The study of harmful and beneficial drug interactions in intensive care, Kerman, Iran

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Since multidrug therapy is common in the intensive care unit (ICU), the risk of drug interactions is high. This study aimed to examine the prevalence of drug interactions and risk factors in patients who were admitted to ICUs. In a cross-sectional study, the medication flow sheet of 101 patients was investigated in terms of the number and the type of drug interactions. The Drug Interaction Facts reference text book (2010 edition) was used to determine the type and the number of drug interactions. In total, 609 potential drug interactions were found. The mean number of drug interactions per patient was 6.1 (SD=5.6). Of all observed drug interactions, 66.9% were classified as harmful and 33.1% beneficial. In terms of the nature of interactions, delayed, moderate, and possible were the most common types. The most frequent harmful interaction was between phenytoin and omeprazole (63 occasions). Critically ill patients are at a higher risk of drug interactions. Although 33.1% of the drug interactions were considered beneficial, medical teams should be aware that even beneficial interactions can have undesirable side-effects in the critically ill.

Keywords: *intensive care unit; drug interactions; beneficial; harmful*

Introduction

A drug interaction occurs when the effect of a drug is altered by other drugs; it may affect the drug's pharmacokinetics or pharmacodynamics.[1] In pharmacokinetic interactions, a drug alters the absorption, distribution, metabolism, or excretion of another drug; in pharmacodynamic interactions, the action of a drug is altered by other drugs.[2] The occurrence and the severity of a drug interaction is affected by many factors such as the number of prescribed drugs, treatment duration, patient's age, disease stage, and the number of physicians prescribing the drugs.[1,3] Critically ill patients are particularly prone to drug interactions, as they have several related risk factors such as higher age, multidrug therapy, and long duration of hospital stay.[1,2,4-6]

Almeida *et al*[1] conducted a study on the assessment of drug-drug interactions in the adult intensive care unit (ICU) of a large private tertiary care hospital over a period of 30 days. They reported that potential drug interactions are common in ICU patients and may potentially produce a significant economic and clinical impact. In another study carried out by Rais *et al* in 2011, drug interactions in three different time periods were studied.[7] They reported a high prevalence of drug interactions in ICU, and found that factors such as the number of drugs taken, the duration of stay in ICU, and the types of drugs used were the most important factors. Moura *et al* studied the correlation between drug interactions and the duration of stay in the ICU.[8] They reported that patients staying longer in ICU suffer more from drug interactions. In our previous study, we observed a high risk of drug interaction in patients after the first 24 hours in ICU. In addition, we found that reasons such as number of administered drugs, the number of physicians visiting a patient, and the patients' ages, were the most important factors increasing the risk of drug interactions in ICU patients.[9]

Although drug interactions have already been studied in ICU, most of these studies were limited in two ways – either they considered theoretical interactions without taking account of the duration of action of the drugs and/or they ignored beneficial drug interactions. As an example of the first limitation, a theoretical interaction between two drugs (one administered in the morning and the other in the evening) was considered a drug interaction, which might not be the case considering the duration of the effect of the drugs. The second confounder, which has been ignored in previous studies, was beneficial drug interactions, ie interactions which the medical team had been aware of and had intentionally used. For example Reis *et al* have reported severe drug interactions between fentanyl and midazolam, without considering this was probably intentional.[7]

The aim of the current study was to determine the prevalence of drug interactions in different work shifts and also to determine the number of beneficial *versus* harmful interactions in ICU patients.

Methods

This cross-sectional study was approved by the ethical committee of Kerman Medical University. Each patient (if the patient was able to respond) or their relative, was asked to fill in a written consent form. All research in Iran requires approval by a local ethical committee. These committees usually comprise about 20 people who are specialist nurses or doctors. In the Iranian healthcare system, hospitals and their

Classification	Morning			Evening			Night		
Severity	Major	8	2.4%	Major	4	4.0%	Major	3	1.6%
	Moderate	230	71.1%	Moderate	73	73.7%	Moderate	152	81.3%
	Minor	85	26.5%	Minor	22	22.3%	Minor	32	17.1%
Onset of action	Rapid	36	11.1%	Rapid	18	18.1%	Rapid	20	10.6%
	Delayed	287	88.9%	Delayed	81	81.9%	Delayed	168	89.4%
Documentation	Established	23	7.1%	Established	10	10.1%	Established	15	8.9%
	Probable	21	6.5%	Probable	6	6.1%	Probable	8	4.8%
	Possible	143	44.3%	Possible	50	50.3%	Possible	84	50.0%
	Suspected	127	39.4%	Suspected	25	25.1%	Suspected	53	31.5%
	Unlikely	9	2.7%	Unlikely	8	8.1%	Unlikely	8	4.8%

Table 1 Drug interactions classified by severity, onset of action and documentation.

ICUs are categorised in three levels. This study was performed in a level one unit. In such a unit the head must be an intensivist. These ICUs usually have more than 20 beds. The Iranian Society of Intensive and Critical Care Medicine is responsible for designing programmes and guidelines for ICU, but has no guidance regarding drug-drug interactions.

Sampling was done in four distinct time periods in three different work shifts – morning, evening, and night. Our previous studies in the same hospital had shown that the average duration of stay in ICU was about 18 days.[9,10] Therefore, four distinct samplings were done at intervals of 20 days. To collect the required data, the ICU flow sheets completed by the ICU nurses were used because they were considered the most reliable. The data on the number of drugs taken, the name of the drugs, the routes of administration, and demographic variables, including the patients' age and gender, were obtained. The extent of occurrence and frequency of potential drug interactions were investigated based on the reference textbook '*Drug Interaction Facts*' published in 2010.[11] This textbook is considered the gold standard for identifying drug interactions in Iran.

Potential drug interactions identified were classified by:

- severity
  - *minor*: 'the effects are usually mild; consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome. Additional treatment is usually not required'
  - *moderate*: 'the effect may cause deterioration in a patient's clinical status. Additional treatment, hospitalisation or an extended hospital stay may be necessary'
  - *major*: 'the effects are potentially life-threatening or capable of causing permanent damage'.
- onset of action
  - *rapid*: 'the effect will be evident within 24 hours of administration of the interacting drug'
  - *delayed*: 'the effect will not be evident until the interacting drug is administered for a period of days or weeks'.
- documentation
  - *established*: 'proven to occur in well controlled studies'
  - *probable*: 'very likely but not proven clinically'
  - *suspected*: 'may occur; some good data; need more study'
  - *possible*: 'could occur but data are limited'
  - *unlikely*: 'doubtful; no good evidence of an altered clinical effect'.

According to this textbook drug interactions, which the medical team had been aware of and had been intentionally induced to gain advantage, were considered beneficial interactions (eg, interactions between antibiotics). Interactions that the medical team had not been aware of were considered harmful. Nutritional supplements, ointments, drops, serums, electrolytes, and vitamins were excluded from the data collection. Drugs which are not registered in the textbook were considered to be without potential drug interaction All data were analysed using SPSS 18·00 statistical software and a variable was found to be statistically significant if $p < 0{\cdot}05$. Descriptive statistics (expressed as mean and standard deviation (SD)), Pearson correlation test and independent t-test were used.

Results

The sample consisted of 101 patients, 75.2% of whom were men. The mean age was 37.2 ± 21.5 years. The mean number of administered drugs for each patient was 23.6 ± 9.1. Of all the drugs administered, 44.5% were during the morning shifts, 23.3% in evening shifts, and 32.2% in night shifts. Overall 58.5% of the drugs were injected and the rest taken orally. Six hundred and nine drug interactions were documented in patients' flow sheets (6.1 ± 5.6 per patient). Of all the drug interactions, 66.9% were potentially harmful, and 33.1% beneficial. Of 202 beneficial drug interactions, 100 cases were related to interaction between phenytoin and midazolam. In terms of distribution among various work-shifts, 53% of interactions were in the morning shifts, 16.1% in the evening shifts, and 30.9% in the night shifts. With regard to the types of interactions, most of the interactions were of delayed, moderate, and possible types. **Table 1** shows the types of interactions in terms of starting time, severity, and the degree of proof in the three various shifts. In terms of the number of drug interactions, the highest frequency of interaction occurred between phenytoin and omeprazole, (**Table 1**). Of all the interactions, 15 were major (**Table 3**) and 74 cases of

Drug Interaction (n)	Type of interaction	Drug Interaction	Type of interaction
Phenytoin + omeprazole (63)	Delayed, moderate, possible	Paracetamol + phenytoin (24)	Delayed, moderate, suspected
Omeprazole + midazolam (52)	Delayed, minor, suspected	Furosemide + phenytoin (19)	Delayed, minor, suspected
Phenytoin + dexamethasone (39)	Delayed, moderate, established	Methadone + phenytoin (16)	Delayed, moderate, suspected
Metronidazole + phenytoin (31)	Delayed, moderate, possible	Ranitidine + midazolam (12)	Delayed, moderate, possible
Ranitidine + phenytoin (29)	Delayed, moderate, possible	Haloperidol + phenytoin (8)	Rapid, minor, unlikely

Table 2 Ten most common harmful drug interactions.

Drug Interaction (n)	Type of interaction	Drug interaction (n)	Type of interaction
Ranitidine + midazolam (16)	Rapid, minor, unlikely	Theophylline + midazolam (5)	Rapid, minor, suspected
Atracurium + vancomycin (12)	Rapid, moderate, probable	Omeprazole + theophylline (6)	Rapid, minor, probable
Atracurium + phenytoin (8)	Rapid, moderate, probable	Atracurium + amikacin (5)	Rapid, major, probable
Erythromycin + midazolam (6)	Rapid, moderate, suspected	Furosemide + ciprofloxacin (5)	Rapid, minor, possible
Furosemide + amikacin (8)	Rapid, major, probable	Furosemide + tobramycin (3)	Rapid, major, probable

Table 4 List of harmful rapid drug interactions.

interaction were rapid (**Table 4**). Among the drugs used in the ICU, the most frequently used ones were morphine (222 times), phenytoin (170 times), and midazolam (155 times). Drug reactions appeared to be commoner among men than women (7.1 *vs* 6.2) but this was not confirmed statistically. Pearson correlation test showed a significant correlation between number of potential drug interactions and number of prescribed drugs ($r=0.561$, $p<0.05$).

Drug Interaction (n)	Type of interaction
Furosemide + amikacin (6)	Rapid, major, probable
Atracurium + amikacin (5)	Rapid, major, probable
Furosemide + tobramycin (3)	Rapid, major, probable
Furosemide + digoxin (1)	Delayed, major, probable

Table 3 List of harmful major drug interactions.

Discussion

There were 690 interactions documented confirming that ICU patients are at high risk of this complication. Although the findings showed that approximately one third of the interactions were beneficial, it remains important for the clinical team to remain aware of all reactions.

Previous studies have reported that the incidence of drug interactions is high in ICU patients,[1,2,4-6,12] however, there remains controversy. For example, in our previous study, we assessed drug interactions only in the first 24 hours after admission.[9] We reported that on average, each patient received 5.6 drugs, which is lower than what we found in the current study (23.6 drugs per patient). Unsurprisnigly therefore, the 6.1 drug interactions per patient, observed in this study, is more than reported in our previous study (mean of 1.9 interactions per patient).[9] Apparently, the longer the patients stay in ICU, the higher the number of drugs is prescribed and the greater the possibility for drug interactions.

Results of the present study showed that the most common type of potential drug interactions among critically ill patients were delayed, moderate and possible. Similarly, Hammes *et al* found that 59.7% of potential drug interactions in ICU are delayed.[4] They also reported that moderate and possible interactions are higher than other types of interactions among critically ill patients.[4] This issue could be explained by two facts: phenytoin was responsible for a high percentage of interactions in our study, and phenytoin's interactions are mostly delayed, moderate, and possible; therefore these types of interactions would be more frequent than others.

The interaction between phenytoin and omeprazole is the most frequent in our study. Phenytoin and omeprazole are the most common anticonvulsant and antacid drugs used in the ICU respectively.[13,14] Omeprazole inhibits CYP2C19 and decreases the clearance of phenytoin.[15] In Iranian ICUs both phenytoin and omeprazole are administered enterally. Omeprazole is administered once daily (9 am) and phenytoin three doses daily (9 am, 5 pm and 1 am). Omeprazole has a short plasma half-life (0.5-2 hours),[15] but considering the use of omeprazole and phenytoin simultaneously (9 am), the chance of an actual interaction between the two drugs in patients in the present study is high.

In line with the results obtained by other studies[1,2,5] the present study found that the risk of drug interactions increased with increasing number of prescribed drugs for patients. It seems intuitive that with increasing numbers of prescribed drugs there would be an increased rate of drug reactions, but in addition critically ill patients are often seen by many different clinicians who may prescribe without proper consideration of the risk of interactions.

Conclusion

Critically ill patients are at a high risk of drug interactions. Although one-third of drug interactions were beneficial, medical teams should be aware that even beneficial interactions could have unfavorable side effects in the critically ill. Factors such as multidrug therapy, administering phenytoin,

omeprazole, dexamethasone, furosemide, atracurium, midazolam, amikacin, and paracetamol simultaneously, absence of clinical pharmacologists, high number of prescribing physicians and poor knowledge of medical and nursing teams could all be important causes. Use of suitable software to detect drug interactions may be helpful in decreasing rate of drug interactions in ICU, although this needs more study. Finally, it is important to highlight that drug interactions and their side-effects could be lethal and costly; therefore it is necessary to limit this risk through correct planning by the medical and nursing team.

Disclosure

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