Original Article:

Drug-drug interactions: experience at a tertiary care hospital

S. Radhika,[1] M.V.S. Subbalaxmi,[2] P. Usharani[1]

Departments of [1]Clinical Pharmacology and Therapeutics, [2]General Medicine, Nizam's Institute of Medical Sciences, Hyderabad

ABSTRACT

Background: Drug-drug interaction (DDI) is one important factor that influences relationship between prescribed dose and drug-effects by interfering with either pharmacokinetics or pharmacodynamics of the co-administered drug. DDIs can cause toxicity or inhibit the drug effect, both of which have deleterious effect on patient care. This study was done to report the impact of prevention of DDIs.

Methods: In this retrospective study, demographic details, relevant clinical information of the cases with suspected DDIs and the opinion given regarding suspected DDIs, with anticipated outcomes and further management were recorded and analyzed.

Results: Of the 124 cases, 21 (16.9%) cases had suspected DDIs, among them 5 (23.8%) were pharmacodynamic and 13 (61.9%) were pharmacokinetic. Of the 21 DDIs, in 38.1% interactions, concomitant administration of interacting drugs was to be avoided and in 33.3% interactions, monitoring of effect was necessary to guide dosage adjustment. In ten (47.6%) cases, the DDIs were identified on day one and necessary action was taken to prevent the deleterious outcome and in rest of the 11 (52.4%) cases, adverse events have occurred due to DDIs, for which most of the patients were hospitalized.

Conclusion: The present demonstrated that early identification of DDIs on day one, could prevent undesired consequences in 10 cases (47.6%). As DDIs is an important factor that can be prevented, if identified early, clinicians should be vigilant regarding DDIs when more than two drugs are prescribed.

Key words: *Drug to Drug Interactions, Adverse events, Pharmacokinetic interactions*

Radhika S, Subbalaxmi MVS, Usharani P. Drug-drug interactions: experience at a tertiary care hospital. J Clin Sci Res 2017;6:208-15; DOI:http://dx.doi.org/10.15380/2277-5706.JCSR.17.01.002.

INTRODUCTION

The therapeutic success of any medication depends on its efficacy and safety of a drug though the response depends on several other factors. There are several factors responsible for inter-individual variability in the dose to obtain optimal therapeutic effect with minimal adverse effects. The factors include co-administration drugs, physiological variables, pathological variables, genetic factors, development of tolerance and desensitization.[1] A drug-drug interaction (DDIs) can occur with not only drugs but can occur with food, dietary supplements, formulation excipients, environmental factors or disease. DDIs may be beneficial or harmful.[2]

Generally, patients benefit from pharmacotherapeutic interventions; however, adverse events, ranging from minor side effects to death, may occur. Any deviation from the intended beneficial effect of a medication results in a drug- related problem. Costs associated with drug related problems can exceed the expenditures for initial drug therapy. Johnson and Bootman developed a decision-analytic model for eight possible negative outcomes of drug therapy, which includes drug interactions.[3]

Received:January 25, 2017, Accepted: February 08, 2017.

Corresponding author: Dr MVS Subbalaxmi, Additional Professor, Department of General Medicine, Nizam's Institute of Medical Sciences, Hyderabad. India.
e-mail: subbalaxmimvs@gmail.com

Online access
http://svimstpt.ap.nic.in/jcsr/oct-dec17_files/2oa.17.01.002.pdf
DOI:http://dx.doi.org/10.15380/2277-5706.JCSR.17.01.002

Harmful DDIs can cause 10%–20% of the adverse drug reactions (ADRs) requiring hospitalisation.[2] Elderly patients are especially vulnerable, as evidenced by a strong relationship between increasing age, the number of drugs prescribed and the frequency of potential DDIs.[2]

DDIs may be pharmacokinetic or pharmacodynamic. Pharmacodynamic DDIs occur when interacting drugs have either additive effect or antagonizing effect. Pharmacokinetic DDIs occur when one drug changes the concentration of another drug at the site of action.[2]

Drug interactions always should be considered when unexpected responses to drugs occur. Prescribers should recognize that patients often come to them with a legacy of drugs during previous medical experiences, often with multiple physicians who may not be aware of all the patient's medications. A meticulous drug history should include examination of the patient's medications and, if necessary, call to the pharmacist to identify prescriptions. Understanding the mechanism of drug interaction provides a framework for preventing harmful DDIs.[4]

In this study, an effort is made to review the data of cases with suspected DDIs with their clinical outcomes at a tertiary care hospital, so as to emphasize the importance of prevention of drug-to-drug interactions.

MATERAIAL AND METHODS

This study is a retrospective analysis of two years data of cases with suspected DDIs at the department of Clinical Pharmacology and Therapeutics at our tertiary care institute with an objective to emphasize the importance of prevention of drug-to-drug Interactions.

Clinical pharmacology department offers drug information services at our institute which is a tertiary care hospital. These services were offered to clinicians. Clinicians referred cases when they suspect drug-related therapeutic issues, like dosage adjustment in special populations like renal impairment, hepatic dysfunction, pregnancy, paediatric cases, geriatric cases/ suspected drug-drug interactions/suspected ADRs and/or rechallenge options etc., for opinion to the clinical pharmacologists.

For this study, demographic details, relevant clinical information of the cases with suspected DDIs and the opinion given regarding suspected DDIs, with anticipated outcomes and further management of the cases were recorded and analyzed.

Information on DDIs was given from the updated label information of the medication and case reports of a similar interaction. Once identified, precautions were suggested to prevent them. If the drugs were already co-prescribed and an adverse event has occurred, it was documented and further line of management of the ADR and alternative strategy for treatment was advocated and follow up was done till the patient was placed on safe and effective regimen. All these details were recorded and used for analysis.

Statistical analysis

The data are presented as mean ± standard deviation (SD) for continuous variables and proportions for categorical variables.

RESULTS

During the two-year study period, 124 cases were referred to Clinical Pharmacology and Therapeutics Department for various drug-related issues. Of the 124 cases, 21 (16.9%) cases had DDIs. The cases with DDIs had a mean age of 41.9 yrs, of them 11 (52.4%) were males. The mean number of medications prescribed was 6.5 in out-patients, 8.3 in in-patients and 10.1 in intensive care unit (ICU) patients.

Among the 21 suspected DDIs, 5 (23.8%) were pharmacodynamic and 13 (61.9%) were pharmacokinetic in nature. Of which, all 5 pharmacodynamic interactions and 8 pharmacokinetic interactions are known to lead to adverse effects, whereas the rest 8 pharmacokinetic interactions would lead to either subtherapeutic effect or loss of therapeutic effect. The details are shown in Table 1.

Of the 13 DDIs for which the anticipated outcome was an adverse effect, 5 (38.5%) were CYP inhibitor mediated interactions, 2 (15.4%) were multidrug-resistance protein (MRP) inhibitor mediated, 3 (23.1%) were synergistic and 3 (23.1%) were due to other mechanisms and of the 8 DDIs which had the potential to cause either loss of therapeutic effect or subtherapeutic effect, 6 (75%) were Cytochrome p450 (CYP) inducer mediated and 2 (25%) were chemical interactions. The details of the same are shown in Table 2.

In the 21 suspected DDIs that we encountered, there was one interaction in which concomitant administration of interacting two drugs was contraindicated; eight (38.1%) interactions in which concomitant administration of interacting drugs was to be avoided; seven (33.3%) interactions in which monitoring of effect was necessary to guide dosage adjustment. Based on the monitoring, drug dosage was tailored when the interacting drugs were co-administered; three (14.3%) interactions in which dosage was adjusted according to guidelines when the drugs were co-administered and two (9.5%) interactions in which the interacting drugs were to be administered at different times to avoid

Table 1: shows the details of anticipated outcome and the mechanism of the suspected DDIs

Nature of Interaction	Suspected DDIs (n=21)			Anticipated outcome
Pharmacokinetic	Ganciclovir	-	tenofovir	
	Voriconazole	-	warfarin	
	Ritonavir	-	tenofovir	
	Ritonavir	-	atorvastatin	
	Ketoconazole	-	sulphonylureas	Adverse effect
	Amiodarone	-	digoxin	
	Ritonavir	-	rifabutin	
	Amiodarone	-	warfarin	
	Rifampcin	-	fluconazole	
	Rifampcin	-	voriconazole	
	Ritonavir	-	phenytoin	
	Carbamazepine	-	warfarin	Loss of therapeutic effect
	Rifampcin	-	lopinavir/r	
	Rifampcin	-	nevirapine	
	Fe + mulltivit	-	levofloxacin	
	Sucralfate	-	levofloxacin	
Pharmacodynamic	Pencillin V	-	warfarin	
	Amphotericin B	-	amikacin	
	Moxifloxacin	-	quetiapine	Adverse effect
	Ganciclovir	-	zidovudine	
	Ganciclovir	-	amphotericin B	

DDI = drug-drug interaction

Table 2: showing the mechanism of interaction and anticipated outcome of the suspected DDI

Mechanism of Interaction	Suspected DDI (n=21)			Anticipated outcome
CYP. inhibitor mediated	Voriconazole	-	warfarin	
	Ritonavir	-	attorvastatin	
	Ketoconazole	-	sulphonylureas	
	Ritonavir	-	rifabutin	
	Amiodarone	-	warfarin	
MRP. inhibitor mediated	Ganciclovir	-	tenofovir	
	Ritonavir	-	tenofovir	
Synergistic	Amphotericin B	-	amikacin	
	Moxifloxacin	-	quetiapine	Adverse effect
	Ganciclovir	-	zidovudine	
Others	Amiodarone	-	digoxin	
	Pencillin V	-	warfarin	
	Ganciclovir	-	amphotericin B	
	Rifampicin	-	fluconazole	
	Rifampicin	-	voriconazole	
CYP. inducer mediated	Carbamazepine	-	warfarin	
	Rifampicin	-	lopinavir/r	
	Rifampicin	-	nevirapine	
	Ritonavir	-	phenytoin	Loss of therapeutic effect
	Sucralfate	-	levofloxacin	
Chemical	Iron + Multivitamin	-	levofloxacin	

CYP. = cytochrome p450; MRP. = multidrug resistance associated protein

interaction and not to be administered at the same time as shown in Table 3. Necessary action was taken to prevent these interactions on a case-by-case basis.

Of the 21 cases, in 10 (47.6%) cases, DDIs were identified on day one and necessary action was taken to prevent the deleterious outcome from occurring. The details of the same are shown in Table 4. In rest of the 11 (52.4%) cases, adverse events have occurred due to DDIs, for which most of the patients were hospitalized, and taking appropriate action treated patient and later after the patient was stabilized, they were started on an alternative safe and effective regimen.

DISCUSSION

This study clearly emphasizes the importance of prevention of suspected drug-drug interactions as most of the drug –drug interactions are preventable once identified. We have prevented deleterious outcomes, which would result from 10 (47.6%) DDIs had the adequate precautions not been taken.

Whenever a case was referred for any drug related therapeutic issue, the prescription was holistically reviewed for all possible concerns related to drugs, including drug interactions. In this way, identification of drug interactions on day one of prescription became possible.

Table 3: Precautions to be taken for DDIs that were encountered

Suspected DDI	Precaution to be taken
Rifampcin- voriconazole	Concomitant administration of interacting two drugs was contraindicated
Ganciclovir-tenofovir Ritonavir-tenofovir Ritonavir- attorvastatin Ketoconazole-sulphonylureas Amphotericin B-amikacin Ganciclovir-amphotericin B Rifampicin- lopinavir/r Rifampicin-nevirapine	Concomitant administration of interacting drugs was to be avoided
Voriconazole-warfarin Rifampicin-fluconazole Pencillin V-warfarin Moxifloxacin-quetiapine Ritonavir- phenytoin Carbamazepine-warfarin Ganciclovir-zidovudine	Monitoring of effect is necessary and based on the monitoring, drug dosage needs to be tailored when the interacting drugs were co-administered
Amiodarone-warfarin Ritonavir-rifabutin Amiodarone- digoxin	Dosage needs to be adjusted according to guidelines when the drugs are co-administered
Fe+Multivit-levofloxacin Sucralfate- levofloxacin	Interacting drugs should be administered at different times to avoid interaction but should not be administered at the same time

DDIs = drug-drug interactions

We observed that ten DDIs were encountered in patients with dual infections, when first line treatment for each of the infection was prescribed in the best interest of the patient. A patient diagnosed with pulmonary aspergillosis, (Table 3) was prescribed voriconazole. Later when sputum cultures showed mycobacterial growth, the patient was started on first-line antituberculosis therapy with isoniazid, rifampicin, ethambutol and pyrazinamide. After a month, the patient's condition deteriorated with increasing breathlessness. When the patient was reevaluated, rifampicin-voriconazole interaction was noticed and immediately, voriconazole was withdrawn and patient was started on amphotericin B for three months and the patient responded. Rifampicin (a CYP450 inducer; 600 mg once daily) decreases the maximum plasma concentration (Cmax) and area under the plasma concentration-time curve within a dosing interval (AUC) of voriconazole by 93% and 96%, respectively. Coadministration of voriconazole and rifampicin will result in a loss of the therapeutic efficacy of voriconazole due to the massive reduction of systemic voriconazole exposure due to induced metabolism.[5]

Table 4: Details of ten drug to drug interactions that were identified on day one and necessary action that was taken to prevent the deleterious outcomes

Suspected DDI	Anticipated Outcome	Action that was taken
Rifampicin- fluconazole	Rifampcin decreases fluconazole levels causing subtherapeutic effect	Fluconazole was stopped
Ketoconazole- sulphonylureas	Ketoconazole can increase sulphonylurea concentration, leading to hypoglycemic events	Ketoconazole was withdrawn
Penicillin V –warfarin	Penicillin by decreasing gut flora decreases synthesis of Vitamin K, thereby increases efficacy of warfarin, causing bleeding episodes	INR monitored and warfarin dosage adjusted accordingly Voriconazole was withdrawn
Voriconazole-warfarin	Voriconazole increases efficacy of warfarin by increasing concentrations, can cause bleeding episodes	
Moxifloxacin - quetiapine	Both the drugs prolong QTc, can cause Torsades pointes	QTc interval was intensively monitored
Ganciclovir- zidovudine	Both cause pancytopenia, so can cause synergistic toxicity	Complete blood picture was monitored
Ritonavir – rifabutin	Ritonavir increases rifabutin levels, leading to untoward effects	Rifabutin dosage was reduced and LFTs monitored
Rifampicin- lopinavir/r	Rifampicin decreases ritonavir levels, thereby contributing to loss of efficacy of lopinavir	Lopinavir/r was withdrawn
Rifampicin - nevirapine	Rifampicin decreases Nevirapine concentrations, making it ineffective	Nevirapine was withdrawn
Carbamazepine- warfarin	Carbamazepine decreases warfarin levels causing subtherapeutic effect	INR monitored and warfarin dosage adjusted accordingly

DDIs = drug-drug interactions; LFT = liver function tests; INR = international normalized ratio

In a patient with human immunodeficiency virus (HIV) infection who was on tenofovir, ganciclovir was started for cytomegalovirus (CMV) gastritis. Subsequently, patient developed acute kidney injury (AKI), which was later identified to be due to tenofovir-ganciclovir interaction.[6] Similarly, in another case with HIV infection, ritonavir-tenofovir interaction resulted in tenofovir induced nephrotoxicity[7]; while interactions between amphotericin B- amikacin, ganciclovir-zidovudine, rifampicin- lopinavir/r, rifampicin – nevirapine, rifampicin- fluconazole, ganciclovir- amphotericin B were identified early and thus interactions were prevented. The World Health Organization (WHO) guidelines on use of antiretroviral drugs for treating and preventing HIV infection, 2016, have referred to interaction of lopinavir/r and nevirapine with rifampicin among key drug interactions for antiretroviral drugs.[8]

Four DDIs were identified with warfarin. Usually in any case, when the patient is on oral anticoagulant; the prescription is reviewed very meticulously for any concern of interaction. This approach helped us to identify interaction between voriconazole- warfarin, penicillin V-warfarin and carbamazepine-warfarin on day one of prescription and prevent adverse outcomes. However, one case on treatment with amiodarone and warfarin, presented with high (INR) with no bleeding event. Warfarin was

stopped and when therapeutic INR was attained, it was restarted and patient was stabilized on a low dose of warfarin with careful monitoring of INR. The interactions of warfarin with voriconazole, antibiotics, azole antifungals,[9] amiodarone[10] and carbamzepine [11] are known and have been reported.

Similarly, with meticulous review of prescription of any patient on treatment with known CYP inducer or inhibitor, prevention of two DDI between ketoconazole-sulphonylureas and moxifloxacin- quetiapine became possible, while ritonavir- phenytoin, amiodarone – digoxin, ritonavir- atorvastatin interactions resulted in adverse events. Similar interactions were reported. [12,13, 14]

Two DDIs of levofloxacin, one with sucralfate and other with Fe-multivitamins were identified and prevented. Absorption of the fluoroquinolones is markedly decreased by ingestion of medications containing divalent cations (calcium, iron, zinc), including antacids; supplements or vitamins containing calcium, iron or zinc, sucralfate ; and the chewable tablet formulation of didanosine. These drug interactions can be avoided by assuring that medications containing divalent cations are ingested at least 2 hours apart from doses of fluoroquinolones.[15,16]

The (FDA) emphasizes in its teaching module on Preventable Adverse Drug Reactions: A focus on drug interactions, that the rate of ADRs increase exponentially when a patient is on 4 or more medications. Although, efforts to reduce polypharmacy are important, many a times, the number of medications cannot be reduced without doing harm. That is why it is important to understand the basis for drug interactions. This will allow us to make the most appropriate choices in prescribing and avoiding preventable ADRs by developing a stepwise approach to identify them.[17] Drug-related morbidity and mortality continue to pose a serious medical and economic problem for society.[3]

More attention should be directed toward developing solutions that reduce preventable morbidity, mortality, and costs associated with drug related problems. In a study done by Ernst and Grizzle, on drug related morbidity and mortality in 2000, it was estimated that the drug-related morbidity and mortality cost-of-illness was $177.4 billion annually, compared with the $76.6 billion arrived at by Johnson and Bootman in 1995 and concluded that since 1995, the costs associated with drug related problems have more than doubled.[3]

Drug interactions always should be considered when unexpected responses to drugs occur. It is very important to review the entire prescription for any drug-drug interaction meticulously, if possible by a clinical pharmacologist, especially if the patient has multiple co-morbidities (HIV, tuberculosis, fungal infections, diabetes), or if the prescription contains drugs with narrow therapeutic index (warfarin) and/or drugs which are known potential CYP inhibitors (voriconazole, amiodarone) or inducers (rifampcin, carbamazepine).

In this study, it is demonstrated that early identification of drug-drug interactions on day one, could prevent undesired consequences in 10 cases (47.6%). As, drug- drug interactions is an important factor that can be prevented, if identified early, clinicians should be vigilant regarding DDIs when more than 2 drugs are prescribed.

It is very important to review the entire prescription for any DDI especially if the patient has multiple co-morbidities. More so, when the patient is in intensive care unit under care of a team of doctors from different specialties, in order to promote rational use of medicines, to reduce healthcare associated costs and prevent deleterious outcomes in patients.

REFERENCES

1. Blumenthal DK and Garrison JC. Pharmacodynamics: Molecular mechanisms of drug actions. In: Brunton L, editor. Goodman & Gilman's The Pharmacological basis of Therapeutics, 12th ed. New York: Mc Graw –Hill; 2011 .p. 49-50.
2. Snyder BD, Polasek TM and Doogue MP. Drug interactions: principles and practice. Aust Prescr 2012;35:85-8.
3. Ernst F R, Grizzle A J. Drug-Related Morbidity and Mortality: Updating the Cost-of-Illness Model. J Am Pharm Assoc 2001;41:192-9.
4. Roden DM. Principles of Clinical Pharmacology. In: Longo, Fauci, Kasper, Hauser, Jameson, Loscalzo, editors. Harrison's Principles of Internal Medicine, 18th ed. New York: McGraw-Hill; 2012. p.45 .
5. Geist MJ, Egerer G, Burhenne J, Riedel KD, Mikus G. Induction of voriconazole metabolism by rifampin in a patient with acute myeloid leukemia: importance of interdisciplinary communication to prevent treatment errors with complex medications. Antimicrob Agents Chemother 2007 ;51:3455-6.
6. Soanker R, Udutha SJ, Subbalaxmi MV, Raju Y. Ganciclovir-tenofovir interaction leading to tenofovir-induced nephrotoxicity . J Pharmacol Pharmacother 2014;5:265-7.
7. Krishna M M, Subbalaxmi M, Uppin M, Radhika S. Delayed onset renal failure in a patient on tenofovir based antiretroviral regimen. Indian J Pharmacol 2014;46:230-1.
8. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. World Health Organization 2016.
9. Baillargeon J, Holmes HM, Lin YL, Raji MA, Sharma G, Kuo Y-F. Concurrent Use of Warfarin and Antibiotics and the Risk of Bleeding in Older Adults. Am J Med 2012;125:183-9.
10. Hamer A, Peter T, Mandel WJ, Scheinman MM and Weiss D. The potentiation of warfarin anticoagulation by amiodarone. Circulation 1982;65:1025-9.
11. Mannheimer B, Andersson ML, Jarnbert-Pettersson H and Lindh JD. The effect of carbamazepine on warfarin anticoagulation: a register-based nationwide cohort study involving the Swedish population. J Thromb Haemost 2016;14:765-71.
12. Lim ML, Min SS, Eron JJ, Bertz RJ, Robinson M, Gaedigk A, et al. Coadministration of lopinavir/ritonavir and phenytoin results in two-way drug interaction through cytochrome P-450 induction. J Acquir Immune Defic Syndr 2004;36:1034-40.
13. Nademanee K, Kannan R, Hendrickson J, Ookhtens M, Kay I, Singh BN. Amiodarone-digoxin interaction: clinical significance, time course of development, potential pharmacokinetic mechanisms and therapeutic implications. J Am Coll Cardiol 1984;4:111-6.
14. Causevic-Ramosevac A, Semiz S. Drug interactions with statins. Acta Pharm 2013;63:277-93
15. Oliphant CM, Green GM. Quinolones: A Comprehensive Review. Am Fam Physician 2002;65:455-64.
16 Centers for Disease Control and Prevention. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. Morb Mortal Wkly Rep 2003;52 (No. RR-11):[inclusive page numbers].
17 Preventable Adverse Drug Reactions: A Focus on Drug Interactions. U.S. Food and Drug Administration. Available from: http://www.fda.gov/Drugs/Development Approval Process / Development Resources / Drug Interactions Labeling / ucm110632.htm. Accessed on June 18, 2014.