Common drug interactions leading to adverse drug events in the intensive care unit: Management and pharmacokinetic considerations

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Critically ill patients are predisposed to drug interactions because of the complexity of the drug regimens they receive in the intensive care setting. Drugs may affect the absorption, distribution, metabolism, and/or elimination of an object drug and consequently alter the intended pharmacologic response and potentially lead to an adverse event. Certain disease states that afflict critically ill patients may also amplify an intended pharmacologic response and potentially result in an unintended effect. A team approach is important to identify, prevent, and address drug interactions in the intensive care setting and optimize patient outcomes. (Crit Care Med 2010; 38[Suppl.]:S126–S135)

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Critically ill patients frequently receive multidrug regimens with the goal of providing pharmacotherapeutic support and cure of a medical condition. These patients are at risk for drug interactions because of the complexity of this polypharmacy, as well as the frequent presence of altered organ function. Furthermore, elderly, critically ill patients are particularly vulnerable to adverse events from drug interactions because of the additional presence of multiple comorbid disease states. Published data that delineate the prevalence of drug–drug interactions (DDIs) and outcomes in intensive care unit (ICU) patients are scarce. A single-center, prospective, observational study of patients admitted into a medical ICU found that 7.5% (21 of 281 patients) were admitted for an adverse drug-related event; approximately 50% of these events were related to a DDI (1). A retrospective, cross-sectional analysis showed that 6.3% (25 of 397) of elderly, veteran affairs, noncritically ill patients had a drug–drug interaction with a detectable adverse outcome (2). Drug interactions may be either 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 pharmacologic response of another agent in an additive, synergistic, or antagonistic way. This review focuses on DDIs and drug–laboratory interactions that are pharmacokinetic in nature.

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DDIs

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

DDIs and absorption

Enteral drug absorption and net bioavailability are complex processes that are affected by many variables, including pharmaceutical dosage form utilized, gastric pH, gastric motility, extent of gastrointestinal drug metabolism, presence of a binder or chelator, and disruption of intestinal microflora. The small intestine is the primary site for drug absorption, because few drugs are absorbed in the stomach (e.g., aspirin). The pharmaceutical dosage form utilized may affect the rate of disintegration and dissolution with greater dissolution times ranked as follows: tablets > capsules > suspensions > liquids.

Gastric pH

Weak acids and weak bases transverse intestinal membranes and reach the bloodstream when they exist in an unionized state (i.e., weak acids in an acidic environment and weak bases in a basic environment). Common utilized intensive care drugs (e.g., H_2-receptor antagonists, proton pump inhibitors, antacids) may change the gastrointestinal pH and alter the rate and extend of an object drug's absorption. When the gastrointestinal pH is increased, the absorption of weak acids (e.g., aspirin, diazepam, furosemide, itraconazole) may be impaired, whereas the absorption of weak bases (e.g., chlorpromazine, indomethacin, tetracycline) may be enhanced (3). This type of interaction may be significant for narrow-spectrum drugs or agents when outcomes may be linked to specific drug concentrations (e.g., itraconazole, dipyridamole). When itraconazole capsules are utilized in the setting of elevated gastrointestinal pH, it is recommended that itraconazole be administered with food or cola beverages to increase the acidity of the stomach (4–6). Dipyridamole requires a pH $\leq$4 for optimal absorption and is clearly affected by concomitant proton pump inhibitor pharmacotherapy

(7). The combination of aspirin/extended-release dipyridamole (Aggrenox, Boehringer Ingelheim, Ridgefield, CT) is preferred in this setting, because it is formulated with tartaric acid to create an acidic environment for maximal dipyridamole absorption (8). An increase in stomach pH can also interfere with the location of dissolution of enteric-coated medications (e.g., aspirin, bisacodyl). These medications may cause stomach irritation in this altered environment. To minimize the impact of this drug interaction, enteric-coated medications should be administered 2 hrs before or after the administration of a medication that elevates stomach pH (9, 10).

Gastric motility

Critically ill patients frequently have alterations in gastric motility and emptying. Impaired gastric emptying was demonstrated in a medical/surgical population through the use of an acetaminophen absorption model. Additional variables that alter gastric emptying in this ICU population were demonstrated to include age, gender, and the use of opioids for sedation and analgesia (11). The rate, but usually not the extent, of bioavailability is affected by alterations in gastric motility. Medications that increase gastric motility include metoclopramide, polyethylene glycol electrolyte solution, cisapride, and erythromycin (9). A 30% increase in cyclosporine bioavailability is observed when coadministered with metoclopramide (12). When this combination is necessary, monitoring of cyclosporine levels and appropriate cyclosporine dosage adjustment should be made to prevent toxicity (13). Anticholinergic medications (e.g., diphenhydramine, benztropine, hyoscyamine) and narcotics can decrease gastric motility and can result in an effect opposite of agents that increase gastric motility, such as metoclopramide (9).

Extent of gastrointestinal drug metabolism

Significant presystemic drug metabolism can occur in the gastrointestinal tract, because there are a number of metabolizing enzymes along the small intestine wall that can biotransform many compounds. Cytochrome P-450 3A4 (CYP3A4) is the predominant enzyme; however, glucuronidation, sulfation, and monoamine oxidation biotransformation can also occur in the gastrointestinal tract. Cyclosporine is a calcineurin inhibitor that is extensively metabolized in the liver by CYP3A and, to a lesser extent, in the intestine (14). However, it has been demonstrated that when administered in combination with rifampin, there is notable induction of the CYP gut enzymes, resulting in a 63% decrease in oral bioavailability of cyclosporine (15, 16). Although not a common beverage in the ICU setting, grapefruit juice is well-known to impair the gastrointestinal CYP3A4 metabolism of a number of agents, including amiodarone, carbamazepine, cisapride, cyclosporine, felodipine, nicardipine, and nifedipine. In one study, concomitant administration of grapefruit juice with amiodarone resulted in an 84% increase in peak amiodarone concentrations (17). In another study, concomitant grapefruit juice increased the area under the curve of felodipine by 200% and nifedipine by 34% compared with the administration of water (18).

Presence of a binder or chelator

Commonly utilized enteral agents in the ICU setting may be able to alter the bioavailability of an object drug if administered concomitantly with a drug that has binding or chelation capabilities. Phenytoin absorption has been demonstrated to be reduced when coadministered with enteral tube feedings and antacids (19, 20). The package insert recommends that phenytoin be fluoroquinolone-form (e.g., ciprofloxacin, levofloxacin) complexes with metal ions (e.g., iron), antacids (e.g., aluminum hydroxide), and calcium-containing products. Concomitant gastrointestinal administration can decrease the bioavailability of the fluoroquinolone and may result in therapeutic failure (21, 22). It was demonstrated that when ciprofloxacin is administered with calcium carbonate or aluminum hydroxide, the relative bioavailability of ciprofloxacin is 60% and 15%, respectively (21). It is recommended that the fluoroquinolone be ingested at least 2 hrs before or 6 hrs after the administration of the binding or chelating drug to minimize this interaction (23). Cholestyramine, a bile acid sequestrant, can also reduce the bioavailability of several medications if administered concomitantly. Digoxin, levothyroxine, and warfarin are among several drugs that are bound by cholestyramine and, if coadministered, can result in decreased systemic absorption. The recommended management is to separate the administration times of the affected medications by at least 2 hrs before and 4 hrs after the administration of cholestyramine (24–26).

Disruption of intestinal microflora

Commensal intestinal microorganisms may be involved in the presystemic metabolism of certain medications. The alteration of bacterial flora by antimicrobials has been shown to affect the absorption of medications that are either absorbed incompletely in the small intestine or undergo enterohepatic circulation. One specific example is the use of oral contraceptives with antimicrobials. The alteration of intestinal flora results in a reduction in the circulation of active estrogen metabolites, which could lead to the loss of effectiveness of the oral contraceptive (27). The concomitant administration of warfarin and antimicrobials can result in excessive anticoagulation. The antimicrobial may reduce the synthesis of endogenous vitamin K by intestinal microflora. An elevated international normalized ratio (INR) and potential bleeding may occur if the warfarin dose is not adjusted to accommodate for this altered vitamin K production. INR monitoring should be increased with appropriate warfarin dosing adjustments while administering concomitant pharmacotherapy (28). Monitoring should continue after the antimicrobial is discontinued and until the gastrointestinal flora is believed to be restored. The alteration of gastrointestinal flora that metabolizes digoxin has also been shown to be affected by antimicrobials that have activity against *Eubacterium lentum* (a Gram-positive anaerobic bacillus). The coadministration of digoxin with macrolides has resulted in an increase in digoxin bioavailability with resultant digoxin toxicity (29, 30). Digoxin levels should be monitored while patients are concurrently using macrolide pharmacotherapy. The risk of this interaction may be reduced by using digoxin capsules (Lanoxicaps), because the extent and probably the rate of absorption are increased with this dosage form (31).

Intestinal p-glycoprotein activation

P-glycoproteins are efflux pumps that are located on the luminal surface of the intestinal wall. They are capable of ex-

truding drug from the circulation back into the lumen of the intestine. These pumps work in concert with the CYP450 system and can be either inhibited or activated. Digoxin is a substrate of both renal and intestinal P-glycoproteins, and clearance can be affected by inducers or inhibitors of this system. Rifampin is a potent inducer of cytochrome P-450 and P-glycoproteins and can decrease the plasma concentration of concomitant enterally administered digoxin to a greater extent than intravenous digoxin (32). Concomitant administration of digoxin with known P-glycoprotein inhibitors (e.g., erythromycin, itraconazole, cyclosporine) can result in an increase in serum digoxin levels and potential toxicity, thus necessitating extra pharmacovigilance (33–36). Another clinically significant interaction can occur between linezolid and rifampin. The serum concentrations of linezolid, which is not metabolized by the cytochrome P-450 enzyme system, has been show to be decreased when used in combination with rifampin (37, 38). It is postulated that this interaction may be attributable to the induction of intestinal P-glycoprotein by rifampin (37, 38). Concomitant pharmacotherapy should be avoided until we have more data to better delineate this potentially significant interaction.

DDIs and distribution: displacement from a carrier protein

Plasma proteins act as a carrier for many drugs, transporting them either to a site of action or to an organ for elimination. The binding of drugs to these plasma proteins depends on the physiochemical properties of each drug or, more specifically, the drug's electrical charge at physiologic pH. Several circulating plasma proteins exist; however, albumin and alpha$_1$-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. Albumin is the major carrier protein for acidic drugs (e.g., warfarin), because it is negatively charged at a pH of 7.4. Concentrations of albumin may decrease in the setting of critical illness, acute renal failure, nephrotic syndrome, and cirrhosis. If two or more acidic drugs compete for binding sites, then the drug with the higher affinity will bind and displace the other agent. This will increase the free fraction and potentially the pharmacologic effects of the displaced drug. However, this additional drug effect may be temporary and self-correcting, because the volume of distribution and the rate of elimination of the displaced drug are increased.

The albumin binding of phenytoin can be decreased with an increase in free fraction when administered concomitantly with an nonsteroidal anti-inflammatory drug (39). The combination of phenytoin with ceftriaxone, nafcillin, or sulfamethoxazole can also result in an increase in free phenytoin levels because of displacement (40). Management of these interactions includes vigilant monitoring of total or free phenytoin concentrations and signs and symptoms of phenytoin toxicity. Warfarin can also be displaced by nonsteroidal anti-inflammatory drugs from albumin, with a resultant increase in free warfarin concentrations (41, 42). However, the clinical significance of this displacement is questionable. Clinicians should consider avoiding this combination, not only because of the potential for displacement but also because of the antiplatelet activity and increased bleeding risk associated with nonsteroidal anti-inflammatory drugs (43).

Alpha$_1$-acid glycoprotein (AAG) is the major carrier protein for basic drugs (e.g., amitriptyline, lidocaine, propranolol). AAG is an acute-phase plasma protein whose concentrations increase in critical illness. As a result, the free fraction and thus the pharmacologic effect of drugs bound to AAG may decrease under periods of acute stress. An example of this interaction is the decrease in unbound fraction of lidocaine as the concentrations of AAG increase in trauma patients (44). To counter the decrease in free fraction, higher doses and total concentration of lidocaine have been needed to achieve an adequate pharmacologic effect (44). AAG has also been shown to increase during an acute myocardial infarction, with a resultant increase in lidocaine binding (45, 46). Monitoring for clinical response and possibly free lidocaine concentrations (if available) are warranted when increased AAG binding is suspected.

DDIs and hepatic clearance

The liver is the most important drug-metabolizing organ, although it is generally recognized that some drug biotransformation and clearance may take place in the gastrointestinal tract, kidney, lung, integument, and blood. Drug metabolism is divided into phase I (oxidation, hydrolysis, and reduction [CYP450 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. The cytochrome P-450 isoenzymes are a group of heme-containing proteins that are embedded in the lipid membrane of the endoplasmic reticulum of hepatocytes (47). The three-tiered classification widely utilized today was first suggested by Nebert et al in 1987 (47). The name was derived from the spectral absorbance maximally produced near 450 nm when carbon monoxide binds to the enzyme at its reduced state (48). Drug-metabolizing enzymes are grouped into families and subfamilies. Enzymes with 40% genetic common identity are grouped into the same family with an Arabic number designation (e.g., CYP1, CYP2, and CYP3). Enzymes with 55% genetic common identity are grouped into the same subfamily (e.g., CYP1A, CYP2D, CYP3A). Last, individual enzymes with 97% genetic common identity are named with another Arabic number (e.g., CYP1A2, CYP2D6, CYP3A4). There are several cytochrome P-450 enzymes with different xenobiotic specificity. Appendix A lists CYP450 isoforms and some common ICU medication substrates. Enzyme induction generally affects phase I enzymes and results in the production of new metabolizing enzyme.

CYP3A4 DDIs

DDIs involving CYP3A4 are particularly concerning, because this enzyme system can metabolize up to 50% of utilized medications (49). Protease inhibitors (e.g., ritonavir), macrolides (e.g., erythromycin), and azoles (e.g., fluconazole, posaconazole, voriconazole) are CYP3A4 inhibitors, and serious drug interactions may develop in the ICU if coadministered with a CYP3A4 substrate with a narrow therapeutic index (e.g., midazolam, HMG-CoA reductase inhibitors, cyclosporine, tacrolimus, verapamil, diltiazem, voriconazole, amiodarone, cisapride) (6, 49–51). Transplant recipient patients commonly receive concomitant azole antifungal agents with their maintenance immunosuppressant agent (e.g.,

cyclosporine, sirolimus, tacrolimus). When itraconazole is combined with cyclosporine or tacrolimus, the interaction results in a two-fold and six-fold increase in cyclosporine and tacrolimus levels, respectively (14, 52–53). Conversely, enzyme induction with antiepileptic medications (e.g., phenytoin, phenobarbital, carbamazepine) can decrease plasma tacrolimus or cyclosporine concentrations, thus necessitating plasma level monitoring (54). Midazolam, a commonly utilized sedative in the ICU, can also be involved in CYP3A4 drug interactions because it is a substrate for this enzyme system. Macrolides or azoles are known to prolong sedation when administered with midazolam. Decreasing the dose and daily midazolam infusion interruption may help prevent accumulation and avoid prolonged sedation, an important end point to minimize the number of ventilator days (55, 56).

CYP2C9/2C19 DDIs

Warfarin is metabolized by several CYP enzymes, including CYP3A4, CYP1A2, CYP2C9, and CYP2C19. Medications that inhibit or induce these enzymes may produce a significant change in warfarin plasma concentrations and pharmacologic effect. Trimethoprim/sulfamethoxazole, fluconazole, metronidazole, and amiodarone inhibit CYP2C9 and can increase the effect of warfarin. Rifampin is an inducer of CYP2C9 and can result in a decreased warfarin effect. A patient's INR should be carefully monitored when warfarin is combined with a CYP2C9 inhibitor or inducer to maintain a therapeutic INR (57). A common example of a significant interaction is the combination of warfarin and amiodarone. The anticoagulant effects of warfarin are dramatically increased because of impaired metabolism and clearance. Each clinician should anticipate a warfarin dose reduction (e.g., 25%–50%) when amiodarone is initiated with concurrent warfarin therapy. In the circumstance of amiodarone discontinuation, increased monitoring of a patient's INR should also occur to ensure that there is not a loss of therapeutic levels (58).

Effects of genetic polymorphisms

Warfarin is administered as a racemic mixture with an (R)-enantiomer and (S)-enantiomer. The (S)-enantiomer is three to five times more potent than the (R)-enantiomer. Genetic polymorphism of the CYP2C9 enzyme may affect the metabolism and pharmacologic activity of the (S)-enantiomer of warfarin (60, 61). Genetic testing is available to assist in the identification of allele variants, although the clinical utility of these tests is in question. CYP2D6 and CYP1A2 genetic polymorphisms may also play a role in the pharmacologic activity of commonly utilized medications in the ICU. High serum concentrations and extrapyramidal symptoms associated with haloperidol, a CYP2D6 substrate, have been identified in slow metabolizers (61). Beta-blockers, such as metoprolol, carvedilol, and propranolol, are substrates of CYP2D6. The blood pressure and heart rate-lowering effects of these agents can be affected by genetic variations of the CYP2D6 enzyme (62). Theophylline is a substrate of CYP1A2 and can be affected by genetic polymorphisms. Therapeutic failure and toxicity have been reported in patients who are rapid and poor metabolizers, respectively (63).

DDI time of onset

Predicting the time of onset for a particular DDI may be a challenge, because numerous factors can affect evolution and eventual manifestation of a particular DDI. This 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 taken into consideration. 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 peaks after the steady-state of any precipitant drug. At this point, 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 between 53 and 140 hrs) and rifampin (half-life between 3 and 4 hrs) are two well-known hepatic enzyme inducers. If each is added separately to a regimen of warfarin, then it may take approximately 7 to 14 days for phenobarbital to reach steady-state compared to 1 to 2 days for rifampin, with a 10-day to 14-day onset for a phenobarbital-warfarin DDI vs. a 2-day 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 it takes time for the inducing drug to be cleared and time for the enzymatic activity of the liver to abate. Thus, any effect of phenobarbital on warfarin may take more than 14 to 21 days to abate vs. 5 to 7 days for rifampin-warfarin.

Enzyme inhibition is usually competitive, because 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 timeframe. Cimetidine (half-life approximately 2 hrs) and amiodarone (half-life between 50 and 150 days) are two well-known enzyme inhibitors. If each is added separately to a regimen of warfarin, then it may take approximately 1 day to reach steady-state with cimetidine as compared to many weeks with amiodarone. The time course of onset for a cimetidine-warfarin drug interaction may be within 1 to 2 days, whereas the effects of an amiodarone-warfarin drug interaction may take 2 or more months to be fully expressed. To make matters more complicated, the dose of the precipitant drug complicates the predictive process whether the object drug has a narrow-therapeutic index, whether the clearance of the object or precipitant drug follows zero-order pharmacokinetics (i.e., phenytoin), whether there is the presence of other enzyme inducers or enzyme inhibitors, and whether there is the presence of any hepatic dysfunction or altered genotypic phenotype (e.g., CYP2C19 deficiency in patients from Asian descent).

DDIs and renal elimination

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

Glomerular filtration

Glomerular filtration is a passive process as a drug diffuses across the glomer-

ular capillary membrane into Bowmann's capsule and the proximal convoluted tubule. Filtration is impeded by a molecular weight >60 daltons, negative charge of the glomerular membrane, and if a drug is bound to a carrier protein as it reaches the glomerular membrane. Agents that increase cardiac output (e.g., inotropes) can have a direct effect on the clearance of renally eliminated drugs (e.g., aminoglycosides). The clearance of these medications is flow-dependent and affected by an increase in renal blood flow and filtration, respectively (64). In response to this possible alteration in drug clearance, the clinician should obtain levels of the aminoglycoside to ensure adequate plasma concentrations (65).

Tubular secretion

Tubular secretion is a carrier-mediated active transport process. It facilitates removal of drugs from plasma into the tubular lumen. There are four distinct channels that can secrete drugs: anionic system that secretes acidic drugs; cationic system that secretes basic drugs; nucleoside transporters; and the P-glycoprotein transporters. Substrates for these systems are listed in Appendix B. The elimination of methotrexate through glomerular filtration and proximal tubule anionic secretion can be affected by weak organic acids, including ascorbic acid, penicillin, and nonsteroidal anti-inflammatory drugs. Delayed methotrexate excretion resulting from this interaction has been reported to cause serious toxicity (66, 67). It is prudent to avoid the administration of nonsteroidal anti-inflammatory drugs within 10 days of high-dose methotrexate pharmacotherapy. Increased monitoring (e.g., plasma levels and signs/symptoms of toxicity) is warranted if concomitant therapy with a competitor for tubular secretion is unavoidable (68). Competition for active tubular cationic secretion can occur between procainamide and cimetidine, resulting in elevated procainamide levels (69). Increased monitoring of procainamide levels and dose reductions are necessary to prevent toxicity. Digoxin toxicity has resulted from competition of tubular cationic secretion when given with quinidine. A 50% decrease is digoxin dose is warranted when quinidine is added to a patient's digoxin regimen (70, 71). The renal tubular anionic secretion of penicillins is affected by a concomitant administration with probenecid. The competition for tubular secretion results in increased and prolonged blood levels of these penicillins, which sometimes is utilized for therapeutic reasons (72).

Tubular resorption

Tubular resorption is mostly a passive process that occurs in the distal convoluted tubule. The extent of drug reabsorption is influenced by urine flow rate, the drug's lipophilicity, and the pH of the urine with subsequent ionization rate of the drug. In acidic urine, weakly acidic drugs tend to be reabsorbed whereas weakly basic drugs tend to be eliminated. Conversely, weakly basic drugs tend to be reabsorbed and weakly acidic drugs tend to be eliminated in basic urine.

Drugs that alkalinize the urine (e.g., acetazolamide, sodium bicarbonate) decrease the renal elimination of quinidine and can result in significant increases in serum quinidine levels (73, 74). Quinidine levels should be monitored when initiating, changing the dose, or discontinuing medications that alter urine pH.

Specific disease-state drug interactions

Critically ill patients are at an increased risk for the development of adverse effects of a drug interaction because of polypharmacy, impaired organ function, and altered drug disposition and/or protein binding (75, 76). The importance of patient-specific characteristics with specific disease states should also be considered when assessing the significance of a drug interaction. The prevalence may vary because of interpatient variability based on multiple patient-specific factors, such as smoking status, alcohol consumption, gender, age, body habitus, and genetics (9). One study that evaluated the significance of drug interactions in the cardiac and cardiothoracic ICU observed that drug interactions occurred frequently in the ICU, with 287.5 noted drug interactions per 100 patient days (77).

Sepsis, surgery, trauma

Critical illness is complicated by infections and stress-related events (e.g., surgery, trauma) that result in increased release of cytokines. Studies have illustrated that the CYP450 metabolism of medications may be inhibited by the production of interleukin-6 and tumor necrosis factor-α and can predispose the critically ill patient to DDIs (78, 79). Theophylline is one example of a medication that has caused toxicity in patients who had critical illness when they previously had been stabilized on a regimen (80). A prolonged elimination rate of theophylline has also been reported in patients acutely infected with a respiratory virus (81).

Not only can the increased release of cytokines affect the metabolism of medications but also changes in hepatic blood flow also may later effect drug metabolism by changes in the delivery rate of a drug to the hepatocyte (10). Sepsis is one particular manifestation in the critically ill that can lead to changes in hepatic blood flow (82). For example, during hyperdynamic sepsis and an increase in cardiac output, hepatic blood flow is increased, which increases the delivery rate of the drug to the hepatocytes. The opposite is true when there is a decrease in cardiac output during late sepsis, which would result in a decrease in hepatic blood flow and a decrease of the clearance of medications (82). Recently, one study evaluated the effects of sepsis on the CYP450 enzyme system. They utilized antipyrine clearance as the gold standard to measure the activity of CYP450 drug metabolism. The authors observed that septic patients had a two-fold reduction in antipyrine clearance compared to controls and that antipyrine clearance was inversely related to interleukin-6, nitrate, and nitrite plasma levels (83).

Prolonged QT-interval syndromes

Torsades de pointes is a life-threatening arrhythmia that can occur in the setting of electrocardiographic prolongation of the QT interval. Medications known to prolong the QT interval include class IA and III antiarrhythmic agents, macrolides, fluoroquinolones, azole antifungals, prokinetic agents, antipsychotics, and certain nonsedating antihistamines (84). These medications cause QT-interval prolongation by blocking the human ether-a-go-go–related gene potassium channels in the cardiac muscle cells and block potassium currents (85, 86). In one evaluation of noncardiac medications, 39% of QT-interval prolongation involved the combination of more than one QT-interval prolonging medication and 38% involve a QT-interval prolonging medication with a drug that inhibited its metabolism (87). The combination of erythromycin with a strong CYP3A4 inhibitor

was shown in one study to increase the risk of sudden cardiac death up to five times as compared to patients not using these medications (88). Additive QT-interval prolongation may result when fluoroquinolone therapy is used concomitantly with either sotalol or amiodarone (89–92). QT-interval prolongation may also occur if azole antifungal agents (e.g., fluconazole, voriconazole) are utilized concomitantly with class III antiarrhythmics (6). The risk and benefit must be weighed when a decision is made to use these combinations. Patients should be evaluated for the risk of an arrhythmia developing and precautions should be taken to minimize the risk if interacting medications are to be continued. Certain precautions can include not exceeding the manufacturer's recommended doses, obtaining a baseline electrocardiogram before therapy initiation, and remaining vigilant in the prevention of additional drug interactions that could produce additive QT-interval prolongation. Clinicians should also consider therapeutic alternatives in patients who are at high risk for an arrhythmia, such as the presence of a dilated cardiomyopathy, hypothyroidism, hypokalemia, hypomagnesemia, hypocalcemia, and anorexia nervosa (93). Please see discussion of management of QT-interval prolongation syndromes elsewhere in this issue.

Coagulopathies

Patients in the ICU are at increased risk for bleeding events because of a multitude of factors, such as trauma, surgical procedures, renal failure, liver failure, and/or stress ulceration (94–96). The critical care clinician should familiarize themselves with common drug interactions that would increase the risk of bleeding in patients on concomitant antiplatelet or anticoagulant pharmacotherapy. For example, selective serotonin reuptake inhibitors, such as paroxetine and fluoxetine, may enhance the antiplatelet effects of aspirin. This is thought to be caused by the blockade of platelet serotonin reuptake leading to platelet serotonin depletion and impaired platelet aggregation (97). Because of the potential platelet dysfunction associated with this drug combination, discontinuation of the selective serotonin reuptake inhibitor is recommended in patients admitted to the ICU for gastrointestinal bleeds. The risk for an upper gastrointestinal bleed may be reduced when a proton pump inhibitor (PPI) is used concomitantly (98). Another potentially problematic drug interaction is the combination of a PPI with clopidogrel. Clopidogrel is metabolized by CYP2C19 to an active metabolite. PPIs are substrates but also inhibitors of this enzyme system. Thus, PPIs may reduce the conversion of clopidogrel to its active metabolite and reduce the intended therapeutic response (99). Retrospective studies suggest that the combination of clopidogrel with a PPI may increase the chance of an adverse cardiac outcome in patients with an acute coronary syndrome (100, 101). In a case-control study, it was observed that the concomitant use of clopidogrel with a PPI increased the risk of re-hospitalization or death from acute coronary syndrome (101). Clinicians should avoid the combination unless a clear indication for both medications exists (102). A histamine-2 receptor antagonist should be utilized for acid reduction in this patient population (103). If the use of a PPI is warranted, then pantoprazole may be the agent of choice because it has been demonstrated that pantoprazole has a lower affinity for the CY2C19 enzyme than the other PPIs and may have less of a propensity to decrease the effectiveness of clopidogrel (104).

Infection

Patients in the ICU are at higher risk for infections than patients in general medicine wards and receive anti-infective agents that are known to cause drug interactions (e.g., azole antifungals, macrolides, fluoroquinolones) (105, 106). The area under the curve and maximum concentration of sirolimus, cyclosporine, and tacrolimus may increase with resultant toxicity when combined with an azole antifungal agent; plasma levels should be closely monitored with these combinations (107, 108). Antifungal agent inhibition (particularly voriconazole) of CYP3A4 may increase the area under the curve of fentanyl, haloperidol and midazolam, possibly resulting in an increased therapeutic effect (109–112). The maximum concentration of midazolam is increased by 3.8-fold when combined with voriconazole and can result in longer arousal times in patients receiving this combination (112). Lorazepam is a logical alterative to midazolam because it does not inhibit the CYP450 enzyme system.

Cases of serotonin syndrome have been reported when linezolid, a weak monoamine oxidase inhibitor, was combined with an selective serotonin reuptake inhibitor (113). It is not clear if linezolid will affect the clearance of catecholamines used in the ICU. Appropriate monitoring is warranted if these combinations are utilized in critically ill patients.

Drug–laboratory interactions

More than 40,000 effects of drugs on laboratory tests have been reported in the literature (114). The interference of laboratory tests by drugs can occur through several mechanisms. The interference may be a result of a pharmacologic or toxic effect or a chemical interference with the testing media or process (115).

A pharmacologic or toxic interference would be considered a change in a laboratory value because of the action of the drug in the body. An example of a pharmacologic effect would be electrolyte abnormalities, such as hypokalemia, resulting from furosemide administration (116). A chemical or analytical interference occurs when the true value of the laboratory test is not measured accurately because of a problem with *in vitro* testing (117). Causes of chemical interferences include a direct interference with a chemical reaction used in the testing process by the interfering drug or by a drug mimicking the substance that is the object of the laboratory test. False results may be reported when a medication or its metabolite share similar properties with the substance that is being tested (115). If a known drug–laboratory interaction can occur between a medication that a patient is using and a needed laboratory test, then the patient should be advised not to use the medication, if possible, for 72 hrs before the test (116).

Several drug–laboratory interactions are of particular importance to the ICU clinician because of the frequent use of the offending medication or laboratory parameter that is affected. Aspirin has been demonstrated to affect several common laboratory tests. Significant increases in laboratory values were found for chloride and a decrease was demonstrated for total protein, calcium, total cholesterol, uric acid, bilirubin, and thyroxine (118). Chloride is also falsely elevated by carbamazepine, cefoxitin, bromide, and fluoride salts (119, 120). Serum creatinine measurements can be falsely increased by cephalosporins and falsely decreased by ascorbic acid and acetylcysteine when the Jaffe method is utilized to determine plasma creatinine con-

centrations (121–125). Argatroban can falsely elevate the INR value by causing a dose-dependent false decrease in fibrinogen and factor X levels (126, 127). Daptomycin is another medication that has been observed to falsely increase INR values and prolong the prothrombin time (128).

Clinician awareness that laboratory results may be altered by pharmaceutical agents is an important step in the accurate assessment of laboratory data. The effects of drugs on laboratory tests have been published in extensive reviews and should be utilized as a reference when needed (115, 120, 129–132).

Team approach to DDI identification and resolution

Each member of the multidisciplinary team can take responsibility for the prevention and resolution of DDIs (132). 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 process

Several resources exist that can assist in the identification of 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. Additionally, 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 their 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 can assist in 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 in the context of the patient involved. The significance, mechanism, and predicted onset should be determined. Whether to continue, discontinue, 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 (e.g., drug levels, laboratory values, electrocardiography). Good communication among all healthcare providers and the patient is essential.

Conclusion

Critically ill patients frequently receive multidrug regimens that can predispose them to significant DDIs. Preliminary data suggest that these events may adversely affect patient outcomes. 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 would be ideal in developing a pharmacotherapeutic regimen designed to optimize patient outcomes and minimize any potential DDIs.

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Appendix A. Select drug substrates/inducers/inhibitors

Isoform	Substrate	Inducer	Inhibitor
CYP1A2	Theophylline, lidocaine, R-warfarin	Omeprazole, phenobarbital	Cimetidine, ciprofloxacin, diltiazem, erythromycin
CYP2B6	Propofol	Phenobarbital	
CYP2C9	Phenytoin, voriconazole, S-warfarin	Phenobarbital, phenytoin, rifampin	Amiodarone, fluconazole, metronidazole, voriconazole
CYP2C19	Clopidogrel, diazepam, phenytoin, proton pump inhibitors, voriconazole, R-warfarin	Phenobarbital, phenytoin, rifampin	Fluconazole, fluoxetine, oxcarbazepine, proton pump inhibitors, voriconazole
CYP2D6	Beta-blockers, haloperidol, phenothiazines, SSRIs		Amiodarone, haloperidol, SSRIs
CYP2E1	Acetaminophen	Isoniazid	Disulfiram
CYP3A4	Alfentanil, amlodipine, cyclophosphamide, cyclosporine, dexamethasone, diazepam, haloperidol, methylprednisolone, midazolam, nicardipine, verapamil, voriconazole, R-warfarin	Carbamazepine, oxcarbazepine, phenytoin, rifampin	Cimetidine, diltiazem, erythromycin, fluconazole, verapamil, voriconazole

SSRIs, selective serotonin reuptake inhibitors.

Appendix B. Proximal tubule transport system substrates

Anionic system substrates
Acetazolamide, amantadine, ampicillin, aspirin, bumetanide, cephalosporins, ciprofloxacin, ethacrynic acid, folate, furosemide, methotrexate, nafcillin, NSAIDs, penicillin G, probenecid, thiazides, zidovudine
Cationic system substrates
Amiloride, amiodarone, cimetidine, digoxin, diltiazem, morphine, NAPA, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin, verapamil
Nucleoside transporters system substrates
Zidovudine, didanosine
P-glycoprotein transporters substrates
Clarithromycin, cyclosporine, digoxin, losartan, procainamide

NSAIDs, nonsteroidal anti-inflammatory drugs; NAPA, *N*-acetyl-procainamide.