ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 8, Issue 1, 2015

ISSN - 0974-2441

Research Article

ASSESSMENT OF PREVALENCE OF POTENTIAL DRUG-DRUG INTERACTIONS IN MEDICAL INTENSIVE CARE UNIT OF A TERTIARY CARE HOSPITAL IN INDIA

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Received: 26 August 2014, Revised and Accepted: 27 October 2014

ABSTRACT

Background: Critically ill-patients frequently receive multidrug regimens (polypharmacy) with the goal of providing the superlative pharmacotherapeutic support. Drug-drug interaction (DDI) is a specific type of adverse event, which develops due to multiple regimen therapy, and that may lead to significant hospitalization and death.

Methods: A retrospective study was conducted for a period of 3 months to assess the prevalence potential DDIs in medical Intensive Care Unit (MICU) patients of a north Indian tertiary care hospital using Lexi Comp drug interact android mobile application.

Results: A total of 72 patients were identified for this study. 65.27% (47) were males, and 34.72% (25) were females. The average age of the study population was 52 years, and average length of stay in hospital was found to be 7 days. An average of 17.09 drugs per patient was administered to the patients during the study period. 90.02% (65) of patients experienced at least one potential DDI. A total of 222 interactions observed during the study period with an occurrence rate of 3.08 DDI per patient. There were 106 types drug pairs was found to get interacted at least 1 time. Corticosteroids, anticonvulsants, central nervous system depressants, sympathomimetics and quinolone antibiotics are the main class of drugs mostly interacted in MICU.

Conclusion: The study shows that, concomitant administration rate of potentially interacting drugs are very high in MICU. We suggest that, special safety measures must be followed by physicians, pharmacists, and nurses to prevent and monitor DDIs in all departments of the hospital especially in intensive care departments. Health providers must be able to identify and classify drug interactions (DIs), and know how to manage them clinically, that is, how to minimize or more over prevent them. Practice of a computer assisted DI checker before prescribing/administering of the drugs can avoid DDIs. In settings with multiple drug use like in ICUs, attendance of a pharmacist or clinical pharmacist, taking the responsibility for monitoring DIs and notifying the physician about potential problems could decrease the harm inpatient and ensure the patient safety.

Keywords: Drug interaction, Intensive care, Patient safety, Rational therapy.

INTRODUCTION

Recent developments in pharmacotherapy have contributed considerably to improve patients' safety and quality of life. As a result of such developments, the number of available medications and their uses is increasing. Although drugs are used to achieve beneficial therapeutic effects, they can also lead to many undesirable consequences. One of such consequences is the development of drug-drug interactions (DDIs). DDI is a specific type of adverse event (AE) that occurs when the effects of the drug is modified, when another drug or food is taken concomitantly. This interaction can cause reduced, null or increased drug effect [1,2]. Evidence from epidemiologic studies suggests that DDIs contribute to 6-30% of AEs [3] with significant hospitalizations or death [4-6]. However, the decision to prescribe two drugs simultaneously is sometimes intentional, with the aim of obtaining a specific pharmacological synergism [7].

Intensive care medicine provides great benefits to patients with life-threatening acute illness or trauma. These benefits are a consequence of advancements in diagnostic testing, technological interventions and pharmacotherapy [8]. Critically ill-patients frequently receive multidrug regimens with the goal of providing pharmacotherapeutic support and cure of a medical condition. These patients are at risk for drug interactions (DIs) because of the complexity of this polypharmacy, as well as the frequent presence of altered organ function. Furthermore, elderly, critically ill patients are particularly vulnerable to AEs from DIs because of the additional presence of multiple co morbid disease states. Published data that delineate the prevalence of DDIs and outcomes in Intensive Care Unit (ICU) patients are scarce [9].

About 5% of all adverse drug reactions in hospitals are caused by DDIs, and the majority of which are avoidable [5,10]. With the increase in the number of patients, multiple diseases, and complex therapeutic regimens, polypharmacy becomes unavoidable in ICU. Polypharmacy increases the risks of drug AEs, especially the DDIs, and that leads to elevated healthcare costs, morbidity and mortality [11]. Within the context of above facts, it is important to investigate potential DDIs in ICUs.

METHODS

A retrospective study was conducted to assess the prevalence of DDIs and to determine drugs involved in potential DDIs in the medical ICU (MICU) of Narayana Hrudayalaya (NH) Hospital, a 200 bedded multispecialty tertiary care hospital at Jaipur, India. Randomly selected patients aged 18 years or older admitted to the MICU from May 2012 to October 2012 who had a length of stay >48 hrs and had more than two medicines in their treatment chart were included in the study.

The data entry form is used to collect the information's from the medical record department of the hospital. Patient demographic details, drug usage, and its administration were collected from the patient file. The DDIs in the medicine chart were assessed by using Lexi Comp drug interact android mobile application trail version [12]. Lexi Comp drug interact [13] classifying the DDIs on the basis of its severity, risk and reliability as follows:

Severity

Major: Effects may result in death, hospitalization, permanent injury, or therapeutic failure.

Moderate: Medical intervention needed to treat effects; effects do not meet criteria for major.

Minor: Effects would be considered tolerable in most cases; no need for medical intervention.

Risk rating

Risk rating	Action	Description
A	No known interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions
B	No action needed	May interact with each other, but there is no evidence of clinical concern
C	Monitor therapy	The benefits of concomitant use of these two medications usually outweigh the risks
D	Therapy modification	Assess whether the benefits of concomitant therapy outweigh the risks or not
X	Avoid combination	The risks associated with concomitant use outweigh the benefits

Reliability

The reliability in documentation of DDIs was categorized as excellent, good fair and poor documentation.

The prevalence of DDIs from each medicine chart were analyzed using the study tool and categorized on the basis of its severity, risk rating and reliability as per the study tool. Prevalence of DDIs of the medicines that are administered together (concomitant) and has major or moderate severity were only included in the study. The interactions of drugs that are not available in Lexi Comp Drug Interact were excluded from the study.

RESULTS

A total of 72 patients were identified for this study. 65.27% (47) were males, and 34.72% (25) were females. The mean age of the study population was 52 (±20.5). The average length of hospital stay was found to be 7 days. A summarized data of DIs determined from this study is illustrated in Fig. 1. A total of 1231 numbers of medicines were used for whole study population during the hospital stay with an average of 17.09 (±6) drugs per patient. Majority of the patients, i.e. about 70.91% (873) received medicine parenterally and for 29.08% (358), drugs administered through other routes.

90.02% (65) of the patient experienced at least one potential DDI. Only 9.72% (7) patients were found without any interaction in their treatment chart. A total of 222 numbers of DDIs were established during the study period with an occurrence rate of 3.08 DDIs per patient. The incidence of major DDIs per patient was found to be 1.05 per patient and for moderate it was 2.03 DDIs per patient (Fig. 2). Graphical representation (Fig. 3) of the relationship of the number of drugs used with the prevalence of DDIs shows that, DDIs increased with increase in a number of drugs. Of the 222, 32.88% (73) were major interactions and 67.11% (149) were moderate interactions (Fig. 1). In terms of the risk rating of the 222 interactions, combination should be avoided (X), combination must consider therapy modification (D) and combination which must be monitor (C) were found to be 7.20% (16), 35.59% (79) and 57.21% (127) respectively. With respect to the reliability of the DDIs, 17.11% of DDIs had excellent documentation, followed by 32.43% DDIs with good documentation. Fig. 4 represents the percentage of prevalence of DDIs according to the severity, risk rating and reliability.

The maximum DDI for one patient was found to be 10 (5 major and 5 moderate). There were 106 types of two drug combinations that were found to get interacted at least 1 time. Of this 106 combinations, 35.84% (38) were major, and 64.15% (68) were moderate (Fig. 1). 51 combinations interacted more than 1 time by producing 167 DDIs and 55 combinations interacted only 1 time (55 DDIs).

Phenytoin followed by hydrocortisone, clarithromycin and fentanyl are the most frequently interacting individual drugs in our study set up. Table 1 shows 10 most frequent interacting individual drug, number of drugs interacted, number of interactions, severity, risk and its reliability. Coming to the most interacted drug combinations, dopamine *Plus* noradrenaline combination is most prominently interacted (7 times) followed by adrenaline *Plus* sodium bicarbonate (6 times), dexametasone *Plus* sodium bicarbonate (6 times) and hydrocortisone *Plus* ofloxacin (6 times) are the focal drug pairs found frequently interacted. Table 2 describes the frequency of interaction, interaction effect, severity, reliability and risk often most frequently interacting combinations.

Assessment of the drug class and combinations, which are mostly involved in the development of interactions in MICU setup were demonstrated in Tables 3 and 4. Corticosteroids (17.1%) are the main class of drug, which has a key role in the development of DDIs in MICU, followed by anticonvulsants (14.9%), central nervous system (CNS) depressants (11.7%) and sympathomimetics (11.2%) (Table 3). Corticosteroids *Plus* quinolone antibiotics (15 times), moderate risk QTc prolonging agents *Plus* other moderate risk QTc prolonging agents (12 times), CYP3A4 substrates *Plus* CYP3A4 inducers (11 times), CNS depressants *Plus* other CNS depressants (10 times), CYP2C19 Substrates *Plus* CYP2C19 inducers (7 times) are the five most frequently interacted drug class combinations observed in our study (Table 4).

DISCUSSION

The present study assessed the prevalence of potentially interacting drugs in MICU patients. This study established a 90.02% of prevalence of DDIs at the investigated MICU during the study period. A wide variation of research conclusion data exists for prevalence of DDIs in ICUs with range between 44.3% and 87.9% [14-18]. The differences in the studied group, study design, and DDI checker sensitivity and specificity make it difficult to compare our study with previous studies. However, comparatively we found there is a higher prevalence of DI in MICU patients of our study.

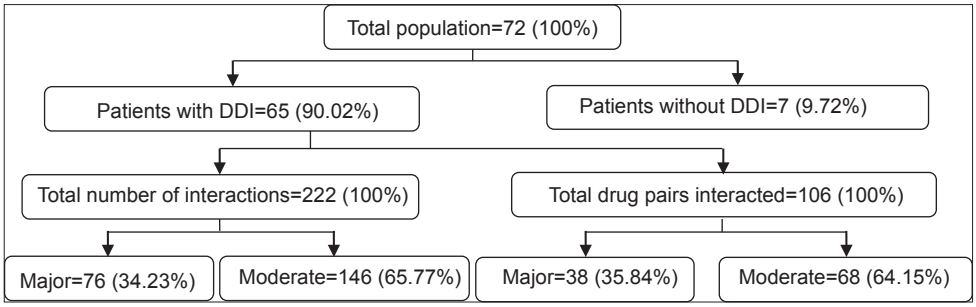

Fig. 1: Summarized data of prevalence of drug-drug interaction

Critically ill patients frequently receive multidrug regimens with the goal of providing pharmacotherapeutic support and cure of a medical condition. Our study confirms that ICU patients receive many drugs. An average of 17.09 drugs was used to treat MICU patients during the current study period and which lead to 222 DDIs with a 3.08 DIs rate per patient. Fig. 4 shows the relationship of DDIs with polypharmacy in ICU. There is a positive relationship between the number of drugs used and chances of interaction [9]. The number of medications has been shown to be a predictive factor for the occurrence of DIs at hospitals, both in the ICU and in internal medicine units [15,19-21]. Several studies proved the evidence of the relationship between the

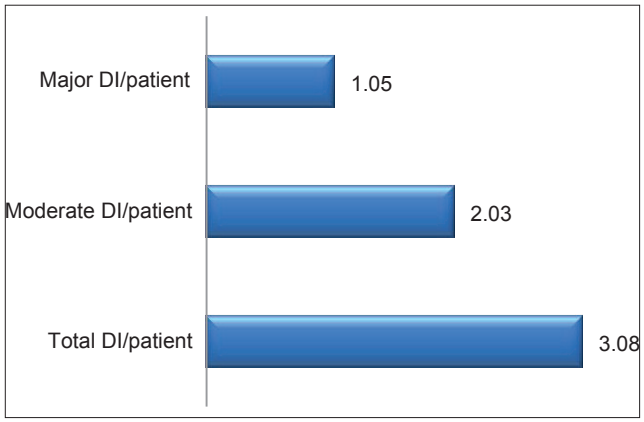

Fig. 2: Rate of drug-drug interactions in medical intensive care unit patients

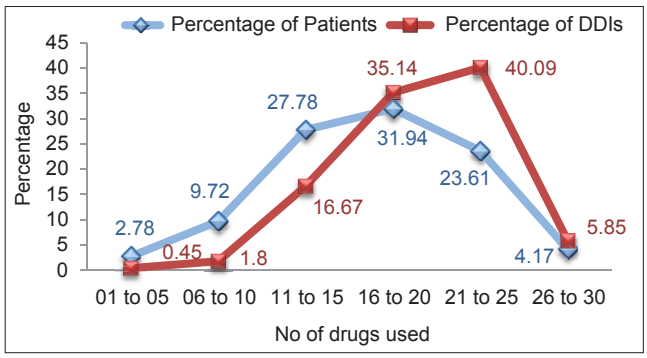

Fig. 3: Drugs usage versus drug interaction and patient population

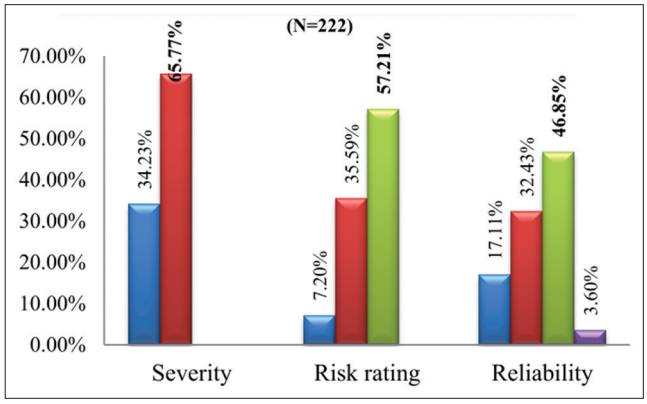

Fig. 4: Percentage of severity, risk and reliability of drug-drug interactions, Severity: MJ=Major; MD=Moderate, Risk rating: X=Combination should be avoided; D=Combination must consider therapy modification; C=Combination which must be monitor; Reliability: E=Excellent; G=Good; F=Fair; P=Poor

polypharmacy in ICU and increased rate of interaction. An average use of 23.6 drugs with 6.1 DIs/patient [22] 18.08 drugs with 3.04 DIs [16], 10 drugs with 2.25 DIs/patient [23], 12 drugs with 2 DIs/patient [17], 9 drugs with 2 DIs/ patient [24] 5.6 drugs with 1.9 DIs/patient [25] are different significant conclusions by many authors, which describes the direct relationship of DIs and polypharmacy in ICU. Our study has a similar result with the study by Lima and De Bortoli Cassiani [16]. The divergence in ICU set up i.e.; neonatal ICU, MICU, coronary care unit (CCU), surgical ICU, intensive therapy unit, etc., and the diversity in therapeutic regimen decides the occurrence rate of DDIs. In line with the results obtained by above authors and other investigations [16,26,27], our study findings exhibited that there are more number of drugs using for the ICU patients, which leads to higher possibility of DI.

The severity is one of the major things to be considered while monitoring the DDIs. It is crucial that health providers are able to identify and classify DIs, and knows how to clinically manage them that is, how to minimize or more over prevent them. Due to the difference in study set up and study tool used, the accuracy of the comparison of severity, reliability, and risk of DDIs with other studies is uncertain. We found 34.23% of major interactions. A study conducted by Rafiei *et al*. in 371 patients found 726 DIs, but of which only 3.44% DIs was major [25]. At the same time, 60% of major interactions reported in a cross-sectional study performed by Carib *et al*. [18]. While discussing the risk rating of DDIs, categories X, D, C were found to be 7.20% (16), 35.59% (79) and 57.21% (127) respectively. It means that any one of the action like, avoidance of the combination, therapy modification or monitoring is essential for all the interactions found in our study. Haji Aghajani *et al*. conducted an investigation to assess the DDIs in CCU using the Lexi Comp drug interact found that category C is more (75.03%), followed by B (14.61%), D (5.42%), X (2.32%) [28]. It reveals that our study group is more in risk when compared to the above population in ICU.

The present study shows that phenytoin is one of the principal individual drug interacted with other 15 drugs and leads to the development of a total of 37 (16.7%) interactions. In ICU setup, the increased use of phenytoin and its role in the development of DDIs are more. Two studies conducted by Rafiei *et al*. reveals that phenytoin is one of the major drug which leads to most interactions [22,25]. Followed by the phenytoin, lead role of hydrocortisone [11] clarithromycin [17], fentanyl [11,16,17] and moxifloxacin [11] in the development of DDIs in ICU set up were proved in several other studies. The results guide to take a special precaution while administering these drugs with other interacting drugs in the ICU setup to avoid potential DDIs.

More than focusing about the individual drugs involved in the DDIs, it is quite easy and convenient to healthcare providers to focus on the class of drugs interacted. Corticosteroids have a prominent role in the development of interactions in ICU. 38 interactions developed by corticosteroids and corticosteroids *Plus* quinolone antibiotics is the most prevalent drug combination that interacted 15 times. Study conducted by July Plaza stated that corticosteroids *Plus* quinolone antibiotics (6 times) are one of the main combination interacted mainly in ICU that leads to tendon rupture [11]. After corticosteroids, QTc prolonging drugs have a major role in the development of DDIs. The association between the occurrence of DIs due to the concomitant administration of drugs that prolong the QT interval should be stressed because there is a growing concern regarding these drugs that results in the risk of cardiotoxicity with torsade de points and cardiac arrest [29,30] These AEs can be determined by potential pharmacokinetic interactions that inhibit the metabolism of drugs with this property or by pharmacodynamic synergism. Recent data suggest that QT prolongation is quite common in ICU patients and adversely affects patient mortality. Thus, high-risk patients should be sufficiently monitored, and the use of medications known to cause drug-induced QTc prolongation might have to be restricted [31]. Other class of drugs to be discussed here is, the administration of cytochrome P450 inhibitors and inducers and the drugs that affect

Table 1: Individual drugs frequently interacted

S. No	Drug	Interacted with	Total interactions (%)	Major DDIs	Moderate DDIs	Risk	Reliability
1	Phenytoin	15	37 (16.7)	9	28	X=4 D=15 C=18	E=5 G=11 F=16 P=5
2	Hydrocortisone	10	30 (13.5)	16	14	D=9 C=21	E=16 G=14
3	Clarithromycin	9	15 (6.8)	4	11	D=13 C=2	E=6 G=4 F=5
4	Fentanyl	9	19 (8.6)	4	15	X=4 C=15	G=7 F=12
5	Amlodipine	8	10 (4.5)	1	9	D=4 C=6	E=3 G=5 F=2
6	Ondansetron	8	15 (6.8)	12	3	D=12 C=3	G=2 F=13
7	Tramadol	8	8 (3.6)	2	6	D=3 C=5	G=1 F=7
8	Fluconazole	7	13 (5.9)	2	11	D=6 C=7	E=8 G=1 F=4
9	Moxifloxacin	7	15 (6.8)	15	0	X=2 D=5 C=8	E=1 G=10 F=4
10	Labetalol	6	10 (4.5)	1	9	D=8 C=2	G=5 F=5

X: Combination should be avoided, D: Combination must consider therapy modification, C: Combination which must be monitor, E: Excellent, G: Good, F: Fair, P: Poor

Table 2: Drug combinations which are mostly interacted

S. No	Drug 1	Drug 2	Frequency (%)	Severity	Risk	Reliability	Interaction effect
1	Dopamine	Noradrenaline	7 (6.6)	Moderate	C	F	Adverse/toxic sympathomimetic effects
2	Adrenaline	Sodium bicarbonate	6 (5.7)	Moderate	C	E	Decrease in adrenaline excretion
3	Dexametasone	Sodium bicarbonate	6 (5.7)	Moderate	D	F	Decreased bioavailability of dexamethasone
4	Hydrocortisone	Ofloxacin	6 (5.7)	Major	C	G	Risk of tendon related side effects (tendonitis and rupture)
5	Hydrocortisone	Atracurium	5 (4.7)	Major	D	E	Atracurium may enhance the adverse neuromuscular effect of hydrocortisone
6	Hydrocortisone	Fluconazole	5 (4.7)	Moderate	C	E	Decreased metabolism of hydrocortisone
7	Noradrenaline	Sodium bicarbonate	5 (4.7)	Moderate	C	E	Decreased excretion of Noradrenaline
8	Phenytoin	Dopamine	5 (4.7)	Moderate	C	P	Enhanced hypotensive effect of phenytoin
9	Phenytoin	Metronidazole	5 (4.7)	Moderate	C	F	Increased serum concentration of phenytoin and decreased serum concentration of metronidazole
10	Phenytoin	Paracetamol	5 (4.7)	Moderate	C	G	Increased metabolism of paracetamol and risk of liver damage

X: Combination should be avoided, D: Combination must consider therapy modification, C: Combination which must be monitor, E: Excellent, G: Good, F: Fair, P: Poor

glycoprotein P was associated with the occurrence of DIs. The activities of cytochrome P450 and glycoprotein P are determinants of important pharmacokinetic processes in a significant number of drugs and are involved in the mechanisms responsible for DIs with clinical significance in the ICU. The integration between basic and clinical research is essential for identifying the mechanisms and the severity of those interactions, especially in the ICU [32,33]. Study conducted by Reis and Cassiani exhibited the role of both classes of drugs that prolong the QT interval, cytochrome P450 inducing and inhibiting drugs in the development of DDI [17].

Limitations of the study

We acknowledge that this study had a few limitations. It was based mainly on the information obtained from the Lexi Comp drug interact. We did not monitor the patients for the occurrence of DDIs clinically and we did not monitor the significant relationship of co morbidities and length of stay in ICU. Of the interaction found here, the beneficial effect of concomitant administration of these medicines in patient-centered therapy was also not investigated.

CONCLUSION

A total of 90.02% of 72 enrolled patients were exposed to one or more potential DDIs. We found an average of 3.08 potential DDIs per patient. The concomitant administration rates of potentially interacting drugs are very high in MICU. Corticosteroids, anticonvulsants, CNS depressants, sympathomimetics, fluroquinolones, QTc prolonging agents and cytochrome inducing or inhibiting agents are the major class of drugs involved in the development of DDIs in MICU. DIs leading to serious adverse effects must be cautiously watched for when multiple drugs are used simultaneously. We suggest that, special safety measures must be followed by physicians, pharmacists, and nurses to prevent and monitor DDIs in all departments of the hospital especially in intensive care departments. Health providers must be able to identify and classify DIs, and know how to manage them clinically, that is, how to minimize or more over prevent them. Appropriate induction and training programs can be provided for the healthcare professionals to reduce DDIs in hospitals. Practice of a computer assisted DI checker before prescribing/administering of the drugs can avoid DDIs. In

Table 3: Class of drugs which are responsible for interaction

S. No	Drug class	Total interactions produced (%)	Major DDIs	Moderate DDIs	Risk	Reliability
1	Corticosteroids	38 (17.1)	20	18	D=11 C=27	E=16 G=22
2	Anticonvulsants	33 (14.9)	0	33	X=4 D=7 C=22	E=5 G=13 F=10 P=5
3	CNS depressants	26 (11.7)	0	26	C=26	G=20 F=6
4	Sympathomimetics	25 (11.2)	0	25	D=5 C=20	E=11 G=6 F=8
5	Quinolone antibiotics	17 (7.7)	0	17	D=1 C=16	E=1 G=15 F=1
6	Calcium channel blockers	14 (6.3)	1	13	X=4 D=4 C=6	E=3 G=9 F=2
7	CYP3A4 substrates	12 (5.4)	8	4	D=12	F=12
8	CYP3A4 inducers	11 (5)	8	3	D=11	F=11
9	Mg salt	10 (4.5)	3	7	C=10	F=7 P=3
10	Loop diuretics	7 (3.2)	0	7	C=7	G=5 F=2

[#]X: Combination should be avoided, D: Combination must consider therapy modification, C: Combination which must be monitor, *E: Excellent, G: Good, F: Fair, P: Poor, DDI: Drug-drug interaction

Table 4: Drug class pairs which are mostly interacted

S. No	Combination class	Frequency (%)	Severity	Risk[#]	Reliability*	Interaction result
1	Corticosteroids *Plus* Quinolone antibiotics	15 (6.8)	Major	C	G	Risk of tendon-related side effects (tendonitis and rupture)
2	Moderate risk QTc prolonging agents *Plus* Moderate risk QTc prolonging agents	12 (5.4)	Major	D	F	Moderate risk QTc prolonging agents may enhance the QTc prolonging effect of other moderate risk QTc prolonging agents
3	CYP3A4 substrates *Plus* CYP3A4 inducers (strong)	11 (5)	Major	D	F	CYP3A4 inducers (strong) may increase the metabolism of CYP3A4 substrates
4	CNS depressants *Plus* CNS depressants	10 (4.5)	Moderate	C	G	Enhanced adverse/toxic effect of CNS depressants
5	CYP2C19 substrates *Plus* CYP2C19 inducers (strong)	7 (3.2)	Major	D	F	CYP2C19 inducers (strong) may increase the metabolism of CYP2C19 substrates

[#]X: Combination should be avoided, D: Combination must consider therapy modification, C: Combination which must be monitor, *G: Good, F: Fair, CNS: Central nervous system

settings with multiple drug use like in ICUs, attendance of a pharmacist or clinical pharmacist, taking the responsibility for monitoring DIs and notifying the physician about potential problems could decrease the harm in patient and increase the patient safety.

AUTHORS CONTRIBUTIONS

SA carried out the collection of data's from medical record department of the study site and assessed the prevalence of drug interaction as per the study protocol. KV designed and developed the study protocols and performed critical assessment. PM interpreted the results and involved in drafting of the manuscript. All authors read and approved the manuscript.

ACKNOWLEDGMENT

The authors acknowledged to the management of Narayana Hrudayalaya Hospitals, Pratap Nagar, Jaipur, India. We widen our heartfelt and truthful thankfulness to Dr. Vivek Bhargava, critical care unit in charge, Narayana Hrudayalaya Hospital, Jaipur, India, for his expensive contribution for this study. We put across our honest thankfulness and gratitude to Mr. Sanjay Agrawal, prescription audit department and all the staffs of medical record department of Narayana Hrudayalaya Hospital, Jaipur.

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