Medication Errors and Drug–Drug Interactions in the Intensive Care Unit

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Medical errors and medication errors may cause patient harm and death and occur in all steps of the medication process and in all settings across healthcare. Some settings, such as the intensive care unit (ICU), involve higher risk of harm from such errors. This increased risk is due to many factors. Sicker patients with organ system(s) dysfunction and use of high-alert medications are two important factors for the risk of medication errors. Other risk factors such as age and comorbidities may also contribute. According to the Institute for Safe Medication Practices, a high-alert medication is "a drug that bears a heightened risk of patient harm when used in error" [1]. Medical toxicologists are sometimes consulted when a medication error occurs to provide expertise in management, to recommend treatment if necessary, and to offer mitigation strategies.

A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer" [2]. An error can result in harm or may be intercepted prior to reaching the patient causing no harm (near miss). The medication use process, with functions such as prescription, transcription, dispensing, administration, and monitoring, lends itself to errors as each function can be broken into additional steps. Numerous strategies have been developed to mitigate errors at each of these functions to reduce harm to patients.

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This chapter will provide an overview and explore the epidemiology of medication errors and drug–drug interactions in the ICU. Factors that lend themselves to causing errors and prevention strategies for errors will also be discussed.

The ICU Setting

Particular areas of the hospital are at increased risk for errors and near misses due to the nature of the area, type of patients, and medications and procedures used as part of patient care. The ICU is one such high-risk area. ICU patients usually have organ dysfunction or multiple organ dysfunction and are routinely exposed to high-alert medications (e.g., adrenergic agonists and antagonists, opioids, insulins, sedation agents, and anticoagulants). In one study involving two medical centers, the strongest predictor or risk factor for an adverse drug event or medication error in an ICU was the patient's illness severity [3]. Another study, involving medical and surgical ICUs compared to general medical and surgical wards, found that patients in an ICU were prescribed twice as many drugs as patients on general wards and had a twofold preventable and potential adverse drug event rate [4]. Another risk factor is the use of weight-based dosing for many medications, including anti-infectives, vasopressors, and anticoagulants. Weights may be estimated which can lead to under- or overdosing of necessary medications. Mathematical calculations are prone to error with weight-based dosing as well [5].

Epidemiology

In 1999, the Institute of Medicine reported, "To Err is Human: Building a Safer Healthcare System." This report estimated between 44,000 and 98,000 patients experienced a medical error and died per year. These errors have an estimated cost of $37.6–50 billion due to the need for extra care, lost income, and disability [6].

Multiple studies have tried to provide further epidemiologic data regarding medication errors in the ICU. The lack of standard definitions for medication errors and adverse drug events and underreporting of these types of medication safety concerns make it difficult to give an exact number to the incidence [7]. Most of these studies are observational. One study, involving a medical ICU and a coronary care unit (CCU) at an academic medical center, found 78% of serious medical events involved medications. These errors were mainly related to medication ordering or executing a particular treatment associated with a medication. The most common medication error was ordering the wrong dose, and the most common medications involved were cardiovascular drugs, anticoagulants, and anti-infectives. The overall medication error rate in the medical ICU was 12.7% and 12.1% in the CCU [8]. A similar observational study also evaluated medical and cardiac ICUs for medication errors. It found that 65% of medication events (1183/1805) had the potential for harm. Some events had more than one error, either the actual order had more than one error or the event led to errors in more than one step of the medication use process (see below for discussion of the "Medication Use Process"). Thirty-eight events (38/1805, 2%) were considered preventable. Seven of these preventable events led to significant patient harm (i.e., diarrhea, nausea, vomiting), 13 lead to serious patient harm (i.e., gastrointestinal bleeding, allergic reaction but not anaphylaxis, or altered mental status), and 18 were considered life-threatening (anaphylaxis, respiratory failure, etc.). Antibiotics were most commonly involved at 26% (10/38) of the events, while diabetic medications were next at 20% (8/38). Most medication errors occurred during the administration (39%) and prescribing/ordering (32%) stages [9]. In a pediatric ICU, an observational study showed that 151 prescribing errors occurred in 1129 orders, with 104 of these errors requiring intervention or resulting in patient harm. Wrong dosage was the most common error followed by wrong drug selection and missing information from the order. The most commonly prescribed medications, analgesics and anti-infectives, had the most frequent errors, with infrequently prescribed drugs (e.g.,

antihypertensives and antimycotics) demonstrating higher errors rates [10]. While it is difficult to compare different types of ICUs, one study did show that medical ICU patients experienced higher rates of medication errors than do patients in surgical ICUs [4].

Medication Use Process

The medication use process is a complicated series of sequential functions leading to a patient receiving medication. Each function of the process has multiple steps to ensure that it is completed correctly. These functions include prescription, transcription, dispensing, administration, and monitoring. Errors can occur at each function of the process. The most error prone functions are prescription and administration [11]. A recent study of prescribing errors in the ICU identified 360 errors in 286 prescriptions out of 534 total prescriptions. The most common prescribing error was omitted information with computer prescriber order entry. Examples of the omitted information included route of administration or diluent needed [12].

Several studies have focused on medication administration in the ICU aimed at determining the epidemiology of administration errors. In one observational study, pharmacists observed nurses in the preparation and administration of medications. Of 2009 medications administered, 132 (6.5%) involved errors. The most common errors were wrong dose (31%, 41/132), wrong rate (22%, 29/132), and wrong preparation technique (18%, 24/132). Almost 20% (26/132) of the errors were potentially life-threatening, and 42% (55/132) of the errors were potentially significant (e.g., underdosing, time errors, and physicochemical incompatibility) [13]. Another observational ICU study for medication administration involved only 3.3% of errors compared to the above but had a multidisciplinary team including pharmacists in place at time of observation [14]. This study supports the use of a multidisciplinary team to reduce medication errors. See "Prevention Strategies" below.

Prevention Strategies

Many prevention techniques, including technological advances, have been developed over the years to try to mitigate medication errors and adverse drug events. These prevention strategies focus on different functions in the medication use process or cross all areas of the medication use process. In general, a comprehensive program to target all parts of medication use and to obtain information in different ways allows for a broader scope of information and highlights different concerns. In one study, a program assessing voluntary reporting, chart review, and computer-based monitoring included monitoring for specific orders (naloxone) and alerts. All of these methods identified different medication safety concerns with little overlap in the problems identified [15]. Another study showed that direct observation revealed a higher incidence of potential and actual events when compared to chart reviews and solicited incident reporting [16]. In one ICU in Australia, a Medication Error Minimization Scheme (MEMS) has been implemented as part of an ongoing quality improvement project. The overall research design uses "Plan-Do-Study-Act cycles" to achieve small steps toward improving medication safety. With this MEMS, the ICU has seen an increased number of reported medication problems from incident reporting, staff surveys, focus groups, and chart review [17]. Once these concerns are known, strategies for prevention can be targeted and tested using methodology such as "Plan-Do-Study-Act cycles."

Prescription writing, or ordering of a medication, is one of the areas more prone to error. Poor handwriting has led to mistakes with transcription in the past. With the introduction of computerized prescriber order entry (CPOE), it is no longer necessary to interpret a prescriber's handwriting. In one study, the error rate of handwritten prescription orders contained 6.7% compared to 4.8% with CPOE. The handwritten prescription errors included omission of key information such as dosing, unit, or frequency. Types of errors for the CPOE orders included dosing errors, omission of writing order for a required drug, and

prescriber's signature [18]. In one ICU, the initiation of CPOE reduced prescribing errors from 27% to 3% when compared to a paper-based unit in the same hospital. Both CPOE and paper-based ordering had errors most commonly with cardiovascular and antibiotic medications [19]. In another study, CPOE implementation in a cardiac care unit showed a decrease in errors from 44.8% with handwritten prescription orders to 0.8% in computerized orders after full implementation of the CPOE system [20]. The evidence supporting the benefit of CPOE in reducing medication errors is grade II-3.

Decision support is considered an essential part of CPOE. This technology incorporates tools into the ordering system to aid providers in appropriate prescribing. It allows providers to automatically check for drug interactions, appropriate medications for elderly patients, and appropriate dosing for renal function among other functions. Some hospitals have even implemented decision support into antibiotic prescribing to ensure quality metrics are met and treatment guidelines are followed. In one recent study, five anesthesia-run ICUs were studied pre- and post-implementation of antibiotic decision support. Prior to implementation, only 61% of antibiotic orders adhered to guidelines. Immediately after implementation, 92% adhered to guidelines. This study also showed more antibiotic free days and a decrease in mortality when antibiotic guidelines were followed [21].

Once medications have been ordered, they must get dispensed and administered. Barcode medication administration has been implemented throughout hospitals as a way to ensure the "rights" of medication administration (i.e., right patient, right medication, right dose, right route, right time, right documentation, right reason, and right response). Using barcodes, one ICU study showed an improvement in correct administration times. This study used a direct observation technique to monitor medication administration errors. Prior to barcode medication administration, 18.8% of were administered at a wrong time. After implementation of barcode administration, the error rate was 7.5% [22]. The evidence supporting the benefit barcodes is grade II-3.

Another technological advance in drug administration has been the use of intelligent infusion pumps for intravenous medications. These infusion pumps have programmable libraries with point-of-care decision support for infusion rates and doses and will alert the nurse to problems related to medication administration. These pumps evaluate dose, dosing unit, rate, and concentration and prevent free-flow or "runaway" medication administration [23]. At the initiation of using this technology, a prospective study found numerous ways that these intelligent pumps could prevent error. The study also showed numerous ways in which providers were bypassing these techniques, such as not using the preprogrammed drug library with correct infusion rates [24]. In one Pediatric Intensive Care Unit, after adapting the drug library to its specific needs and acceptance by nursing staff, smart pumps were found to be very effective in reducing IV medication administration errors [25]. These intelligent pumps have the ability to intercept and log medication errors as well. One study in Germany showed that there were 717 instances of an alert firing for potentially harmful overdosing [26]. These pumps when used with barcode medication administration aid to ensure the "rights" of IV medication administration are met [23]. The evidence supporting the benefit of intelligent infusion pumps is grade II-3.

An additional way to prevent medication errors in the ICU is to have clinical pharmacists as part of the care management team. Clinical pharmacists have been shown to reduce errors, reduce costs, improve individualized care, and serve an educational function in the ICU [27]. A study involving a medical ICU and a coronary care unit at a large teaching hospital showed that preventable prescribing errors were reduced by 66% when a senior pharmacist was a full member of the patient care team [28]. Another study in China showed that pharmacists in the ICU intervened in errors related to medication dosing (152/407 interventions) (e.g., patient with renal insufficiency or on renal replacement therapy), drug omission (83/403 interventions), and potential for an adverse drug reactions (54/407 interventions) over a 6-month observational study [29]. In a

Dutch hospital, clinical pharmacists in the ICU reduced the incidence of prescribing errors from 190.5 per 1000 patient days to 62.5 per 1000 patient days and reduced the number of preventable adverse drug events from 4 to 1 per 1000 patient days [30]. Clinical pharmacists can also develop a training program for providers working in the ICU to teach clinically relevant errors related to preparation and administration of IV medications. A study of a Vietnamese program showed a reduction from 64% to 49% following implementation of such a program, and any residual dosing errors were less likely to be clinically relevant [31]. In addition to reducing errors, pharmacists in the ICU can aid in improving the management of infections, anticoagulation therapy, sedation, and analgesia for ICU patients [32]. The evidence supporting the benefit of ICU-based pharmacists grade II-3.

Drug–Drug Interactions

Drug–drug interactions (DDIs) are common and can lead to patient harm. The severity and drugs involved may differ in the ICU compared to other clinical settings [33]. Similar to medication errors, patients in intensive care units may be at risk for more severe drug–drug interactions due to the complexity of their illness, medications administered and their number, disease severity, and organ system dysfunction [5]. In one Dutch study, a computerized algorithm was developed to determine the frequency of DDIs. The DDIs were classified based on surveys from nine pharmacists and intensivists. After a consensus was reached, the group studied admissions to an ICU. A total of 16,122 DDIs were identified. Most commonly, antithrombotic and antibacterial agents were involved [34]. In another Dutch retrospective observational medical ICU study, 54% of all ICU patients experienced a potential DDI. The most common consequences for the DDIs were increased risk of an adverse drug reaction/side effect or toxicity. Management for the DDIs seen in the ICU often involved increased monitoring of some type (e.g., vital signs, laboratory studies, clinical monitoring for toxicity or effectiveness, or for changes on the electrocardiogram) [35]. DDIs were associated with prolonged lengths of stay, 12 days versus 5 days for patients without DDIs, in the ICU [36]. Another prospective, case–control study showed that 6.65 DDIs occurred per patient. Pharmacodynamic and pharmacokinetic DDIs were common. Risk factors associated with risk of DDIs included female gender, age >50 years, use of >10 drugs, and ICU stay >7 days [37]. One recent study showed that 37% (187/501) of patients in a cardiac ICU have documented QTc ≥ 500 ms. While no patients developed torsades de pointes, 63 patients (34%) had atrial dysrhythmias and 37 patients (20%) had ventricular dysrhythmias [38]. This acquired prolonged QTc syndrome may be a potential serious consequence of ICU stay since critically ill patients are at risk for QTc prolongation in addition to these patients receiving multiple medications and having organ system dysfunction which may lead to electrolyte abnormalities or changes in metabolic function due to reduced renal and hepatic function [39].

In the cardiothoracic ICU, anti-infectives, central nervous system, and cardiovascular agents were the main drugs associated with major DDIs or contraindicated because of another drug present in the patient's medication regimen. The predicted consequences of the identified DDIs included altered GI absorption of antibiotics, inhibition/induction of enzymes for drug metabolism, and QTc prolongation [40]. Another study in a cardiothoracic ICU revealed that 17.7% of DDIs were considered major (i.e., life-threatening and/or require medical intervention to minimize or prevent serious adverse events) or were contraindicated for concurrent use. The most common interactions were drug metabolism and drug synergy effects. Azole antifungals and fluoroquinolones were the most common drugs involved [41]. In another prospective, observational study of a medical ICU, 5–9% of potential DDIs were major or contraindicated for concurrent use. The most common consequences were changes to blood coagulation profiles, QTc prolongation, and inhibition of cytochrome P450 enzymes [33].

Summary of Recommendations

Use *Computer Prescriber Order Entry* with *Decision Support* to Decrease Prescribing Errors

Use Other Technologies, such as *Barcode Medication Administration* and *Intelligent Infusion Pumps* to Decrease Administration Errors

Seek the Aid of *Pharmacists* to Reduce All Errors, Reduce Costs, and Provide Education on Best Medication Practices in the ICU

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