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STUDY THE POTENTIAL DRUG-DRUG INTERACTION THROUGH PRESCRIPTIONS ANALYSIS IN SOME SANA'A CITY HOSPITALS, YEMEN

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ABSTRACT

Drug-drug interactions (DDIs) occur during the co-administration of medications. They are a common cause of adverse drug reactions (ADRs) and lead to increasing healthcare costs. **Objective:** To assessment of frequency, severity and mechanism of DDIs through prescriptions analysis in some Sana'a hospitals. **Methods:** The cross-sectional observation study was performed on some Government and private hospitals in Sana'a city from June 2022 to April 2023. Prescriptions with two or more drugs prescribed were selected for the study stratified by age, sex, and frequency of common interacting drugs. Drugs were analyzed for interactions by using the Medscape drug interaction checker. Potential drug-drug interactions (pDDIs) were classified based on the severity and mechanism of interactions. **Results:** A total of 1321 prescriptions were collected from various section of both Government and private hospitals, 398 prescriptions with one drug were excluded from study and 923 prescriptions analyzed, of which 299 prescriptions had 989 pDDIs. From these, 51.5% was female, and 48.5% male. The study findings showed that the prescriptions for Private hospital had the greatest number of drug interactions. Most of the pDDIs by mechanisms were pharmacokinetic drug interactions (52.8%) followed by pharmacodynamic (47.2%). The Department in the hospital I.C. U had the greatest number of drug interactions. A severity assessment showed that majority of the DDIs were moderate (58.6%) followed by Mild (24.2%) then Sever (16.4%). The study results showed that as the number of drugs increases in a prescription, the number of DDIs also increases. **Conclusion:** In our study, we found that most common pDDIs were more in prescriptions of private hospital in Sanaa, Pharmacokinetic in nature and of moderate severity. The number of pDDI increased with increase the number of drugs prescribed.

KEYWORDS: Drug-Drug Interaction; Adverse Drug Reaction; Prescription; Sana'a city; Yemen.

INTRODUCTION

Drug–drug interactions (DDIs) occur during the co-administration of medications. They are a common cause of adverse drug reactions (ADRs) and lead to increasing healthcare costs.[1,3] Many DDIs are not identified during the clinical trial phase and are reported after the drugs are approved for clinical use. Such DDIs often lead to patient morbidity and mortality, accounting for 3–5% of all inpatient medication errors.[4] Clinical DDIs can also cause serious social and economic problems. Thus, there is an urgent need to detect or determine DDIs before medications are approved or administered.[5] There are different factors for the occurrence of potential DDIs. The age of the patient, common disease state and polypharmacy; pharmacokinetic and pharmacodynamic nature of drugs; the influence of disease on drug metabolism; prescriber issues. Such as multiple drug prescription by multiple prescribers, inadequate knowledge of prescribers' on DDIs or poor recognition of the relevance of DDIs by prescribers are among the risk factors significantly associated with the occurrence of potential DDIs.[6,7]

DDIs are also more frequent in hospitalized patients, patients who stay in the hospital for a longer time, and/or receive more drugs per day.[8,11] Hospitalized patients are more likely to be affected by DDIs because of severe and multiple illnesses, comorbid conditions, chronic therapeutic regimens, poly-pharmacy, and frequent modification in therapy.[12] Among hospitalized patients, elderly patients are at higher risk of potential DDIs, and

the occurrence of potential DDIs ranges from 3 to 69%, depending on the specific area and population.

The increased prevalence was found to be related to the presence of multiple chronic illnesses, the use of multiple medications, and altered pharmacokinetics in elderly patients.[13] Physicians and pharmacists alert fatigue is a common reason for the occurrence of drug-drug interactions for patients receiving interacting drugs. Even though computerized DDI alert systems could decrease the occurrence of DDIs, numerous alerts produced by such system lead physician and pharmacist alert fatigue. This alert fatigue results in a considerable override of DDI alerts. A study done in Japan showed physicians overrode DDI alerts at a high rate in computerized drug interaction alert system.[14]

DDIs may have undesirable or harmful effects in addition to their desirable effects. Clinically significant DDIs may cause potential harm to patients, harmful outcomes, and resulting in an estimated cost of more than $1 billion per year to governmental health care system expenditure.[15]

DDIs are classified as pharmacodynamic or pharmacokinetic, and may result in increased or decreased efficacy, in treatment failure as well as in increased toxicity of medication**s** Pharmacodynamic interactions may be divided into three subgroups: Direct effect at receptor function, Interference with a biological or physiological control process and Additive/opposed pharmacological effect, for example, sedatives can potentiate each other. The same is true of alcohol, which can potentiate the sedative effects of many drugs.[16]

PD DDIs are typically categorized as synergistic, additive, or antagonistic, although these terms are often used inappropriately.[17]

Pharmacokinetics interaction**s:** defined as the influence of a second drug on the study drug. The second drug can affect the absorption, distribution, metabolism, and elimination (ADME) of the study drug. Pharmacokinetic: altered concentration, Bioavailability: absorption or first-pass metabolism, Clearance: metabolism or excretion of active drug, Distribution: cell membrane transport to the site of action.[18]

In Yemen, no previous studies were attempted to document the pharmacoepidemiology of potential DDIs and no attempts has been done to minimize the DDIs in internal medicine wards in hospitals. Therefore, the aim of the study was to assess of frequency, severity and mechanism of pDDIs through prescriptions analysis in some Sana'a hospitals.

MATERIALS AND METHODS

Materials: Prescriptions.

METHODOLOGY

This cross-sectional observation study was performed on some government and private hospital in Sana'a city. The hospital had various wards such as an intensive care unit, surgery ward, emergency, obstetrics & Gynecology, internal medicine wards. The study period was 11 months (June 2022–April 2023), during which the data were collected. The total study sample of 1321 prescriptions were randomly collected. Prescriptions with one drug (n= 398) were excluded from study.

Prescriptions with two or more drugs prescribed (n= 923) were selected for the study stratified by age group sex, and frequency of common interacting drugs, presence and severity of interactions. Information about patient's demographic profile, diagnosis and information about prescribed drugs were collected. The data were analyzed by using the Medscape drug interaction checker, drugs. com checker and stockley`s drug interactions index.[19] This computer program will give information about potential DDI (pDDI). It also informs about its severity, management, and monitoring parameters with scientific references.

Classification of Potential Drug–Drug Interaction On the basis of the profile of medications prescribed, the pDDIs were identified and classified.

According to the mechanism, pDDIs were classified as: (a) pharmacokinetic, and (b) pharmacodynamic.

According to severity, pDDIs were classified as: (1) major (sever), the effects are potentially life threatening or capable of causing permanent damage; (2) moderate, the effects may cause deterioration in patients' clinical status and additional treatment or extension of hospital stay; (3) minor (mild), the effects are usually mild; and (4) contraindication, Consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome.

Pharmacokinetic pDDIs were further classified as either increase/decrease in: (a) absorption, (b) distribution, (c) metabolism, and (d) excretion.

Pharmacodynamic pDDIs were further classified as: (a) synergistic or (b) antagonistic.

Statistical analysis was done using appropriate statistical software (MS Excel, Spss.

RESULTS

A total of 1321 prescriptions were collected from various section of both Government and private hospitals, 398 prescriptions with one drug were excluded from study and 923 prescriptions as 772 from private hospital, 150 prescriptions from government hospital (Table 1). we have found n = 623 (67%) prescriptions without any DDI and remaining n = 299 (32%) prescriptions had at least one interacting combination, showed 989 pDDIs.

Different variables that are in close association with potential DDIs are summarized in Table 2 like age with 60.5% adult, and 39.5% elderly (Figure 1), Further pDDIs in gender was 51.5% female, and 48.5% of male (Figure 2). The study findings showed that the prescriptions for Private hospital had the greatest number of drug interactions on average 81.6% whereas Government hospital had 18.4% of pDDIs. The Prescriptions for patients in ICU had the greatest average number of DDIs (43.5 %), followed by internal medicine (22.1 %) then inpatient was (15.1 %), and 7 %, 4.7 %, 3.3 %, 3% in surgery, emergency, obstetrics, general medicine, respectively (Table 2, Figure 3).

Table 1: Presence of potential drug-drug interactions (pDDI).

Type of hospitals	N (No of prescription)	N (Prescriptions with interaction)
Private	772	244 (32%)
Government	150	55 (37%
Total	923	299 (32 %)

Table 2: Different variables associated with possibility of drug-drug interactions.

	N (Prescriptions with interaction)(N= 299)	Percentage
Age Group		
Adult	181	60.5%
Elderly	118	39.5%
Gender		
Female	154	51.5%
Male	145	48.5%
Type of hospital		
Governmental	55	18.4%
Private	244	81.6%
Department in the hospital		
I.C. U	130	43.5%
Inpatient	45	15.1%
Surgery	21	7.0%
Emergency	14	4.7%
Obstetrics & Gynecology	10	3.3%
Internal medicine	66	22.1%
Neurology	4	1.3%
General Medicine	9	3.0%

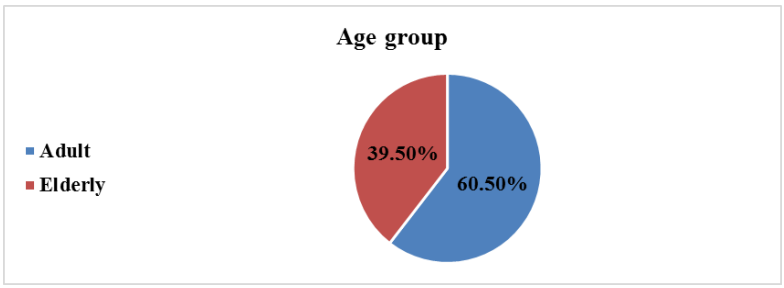

Fig. 1: Correlation of age with possibility of drug-drug interaction.

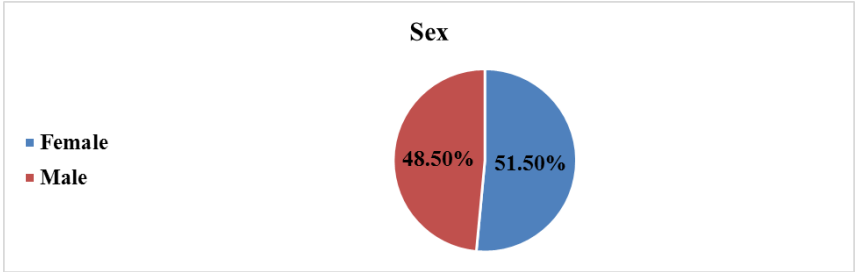

Fig. 2: Correlation of gender with possibility of drug-drug interaction.

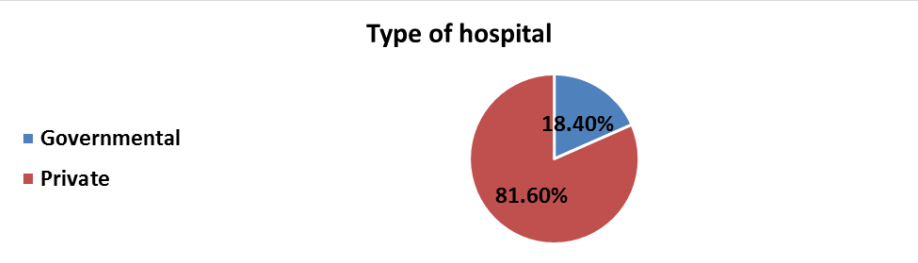

Fig. 3: Correlation of type of hospital with possibility of drug-drug interaction.

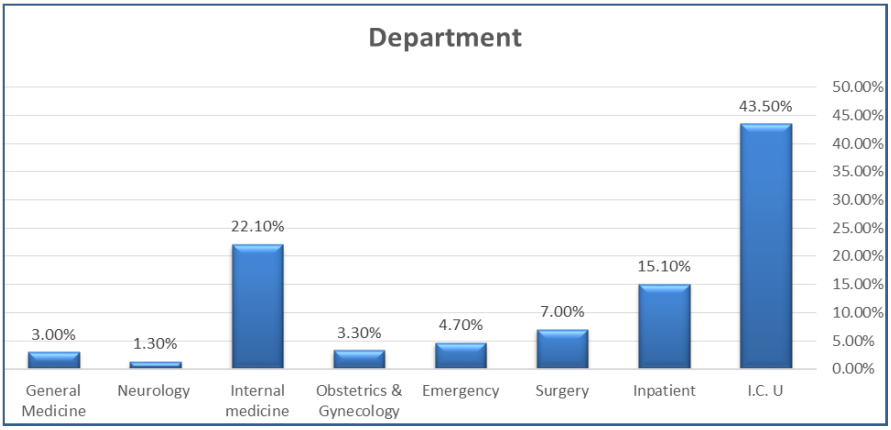

Fig. 4: Correlation of department of hospital with possibility of drug-drug interaction.

Categorization of drug–drug interactions based on severity

There was a greater number of moderate DDIs than sever or mild interactions (68 % DDI & 59% prescription), 21 % & 19 % and 10% & 21 %, respectively; (Table 3 & figure 5).

Table 3: Categorization of drug–drug interactions based on severity.

Severity	Number of drugs interaction (n= 989) %	N (Prescriptions) %
Mild	106 (10 %)	64 (21.4%)
Moderate	675 (68 %)	177 (59 %)
Severe	208 (21 %)	58 (19 %)
Total	989 (100 %)	299 (100 %)

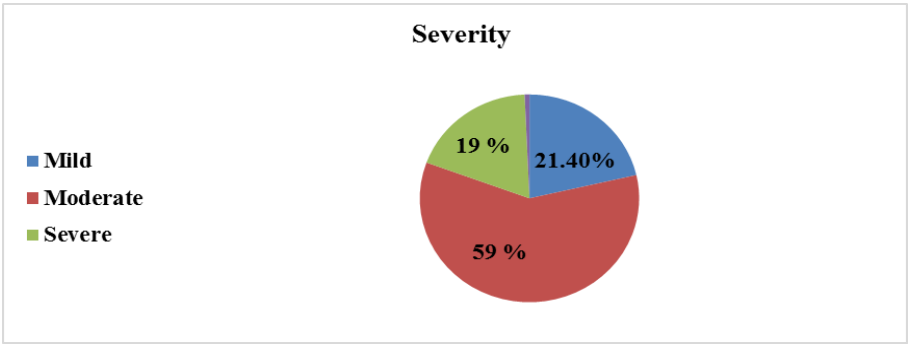

Fig. 5: Categorization of drug–drug interactions based on severity.

Frequency of number of pDDIs per prescription

The study findings showed that the frequency of pDDIs per prescription had at greatest with 13- 18 DDI in one prescription (0.33 %) and one DDI in 91 prescription (30%). The results are represented in Table 4.

Table 4: **Frequency of number of pDDIs per prescription.**

NUMBER OF PDDIS	NUMBER OF PRESCRIPTION (%) N= 923
0	624 (68%)
1	91 (30%)
2	67 (22.5%)
3	39 (13%)
4	31(10%)
5	19 (6%)
6	12 (4%)
7	14 (5%)
8	8 (2.7%)
9	6 (2%)
10	3 (1%)
11	3 (1%)
12	4 (1.3%)
13	1 (0.33%)
18	1 (0.33%)

Categorization of drug–drug interactions based on mechanism

Our study found that among the Pharmacokinetic interaction (158 prescription & 52,8 %), of the (19 %) were absorption, (7 %) were distribution, the greatest causes were 58.9 % were metabolism and 4.4 % were excretion (table 5 & figure 6). Pharmacodynamics interactions: Among this 141 prescription & 47.2 %, of (44.7%) were antagonist, 37.6 % were additive and 17.7 % were synergism (table 5 & figure 6). Unknown mechanism was 10.8 %.

Table 5: Categorization of drug–drug interactions based on mechanism.

Mechanism		Number of prescription (%)	Percentage of drug-drug Interactions
Pharmacokinetic	Absorption	30	19.0%
	Distribution	11	7.0%
	Metabolism	93	58.9%
	Excretion	7	4.4%
	Total	158	52.8%
Pharmacodynamics	Additive	53	37.6%
	Antagonist	63	44.7%
	Synergism	25	17.7%
	Total	141	47.2%
Unknown		17	10.8 %

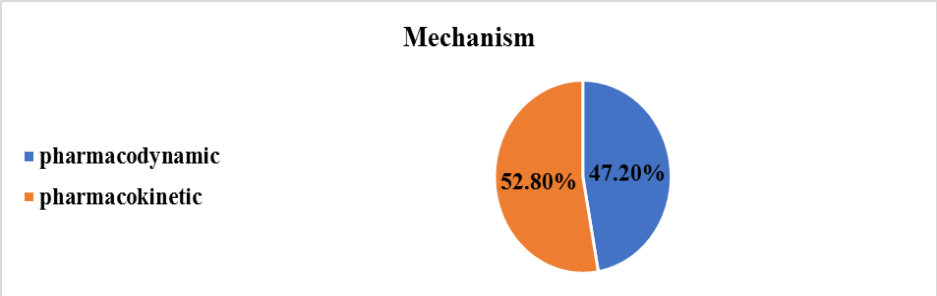

Fig. 6: Categorization of drug–drug interactions based on mechanism.

The type of drug combinations showing DDIs

Our study showed that the type of drug combinations showing DDIs are shown in Tables 6-9 and Figure 7. The most frequent drug interactions were the combination of Phenytoin + pantoprazole, Metoclopramide + acetaminophen (18.75 %). The combination of Phenytoin + Ondansetron was (15.6%). The combination of Amoxicillin + aspirin was (9.38%). Table 6.

Table 6: The drug combinations showing DDI.

Drug- Drug Interaction	frequency in prescription	Percentage
Phenytoin + pantoprazole	18	18.75%
acetaminophen + heparin	7	7.29%
Amoxicillin + aspirin	9	9.38%
Metoclopramide + acetaminophen	18	18.75%
Phenytoin + Ondansetron	15	15.63%
piperacillin + heparin	7	7.29%
TOTAL	**96**	**100%**

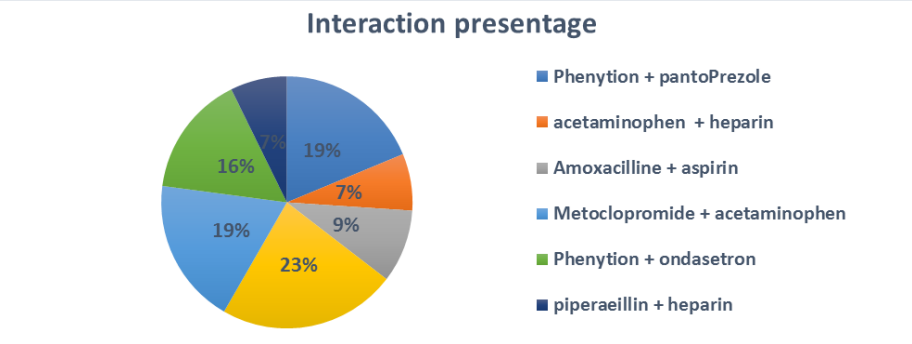

Fig. 7: The drug combinations showing DDIs.

Table 7: Distribution of the study variables by type of hospital.

		Type of Hospital			
		Governmental		Private	
		N	%	N	%
Mechanism	**pharmacodynamics**	29	52.7%	112	45.9%
	pharmacokinetic	26	47.3%	132	54.1%
Type of interaction	**Unknown**	1	1.8%	16	6.6%
	Absorption	8	14.5%	75	30.7%
	Distribution	30	54.5%	44	18.0%
	Metabolism	15	27.3%	103	42.2%
	Excretion	1	1.8%	6	2.5%
Severity	**Mild**	5	9.1%	59	24.2%
	Moderate	34	61.8%	143	58.6%
	Severe	16	29.1%	40	16.4%
	contraindication	0	0.0%	2	0.8%
Number of drugs	**<=5 drugs**	30	54.5%	36	14.8%
	6-10 drugs	23	41.8%	128	52.5%
	11-15 drugs	2	3.6%	56	23.0%
	16-20 drugs	0	0.0%	19	7.8%
	>=21 drugs	0	0.0%	5	2.0%
Number of Interactions	**<5**	47	85.5%	181	74.2%
	5-10	7	12.7%	55	22.5%
	>10	1	1.8%	8	3.3%

Table 8: Distribution of the study variables by sex.

		Sex			
		Female		Male	
		N	%	N	%
Mechanism	**pharmacodynamics**	82	53.2%	59	40.7%
	Pharmacokinetic	72	46.8%	86	59.3%
Type of interaction	**Unknown**	6	3.9%	11	7.6%
	Absorption	45	29.2%	38	26.2%
	Distribution	50	32.5%	24	16.6%
	Metabolism	50	32.5%	68	46.9%

	Excretion	3	1.9%	4	2.8%
Severity	**Mild**	21	13.6%	43	29.7%
	Moderate	100	64.9%	77	53.1%
	Severe	32	20.8%	24	16.6%
	Contraindication	1	0.6%	1	0.7%
Number of drugs	**<=5 drugs**	26	16.9%	40	27.6%
	6-10 drugs	72	46.8%	79	54.5%
	11-15 drugs	39	25.3%	19	13.1%
	16-20 drugs	12	7.8%	7	4.8%
	>=21 drugs	5	3.2%	0	0.0%
Number of Interactions	**<5**	108	70.1%	120	82.8%
	5-10	44	28.6%	18	12.4%
	>10	2	1.3%	7	4.8%

Table 9: Distribution of the study variables by age.

		Age			
		Adult		**Elderly**	
		N	**%**	**N**	**%**
Mechanism	**pharmacodynamics**	75	41.4%	66	55.9%
	Pharmacokinetic	106	58.6%	52	44.1%
Type of interaction	**Unknown**	14	7.7%	3	2.5%
	Absorption	52	28.7%	31	26.3%
	Distribution	41	22.7%	33	28.0%
	Metabolism	71	39.2%	47	39.8%
	Excreation	3	1.7%	4	3.4%
Severity	**Mild**	42	23.2%	22	18.6%
	Moderate	108	59.7%	69	58.5%
	Severe	29	16.0%	27	22.9%
	contraindication	2	1.1%	0	0.0%
Number of drugs	**<=5 drugs**	38	21.0%	28	23.7%
	6-10 drugs	84	46.4%	67	56.8%
	11-15 drugs	39	21.5%	19	16.1%
	16-20 drugs	15	8.3%	4	3.4%
	>=21 drugs	5	2.8%	0	0.0%
Number of Interactions	**<5**	140	77.3%	88	74.6%
	5-10	35	19.3%	27	22.9%
	>10	6	3.3%	3	2.5%

DISSCUSION

DDIs are becoming serious issue with complex drug therapies. DDIs can result in anything from minor morbidities up to fatal consequences. Our studies have shown that up to 32% of private hospital prescription associated with DDIs and DDIs are responsible for up to 37% of government hospital. The incidence of the pDDIs in our study patient population was 32%. In other studies, incidence of pDDIs were quiet variable from 44% to 80%.[20,22] Among them sever potential DDIs were 18.7% (n=56), moderate interactions 59.2% (n=177) and mild interactions 21.4% (n=64) observed in I.C.U ward.

These results were contradictory to results obtained in Ismail et al.[23] study, where major interactions 12.8% (n=53), moderate interactions 61.2% (n=253), and minor interactions of 26% (n=107). Our study found that among the 989 interactions, 52% were pharmacokinetic DDIs, 47.2% were pharmacodynamic DDIs and 10.8% involved unknown mechanisms. These findings were different from another study reported in the literature where the discharge medications of the inpatients were of concern and pharmacodynamic DDIs were dominant.[24] In our study, from 158 pharmacokinetic pDDIs were affecting absorption (19%), followed by metabolism (58.9%) and excretion (4.4%) processes. This finding was similar to another published report where affected the metabolism, followed by absorption, distribution and excretion of the drugs.[25]

Among 141 pharmacodynamic pDDIs, were antagonistic (44.7%) followed by additive (37.6%) and synergistic (17.7%). These findings were different from another study, 523 significant potential pharmacodynamic DDIs were detected, of which [298 (56.98%)] were synergistic, followed by 209 (39.96%) showing a potential for antagonism.[26] Our study found that the average number of DDIs per patient increased as the number of drugs in the prescription increased. This finding was similar to

another published report where the potential for a drug interaction increased from 13% to 82% as the number of medications increased from 2 to 7 or more.[27]

In our study frequently occurring pair of drug-drug interaction were the combination of Phenytoin + pantoprazole, Metoclopramide + acetaminophen (18.75 %). The combination of Phenytoin + Ondansetron was (15.6%). The combination of Amoxicillin + aspirin was (9.38%), piperacillin and heparin (2.3 %). It is known that Phenytoin acts as an induction of hepatic drug metabolizing enzyme and decrease the level and effect of pantoprazole. It is also known that Metoclopramide an increase the absorption of acetaminophen. Phenytoin acts as an induction of hepatic drug metabolizing enzyme and decrease the level and effect of Ondansetron. More over a serious interaction may occur if combination of piperacillin and heparin is used, piperacillin will increase the level or effect of heparin by anticoagulation.

CONCLUSION

This study showed that the overall incidence of pDDIs was 32%. It was observed that the number of pDDIs increased linearly with the number of drugs. The majority of interactions was pharmacokinetic in mechanism and showed moderate severity. This study provided a reference data for the surveillance of pDDIs in I.C.U department of a hospitals in Sana'a, Yemen. The major potential DDIs were observed with piperacillin and heparin. Similarly, ciprofloxacin and Ondansetron. Drug-drug interaction should also be included in the curriculum of undergraduate medical and dental students. Pharmacists should be included as member of the healthcare team to raise the standard of rational prescribing and ensuring patient safety.

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DECLARATION OF INTERESTS

None.

AUTHORS CONTRIBUTION

Mohammed A Alkhawlani carried out experiments, collected data, interpreted results and participated in writing manuscript, Ahmed M. Al-Ghani designed and supervised the carry out of experiments and collection of data, Mahmoud Alburyhi conceived and supervised the study.

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