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A QUESTIONNAIRE STUDY ON THE EVALUATION OF DIFFERENT PHARMACOKINETIC DRUG INTERACTIONS IN THE INTENSIVE CARE UNIT OF AL-THOURA TEACHING HOSPITAL IN EL-BEIDA, LIBYA

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Abstract: **The concomitant use of many drugs by ICU (Intensive Care Unit) patients is almost unavoidable. In these patients, pharmacokinetic drug interactions are terribly possible. This current questionnaire study was designed to evaluate the drug interactions in the ICU patients of Al-Thoura Teaching Hospital in El-beida city, Libya. A questionnaire study was designed and used to collect the requisite knowledge. The present study was conducted in the ICU of Al-Thoura Teaching Hospital affiliated to Omar Al-Mukhtar University, Faculty of Pharmacy. Overall, the data was collected from 450 ICU prescriptions from April 2019 to May 2019. The extent of prevalence and the frequency of potential pharmacokinetic drug interactions were categorized on the basis of the reference text *Drug Interaction Facts*. There were 300 pharmacokinetic drug interactions in the 450 studied ICU prescriptions that were divided into 64 varieties of pharmacokinetic drug interactions. The first observed drug interaction was between ciprofloxacin and sucralfate. The mechanisms of pharmacokinetic drug interactions were associated with absorption (76.66%), metabolism (18.33%), distribution (3.33%), and elimination (1.66%). There was a direct relationship between the frequency of pharmacokinetic drug interactions and the number of drugs per prescription (r=0.97, p<0.0001). During this survey study, we concluded that the higher number of drugs in prescriptions, the higher number of drug interactions. Therefore, the clinical pharmacists should be aware of the drug interactions in the ICU, and careful drug therapy should be performed if applicable.**

Keywords: **Pharmacokinetic drug interactions, intensive care unit (ICU), Al-Thoura Teaching Hospital, El-beida, Libya**

I. INTRODUCTION

A drug interaction may be described as a modification of the consequences of one drug (object drug) by the previous or concurrent administration of another drug (precipitant drug) (Tatro, 2006 and RPSGB, 2009). In a study involving 9900 patients with 83200 drug exposures, 234 (6.5%) of 3600 adverse effects of drug reactions were accredited to drug interactions (Leape et al., 1995). In a study by (Köhler et al., 2000), there were about 221 drug interactions found in the prescriptions of 160 patients in the internal ward; 24 (10.85%) of them were major, 115 (52.03%) were moderate, and 82 (37.10%) were minor interactions. In another study by (Reis and Cassiani, 2011), they evaluated the drug interactions in 2130 prescriptions of four wards in a teaching hospital. Their results showed a total number of 2960 medications with 130 types of drug interactions. The mechanisms of drug interactions were not determined in this study (Reis and Cassiani, 2011). In terms of mechanisms, drug interactions are usually characterized as either pharmacokinetic or pharmacodynamic. Pharmacokinetic interactions influence the disposition of a drug within the body and involve the impact of one drug on the absorption, distribution, metabolism, and excretion of another one (Lubinga and Uwiduhaye, 2011). Pharmacodynamic interactions are associated with the pharmacological activity of the interacting medication. They did not involve changes in the blood serum concentration of the medicine (Leape et al., 1995). Additionally, they need not

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been amply studied or according to textbooks (Tatro, 2006). The ICU is differentiated from other wards due to the high frequency of medicines received by the patients. So, it's rational to expect a high probability of pharmacokinetic drug interactions in ICU prescriptions (Cruciol-Souza and Thomson, 2006). This study was designed to analyze the incidence of pharmacokinetic drug interactions in the prescriptions of the ICU ward in Al-Thoura Teaching Hospital, El-beida city, Libya.

II. METHODS AND MATERIALS

The proposal of this questionnaire study was approved by the ethical committee of Omar Al-Mukhtar University, Faculty of Pharmacy. The questionnaire was designed for gathering data. The initial part of the form contained demographic information of patients as well as their gender and age. The second half of the form contained a table for all medicines prescribed as along with drug names, dosage types, dosage quantities, routes of administration, and timing of administration. For two months in 2019, patients were visited daily and data gathered. A total of 120 ICU patients were visited during the study, and one form was filled per visit. The data for the total number of 450 ICU prescriptions was recorded. The prevalence and frequency of potential pharmacokinetic drug interactions were investigated based on the reference text *Drug Interaction Facts* (2004). The severity of drug interactions is classified under three categories: minor, moderate, and major. In terms of documentation, only the established, probable, and suspected interactions were considered. Regarding significance, only grade 1 and 2 of drug interactions were recorded. Since USP-DI does not divide drug interactions based on their severity, significance, and documentation, so a few pharmacokinetic drug interactions could not be classified.

III. RESULTS

The study was conducted on 120 patients with a mean age (46±5) years. 65 (54.16%) of the patients were males, and 55 (45.83%) were females. From the 450 ICU prescriptions, 300 pharmacokinetic drug interactions were found out. These drug interactions were in 64 varieties of drugs. Five of the most common types are recorded in Table 1.

Table-1 The most common pharmacokinetic drug interactions in ICU prescriptions.

No.	Drug Interactions	Number of 300 Case Interactions	% of Case Interactions
1	Ciprofloxacin-Suclarafate	180	60.00%
2	Metronidazole-Omeparazole	76	25.33%
3	Digoxin-Metoclopramide	25	8.33%
4	Rifampin-Isoniazide	9	3.00%
5	Doxycycline-Clindamycin	10	3.33%

Among the mechanisms of pharmacokinetic drug interactions, the first dominant type was absorption interaction with a total proportion of 76.66%. Table 2 shows the frequency of 300 pharmacokinetic drug interactions based on their mechanisms.

Table-2 Distribution of different mechanisms of the pharmacokinetic drug interactions.

Different Mechanisms	Total Number	%
Absorption	230	76.66%
Metabolism	55	18.33%
Distribution	10	3.33%
Elimination	5	1.66%

Table 3 illustrates the distribution of drug interactions based on the onset, severity, significance, and documentation.
Regarding severity, 6.66% were major interactions, while 50.00% were moderate interactions with less clinical drawbacks. In terms of onset of action, 50.66% were delayed-type that might take several days or weeks to occur, needing no direct concern or medical interference. In terms of significance, 24.00% of them were type 1 that were severe and well-documented interactions, however, the foremost frequent interactions discovered were type 2 (76.00%) that were moderate and documented or suspected interactions. The most current interaction supported the documentation was probable interactions (43.33%). There was an immediate relationship between the frequency of drug interactions and the number of drugs in prescription. Figure 1 shows that relationship ($r=0.97$, $p<0.0001$).

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Table-3 Different categories of drug interactions.

Drug Interaction Type	Total Number of Interactions	%
ONSET		
Delay	152	50.66%
Rapid	148	49.33%
SEVERITY		
Major	20	6.66%
Moderate	150	50.00%
Minor	130	43.33%
DOCUMENTATION		
Suspected	110	36.66%
Probable	130	43.33%
Established	56	18.66%
Unknown	4	1.33%
SIGNIFICANCE		
1	72	24.00%
2	228	76.00%

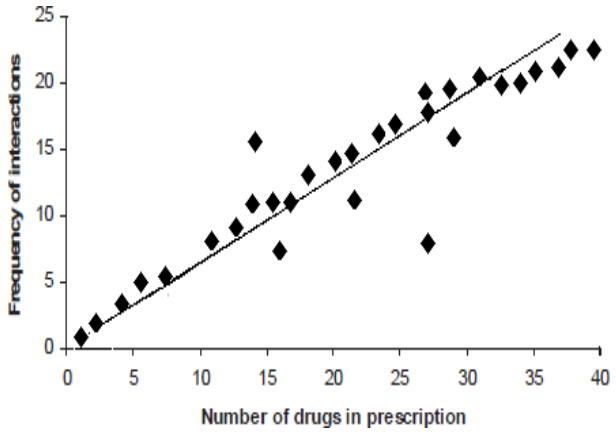

Fig. 1. Relationship between frequency of drug interactions and number of drugs in prescription.

IV. DISCUSSION

There is a chance of a pharmacokinetic interaction whenever a patient receives multiple drugs for treatment. As a result of massive inter-patient and intra-patient variabilities in drug disposition, the pharmacokinetic drug interactions rarely have severe clinical consequences (Tatro, 2006). In previous studies, the total drug interactions were examined (Leape et al., 1995 and Kashuba et al., 2006), but in this study, the pharmacokinetic drug interactions were evaluated severally. This study showed the foremost current pharmacokinetic drug interactions in the ICU and could also be metabolic and those associated with absorption alterations (approximately 76.66%). Interaction between ciprofloxacin and sucralfate, an absorption kind, was the foremost prevalent one (60.00%). In the ICU, nurses sometimes confirm the timing of drug administration; consequently, it is possible that lack of knowledge regarding drug interactions might exacerbate their occurrence (Dresser et al., 2000). This intensifies the importance of awareness of nurses as well as physicians regarding drug interactions, their nature, and also the ways to avoid them. Several absorption interactions can be prevented by considering an appropriate lag time between drug administrations (Andersson et al., 1990). Health care professionals in the ICU should also be alert regarding drugs with catalyst inducing or inhibiting effects to decrease metabolic interactions (Lubinga and Uwiduhaye, 2011). In this study, only potential pharmacokinetic interactions were determined; however, it is possible that these interactions cause changes in drug effects (Bjornsson et al. 2003), so it is necessary to educate physicians and nurses about these interactions. Regarding metabolic interactions, the role of physicians seems to be more necessary than that of nurses. Monitoring could also be particularly useful once there are some coexistent pathophysiological conditions touching drug disposition, for instance, absorption, marked instability of the systemic circulation or renal and internal organ function (Niemi et al., 2003). It appears that with regards to the high prevalence of drug interactions in ICU prescriptions, attending of a clinical pharmacist could prevent and reduce the severity and frequency of different drug interactions.

V. CONCLUSION

We concluded that the higher number of drugs prescribed, the higher number of drug interactions. Therefore, clinical pharmacists should be aware of the drug interactions in the ICU, and careful drug therapy should be performed if applicable.

VI. CONFLICTS OF INTEREST

We hereby declare that there are no conflicts of interest regarding the publication of this questionnaire study.

VII. ACKNOWLEDGMENT

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