Critically ill patients, given the nature and extent of their critical illness, frequently receive complex multidrug regimens. Organ dysfunction and polypharmacy potentially can lead to adverse drug interplay and an adverse event. Drug interactions may be pharmacokinetic or pharmacodynamic. A pharmacokinetic interaction arises when one drug alters the absorption, distribution, metabolism, or elimination of another agent. A pharmacodynamic interaction arises when one agent changes the pharmacological response of another agent in an additive, synergistic, or antagonistic way. This chapter focuses on drug–drug interactions (DDIs) that are pharmacokinetic in nature.

**DRUG–DRUG–INTERACTIONS**

A precipitant drug may alter any portion of an object drug’s pharmacokinetic profile. Absorption, distribution, metabolism, or elimination of the object drug may be affected and can result in either amplification or minimization of the object drug’s intended pharmacological response and a potential adverse event.

**Absorption**

Absorption in the small intestine is a complex process that may be affected by gastric pH, the extent of gastrointestinal drug metabolism, the presence of a chelator or binder, or disruption of intestinal microflora.

**Gastric pH**

Weak acids and weak bases traverse intestinal membranes and reach the bloodstream when they exist in an un-ionized state (ie, weak acids in an acidic environment and weak bases in a basic environment). Commonly used intensive care drugs (eg, H₂-receptor antagonists, proton pump inhibitors) may change the gastrointestinal pH and alter the rate and extent of an object drug’s absorption. The absorption of weak acids (eg, aspirin) may be impaired when the gastrointestinal pH is increased, whereas the absorption of weak bases (eg, tetracycline) may be enhanced. This change in gastric pH may be significant for narrow-spectrum drugs, the outcomes of which may be linked to specific drug concentrations (eg, itraconazole, dipyridamole). It is recommended that itraconazole capsules be administered with food or cola beverages to increase the acidity of the stomach when a patient has elevated gastrointestinal pH. Dipyridamole requires a pH of 4 or less for maximal absorption and is affected by concomitant proton pump inhibitor therapy. The combination of
aspirin and extended-release dipyridamole is preferred in the setting of an increased gastric pH, because it is formulated with tartaric acid to create an acidic environment for maximal dipyridamole absorption.\(^5\)

**Extent of Gastrointestinal Drug Metabolism**

A number of metabolizing enzymes along the small intestinal wall can significantly biotransform many compounds before they are absorbed into the systemic circulation. Cytochrome P4503A4 (CYP3A4) is the predominant enzyme; however, glucuronidation, sulfation, and monoamine oxidation biotransformation can also occur in this area. Substrates for gut CYP3A4 include amiodarone, carbamazepine, cyclosporine, nifedipine, nifedipine, and simvastatin.

**Presence of a Chelator or Binder**

Several medications have the ability to chelate or bind to other medications if administered concomitantly. Fluoroquinolones (eg, ciprofloxacin, levofloxacin) form complexes with metal ions (eg, iron), antacids (eg, aluminum hydroxide), and calcium-containing products. Concomitant gastrointestinal administration can decrease fluoroquinolone bioavailability and may result in therapeutic failure.\(^6,7\) It is recommended that a fluoroquinolone be taken at least 2 hours before or 6 hours after the administration of the chelating or binding drug to minimize this interaction.\(^8\) Bile acid sequestrants (eg, cholestyramine) can also reduce the bioavailability of several medications if administered concomitantly (eg, digoxin, levothyroxine, warfarin). The recommended management is to separate the administration times of the affected medications by at least 2 hours before and 4 hours after the administration of cholestyramine.\(^9\)\(^-\)\(^11\)

**Disruption of Intestinal Microflora**

Commensal intestinal microorganisms are involved in the presystemic metabolism of certain medications. Antimicrobial alteration of this flora has been shown to affect the absorption of medications that either are incompletely absorbed in the small intestine or undergo enterohepatic circulation (eg, estrogen-containing medications). The concomitant administration of warfarin and hepatobiliary-secreted antimicrobials can result in excessive anticoagulation. The antimicrobial may reduce the endogenous synthesis of vitamin K by intestinal microflora. An elevated international normalized ratio and bleeding may occur if the warfarin dose is not adjusted. The alteration of gastrointestinal flora that metabolizes digoxin is affected by antimicrobials that have activity against Eubacterium lentum (a gram-positive anaerobic bacillus). The coadministration of digoxin with macrolides increases digoxin bioavailability, resulting digoxin toxicity.\(^12,13\) Digoxin levels should be monitored while patients are administered concurrent macrolide pharmacotherapy.

**Intestinal P-Glycoprotein Activation**

P-glycoproteins are efflux transport proteins that are located on the luminal surface of the intestinal wall, hepatocannalicular system, and proximal renal tubules. They are capable of extruding drug from the circulation into the lumen of the small intestine, bile duct, and proximal convoluted tubule. These pumps work in concert with the cytochrome P450 system and can be either inhibited or activated. Digoxin is a substrate of the P-glycoprotein system; inducers or inhibitors can affect clearance. Rifampin is a potent inducer of both cytochrome P450 and P-glycoproteins and can decrease the plasma concentration of concomitantly administered digoxin.\(^14\) Concomitant administration of digoxin with P-glycoprotein inhibitors (eg, erythromycin, itraconazole, cyclosporine) can result in an increase in serum digoxin levels and lead to potential toxicity.\(^15\)\(^-\)\(^18\) Another clinically significant interaction can occur between linezolid and rifampin. Serum concentrations of linezolid, which is not metabolized by the cytochrome P450 enzyme system, have been decreased when used in combination with rifampin; this interaction may be due to the induction of intestinal P-glycoprotein by rifampin.\(^19,20\)
**Distribution (Displacement From a Carrier Protein)**

Plasma proteins are carriers for many drugs, transporting them either to a site of action or to an organ for elimination. The physiochemical property of each drug determines the extent of plasma protein binding. Albumin and α₁-acid glycoprotein are the major carrier proteins for acidic and basic drugs, respectively. The extent of plasma protein binding will depend on the concentration of the carrier protein and the presence of any competing agent for binding. If 2 or more drugs compete for binding sites, the drug with the higher affinity will bind and displace the other agent. This will increase the free fraction and potentially the pharmacological effects of the displaced drug. However, this additional drug effect may be temporary and self-correcting, because the volume of distribution and rate of elimination of the displaced drug may be increased.

The albumin binding of phenytoin or warfarin can be decreased with an increase in free fraction when given concomitantly with a nonsteroidal anti-inflammatory drug, ceftriaxone, or sulfamethoxazole. Management of these interactions includes monitoring of free phenytoin concentrations and signs and symptoms of phenytoin or warfarin toxicity. α₁-Acid glycoprotein (AAG) is the major carrier protein for basic drugs (eg, amitriptyline, lidocaine, propranolol). It is an acute-phase plasma protein whose concentrations increase under periods of acute stress. As a result, the free fraction and the pharmacological effect of drugs bound to AAG may decrease during periods of critical illness. An example of this interaction is the decrease in unbound fraction of lidocaine as the concentration of AAG increases in patients with acute myocardial infarction or trauma. To counter the decrease in free fraction, higher doses and total concentration of lidocaine have been needed to achieve an adequate pharmacological effect. Monitoring clinical response and assessing free lidocaine concentrations (if available) are warranted when increased AAG binding is suspected.

**Hepatic Clearance**

The liver is the most important drug-metabolizing organ. Drug metabolism is divided into phase I (oxidation, hydrolysis, and reduction [cytochrome P450 enzymes]) and phase II (glucuronide, sulfate, and glycine conjugation) enzymes. The phase I process usually produces a more hydrophilic metabolite than the parent compound, whereas the phase II process produces an inactive water-soluble product. There are several cytochrome P450 enzymes with different xenobiotic specificities. Enzyme induction generally affects phase I enzymes and results in the greater production of metabolizing enzyme. Table 27-1 lists cytochrome P450 isoforms and provides a partial list of common ICU medication substrates.

**Table 27-1. Select Drug Substrates, Inducers, and Inhibitors for Common ICU Medications**

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Substrate</th>
<th>Inducer</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Theophylline, lidocaine, R-warfarin</td>
<td>Omeprazole, phenobarbital</td>
<td>Cimetidine, ciprofloxacin, diltiazem, erythromycin</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Propofol</td>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Phenytoin, voriconazole, S-warfarin</td>
<td>Phenobarbital, phenytoin, rifampin</td>
<td>Amiodarone, fluconazole, metronidazole, TMP/SMX, voriconazole</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Clopidogrel, diazepam, phenytoin, proton pump inhibitors, voriconazole, R-warfarin</td>
<td>Phenobarbital, phenytoin, rifampin</td>
<td>Fluconazole, fluoxetine, oxcarbazepine, proton pump inhibitors, voriconazole</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>β-Blockers, haloperidol, phenothiazines, SSRIs</td>
<td></td>
<td>Amiodarone, haloperidol, SSRIs</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Acetaminophen</td>
<td>Isoniazid</td>
<td>Disulfiram</td>
</tr>
</tbody>
</table>
DDI Time of Onset
Predicting the time of onset for a particular DDI can be a challenge. Numerous factors can affect the evolution and eventual manifestation of a DDI. However, such a prediction can allow the clinician to develop the most appropriate plan for patient monitoring, dosing adjustments, and follow-up. The half-life of the precipitant drug and object drug must be considered. Maximum enzyme inhibition or enzyme induction will take place as the precipitant drug reaches steady-state levels. The effect on the object drug may begin during initiation of the precipitant drug but will peak following the steady state of any precipitant drug. A new steady state of the object drug will occur based on the “new” half-life of the object drug, at which point the maximum onset of this drug interaction will be observed. Phenobarbital (half-life 53-140 hours) and rifampin (half-life 3-4 hours) are well-known hepatic enzyme inducers. If each is added separately to a regimen of warfarin, it may take approximately 7 to 14 days for phenobarbital to reach steady state compared with 1 to 2 days for rifampin, with a 10- to 14-day onset for a phenobarbital–warfarin DDI versus a 2- to 5-day onset for a rifampin–warfarin DDI. It is generally recognized that hepatic enzyme induction takes time to dissipate after the discontinuation of an enzyme inducer, because time is required for the inducing drug to be cleared and for the enzymatic activity of the liver to abate. Thus, any effect of phenobarbital on warfarin may take 14-21 days or more to abate versus 5 to 7 days for rifampin–warfarin.

Enzyme inhibition is usually competitive, as precipitant drug and object drug compete for binding sites of the metabolizing enzymes; however, the precipitant drug may not always be a substrate for the metabolizing enzyme. Inhibition generally follows the same principles as enzyme induction but usually reaches maximal intensity within 1 to 2 days; offset will generally abate within the same time frame. Cimetidine (half-life approximately 2 hours) and amiodarone (half-life 50-150 days) are well-known enzyme inhibitors. If each is added separately to a regimen of warfarin, it may take approximately 1 day to reach steady state with cimetidine as compared to many weeks with amiodarone. The onset of a cimetidine–warfarin drug interaction may occur within 1 to 2 days, whereas the effects of an amiodarone–warfarin drug interaction may take 2 or more months to be fully expressed. The predictive process is further complicated by factors such as the dose of the precipitant drug, whether the object drug has a narrow therapeutic index, whether the clearance of the object or precipitant drug follows zero-order pharmacokinetics (ie, phenytoin), the presence of other enzyme inducers or enzyme inhibitors, and the presence of any hepatic dysfunction or altered genotypic phenotype (eg, CYP2C19 deficiency in patients from Asian descent).

Renal Elimination
The net renal clearance of a drug depends on the extent of glomerular filtration, tubular secretion, and tubular reabsorption. The proximal convoluted tubule is the site for active tubular secretion of organic acids and bases.
Non-ionized forms of weak acids and weak bases undergo passive reabsorption predominately in the distal convoluted tubule.

Tubular secretion is a carrier-mediated active transport process. It facilitates removal of drugs from plasma into the tubular lumen. Four distinct channels can secrete drugs: the anionic system, which secretes acidic drugs; the cationic system, which secretes basic drugs; nucleoside transporters; and the P-glycoprotein transporters. Substrates for these systems are listed in Table 27-2. Increased monitoring (eg, plasma levels and signs and symptoms of toxicity) is warranted if concomitant therapy with a competitor for tubular secretion is unavoidable.

**Table 27-2. Proximal Tubule Transport System Substrates**

<table>
<thead>
<tr>
<th>Anionic system</th>
<th>Cationic system</th>
<th>Nucleoside transporters</th>
<th>P-glycoprotein transporters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide, amantadine, ampicillin, ascorbic acid, aspirin, bumetanide, cephalosporins, ciprofloxacin, ethacrynic acid, folate, furosemide, methotrexate, nafcillin, nonsteroidal anti-inflammatory drugs, penicillin G, probenecid, thiazides, zidovudine</td>
<td>Amiloride, amiodarone, cimetidine, digoxin, diltiazem, morphine, N-acetyl procaainamide, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin, verapamil</td>
<td>Zidovudine, didanosine</td>
<td>Boceprevir, clarithromycin, cyclosporine, digoxin, losartan, procainamide</td>
</tr>
<tr>
<td>Cationic system</td>
<td></td>
<td></td>
<td>P-glycoprotein inducers</td>
</tr>
<tr>
<td>Amiloride, amiodarone, cimetidine, digoxin, diltiazem, morphine, N-acetyl procaainamide, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin, verapamil</td>
<td></td>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>P-glycoprotein inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin, cyclosporine, itraconazole, quinidine, ritonavir, verapamil</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patient Case**

JS is a 45-year-old, 7-kg male admitted to the medical ICU due to altered mental status and respiratory distress. He was intubated and sedated with a midazolam continuous infusion upon arrival at the medical ICU.

Medical history:
- Renal transplant (5 years ago)
- Deep vein thrombosis (twice)
- Diabetes mellitus type II
- Hypercholesterolemia

Home medications:
- Cyclosporine 100 mg orally 2 times per day
- Trimethoprim–sulfamethoxazole single-strength every Monday/Wednesday/Friday
- Prednisone 5 mg orally once a day
- Warfarin 5 mg orally 4 times per day
- Insulin glargine 20 units subcutaneously at bedtime
- Simvastatin 20 mg orally every night at bedtime
During the first week of his hospitalization, the patient was empirically started on broad-spectrum antibiotics (piperacillin–tazobactam and vancomycin) for a presumed ventilator-associated pneumonia. Fluconazole was also started based on a fungal blood culture that grew *Candida albicans*. He had high gastric residual volumes, for which metoclopramide was initiated. On day 5 of his hospitalization, JS developed rapid atrial fibrillation and became hemodynamically unstable. He was loaded and maintained on digoxin. JS also developed hyperactive delirium that was managed with haloperidol.

**Day 1 Laboratory Results**

<table>
<thead>
<tr>
<th>Sodium 138 mEq/L (136-146)</th>
<th>Calcium 9.5 mg/dL (8.5-10.5)</th>
<th>Alanine aminotransferase 30 IU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium 4.5 mEq/L (3.5-5)</td>
<td>Phosphate 3.0 mg/dL (2.5-4.5)</td>
<td>Aspartate aminotransferase 23 IU/L</td>
</tr>
<tr>
<td>Chlorine 99 mEq/L (95-110)</td>
<td>Magnesium 2.0 mg/dL (1.6-2.5)</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate 25 mEq/L (21-31)</td>
<td>White blood cell count 17 × 103</td>
<td></td>
</tr>
<tr>
<td>Serum urea nitrogen 15 mg/dL (5-20)</td>
<td>Hemoglobin 12 g/dL</td>
<td>Cyclosporine level 125 ng/mL</td>
</tr>
<tr>
<td>Serum creatinine 0.9 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum glucose 102 mg/dL (70-99)</td>
<td>Platelets 150 × 103</td>
<td></td>
</tr>
<tr>
<td></td>
<td>International normalized ratio 2.3</td>
<td></td>
</tr>
</tbody>
</table>

**Day 8 inpatient medications:**

- Cyclosporine 100 mg orally 2 times per day (goal concentration = 100-150 ng/mL)
- Trimethoprim–sulfamethoxazole single-strength every Monday/Wednesday/Friday
- Prednisone 5 mg orally every day
- Warfarin 5 mg orally every day
- Insulin glargine 20 U subcutaneously QHS
- Simvastatin 20 mg orally QHS
- Omeprazole 20 mg orally 2 times per day
- Midazolam 5 mg/h continuous infusion
- Fluconazole 400 mg IV every 24 hours
- Piperacillin–tazobactam 4.5 g IV every 6 hours
- Vancomycin 1.25 g IV every 12 hours
- Digoxin 0.25 mg IV every day
- Metoclopramide 10 IV every 6 hours
- Haloperidol 5 mg IV every 6 hours

Electrocardiogram: atrial fibrillation; QTc = 412 seconds
Day 8 Laboratory Results

<table>
<thead>
<tr>
<th>Substance</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>142 mEq/L (136-146)</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>8.5 mg/dL (8.5-10.5)</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>520 IU/L</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>4.7 mEq/L (3.5-5)</td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>3.5 mg/dL (2.5-4.5)</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>293 IU/L</td>
<td></td>
</tr>
<tr>
<td>Chlorine</td>
<td>101 mEq/L (95-110)</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>2.2 mg/dL (1.6-2.5)</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>2,500 IU/L</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>25 mEq/L (21-31)</td>
<td></td>
</tr>
<tr>
<td>White blood cell count</td>
<td>$10 \times 10^3$</td>
<td></td>
</tr>
<tr>
<td>Serum urea nitrogen</td>
<td>22 mg/dL (5-20)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11 g/dL</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine level</td>
<td>350 ng/ml</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.7 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Digoxin level</td>
<td>4.1 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Serum glucose</td>
<td>142 mg/dL (70-99)</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>$120 \times 10^3$</td>
<td></td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

Electrocardiogram: atrial fibrillation; QTc = 569 seconds

Tubular reabsorption is mostly a passive process that occurs in the distal convoluted tubule. The extent of drug reabsorption and subsequent ionization state is influenced by urine flow rate, the drug's lipophilicity, and the pH of the urine. In acidic urine, weakly acidic drugs tend to be reabsorbed whereas weakly basic drugs tend to be eliminated. Conversely, in basic urine, weakly basic drugs tend to be reabsorbed and weakly acidic drugs tend to be eliminated. Drugs that alkalize the urine (eg, acetazolamide, sodium bicarbonate) decrease the renal elimination of quinidine and can result in significant increases in serum quinidine levels. Quinidine levels should be monitored when initiating medications that alter urine pH, changing the dose, or discontinuing them.

TEAM APPROACH TO DRUG–DRUG INTERACTION IDENTIFICATION AND RESOLUTION

Each member of the multidisciplinary team should take responsibility for the prevention and resolution of DDIs. Physicians should justify and review each drug regularly, screen for DDIs with each drug addition or deletion, and integrate information discussed on multidisciplinary rounds. Nurses should assess and monitor drug administration and document any adverse drug events or change in patient status. Pharmacists should review each medication order for DDIs, assist in drug selection or substitution, and monitor for any adverse drug events.

DDI Identification

Several resources can help clinicians identify DDIs. Tertiary references such as Hansten and Horn’s Drug Interaction Analysis and Management, American Hospital Formulary Service, Physician’s Desk Reference, and Lexi-Comp’s Drug Information Handbook are useful for DDI identification. Several electronic databases such as Micromedex and Clinical Pharmacology are useful. Computer decision support systems and computerized physician order entry systems can be designed to alert the prescriber to potential DDIs. Alert fatigue is a problem with these systems, and careful design is important to maximize the value of these electronic systems. Furthermore, not all DDIs are identified by every DDI detection tool. This necessitates that each clinician become familiar with common DDIs in his or her area of practice. Clinical judgment is required when evaluating any information identified on a particular DDI. A clinical pharmacist can assist in the detection and interpretation of DDI data and the development of an alternative pharmacotherapeutic plan.
**Action Steps When a DDI Is Identified**

It is important that the clinical significance of each identified DDI be assessed under the context of the patient involved. The significance, mechanism, and predicted onset should be determined. Whether to continue a drug, discontinue it, or substitute another drug is an important decision that needs to be made on a case-by-case basis. The decision is easy if a clear therapeutic alternative exists; however, this may not always be possible. A clear plan for monitoring and follow-up is essential to maintain therapeutic effectiveness and avoid toxicity (eg, drug levels, laboratory values, electrocardiogram). Good communication among all healthcare providers and the patient is essential.

**Case Discussion**

Upon evaluation of this patient case, the clinician must investigate all possible DDIs before altering his medication regimen. Additional consideration is warranted when medications that have a narrow therapeutic index (ie, cyclosporine, digoxin, warfarin) are involved. The DDIs in this patient case involve several cytochrome P450 enzyme and P-glycoprotein interactions. Furthermore, several interactions occurred as a result of adsorption and distribution alterations and pharmacodynamic additive effects. The extensive list of interactions is provided in Table 27-3.

**Table 27-3. Drug–Drug Interactions From the Patient Case**

<table>
<thead>
<tr>
<th>Object Drug</th>
<th>Interacting Drug</th>
<th>Interaction Mechanism</th>
<th>Clinical Result</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>Cyclosporine</td>
<td>CYP3A4 and P-glycoprotein inhibition</td>
<td>Increased risk of developing myopathy and rhabdomyolysis; CK elevation⁴³,⁴⁴</td>
<td>In the setting of the elevation of CK, it is recommended to immediately discontinue simvastatin.⁴⁵</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Cyclosporine</td>
<td>CYP3A4 inhibition</td>
<td>Increased risk of myopathy</td>
<td>When this combination is necessary, clinicians should increase their monitoring of signs and symptoms of myopathy or rhabdomyolysis; CK may increase, as seen in the patient case. If muscle pain or an increase in CK occurs, simvastatin should be immediately discontinued.⁴⁶,⁴⁷</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Fluconazole</td>
<td>CYP3A4 inhibition</td>
<td>Increase in cyclosporine serum concentrations</td>
<td>The metabolism of cyclosporine is maximally inhibited by day 4 of concurrent administration with fluconazole, and it is recommended to closely monitor cyclosporine levels and renal function and adjust the cyclosporine dose as needed.⁴⁸ There is large interindividual variability in sensitivity to cyclosporine metabolism, so recommendations for empirical dose reductions cannot be made.⁴⁹</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Omeprazole</td>
<td>CYP3A4 inhibition</td>
<td>Reports of a doubling of cyclosporine serum concentrations</td>
<td>Cyclosporine levels should be monitored closely and adjusted as necessary if omeprazole is required.⁵⁰ Consider a histamine-2 receptor antagonist, such as famotidine, as a possible alternative.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Metoclopramide</td>
<td>Gastric motility increase</td>
<td>Decrease in cyclosporine bioavailability⁵¹</td>
<td>Closely monitor cyclosporine levels when metoclopramide is initiated or discontinued.</td>
</tr>
<tr>
<td>Cyclosporine–warfarin</td>
<td>Cyclosporine–warfarin</td>
<td>Unknown</td>
<td>Reduction in cyclosporine concentration; increase in prothrombin activity</td>
<td>To account for this interaction, patients who are receiving cyclosporine and warfarin should undergo close monitoring of serum cyclosporine levels and INRs to maintain efficacy of the medications.⁵²,⁵³</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Cyclosporine; omeprazole</td>
<td>P-glycoprotein inhibition</td>
<td>Increase in digoxin serum levels due to the down-modulation of the efflux of digoxin⁵¹,⁵²</td>
<td>When digoxin is given in combination with cyclosporine, digoxin levels should be closely monitored 3 to 5 days after discontinuing or adjusting the dose of cyclosporine.</td>
</tr>
<tr>
<td>Object Drug</td>
<td>Interacting Drug</td>
<td>Interaction Mechanism</td>
<td>Clinical Result</td>
<td>Management</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------</td>
<td>-----------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Metoclopramide</td>
<td>Gastric motility increase$^{54}$</td>
<td>Low serum digoxin concentration</td>
<td>Increased monitoring and dose adjustment of digoxin are necessary when metoclopramide is initiated or discontinued. When metoclopramide is withdrawn, digoxin levels should return to normal within 10 days.$^{54}$</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Fluconazole</td>
<td>Inhibitor of 2C9, 2C19, and 3A4</td>
<td>Decrease in warfarin metabolism, which can result in a 2-fold increase in prothrombin time$^{55-57}$</td>
<td>The INR of patients should be closely monitored when initiating, discontinuing, or changing the doses of fluconazole.$^{59}$</td>
</tr>
<tr>
<td>Warfarin−simvastatin</td>
<td>Warfarin−simvastatin</td>
<td>Competition for the CYP3A4 enzyme</td>
<td>Has been associated with an increase in INR and rhabdomyolysis$^{59-61}$</td>
<td>Patients should be monitored for signs and symptoms of rhabdomyolysis and CK elevation. Due to the competition for the CYP3A4 enzyme, the patient’s INR should be closely monitored.$^{62}$</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vancomycin; piperacillin−tazobactam</td>
<td>Reduction of generation of vitamin K by intestinal microflora$^{63}$</td>
<td>Excessive anticoagulation, which can result in overtanticoagulation and bleeding</td>
<td>The patient should be subject to increased monitoring of INR, with adjustment of the warfarin dose as necessary.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Fluconazole</td>
<td>CYP3A4 inhibition</td>
<td>Increase in maximal concentration and area under the concentration−time curve of midazolam</td>
<td>If midazolam is being administered to a patient who is concurrently receiving fluconazole, a lower initial dose of midazolam should be considered. Patients should be monitored closely, and midazolam should be titrated to achieve the desired level of sedation. Midazolam toxicity, such as prolonged sedation, should also be considered in the presence of this drug interaction.$^{54}$</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Fluconazole</td>
<td>CYP3A4 inhibition</td>
<td>Inhibition in metabolism of the glucocorticoid, resulting in higher plasma concentrations</td>
<td>When fluconazole is withdrawn, the metabolism of the steroid is increased, which may result in the precipitation of an Addisonian crisis.$^{55}$ Monitoring for signs of adrenal insufficiency should increase when the fluconazole is discontinued.</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Metoclopramide</td>
<td>Pharmacodynamic interaction</td>
<td>Contraindicated combination that may result in the development of EPS or NMS</td>
<td>If therapy is required, patients should be closely monitored for signs of EPS or NMS. Metoclopramide should be discontinued if any signs or symptoms develop.$^{66}$</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Trimethoprim−sulfamethoxazole</td>
<td>Pharmacodynamic interactions</td>
<td>Can result in QT-interval prolongation that may lead to torsades de pointes$^{67-69}$</td>
<td>These combinations have resulted in QT-interval prolongation that may lead to torsades de pointes. If these combinations cannot be avoided, patients should receive a baseline electrocardiogram, the manufacturer’s dosing recommendations should not be exceeded, and clinicians should monitor for the addition of other medications that could prolong the QT interval.$^{70}$</td>
</tr>
</tbody>
</table>

Abbreviations: CK, creatine kinase; CYP3A4, cytochrome P450 3A4; EPS, extrapyramidal symptoms; INR, international normalized ratio; NMS, neuroleptic malignant syndrome.
A Focus on One of the DDIs

P-glycoproteins are drug transporters that are responsible for the efflux of drugs outside of cells. They transport a wide array of compounds, including many commonly used medications (e.g., digoxin).\textsuperscript{32,33} P-glycoprotein transporters are found in the gastrointestinal tract, liver, kidney, and brain and are an essential part of blood–tissue and blood–brain barriers.\textsuperscript{34-36} An inducer (e.g., rifampin) or an inhibitor (e.g., cyclosporine, omeprazole) of P-glycoproteins can alter the pharmacokinetic parameters of P-glycoprotein substrates and lead to toxicity or loss of efficacy.\textsuperscript{37-38}

Digoxin was involved in several interactions in this patient case. Digoxin is not metabolized by the cytochrome P450 enzyme system; it is a substrate of intestinal and renal P-glycoproteins.\textsuperscript{38,39} Digoxin is considered the gold standard and the most relevant probe for studying clinical P-glycoprotein DDIs.\textsuperscript{40} In the patient case, both cyclosporine and omeprazole impaired digoxin clearance, resulting in increased digoxin serum levels.\textsuperscript{41,42} When digoxin is given in combination with cyclosporine, digoxin levels should be closely monitored 3 to 5 days after discontinuing or adjusting the dose of cyclosporine.\textsuperscript{32}

SUMMARY

Critically ill patients frequently receive complex drug regimens that can predispose them to significant DDIs. Knowledge of the different mechanisms is paramount to either preemptively identify a possible DDI or to address an interaction in a patient’s drug regimen. A multidisciplinary approach is ideal in developing a pharmacotherapeutic regimen designed to optimize patient outcomes and minimize any potential DDIs.

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