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Original Article

Evaluation of Pharmacokinetic Drug Interactions in Prescriptions of Intensive Care Unit (ICU) in a Teaching Hospital

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Abstract

Concomitant use of several drugs by ICU(Intensive Care Unit) patients is often unavoidable. In these patients, pharmacokinetic drug interactions are very likely. The current study was designed to evaluate these interactions in patients hospitalized in an ICU of a teaching hospital in Tehran, Iran.

A questionnaire was designed and used to collect study data. The study was done in the ICU of a teaching hospital affiliated to the Shaheed Beheshti Medical University. Overall information extracted from 567 ICU prescriptions from March 2005 to December 2005. The extent of occurrence and frequency of potential pharmacokinetic interactions were categorized based on the reference text Drug Interactions Facts. All of the pharmacokinetic drug interactions were extracted and evaluated in terms of mechanism, significance, severity, documentation and onset.

There were 413 pharmacokinetic interactions in 567 studied prescriptions, which were divided into 64 types of pharmacokinetic interactions. The most observed interaction was between ciprofloxacin and sucralfate. Mechanisms of the pharmacokinetic interactions were related to metabolism (%60.05), absorption (% 38.26), elimination (%0.97) and distribution (%0.73). There was a direct relationship between the number of drugs per prescription and the frequency of pharmacokinetic interactions ($p<0.001$, $r=0.98$)

Findings obtained in this study revealed that there is a significant number of rapid occurring, moderate, probable and definite interactions among the ICU prescriptions. This highlights the necessity for the presence of a drug specialist (i.e. clinical pharmacist) to rationalize the therapy and minimize major interactions.

Keywords: ICU; Pharmacokinetic; Drug interaction; Teaching hospital.

Introduction

A drug interaction can be defined as the modification of the effects of one drug (the object drug) by the prior or concomitant administration of another drug (the precipitant drug) (1). In a study involving 9900 patients with 83200 drug exposures 234 (6.5%) of 3600 adverse drug reactions were attributed to drug interactions (2).

In a study by Galley et al. it was found that in prescriptions prescribed for a total number of 160 patients in internal ward, 221 interactions exist from which 24(%10.85) were major, 115(%52.03) were moderate and 82(%37.12) were minor interaction(3).

In another study in 2000, Hajebi et al evaluated drug interactions in 3130 prescriptions

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of 4 wards in a teaching hospital. Their results showed total number of 3960 including 156 types of interactions. In this study mechanisms of drug interactions were not determined (4).

In terms of mechanism, drug interactions are often characterized as being either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions influence the disposition of a drug in the body and involve the effect of one drug on the absorption, distribution, metabolism and excretion of another one. Pharmacodynamic interactions are related to the pharmacologic activity of the interacting drugs. They did not involve changes in serum concentration of drugs. Also they have not been amply studied or reported in textbooks (1).

Intensive care unit (ICU) of hospitals is differentiated from other wards because of the high frequency of medications received by patients. Therefore it's rational to expect a high probability of pharmacokinetic interactions in ICU prescriptions. This study was designed to investigate the occurrence and extent of pharmacokinetic drug interactions in prescriptions of ICU ward in a teaching hospital.

Methods and Material

The proposal of the study was approved by the ethical committee of the Shaheed Beheshti Medical University.

At first, a questionnaire was designed for collecting data. First part of the questionnaire contained demographic data of patients including sex and age. In the second part there was a table for writing all drugs prescribed including drug name, dosage form, dosage amount, rout of administration and timing of the administration.

During 6 months of 2005, a pharmacy student visited patients daily and collected the data. A total number of 116 patients of ICU ward were visited during the study and one questionnaire was filled for each visit. Data for total number of 567 prescriptions were recorded. The extent of occurrence and frequency of potential pharmacokinetic drug interactions were investigated based on the reference text Drug Interaction Facts published in the year 2004. Another text named the United States Pharmacopoeia Drug Information(USP- DI), volume 1, publication year 2000 was used for drugs not present in Drug Interaction Facts.

All of the potential pharmacokinetic drug interactions were extracted and classified in terms of mechanism, significance, onset, severity and documentation of pharmacokinetic interactions. Onset shows how rapidly the clinical effects of interaction can occur. This determines the urgency with which preventive measures should be instituted to avoid the consequences of the interaction. Severity of interactions is classified in 3 categories: major (life threatening or permanent damage), moderate (deteriorating patients status), minor (bothersome or with little effect). Purpose of documentation is the confidence that an interaction can occur based on supporting biomedical literature (5). In terms of documentation only established, probable and suspected interactions were considered. Regarding significance, only grade 1 and 2 drug interactions were recorded.

Since USP-DI does not divide drug interactions based on their severity, significance and documentation therefore a few number of pharmacokinetic drug interactions could not be categorized.

Result

A total number of 116 patients were enrolled the study with the mean age (±SD) of 46(± 7) years. 65 (%56.03) patients were male and 51 (%43.97) were female.

From 567 prescriptions, 413 pharmacokinetic interactions were identified. These interactions were in 64 types. Five of the most common types have shown respectively in table 1.

Among the mechanisms of pharmacokinetic interactions, the most dominant type was metabolic interaction with a total percentage of %60.05. Table 2 shows the frequency of 413 pharmacokinetic interactions based on their mechanism.

In terms of the onset of action, %61.00 were delayed-type which could take up to several days or weeks to occur, needing no immediate concern or medical intervention.

Regarding severity, %17.43 were due to major interactions the foremost interactions

Table 1. The most common pharmacokinetic interactions in the studied ICU prescriptions

No	Interaction between	Number in 413 cases of interactions	Percentage in 413 cases of interactions
1	Ciprofloxacin- Sucralfate	137	%33.17
2	Ciprofloxacin-Magnesium sulfate	22	%5.32
3	Rifampin- Isoniazid	21	%5.08
4	Digoxin- Metoclopramide	17	%4.11
5	Theophylline- Rifampin	16	%3.87

were moderate interactions (%73.61) with less clinical problem.

In terms of significance, %17.43 of them were type1 which are severe and well documented interactions but the most frequent interactions observed were type 2 (%73.61) which are moderate and documented or suspected interactions.

The most prevalent interaction based on the documentation was probable interactions (%39.95).

Table 3 shows distribution of drug interactions based on the onset, severity, significance and documentation.

There was a direct relationship between number of medication entries in prescriptions and frequency of prescriptions with at least one pharmacokinetic drug interaction. Figure 1 illustrates this relationship ($r = 0.98$, $p < 0.0001$).

Discussion

Whenever a patient receives multiple drug therapy, the possibility of a pharmacokinetic interaction exists. Because of large interpatient and intrapatient variabilities in drug disposition, pharmacokinetic interactions rarely produce serious clinical consequences (1). In previous studies total drug interactions were examined (2), (4), however in this study pharmacokinetic interactions were evaluated separately. This study shows the most prevalent pharmacokinetic interactions in ICU may be metabolic and those related to absorption alterations (about %98.31). Interaction between ciprofloxacin and sucralfate, an absorption type, was the most prevalent one (%33.17). In the ICU, nurses usually determine timing of drug administration; consequently it is possible that lack of information about the interactions exacerbates their occurrence. This intensifies the importance of awareness of nurses as well as physicians about drug interactions, their nature and the ways to avoid them. Many absorption interactions can be prevented by considering an appropriate lag time between drug administrations. Health care professionals in ICU should also be alert about drugs with enzyme inducing or inhibiting affects in order to decrease metabolic interactions.

In this study only potential pharmacokinetic interactions were determined, nevertheless, it is possible these interactions lead to changes in drug effects, thus education of physicians and nurses seems necessary. About metabolic interactions role of physicians seems to be more

Table 2. Distribution of different mechanisms of the pharmacokinetic interactions

Mechanism	Total number	Percentage
Metabolism	248	%60.05
Absorption	158	%38.26
Elimination	4	%0.97
Distribution	3	%0.72

Table 3. Categories of drug interactions

Interaction type	Number of interactions	Percentage
Onset		
Delayed	251	%61.00
Rapid	162	%39.00
Severity		
Major	72	%17.43
Moderate	335	%73.61
Minor	0	%0.00
Unknown	37	%8.96
Documentation		
Established	102	%24.7
Probable	166	%39.95
Suspected	109	%26.39
Unknown	37	%8.96
Significance		
1	72	%17.43
2	335	%73.61
Unknown	37	%8.96

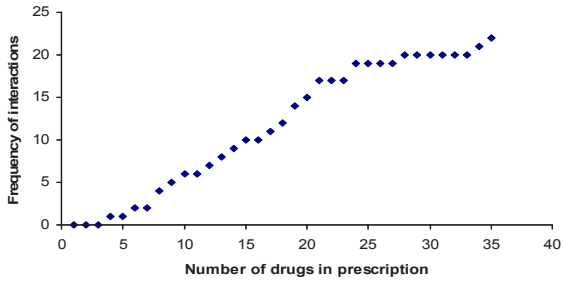

Figure 1. Relationship between number of prescribed drugs and frequency of interactions (P<0.0001, r = 0.98)

important than nurses. Our study showed the higher the number of drugs in prescriptions, the higher the number of interactions. Therefore, polypharmacy should be avoided as much as possible and careful drug therapy should be performed when applicable.

Monitoring may be especially helpful when there is some coexisting pathophysiological conditions affecting drug disposition, for example malabsorption, marked instability of the systemic circulation or of renal and hepatic function (6). It seems that with regards to high prevalence of drug interactions in ICU prescriptions, attendance of a clinical pharmacist may prevent and reduce the frequency and severity of drug interactions interactions.

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