-fold and 70-fold, respectively, when volunteers had steady-state telaprevir exposure.[52] Clinical management could include either significant dose reduction in tacrolimus or cyclosporine or conversion from tacrolimus to cyclosporine and careful postconversion therapeutic drug monitoring; however, experience in this area thus far is very limited.

Conclusion

Overall, the propensity for gastroenterology agents to serve as either the substrates or the causative agents of drug interactions warrants greater attention to medication management. Attention to drug interactions is crucial in order to prevent toxicities and side effects and to avoid decreased efficacy due to subtherapeutic drug levels. Therapeutic drug monitoring of narrow–therapeutic index medications is crucial when drug interactions cannot be avoided. Often, clinicians must make empiric therapeutic adjustments or perform more intensive clinical monitoring to either prevent or manage drug-drug and drug-disease interactions. Ultimately, due to the clinical variability of drug-drug interactions for various agents, it is important to approach medication management with a multidisciplinary team, including physicians, nurses, and pharmacists.

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