Original Article

A Cross Sectional Study About the Prevalance of Potential Drug-drug Interactions in Various Inpatient Departments of a South Indian Government Headquarters Hospital using Prescription Analysis

Murugakadavul Arumugavignesh*, Thenmozhi Prammanathan, Rajaram Abishek, Rajagopal Vigneswaran

Department of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankoil, Virudhunagar, Tamil Nadu, INDIA.

ABSTRACT

Objectives: This study is focused on to identify the prevalence of potential drug-drug interactions among various inpatients' departments of a government headquarters hospital in Tamil Nadu, India. Segregation of potential DDIs which were found in patients' prescriptions according to their severity and examining the distribution of those DDIs in relevance to demographic features like gender and age are other objectives of this study. **Materials and Methods:** A prospective observational cross-sectional study was conducted with the periodicity of six months (between September 2021 and February 2022) in a government headquarters hospital of the state Tamil Nadu. This research includes six hundred and fifty- four (654) inpatients, including both male and female patients from various departments like general medicine, surgery, pediatric, psychiatric, post operative wards. Patients with serious illness and those who are not willing to participate were excluded from this study. **Results:** The average number of drug interaction per patient prescription was said to be 1.09. Number of prescriptions with 1 drug-drug interaction are 219. Fourteen prescriptions were found with more than six drug-drug interactions. Out of 718 potential DDIs, only 2 were contraindicated. The number of major DDIs was 335. Moderate drug interactions outnumbered minor drug interactions in our study. This study identified 2 contraindicated DDIs which were attributed to the same drug pair (ceftriaxone and ringer's lactate solution) in two different pediatric prescriptions. **Conclusion:** Polypharmacy and drug-drug interactions are the widely recognized drug related problems. By mitigating polypharmacy issue, drug-drug interactions in prescriptions can be attenuated.

Key words: Drug-drug interactions, Severity, Inpatients, Polypharmacy, Micromedex, Prescriptions.

INTRODUCTION

Drug-drug interactions (DDIs) have become an important factor of concern, as they are related to adverse drug reactions and hospitalization. The main reason for drug-drug interaction is polypharmacy. Patients with multiple disorders are treated with multiple drug regimens. In such cases drug-drug interactions would become inevitable. Drug-drug interactions occur when pharmacological action of one drug interferes with the pharmacological action of the other drug.[1] As the number of marketed drug increases potential drug-drug interactions have also expected to be increased.[2] Drug-drug interactions may cause different effects, and adverse drug interactions may lead to death or drug withdrawal.[3] Another aspect of drug-drug interaction is therapeutic failure which is less well characterized and also less recognized in health care.[4]

DOI: 10.5530/ijopp.15.2.21

Address for correspondence:
Mr. M Arumugavignesh,
Student, Department of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankoil, Tamil Nadu, INDIA.
Email id: m.arumugavignesh20@gmail.com

www.ijopp.org

In clinical practice drug-drug interactions can be differentiated into pharmaceutical, pharmacokinetic and pharmacodynamic interaction. Pharmaceutical DDIs occur when two physically or chemically incompatible compounds are combined together. Pharmacokinetic interaction occurs when two or more drugs metabolized by same enzyme. Pharmacodynamic interaction occurs when two or more drugs have similar type of mechanism of action which usually enhances the pharmacological action.[5] Clinical pharmacists are the righteous professionals for the purpose of finding out and abating the untoward effects which would be experienced by patients by these potential drug-drug interactions. A good collaboration if exists between physicians and clinical pharmacists in providing healthcare services will yield fruitful economic, clinical and humanistic outcomes.[6]

A study predicted 66% of DDIs in a medicinal department of a tertiary care hospital in Karnataka, India.[7] Yet another study in Chandigarh ruled out that 8.3% of prescriptions had multiple DDIs.[8] This study is focused on to identify the prevalence of potential drug-drug interactions among various inpatients' departments of a government headquarters hospital in Tamil Nadu, India. Segregation of potential DDIs which were found in patients' prescriptions according to their severity and examining the distribution of those DDIs in relevance to demographic features like gender and age are other objectives of this study.

MATERIALS AND METHODS

Study design and site

A prospective observational cross-sectional study was conducted with the periodicity of six months (between September 2021 and February 2022) in a government headquarters hospital of the state Tamil Nadu which is now upgraded into medical college and teaching hospital. The case sheets of inpatients required for this study was collected during our clerkship which was legally permitted by the authorities of the above-mentioned hospital.

Ethical clearance

The institutional human ethical committee of the Virudhunagar government headquarters hospital, Tamil Nadu gave us approval for conducting this study. The reference number of the ethical certificate provided by them for conducting this study was R.No 110 / HS / GHQH - VNR / SEP 2019.

Sample size

This research includes six hundred and fifty-four (654) inpatients, including both male and female patients from various departments like general medicine, surgery, pediatric, psychiatric, post operative wards of Virudhunagar District Headquarters Hospital. Patients with serious illness and those who are not willing to participate were excluded from this study. The sampling was done by systematic random sampling method upon considering the margin of error of ±5% with a confidence interval of 95% though the population data was taken accurately enough for the study.

Data collection and analysis

The data collected for this study includes age, gender, lab parameters, diagnosis, drugs prescribed etc. These data were collected from case sheets. Separate data collection form was used for this purpose. The data about prevalent drug-drug interactions were separated using MS EXCEL 2007 spreadsheets. Drug interactions were identified using IBM MICROMEDEX drug interaction checker software subscription version.

Classification of potential drug-drug interactions

Micromedex software is a well-established database for checking drug-drug interactions. It also contains literature citations for every drug-drug interaction. Classification of drug-drug interactions prevalent in the prescriptions of case sheets was done using this database. The drug interaction checker was well built by three major criteria known as severity, documentation and summary.

Severity section is further segregated into five clinically significant categories known as contraindicated, major, moderate, minor and unknown. The term 'contraindicated' means that the pair of drugs are not recommended or to be avoided strictly for concurrent use. The term 'major' means that the interaction might be life-threatening and requires medical intervention to minimize or prevent serious adverse effects. The term 'moderate' refers to the interaction that would result in exacerbation of patient's condition and/or require an alteration in therapy. The term 'minor' refers to the interaction with limited clinical effects. These manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy. The term 'unknown' is used to refer the interaction which is not well established in medical literature.

Documentation section is further expanded into four categories known as excellent, good, fair and unknown. The rank 'excellent' is given for the drug-drug interactions

which were well established using controlled clinical trials. The rank 'good' is given for the interactions which were not established by controlled studies but by other pharmacoepidemiological study designs. The rank 'fair' is given for the interactions with poor documentation but having pharmacologic considerations which lead the clinicians to suspect the interaction exists or having good documentation for a pharmacologically similar drug. The rank 'unknown' is given for the interactions which lack both documentation and pharmacologically relevant mechanism.

The summary section of this database briefly explains the clinical manifestations and pathogenic attributes which is anticipated in patients whom are administered with the pair of drugs which have any form of interactions concurrently.

RESULTS

Totally 654 inpatients' prescriptions were scrutinized during the study period. Out of 654 prescriptions, 288 prescriptions (44.03%) were found to be with no drug-drug interactions. Remaining 366 (55.96%) prescriptions have potential drug-drug interactions. Total number of drugs prescribed in overall 654 prescriptions was found to be 3972. The average number of drugs per prescription was calculated as 6.07. Total number of drug-drug interactions in 654 prescriptions was enumerated as 718. The average number of drug interaction per patient prescription was said to be 1.09. Number of prescriptions with 1 drug-drug interaction are 219. Fourteen prescriptions were found with more than six drug-drug interactions. This data representing the number of DDIs in patients' prescriptions are enlisted in Table 1.

Out of 718 potential DDIs, only 2 were contraindicated. The number of major DDIs was 335. Moderate drug interactions outnumbered minor drug interactions in our study. These details regarding severity of DDIs are presented in Table 2.

Totally 654 patients were enrolled in our study. Out of those, number of male patients was 392 (59.93%) and number of female patients was 262 (40.06%). There was a male preponderance in our study. Gender wise distribution of potential DDIs is provided in Table 3.

Among 654 cases, 125 were pediatrics; 402 were adolescents and adults and 127 were geriatrics. Out of 125 pediatric prescriptions, 28 were recognized with potential DDIs. 104 prescriptions were identified with potential DDIs among 127 geriatric prescriptions. The individual category wise percent of prescriptions with potential DDIs shows a high value among geriatrics (81.88%). This data representing age wise categorization of patients' prescriptions with interactions is expressed in Table 4.

This study identified 2 contraindicated DDIs which were attributed to the same drug pair (ceftriaxone and ringer's lactate solution) in two different pediatric prescriptions. 51 out of 194 moderate interactions are occurred due to the drug pair ranitidine and theophylline. Table 5 lists the most frequently identified DDIs in each severity category with its respective significance.

Table 1: Segregation of patients' prescriptions based on number of DDIs.

	No. of prescriptions (*N*=654)	Total DDIs in 654 prescriptions (*N*=718)
Zero DDI	288 (44.03%)	0
One DDI	219 (33.48%)	219
Two DDIs	74 (11.31%)	148
Three DDIs	32 (4.89%)	96
Four DDIs	15 (2.29%)	60
Five DDIs	6 (0.91%)	30
Six DDIs	6 (0.91%)	36
Seven DDIs	4 (0.61%)	28
Eight DDIs	5 (0.76%)	40
Nine DDIs	1 (0.15%)	9
Ten DDIs	1 (0.15%)	10
Twelve DDIs	1 (0.15%)	12
Thirteen DDIs	1 (0.15%)	13
Seventeen DDIs	1 (0.15%)	17

Table 2: Segregation of DDIs based on severity.

Severity	DDIs (*N*=718)	%
Contraindicated	2	0.27
Major	335	46.65
Moderate	194	27.01
Minor	187	26.04

Table 3: Gender wise distribution of DDIs.

Gender	No. of patients (*N*=654)	No. of DDIs (*N*=718)
Male	392	446
Female	262	272

DISCUSSION

In this study, we analyzed 654 inpatients' prescriptions from various wards. More than half (55.96%) of the

Table 4: Age wise categorization of patients' prescriptions with interactions.

Age	No. of cases (N=654)	No. of prescriptions with interactions (N=366)	% of prescriptions with interactions in individual category
0-12 years (pediatrics)	125	28	22.40
13-60 years (adolescents and adults)	402	234	58.20
Above 60 years (geriatrics)	127	104	81.88

Table 5: Most common DDIs in each severity category with its respective significance.

Drug pair	Severity	No. of times repeated in prescriptions	Significance of interaction
Ringer's lactate solution/ ceftriaxone	contraindicated	2	formation of ceftriaxone-calcium precipitate in blood
Haloperidol/ risperidone	major	16	increased risk of an irregular heart rhythm
Ranitidine/ theophylline	moderate	51	increased risk of theophylline toxicity (nausea, vomiting, insomnia, seizures)
Ranitidine/ paracetamol	minor	24	increased risk of hepatotoxicity

prescriptions were identified with potential drug-drug interactions. Our study differed from the study conducted at a different hospital in South India in which only 19.3% of prescriptions were identified with potential DDIs.[9] The average number of drug per prescription encounter was 6. This indicates polypharmacy which is one of the drug related problems (DRPs). Drug-drug interaction in each prescription with at least one DDI ranges from one to seventeen in number. Among the prescriptions with potential DDIs, most of them have 1 DDI (219 out of 366).

Based on the severity index, 2 contraindicated drug-drug interactions were identified in our study. The 2 interactions were attributed to the same drug pair (ceftriaxone and calcium containing ringer's lactate solution) in two different pediatric prescriptions. Neonatal deaths were reported in medical literature due the precipitation of calcium and ceftriaxone in blood which is caused by the concomitant administration of ceftriaxone and calcium containing ringer's lactate solution.[10] Concomitant administration of both of these medications should be avoided strictly.

Major DDIs surpassed both moderate and minor DDIs in our study. This is not in line with another study which reported moderate DDIs as the most prevalent one at internal medicine departments of a teaching hospital in Iran.[11]

Male inpatients were more in our study when compared with female inpatients. This trend goes hand in hand with another study which was conducted among hospitalized inpatients in Goa medical college.[12]

Out of 127 geriatric prescriptions, 104 (81.88%) were witnessed with potential DDIs. This is due to multiple co-morbidities, polypharmacy and declining pharmacokinetic and pharmacodynamic functions with increase in age. This finding resembles another study conducted at different internal wards of the JIPMER hospital, Pondicherry, India which enrolled 211 geriatrics' prescriptions and found 128 (60.66%) of them with potential DDIs.[13]

Among major interactions, interaction due to haloperidol and risperidone is the most common one. It is also the most common interaction in psychiatric ward of the hospital. Studies had proved the risk of QT interval prolongation associated with the concomitant administration of haloperidol and risperidone.[14,15] Interaction associated with ranitidine and theophylline is the most common one in moderate severity index. Many case reports were presented with the patients showed signs of theophylline toxicity like nausea, vomiting, tremor, seizures after the simultaneous administration of ranitidine and theophylline.[16,17] Interaction caused by paracetamol and ranitidine is the most common one among minor drug-drug interactions. Ranitidine when given at very high doses would bind to P-450 and inhibits the metabolism of paracetamol. This would result in paracetamol induced hepato toxicity.[18]

LIMITATIONS OF THE STUDY

This is an observational study not a controlled study. Prescribers of the hospital were not informed about these findings. This study lacks intervention component or stewardship program.

CONCLUSION

Polypharmacy and drug-drug interactions are the widely recognized drug related problems. By mitigating polypharmacy issue, drug-drug interactions in prescriptions can be attenuated. The study stresses the need for the establishment of drug information centers recruited with trained and obliging clinical pharmacists in every hospital across India. This will be advantageous for overburdened government hospitals to provide patient centric health care. Therapeutic drug monitoring service is still in rudimentary state in India. If utilized optimally, this service can act as a good supporting tool for subsiding potential drug-drug interactions and also marshal the prescribing practices towards evidence based personalized medicine and rational drug therapy.

ACKNOWLEDGEMENT

We would like to render our heartfelt thanks to our esteemed mentor and professor Late (Dr.) P L Haroled Peter for being a torch bearer towards our academic curriculum. May his soul rest in peace! We are indebted to express our gratitude and sincere thanks to the member secretary of Virudhunagar government headquarters hospital for providing us human ethical committee certificate. We also express our whole hearted thanks to all physicians, nurses and staff members of the concern hospital for being the chief provider of medical care and management for the patient and granting access to the patient's medical records.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DDI: Drug-Drug Interaction; **DRP:** Drug Related Problem; **JIPMER:** The Jawarharlal Institute of Postgraduate Medical Education and Research.

SUMMARY

Drug-drug interactions may lead to serious adverse outcomes. The main aim of this study is to identify the prevalence of drug-drug interactions in prescriptions of inpatients from different internal medicine departments of the concern hospital. This study also emphasizes the need to establish drug information centers in hospitals. Clinical pharmacists in drug information centers can monitor patients' prescriptions for all drug related problems and also provoke prescribers to adhere to good prescribing practices.

REFERENCES

1. Johnell K, Klarin I. The relationship between number of drugs and potential drug–drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. Drug Saf. 2007;30(10):911-8. doi: 10.2165/00002018-200730100-00009, PMID 17867728.
2. Malone DC, Hutchins DS, Haupert H, Hansten P, Duncan B, Van Bergen RC, *et al*. Assessment of potential drug–drug interactions with a prescription claims database. Am J Health Syst Pharm. 2005;62(19):1983-91. doi: 10.2146/ajhp040567, PMID 16174833.
3. Zhang W, Chen Y, Liu F, Luo F, Tian G, Li X. Predicting potential drug–drug interactions by integrating chemical, biological, phenotypic and network data. BMC Bioinformatics. 2017;18(1):18. doi: 10.1186/s12859-016-1415-9, PMID 28056782.
4. Böttiger Y, Laine K, Andersson ML, Korhonen T, Molin B, Ovesjö ML, *et al*. SFINX-A drug–drug interaction database designed for clinical decision support systems. Eur J Clin Pharmacol. 2009;65(6):627-33. doi: 10.1007/s00228-008-0612-5, PMID 19205683.
5. Bhagavathula AS, Berhanie A, Tigistu H, Abraham Y, Getachew Y, Khan TM, *et al*. Prevalence of potential drug–drug interactions among internal medicine ward in University of Gondar Teaching Hospital, Ethiopia. Asian Pac J Trop Biomed. 2014;4(Suppl 1):S204-8. doi: 10.12980/APJTB.4.2014C1172, PMID 25183081.
6. Ballerie A, Alix L, Bajeux E, Jégo P, Lescoat A, Hue B. The collaboration of clinical pharmacists and physicians for medication safety. The Lancet. 2019;394(10216):2240. doi: 10.1016/S0140-6736(19)32608-X.
7. Soherwardi S, Chogtu B, Faizal P. Surveillance of the potential drug–drug interactions in the Medicine Department of a tertiaryCare Hospital. J Clin Diagn Res 2012Sep1;6(7).
8. Kashyap M, D'Cruz S, Sachdev A, Tiwari P. Drug–drug interactions and their predictors: Results from Indian elderly inpatients. Pharm Pract. 2013;11(4):191-5. doi: 10.4321/s1886-36552013000400003, PMID 24367458.
9. Ahmad A, Khan MU, Haque I, Ivan R, Dasari R, Revanker M, *et al*. Evaluation of potential drug–drug interactions in general medicine ward of teaching hospital in southern India. J Clin Diagn Res. 2015;9(2):FC10-3:FC10. doi: 10.7860/JCDR/2015/11264.5608, PMID 25859467.
10. Gin A, Walker S. Notice to hospitals regarding ceftriaxone–calcium in compatibility: What's a clinician to do? Can J Hosp Pharm. 2009;62(2):157-8. doi: 10.4212/cjhp.v62i2.447, PMID 22478884.
11. Mousavi S, Ghanbari G. Potential drug–drug interactions among hospitalized patients in a developing country. Caspian J Intern Med. 2017;8(4):282-8. doi: 10.22088/cjim.8.4.282, PMID 29201319.
12. Khandeparkar A, Rataboli PV. A study of harmful drug–drug interactions due to polypharmacy in hospitalized patients in Goa Medical College. Perspect Clin Res. 2017;8(4):180-6. doi: 10.4103/picr.PICR_132_16, PMID 29109936.
13. Bethi Y, Shewade DG, Dutta TK, Gitanjali B. Prevalence and predictors of potential drug–drug interactions in patients of internal medicine wards of a tertiary care hospital in India. Eur J Hosp Pharm. 2018;25(6):317-21. doi: 10.1136/ejhpharm-2017-001272, PMID 31157049.
14. Drici MD, Wang WX, Liu XK, Woosley RL, Flockhart DA. Prolongation of QT interval in isolated feline hearts by antipsychotic drugs. J Clin Psychopharmacol. 1998;18(6):477-81. doi: 10.1097/00004714-199812000-00011, PMID 9864081.
15. Sala M, Vicentini A, Brambilla P, Montomoli C, Jogia JR, Caverzasi E, *et al*. QT interval prolongation related to psychoactive drug treatment: A comparison of monotherapy versus polytherapy. Ann Gen Psychiatry. 2005;4(1):1. doi: 10.1186/1744-859X-4-1, PMID 15845138.
16. Hegman GW, Gilbert RP. Ranitidine-theophylline interaction--fact or fiction?. DICP. 1991;25(1):21-5. doi: 10.1177/106002809102500104, PMID 2008782.
17. Cukier A, Vargas FS, Santos SR, Donzella H, Terra-Filho M, Teixeira LR, *et al*. Theophylline-ranitidine interaction in elderly COPD patients. Braz J Med Biol Res. 1995;28(8):875-9. PMID 8555989.
18. Panella C, Makowka L, Barone M, Polimeno L, Rizzi S, Demetris J, *et al*. Effect of ranitidine on acetaminophen-induced hepatotoxicity in dogs. Dig Dis Sci. 1990;35(3):385-91. doi: 10.1007/BF01537419, PMID 2307085.