Prescribing pattern of angiotensin receptor blocker: A study of errors and drug-drug interactions

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Abstract: Prescriptions comprising multi-drug therapy mostly illustrate the prescribing error. The phenomenon of error is bonded with human inaccuracy. The erroneous practice is observed in under developed countries like Pakistan, Bangladesh and also in developed ones. Consequently drug-drug interaction is one of the most common error associated with potentially serious adverse response even death. Accordingly the present study was conducted to assess the prevalence of prescribing errors and drug-drug interactions in out-patients receiving angiotensin receptor blockers. The study was done with population size one hundred fifty prescriptions obtained from different out-patient settings in Karachi. The prescriptions were screened for prescribing errors and risk factors for drug-drug interactions. Drug-drug interactions were recognized by Micromedex.2.0.Drug-Reax® database. The most common type of error was omission error. These errors were patient's age, weight and diagnosis found in 51.3%, 97.3% and 74% of prescriptions, respectively. The prevalence of drug-drug interaction was 38%. A total of 746 drugs were prescribed with an average of 5 drugs per prescription and 450 medication errors were detected. Majority of the interaction were moderate (19.33%), others were minor (14%) and major (6%) in severity. Patients who prescribed many drugs (more than 5 drugs in a while) had a higher risk of developing drug-drug interactions (OR=4.76; 95% CI=2.30-9.64; *p*=0.0001*).The study data reports the occurrence of prescribing errors in Karachi and also necessitate the need of clinical pharmacist's services in health care system. The step will help to minimize the risk factors by having the drug prescriptions reviewed by the pharmacists.

Keywords: Prescribing errors, drug-drug interactions, angiotensin receptor blockers, out-patients.

INTRODUCTION

Prescribing errors (PEs) are the errors, leading to inapt use or injury though the medication is in the control of health care experts. The contributors of PE might be associated with administration, techniques, and personnel. PEs can cause adverse drug reactions, which lead patients at risks and might not only result in maltreatment but also upsurge the medical expenses (van den Bemt, Postma *et al*. 2002). Drug-drug interactions (DDIs) are one of those preventable prescribing errors and may be defined as when more than two drugs are prescribed in such a way that the potency and effectiveness or toxicity of one drug is altered by the presence of another drug. Majority of drug interactions although preventable, but associated with serious adverse effects and sometimes death (Peterson and Bates 2001, Gurwitz, Field *et al*. 2003; Juurlink, Mamdani *et al*. 2003, Ray, Murray *et al*. 2004, Becker, Kallewaard *et al*. 2007). Previously different studies have reported that concomitant use of more than two drugs increases the incidence of DDIs (Nobili, Garattini *et al*. 2011, Nesar, Shoaib *et al*. 2014).

Cardiovascular patients are the victims of PEs due to poly-pharmacy. PEs occurred most commonly with diuretics and antihypertensive agents among all cardiovascular drug classes. Previous study reported that medication errors in out-patient settings were more frequent and cause serious adverse effects (Friedman, Geoghegan *et al*. 2007). Reasons include simultaneous procedures going on in such setting and also more hazardous and less regulated than hospital settings (Lapetina and Armstrong 2002). Therefore, the present study was executed to assess the incidence of PEs and pattern of DDIs in out-patients receiving angiotensin receptor blockers (ARBs) in Karachi, Pakistan

ARBs signify relatively a new-fangled class of antihypertensive drugs. Their mechanism of action diverges from that of the angiotensin-converting enzyme (ACE) inhibitors. These drugs have shown interference with the renin-angiotensin system. Overall, the ARBs are well tolerated. These drugs have a specific, dose-related adverse effect. Comparison of drugs within the class divulges that losartan has potential for DDIs due to its engrossment with enzyme system of liver i.e. cytochrome P450 (Khairnar, Baviskar *et al*. 2012). The ARBs can be safely prescribed in the elderly or patients with renal or

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hepatic impairment without any specific considerations as in case of ACE inhibitors (Burnier and Brunner 2000). Several clinical trials have appraised the relative antihypertensive efficacy of the ARBs in patients with mild to moderate hypertension. ARBs cannot be considered as first-line therapy in place of ACE inhibitors, but both endure a rational substitute for patients unable to tolerate ACE inhibitors (Böhler, Pittrow *et al*. 2005). No recent data of retrospective analysis of patients receiving ARBs from Pakistan was available in the medical literature. The study outcome was to provide sound evidences of PEs and DDIs in prescriptions having ARBs.

MATERIALS AND METHODS

Study design and period

Design of the current study was prospective and conducted from August 2012 till December 2013 in out-patient settings of Karachi, Pakistan after due permission from BASR (Board of Advanced Studies and Research), University of Karachi.

Data collection and analysis

Prescriptions containing ARBs prescribed with other drugs were collected from different out-patient settings. Collected prescriptions were scrutinized keeping in view inclusion criteria (patients of both the sexes taking ARB) and exclusion criteria (prescriptions that were scrawled or not visibly written and did not fall in the inclusion criteria) and analyzed for PEs. Number of drugs prescribed per prescription was also noted down. The occurrence and severity of DDIs were analyzed using Micromedex.2.0. Drug-Reax® database.

STATISTICAL ANALYSIS

All the statistical analysis was performed using Statistical Package for Social Sciences (SPSS 20.0, Chicago, IL) software. Prescriptions were classified into two groups that is prescriptions containing less than five drugs and those containing more than or equal to five drugs. Pearson correlation and binary logistic regression were performed to analyze the association between number of drugs per prescription and prevalence of DDIs.

RESULTS

In the current study, a sample of 150 prescriptions with ARBs was scrutinized. A total of 450 PEs were perceived in prescriptions evaluated. The most recurrent PE was the patient's weight not stated (n=146; 97.3%) trailed by missing diagnosis (n=111; 74%) (table 1). Patient's age was not written in (n=77; 51.3%). DDIs were present in 57 prescriptions (38%). A total of 746 drugs were prescribed. The average number of drugs per prescriptions was 5 and approximately 26% of prescription has 4 drugs (fig. 1).

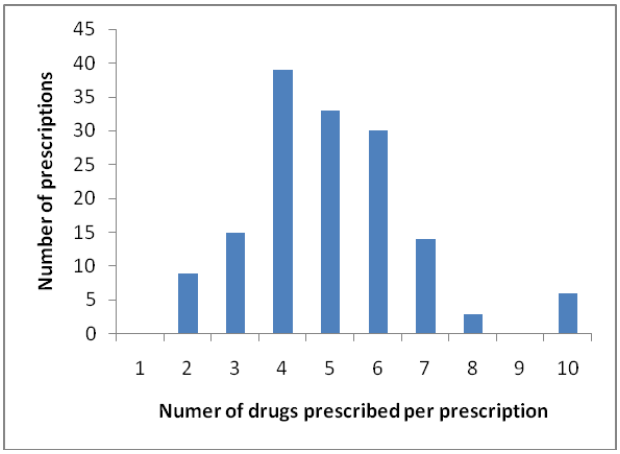

Fig. 1: Prescriptions having different number of drugs prescribed with ARBs.

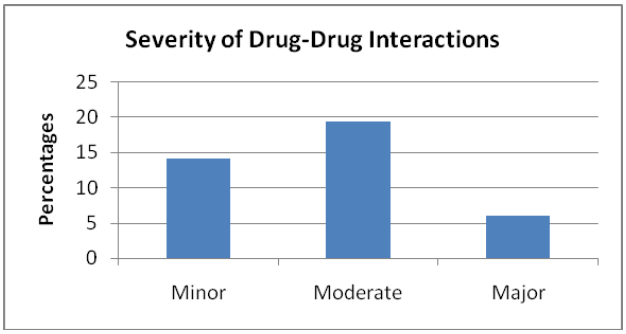

Fig. 2: Severity of drug-drug interactions of ARBs' prescriptions according to Micromedex®.

The prescriptions were classified depending on number of drugs. Those groups of prescriptions were compared for DDIs by Pearson correlation and binary logistic regression and found statistically significant (p=0.0001*). Statistical analysis of PEs in prescriptions of ARBs and the incidence of DDIs were significantly amplified with the increase in number of drugs per prescription. Majority of DDIs (n=29; 19.33%) were moderate. Some DDIs were major (n=9; 6%) and certain were minor (n=21; 14%) (fig. 2).The top seven drug pairs with the potential for interacting are summarized in table 2. DDI of ARBs was observed with spironolactone, furosemide and lisinopril. The results of logistic regression showed that prescriptions with >5 drugs increase the odds ratio by 4.76. Therefore, it was established that the incidence of DDIs is approximately five times more in prescriptions containing more than or equal to 5 drugs.

DISCUSSION

Prescriptions errors (PEs) are arising problem in the health profession. PEs can transpire on different levels of the medication cycle, including, diagnosis, treatment, administration and discharge. Health care team including physicians and pharmacists are responsible to avoid occurrences of such errors. The role of clinical pharmacist

Table 1: Medication errors in angiotensin receptor blocker (ARBs) prescriptions (n=150)

Name of Prescribing Errors	Incidence of error N (%)[a]
Ambiguous medication order	3(02)
Patient age not given	77(51.3)
Patient weight not given	146(97.3)
Patient sex not given	60(40.0)
Omission of prescriber Signature	3(02)
Drug-Drug Interaction	57(38)
Missing diagnosis	111(74)

a = Number and percentages of prescriptions having medication error. Errors, which were 0%, are not mentioned in the above table.

Table 2: Frequency of drug-drug interactions in ARBs' prescriptions

Interactions	Drug Combinations	Frequency n (%)
Minor Drug-Drug Interaction	Aspirin + Clopidogrel	21(14)
Moderate Drug-Drug Interaction	Losartan potassium+Spironolactone + Furosemide	15(10)
	Aspirin + Amiloride + Furosemide	3(2)
	Aspirin + Nitroglycerine	6(4)
	Atenolol + Glimepiride	3(2)
	Aspirin + Furosemide	2(1.33)
Major Drug-Drug Interactions	Losartan potassium + Lisinopril	9(6)

is not well recognized in Pakistan. Also in the health care system, physicians and other health care professionals are not trained to reduce PEs (Nousheen *et al*., 2012, WHO, 1988).

Consequences are the increased rates of PEs and DDIs causing injury and even death. It is necessary to determine the frequency and type of PEs and DDIs which was executed in the present study. A total of 450 prescribing errors were identified in ARB prescriptions (n=150). Patient's weight was not mentioned in prescriptions (97.3%, n=146) followed by missing diagnosis (74%, n=111) contributing to the second most frequent PE and patient's age was not written in 51.3% (n=77) (table 1). Reports from different countries also documented that recommended doses were not mentioned in prescriptions (Najmi, Hafiz *et al*. 1998, Chareonkul, Khun *et al.* 2002, Ravi, Partha *et al.* 2002).

In current study, 746 drugs were prescribed in 150 ARBs prescriptions and average number of drugs per prescription was 5. Prescriptions with four drugs were 39 (26%) and then with five and six drugs were 33 (22%) and 30 (20%), respectively (fig. 1). A similar study conducted in Bangladesh reported an average of 3.8 drugs per prescription (Guyon, Barman *et al*. 1994) , but previously 1.4 drugs per prescription was prescribed. The fig. 3.8 drugs per prescription are higher than WHO recommendation limit (Organization 1993) . Researcher from India stated 2.9 drugs per prescription (Karande, Sankhe *et al*. 2005). Risk of DDIs is increased with the increase in number of drugs. In present study, DDIs were present in 38% prescriptions of ARBs. DDIs were more observed in those prescription orders having equal to or more than 5 drugs. Pearson correlation and binary logistic regression was applied to analyze prescription for DDIs and found that prevalence of DDIs is remarkably amplified as there is an increase in number of drugs per prescription (p=0.0001*). Through binary logistic regression, it was proved that there was a In another study, DDIs were observed in 68.2% prescription orders (Lisby, Nielsen *et al*. 2005). Alexander and his fellow workers also reported PEs in cardiovascular patients(Alexander, Bundy *et al*. 2009) . A similar study stated that frequency of DDIs was higher in outpatient prescriptions of cardiologist due to poly-pharmacy (Ahmadizar, Soleymani *et al*. 2011). Another study also reported that incidence of DDIs increased with poly-pharmacy (Egger, Bravo *et al*. 2007).In present study, most potential DDIs were moderate in severity (fig. 2). Aspirin was the most implicated drug for potential drug-drug interactions followed by Furosemide and Losartan potassium (table 2). Murtaza and his co-workers conducted a similar study on inpatients and reported such type of interactions (Murtaza, Khan *et al*. 2016). Other study also documented such types of moderate and major drug-drug interactions (Chelkeba, Alemseged *et al*. 2013; Mateti, Rajakannan *et al*. 2011). The current study was successful in identifying the PEs and prevalence of DDIs in out-patients receiving ARBs.

A prodigious asset of this study was that the prescriptions data analyzed were based on actual parallel use of ARBs with other drugs. Other métiers included the multi-centre sample size, prospective design, identification of DDIs based on highly delicate screening tool, Micromedex. 2.0. Drug-Reax® database. The risk for DDIs will consequently increase with the increasing numbers of newer

antihypertensive drugs that become available. Different combinations of interacting drugs are unavoidable and may be administered together if appropriate precautions have to be taken. This entails a compact and comprehensive medication review of drug usage. Therefore, ideally all drugs prescribed by general physicians, and cardiologists should be reviewed by clinical pharmacist to identify and prevent potentially harmful DDIs (Nabeel *et al*., 2014).

The flaw of current study is that it does not explore the clinical impression of DDIs. In cardiovascular patients, impact of DDIs remains unknown and in future further studies should be done to investigate the actual picture. It is also unidentified to what extent pharmacies and prescribers were familiar with drug-drug interaction and took specific measures to rectify these DDIs and adverse drug events and improve prescription writing.

CONCLUSION

The data obtained from present study reveals the usual episodes of prescribing inaccuracies high in Karachi, a metropolitan city, which escort the need and significance of Pharmacist at clinical settings. The practice of reviewing by the pharmacist will apparently reduce the jeopardy of drug prescription.

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