The Journal of Clinical Pharmacology
2015, 55(2) 132–136

DOI: 10.1002/jcph.421

# Potential Drug-Drug Interactions in Cardiothoracic Intensive Care Unit of a Pulmonary Teaching Hospital

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## Abstract

Little is known about clinically significant drug-drug interactions (DDIs) in respiratory settings. DDIs are more likely to occur in critically ill patients due to complex pharmacotherapy regimens and organ dysfunctions. The aim of this study was to identify the pattern of potential DDIs (pDDIs) occurring in cardiothoracic intensive care unit (ICU) of a pulmonary hospital. A prospective observational study was conducted for 6 months. All pDDIs for admitted patients in cardiothoracic ICU were identified with Lexi-Interact program and assessed by a clinical pharmacologist. The interacting drugs, reliability, mechanisms, potential outcomes, and clinical management were evaluated for severe and contraindicated interactions. The study included 195 patients. Lung cancer (14.9%) was the most common diagnosis followed by tracheal stenosis (14.3%). The rate of pDDIs was 720.5/100 patients. Interactions were more commonly observed in transplant patients. 17.7% of pDDIs were considered as severe and contraindicated interactions. Metabolism (54.8%) and additive (24.2%) interactions were the most frequent mechanisms leading to pDDIs, and azole antifungals and fluoroquinolones were the main drug classes involved. The pattern of pDDIs in cardiothoracic ICU differs from other ICU settings. Specialized epidemiological knowledge of drug interactions may help clinical practitioners to reduce the risk of adverse drug events.

## Keywords

cardiothoracic, clinical pharmacology, drug-drug interaction, intensive care unit, pulmonary hospital

Drug-drug interactions (DDIs) are a significant threat to hospitalized patients especially in intensive care units (ICUs). ICU-admitted patients are at an increased risk of DDIs due to the complexity of pharmacotherapy, large number of medications, disease severity, and organ failure (that changes the pharmacokinetics of drugs).[1–5] Although different studies describe the pattern of DDIs in medical and surgical ICUs[1,6], little has been done to study clinically significant DDIs occurring in pulmonary patients.

Several factors such as number of prescribed drugs, pharmacological characteristics of the medications, and duration of treatment are associated with the pattern of DDIs in a hospital.[7–10] Sex, age, genetics, comorbidities, and state of health are also determinant factors of DDIs.[11,12]

DDIs may cause lack of efficacy, therapeutic failure, toxicity, and serious adverse events[13–15] that could be identified and managed by clinical pharmacologists.[16,17] In the age of information technology (IT) systems, the use of DDIs software helps to improve patient safety,[18–21] but final decisions should be made by specialists. Therefore, objectives of the present study were to investigate the incidence, mechanisms, clinical significance, and management of potential drug-drug interactions (pDDIs) in the cardiothoracic ICU of a university-affiliated pulmonary hospital in Iran.

## Methods

### Setting and Study Population

This prospective study was carried out in a 13-bed cardiothoracic ICU of a pulmonary teaching hospital. It delivers care in cardiovascular surgery, thoracic surgery, and transplantation of solid organs (lungs and heart). The study received ethical approval from the hospital board review.

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Submitted for publication 21 August 2014; accepted 2 November 2014.

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All patients admitted to the ICU and those who were on medication between July and December 2013 entered the study.

### Data Collection

A clinical pharmacologist reviewed the medication record of each patient in the ICU twice a week. Demographic and clinical data were collected (by a data collection form). Lexi-Interact database was used to assess the presence and clinical significance of pDDIs. Lexi-Interact is a complete drug and herbal interaction analysis program capable of assessing pDDIs, drug-allergy interactions, and duplicate therapy interactions.[22]

The severity rating of pDDIs was scaled as A (unknown), B (minor), C (moderate), D (major), and X (contraindicated).[23] The interacting drugs, reliability, potential outcomes, and clinical management were recorded for D and X interactions. The physicians were notified of these interactions. This notification might have led to alterations in drug therapy. The ratings of reliability were indicated as excellent (E = the interaction has been clearly demonstrated in well-controlled studies), good (G = the studies strongly suggest that interaction exists; however, the proof of well-controlled studies is lacking), and fair (F = available evidence is poor, but clinicians suspect interaction on the basis of pharmacologic considerations; or, evidence is good for an interaction of pharmacologically similar drug).[24]

### Data Analysis

Data were analyzed by SPSS software v.22.0 for Windows (SPSS, Chicago, Illinois). The median, range, and percentage were applied to present the results where appropriate. The frequency of pDDIs was calculated as the number of pDDIs per 100 patients and the number of patients that exposed to at least 1 pDDI.

Descriptive statistics was performed on collected data to enable development of a list of pharmacokinetics and pharmacodynamics interactions. Interactions with severity ratings of A, B, and C were excluded due to lack of clinical significance.

Logistic regression analysis was applied to evaluate the relationship between occurrence of pDDIs and patients' age, gender, number of prescribed medications, and length of hospital stay before DDI assessment.

## Results

The study included a total population of 195 patients (male, 60%; median [range] age, 48 [3–85] years). Lung cancer (14.9%) was the most common diagnosis followed by tracheal stenosis (14.3%). A median number of 12 medications (range 2–18) were administered per patient. A total of 79.5% of the patients exposed to at least 1 pDDI. The rate of pDDIs was 720.5/100 patients. Interactions were more commonly identified in transplant patients (2182.3 pDDIs/100 patients).

Severity ratings of A, B, and C were 1.6%, 8.4%, and 72.3% of total interactions, respectively. About 17.7% (248/1405) of pDDIs were considered as D and X severity. These interactions were categorized according to mechanisms. The total incidence of pharmacokinetics interactions was 71.4% which included drug absorption (17.5%), distribution (1.7%), metabolism (76.8%), and excretion (3.9%) (Table 1). On the other hand, additive/synergistic (87%) and antagonist/opposing (13%) made the most important interactions in pharmacodynamics category (27.8% of total interactions) (Table 2). 0.8% of the interactions were caused by unknown mechanisms. Tables 1–7S show frequency, severity, reliability, potential adverse outcomes, and recommendations for all interactions.

In univariate logistic regression analysis, occurrence of pDDIs was significantly associated with the number of prescribed medications ($\geq$6 medications), length of hospital stay before pDDI assessment ($\geq$3 days), and patients' age. Variables with univariate $P$ value less than .1 were analyzed by multivariate logistic regression model. In multivariate analysis, a significant association was observed between occurrence of pDDIs and the number of prescribed medications ($\geq$6 medications) (Table 3). The probability of the occurrence of DDIs among the patients taking $\geq$6 medications was approximately 14 times of the patients taking $<$6 medications.

## Discussion

This study identifies the frequency, severity, and pattern of pDDIs in the cardiothoracic ICU of a pulmonary teaching hospital. The main reasons for designing this study were limited number of reports on pDDIs pattern in cardiothoracic ICUs, lack of pDDIs data in patients with pulmonary diseases, and the absence of a regular program for pDDIs detection and prevention in Iran.[25]

The present data reveal the potential for DDIs is common in patients admitted to the cardiothoracic ICU. Several studies have assessed the pattern of pDDIs in ICU settings and compared the results with general wards.[26,27] The main differences between ICU and general wards are prescribing large number of medications, changing dose and type of drugs, and administering high risk medications in ICUs.[6,28] On the other hand, variation of practices and medications between ICU settings may lead to different pDDIs pattern. Smithburger et al[29] identified 287.5 pDDIs/100 patients in a cardiovascular and cardiothoracic ICU by means of 2 interaction databases during 8 weeks. They emphasized that their data from a large university hospital with various patient population cannot generalize to other types of ICUs, community hospitals, and institutions without DDI surveillance system.

**Table 1.** The Number and Percentage of DDIs Based on Pharmacokinetics Mechanisms, Severity, and Reliability Rating

| | | Rate of Severity | | | | | |
|---|---|---|---|---|---|---|---|
| | | D (n = 170) | | | X (n = 7) | | |
| | | Rate of Reliability | | | | | |
| Mechanism of DDI % (n) | | Excellent % (n) | Good % (n) | Fair % (n) | Excellent % (n) | Good % (n) | Fair |
| Absorption 17.5% (31) | | 3.4% (6) | 6.8% (12) | 6.8% (12) | – | – | 0.6% (1) |
| Distribution 1.7% (3) | | – | – | 1.7% (3) | – | – | – |
| | Induction 34.5% (n = 61) | 1.7% (3) | 3.4% (6) | 28.8% (51) | – | 0.6% (1) | – |
| Metabolism 76.8% (136) | Inhibition 37.3% (n = 66) | 7.9% (14) | 13% (23) | 14.7% (26) | 0.6% (1) | 0.6% (1) | 0.6% (1) |
| | Both 5.1% (n = 9) | 1.7% (3) | 2.2% (4) | – | – | 1.1% (2) | – |
| Excretion 3.9% (7) | | 0.6% (1) | 1.7% (3) | 1.7% (3) | – | – | – |
| Total 100% (177) | | 15.2% (27) | 27.1% (48) | 53.7% (95) | 0.6% (1) | 2.2% (4) | 1.2% (2) |

**Table 2.** The Number and Percentage of DDIs Based on Pharmacodynamics Mechanisms, Severity, and Reliability Rating

| | Rate of Severity | | | | | |
|---|---|---|---|---|---|---|
| | D (n = 49) | | | X (n = 22) | | |
| | Rate of Reliability | | | | | |
| Mechanism of DDI % (n) | Excellent % (n) | Good % (n) | Fair % (n) | Excellent % (n) | Good % (n) | Fair % (n) |
| Additive 87% (60) | 17.4% (12) | 5.8% (4) | 39.1% (27) | – | 13% (9) | 11.6% (8) |
| Antagonistic 13% (9) | 2.9% (2) | 2.9% (2) | – | – | – | 7.2 (5) |
| Total 100% (69) | 20.3% (14) | 8.7% (6) | 39.1% (27) | – | 13% (9) | 18.8% (13) |

High percentage of pDDIs in our study may be due to several factors such as prescribing new drugs without considering previous medications, shortage of clinical pharmacologists, and lack of computerized physician order entry. Sweileh et al[30] also reported the aforementioned reasons for high incidence of pDDIs. The occurrence of pDDIs was significantly associated with the increasing number of prescribed drugs and length of hospital stay, that is in accordance with previous reports.[31,32]

**Table 3.** Logistic Regression Analysis

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| Variable | OR (95%CI) | *P* Value | OR (95%CI) | *P* Value |
| Age (years) | | | | |
| <50 | 2.1 (1–4.3) | <.05 | 2 (0.9–4.6) | .1 |
| ≥50 | | | | |
| Sex | | | | |
| Female | 1.3 (0.7–2.7) | .4 | – | – |
| Male | | | | |
| Hospital stay (days) | | | | |
| <3 | 4 (1.2–13.7) | <.05 | 1.5 (0.4–6.2) | .6 |
| ≥3 | | | | |
| Number of drugs | | | | |
| <6 | 15.2 (6–38.9) | <.001 | 14.1 (5.4–37.2) | <.001 |
| ≥6 | | | | |

Variables with univariate *P* values of less than .1 were included in multivariate analysis.

In terms of mechanisms, pDDIs could be categorized into pharmacokinetics and pharmacodynamics interactions. The pharmacokinetics affect the processes of absorption, distribution, metabolism, and excretion, whereas pharmacodynamics occur when the effects of a drug changed in the presence of another one at the site of actions.[33] In this study, metabolism interactions were the most frequent ones in pharmacokinetics category (136/177). Our results are in accordance with Smithburger et al[29] who reported cytochrome P450 (CYP) enzyme system, specifically CYP3A isoenzyme inhibition as a common mechanism for pDDIs.

Rifampin, dexamethasone, and carbamazepine were the main inducers (Table 3S) that probably increase metabolisms and decrease serum concentrations of a pair drug. Induction of oxidative metabolic systems, such as CYP isoenzyme system, transmembrane efflux pumps, such as P-glycoprotein, and conjugative enzyme systems, such as UDP-glucuronosyltransferase, are the mechanisms that rifampin may interact with other drugs.[34] Although dexamethasone induces CYP3A isoenzyme, reliability rating of its interaction is usually fair and the clinical outcome is unknown. Dexamethasone weakly

activates pregnane X receptor and induces CYP3A isoenzyme activity.[35]

Antifungal agents (itraconazole, voriconazole, and posaconazole) and macrolides were the most common inhibitors (Table 3S) that may decrease metabolism and enhance the toxic effects of a co-administered medication. All azole antifungal agents inhibit CYP3A isoenzyme that is the principal drug metabolizing enzyme in human. The azoles also interact with commonly used immunosuppressive agents (ie, calcineurin inhibitors, corticosteroids, sirolimus). Management of these interactions is an important issue in transplant patients. Dose adjustments and blood concentration monitoring of calcineurin inhibitors should be considered before, during, and after administration of azole.[36] The macrolides (erythromycin and clarithromycin) are associated with numerous drug interactions. Inhibition of the CYP450 system and P-glycoprotein are the main mechanisms for such interactions.[37]

Most of the absorption interactions were due to complex formation between medications and divalent or trivalent ions (Table 1S). These interactions can be prevented by separating doses of paired drugs in an appropriate interval. Change of gastrointestinal pH was another mechanism that may noticeably reduce effects of azole derivatives.[38]

The QTc prolonging effect was the most significant interaction outcome in the category of additive mechanism. The pDDIs that increase the risk of QT prolongation, and ultimately torsades de pointes, may lead to sudden death.[39] Fluoroquinolones (ciprofloxacin) was the main drug class involved in QTc prolongation effect in our setting (Table 5S).

Administration of 2 drugs with opposing activities especially by certain receptors (such as nonselective beta-blockers and beta-2 agonists) led to important antagonistic interactions (Table 6S).

In this study, fair scientific evidence was identified for 56% of severe and contraindicated pDDIs. Good scientific evidence has been reported as the most common reliability rating of pDDIs in other studies.[24,40] The pDDIs with severity ratings of D and/or X and reliability ratings of excellent and/or good may have considerable harmful effects on patients' clinical condition or therapeutic response. Careful monitoring is necessary in order to avoid and minimize negative consequences of these types of interactions.

Lexi-Interact database was used to compile the DDIs' profiles. It is a commonly used resource providing detailed DDI information,[23] and available in our hospital. Some DDIs' software may overestimate pDDIs and cause extra concern about interactions. These software cannot make a distinction between interactions that are well documented, and those that have only been encountered in a single patient.[33] Lexi-Interact database with a documentation rating that is useful to recognize well-documented interactions would limit clinical repercussions. In conclusion, our results show different patterns of pDDIs between cardiothoracic ICU and other ICU settings. It would be helpful to provide specialized information in order to manage and prevent harmful adverse drug events, especially in developing countries.

## Declaration of Conflicting Interests

The authors declare no conflicts of interest.

## Funding

This study has no funding resources.

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