ISSN 2394–806X (Print), ISSN 2454-5139 (Electronic)
IJHRMLP, Vol: 03 No: 01 January, 2017
Printed in India
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ORIGINAL PAPER

Profile of Adverse Drug Reaction in Patients with Renal Disorders

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***Received** on July 12, 2016; **editorial approval** on August 03, 2016*

ABSTRACT

***Introduction**: Lot of drugs cause renal dysfunctions. As renal patients are prescribed medications with utmost care and attention, and with dose modifications according to GFR, adverse drug reactions in renal patients are expected to be very low. **Aim**: To find out the incidence of adverse drug reaction (ADR), to ascertain the association of the offending drugs with the type of ADR, and to assess the severity of ADR, in indoor and outdoor renal patients. **Methods**: This is prospective observational case control study, which was conducted in 850 patients, who had either attended the Nephrology dept. OPD or were admitted in the Nephrology ward of Guwahati Medical College hospital with various renal disease, from January to June 2012. **Results**: Out of the 850 patients, 72 (8.4%) patients were found to have one or more ADR, comprising of total 89 episode of ADR. Out of these male were 40 and female were 32 in number. Commonest age group was 18- 60 years of age. Commonest ADR was Moon face (18.6%), followed by Allergic reactions (10.4%). In the causality assessment scale: most of the ADR were highly probable for offending drugs (65%). Regarding severity, most of the patients had mild ADR (51.6%), latent in onset, and only 12.3 % were preventable. **Conclusion:** Even after careful monitoring, ADR is not uncommon in renal patient and most of them are not preventable.*

***Keywords**: ADR: Adverse drug reaction. GFR: Glomerular filtration rate*

INTRODUCTION

As per World Health Organization definition (WHO), "an adverse drug reaction (ADR) is a noxious, unintended effect of a drug, occurring at normal doses in human for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function".[1] It is considered to be 4th leading cause of death among hospitalized patients. About 2.9-5.6% of all admissions are caused by ADR. As per Journal of American medical association, about 2 million serious ADR are reported annually, 350000 hospitalized patients experiences an ADR per year, and 100000 deaths occurred due to ADR.[2] ADR may vary from mild manifestation, requiring no medical treatment to serious ADR. American Food and Drug Administration defines a serious adverse event as one when the patient outcome is one of the following: death, hospitalization, disability, congenital anomaly, and requires intervention to prevent permanent impairment or damage.[3]

Therefore for ensuring safety and efficacy of drug or health related product, a very important tool is post marketing survey or pharmaco-vigilance. WHO defines pharmaco-vigilance as "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems".[4, 5]

Principle route for elimination of most of the drugs and its metabolite from the human body is the Kidney. In comparison with lipophilic drugs, hydrophilic drugs are mainly cleared by the kidneys. Reduction of renal reserve, which occurs in elderly as well as various diseases, lead to delayed renal clearance of many drugs. Therefore in patient with renal dysfunction, adverse drug reactions may be substantially high.

Aim of the Study: This study was conducted to find out the incidence of adverse drug reaction (ADR) in indoor and outdoor renal patients. Moreover, this study tried to ascertain the association of the offending drugs with the type of ADR, to

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assess the severity of various ADR and find out the preventability of the ADR.

METHODS

This is prospective observational case control study, which was conducted in 850 patients, who had either attended the Nephrology OPD or were admitted in the wards of Guwahati Medical College hospital with various renal disease, from January to June 2012. The renal diseases comprises of Nephrotic Syndrome, Glomerulo-nephritis, Acute kidney Injury, Chronic kidney disease with or without requiring dialysis, renal stone diseases, and post renal transplant recipients.

Inclusion criteria: Patients who either attended or were admitted in the nephrology ward with renal diseases. Ages of the patient ranged from 2 years to 74 years.

Exclusion criteria: patients who didn't give a written consent for this study.

Incidence of ADR was determined by Chart Review method. The **association** of the offending drugs with the type of ADR, - **causality** was ascertained by Naranjo's algorithim[6], using questionnaires, with score ranging from -1 to + 2. Total score then calculated for an offending drug and association is termed as:

0 : Doubtful; 1 – 4 : possible; 5 – 8 : Probable; > 9 : Highly probable

Severity of ADR and preventability were assessed by Hartwig severity scale.[7]

Mild: reaction that does not require treatment. **Moderate:** reaction that requires treatment or hospitalization. **Severe**: life threatening.

Onset of the ADR: Acute: ADR occurring within 60 minutes after administration of the drug. **Sub-Acute**: ADR occurring within 60 minutes to 24 hours after administration of the drug. **Latent:** ADR occurring after 2 days of administration of the drug.

Preventability of ADR was ascertained by seven point questionnaires of Schumock and thorton preventability criteria[10]. Answering "YES" to one or more questions will substantiate the preventability.

STATISTICAL ANALYSIS

The descriptive data are represented by mean, standard deviation, and percentage. The differences between the groups were determined by the parametric t-test and non-parametric Fisher's exact test or chi-square test. For data analysis Graph Pad InStat version 3.12 was used. Odd ratio and 95% confidence interval (CI) were calculated. $P< 0.05$ is considered to be significant.

OBSERVATION AND RESULTS

Out of the 850 patients, 72 patients had ADR. Out these 40 /490 were male (8.16%) and 32 /360 were female (8.8%). In the t-test, it is found to be significant ($p<0.042$). Females were found to be more prone for ADR.

According to age, the patients were analyzed in three groups: Child (0 – 18 yrs), Adult (19 – 60 yrs) and Elderly (>60 yrs).

In the child group: 9/96 had ADR (9.37%); Adult group 57/714 (7.9%) had ADR and Elderly group 6/40 had ADR (15%, $p<0.001$). In this study, elderly were more susceptible for ADR than the other group.

Types of ADR: A total of 37 different types of ADR were reported. Moon face (18%) was the commonest, followed by Allergic reaction (10.4%).

Table 1 Types of ADR

ADR	Frequency
Moon Face	16 (18.6%)
Allergic reaction	9 (10.4)
Constipation	8
Fluid & Electrolyte balance	4
Hirsutism	4
Tachycardia	3
Melaena	3
Tremor	3
Cataract	3
Blurred vision	3
Acne	2
High Blood Pressure	2
Glucoma	2
Ulcer	2
Thrombocytopenia	2
Tinitus	2
Pruritus	1
Arthralgia	1
Dry Mouth	1
Hyperglycaemia	1
Ototoxicity	1
Nausea	1
Vomiting	1
Pancytopenia	1
Diarrohea	1
Dry Cough	1
Hypotension	1
Pain abdomen	1
Chest Pain	1
Dyspnoea	1
Palpitation	1
Hepatotoxicity	1
Gum Hyperplasia	1
Myalgia	1
Necrosis of finger tips	1
Depression	1
Memory Loss	1

Causality Analysis: Naranjo's scale,[6] with score ranging from -1 to + 2 was used to analyze the causality. Total score then calculated for an offending drug and association is termed as: 0 : Doubtful; 1 – 4 : possible; 5 – 8 : Probable; > 9 : Highly probable.

Majority of ADR were found to be highly probable (47/72, 65%), followed by Probable (18/72, 25%), then Possible 7/72 cases.

Severity Assessment: Severity of ADR was assessed by Hartwig severity scale.[7] **Mild group**: a reaction that does not require treatment. **Moderate group:** a reaction that requires treatment or hospitalization. **Severe group**: life threatening ADR.

Majority of ADR were found in this study to be mild in severity (47/89, 52.8%), followed by of Moderate severity (38/89, 42.6%), and finally 4.4 % (4/89) were in the severe group.

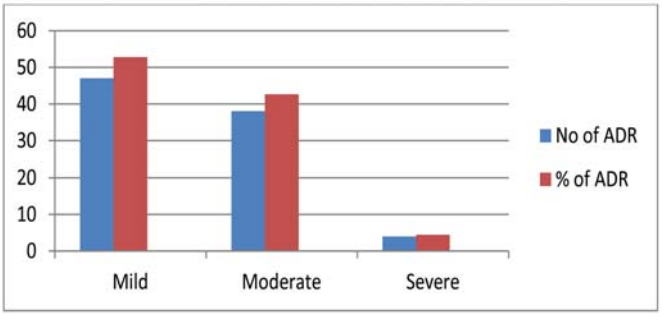

Figure 1 Severity assessment

Onset of ADR: ADR were grouped according to the onset into following three groups: **Acute:** ADR occurring within 60 minutes after administration of the drug. **Sub-Acute**: ADR occurring within 60 minutes to 24 hours after administration of the drug. **Latent:** ADR occurring after 2 days of administration of the drug.

In this study, it was found that most of the ADR occurred in the Latent group (58.1%, 53/89), followed by Sub-acute group (33.7%, 30/89), and finally the acute group with 6.7% (6/89).

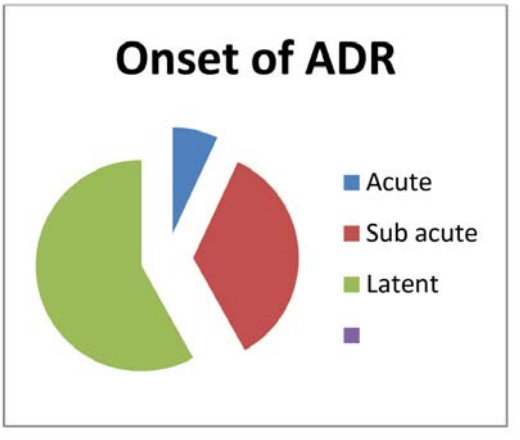

Figure 2 Onset of ADR

Preventability of ADR: Preventability of ADR was ascertained by seven point questionnaires of Schumock and thorton[8] and the preventability criteria. Out of these 89 episode of ADR, only 11 (12.3 %) were preventable and remaining 87.6 % (78/89) were non-preventable. These large numbers were non-preventable because susceptibility of these ADR is still not defined and they require further study.

DRUG CAUSING ADVERSE REACTIONS

About 450 medicines were prescribed in these patients with ADR. Prednisonle was the most common offending drugs in 23 (26.7%) cases, followed by analgesics.

Table 2 Most commonly ADR causing Drugs

DRUGS	No (%)	ADR
Prednisolone	23 (26.7%)	Moon Face, Hyperglycaemia, Cataract, Glucoma, Hirsutism, Melaena, Acne, Depression
Nimesulide (taken over the counter, outside the hospital)	12 (13.9%)	Melaena, Gastritis, Thrombocytopania
Diclofenac (taken over the counter, outside the hospital)	11 (12.7%)	Melaena, Gastritis, Allergic reaction
Furosemide	10 (11.6%)	Dry Mouth, Fluid & electrolyte imbalance
Cyclosporin	8 (9.3%)	Tachycardia, gum hyperplasia, Hair Growth
Atorvastatin	4 (4.65 %)	Myelgia, hepatotoxicity, Memory loss

RELATIONSHIP OF MULTIPLE MEDICATIONS WITH ADR

For analysis of the relationship, the patients were divided into 3 groups: Group1: that receiving 1 – 5 numbers of medications. Group2: those receiving 6 – 10 number of medications. Group3: those receiving > 10 number of medications.

It was found that Group 3 patients had the highest number of ADR 48.6 % (35/72 cases; prevalence of ADR 9.45%, or 1.06 (0.4-1.5), followed by Group 2, with 26.3 % (19/72 cases; prevalence of ADR 6.7 %, or 0.73 (0.4-1.3), and finally Group 1 with 25% (18/72 cases; prevalence of ADR 9 %, or 1.00 (reference). So it implies that patient receiving more than 5 medications are at higher risk of ADR.

DISCUSSION

This was a prospective observational study, to evaluate the incidence of ADR in OPD and Indoor patient. Out of 850 patients included in the study, 72 (8.47 %) patients were found to have one or more ADR. Total numbers of ADR were 89. This is significantly lower than data reported from other countries, which ranges from 10% to 18% of cases.[11,12]

The number of Male patient was 40 and female 32. In the t-test, it is found to be significant ($p<0.042$). Females were found to be more prone for ADR than male. Tharpe et al reported that women have a nearly 2-fold greater risk for developing ADRs than men[11]. Redmaker et al. reported that women have 1.5 times more at risk of developing ADR than male.[12] In an analysis of 48 community-based cohort studies from the UK, the overall incidence of suspected ADRs in males was 12.9 per 10 000 patient-months of exposure, and in females was 20.6 per 10 000 patient-months of exposure. The overall age-standardized odds ratio of an ADR in females compared with males was 1.6 [95% confidence interval (CI) 1.5 to 1.7].[13]

Female patients have a 1.5- to 1.7-fold greater risk of developing an ADR Female patients have a 1.5- to 1.7-fold greater risk of developing an ADR. In an analysis of 48 community-based cohort studies from the UK, the overall incidence of suspected ADRs in males was 12.9 per 10 000 patient-months of exposure, and in females was 20.6 per 10 000 patient-months of exposure.[9]

The overall age-standardized odds ratio of an ADR in females compared with males was 1.6 [95% confidence interval (CI) 1.5 to 1.7]. This may be due to pharmacokinetic, immunological

and hormonal factors as well as gender-related differences in the use of medications. Further studies are required with adequate number and strength in this regard.

Commonest age group of patient with ADR was 19 - 60 years of age. Lot of other studies also has confirmed this. Stewart et al. reported that increase in the incidence of ADR in elderly is due to polypharmacy.[14] A meta-analysis of 68 observational studies reported that the proportion of admissions related to ADRs in older people was four times higher than in younger people.[15] ADRs in elderly are largely contributed by polypharmacy, prescribing error, the effect of age and frailty on drug disposition, especially renal and hepatic clearance, increased pharmacodynamic sensitivity of the elderly to several commonly used drugs, e.g., central nervous system and cardiovascular drugs.

In this study, prednisolone was found to be responsible for maximum number of ADRs (26.7%). Its use was associated moon Face, hyperglycaemia, cataract, glucoma, hirsutism, melaena, acne, depression. Joshua et al also reported the about similar incidence with use of prednisolone.[9] Moon face was the commonest ADR (18.6%) in this study. But in a study evaluating the incidence of moon faces in 88 patients on long-term systemic corticosteroid therapy for all diseases, Fardet et al. reported as 61% at 3 months and 70% at 12 months.[16] Prednisonole is one of the most commonly used medications in various renal diseases. Probably because of monitoring and stepwise reduction of steroid dose to bare minimum, in this study incidence of moon face is lower.

Second ADR in this study is found to be Allergic reactions (10.4%). The patients with Nephotic syndrome, or Glomerulonephritis, or renal failure or post renal transplant are in a hypo-immunity state, so they develop lot of infections. To prevent or treat these infections lot of antibiotics, antifungal or antiviral medications are often prescribed. These may be implicated for the high incidence of allergic reaction encountered in this study.

Regarding severity, in this study, most of the patients had mild ADR (44/72, 51.1 %), which did not require hospitalization. These ADR responded quickly with either stoppage or modification of the offending drugs. This may be due to active monitoring and timely withdrawal of the offending drugs.

In this study, it was found that most of the ADR occurred in the Latent group (58.1%, 53/89), followed by Sub-acute group (33.7%, 30/89), and finally the acute group with 6.7% (6/89).

In this study, out of these 89 episode of ADR, only 11 (12.3 %) were preventable and remaining 87.6% (78/89) were non-preventable. These large numbers were non-preventable because susceptibility of these ADR is still not defined and they require further study.

Majority of ADR reported in this study were highly probable (47/72, 65%) of a single or more than two medications, which are known to cause these type of ADR. But as these drugs are of proven efficacy or they have been recommended in clinical practice guidelines, these drugs had to be used.

Finally, poly-pharmacy, or use of more than five drugs in a patient was found to be significantly associated with higher incidence of ADR (48.6%). In a similar study, Joshua et al. reported this incidence to be as high as 91%.[9] As most of the renal diseases are associated with co-morbidities like diabetes, hypertension, anaemia, cardiac disease, etc, polypharmacy is unavoidable and this increases the risk of ADR.

CONCLUSION

ADR is common in renal patient, inspite of careful monitoring and timely follow. Commonly used nephrological drugs have known adverse effects. But as they are of proven efficacy or have been recommended in various clinical practice guidelines, these drugs have to be used frequently and for considerable duration of time. This may be the reason most of ADR recorded in this study are not preventable. But clinician should always remain alert and vigilant for these ADR in a renal patient.

Acknowledgement: We express our gratitude to Professor (Dr) Anup Kr Barman, for his encouragement to undertake the study. Moreover we like to thank Mr Rama Krishna Prudhivi for helping us collecting the data.

Conflict of interest: None

Ethical clearance: Taken

Source of funding: None.

Contribution of authors: We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors". The first author conceived, designed the study and second author analyzed the data.

REFERRENCE

1. International drug monitoring: The role of national centers. Technical report series 498. WHO: Geneva; 1972. [cited 2016 September 17]; Available from: URL:http://who-umc.org/graphics/24756.pdf
2. Hussain MM, Girhepunje K, Pal R, Siddiqua SS. Incidence of Adverse Drug Reactions in a Tertiary Care Hospital: A Systematic Review and Meta-Analysis of Prospective Studies. Der Pharmacia Lettre 2010;2(3):358-368.
3. MedWatch - What Is A Serious Adverse Event?. 2007-09-18. [cited 2016 September 17]; Available from: URL:http://www.fda.gov/medwatch/report/DESK/advevnt.htm
4. *WHO definition of Pharmaco-vigilance*. 2002 [cited 2016 September 17]; Available from: URL: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/
5. Sainul AP. Practical Implications Of Spontaneous Adverse Drug Reaction Reporting System In Hospitals - An Overview Asian journal of pharmaceutical and clinical research 2013;6(4):10-15.
6. Naranjo CA. A method for estimating the probability of adverse drug reaction. Clinical Pharmacol ther 1981 Aug;30(2):295-45.
7. Hartwig SC. Preventibility and severity assessment in reporting adverse drug reaction. American journal of Hospital Pharmacology 1992;49;2291-31.
8. Schumock and thorton. A method for estimating the preventability of adverse drug reaction. Clinical Pharmacol ther 1992 Aug 30(2):239-45.
9. Joshua L. Adverse drug reactions in Nephrology wards inpatient of tertiay care hospital. Indian J Med Sci 2007;61(10):
10. Jick H. Adverse drug reaction: the magnititude of the problem. J Allergy clin immunol 1984;74:555-557.
11. Tharpe N. Adverse drug reactions in women's health care. J Midwifery Womens Health.2011 May-Jun;56(3):205-13.
12. Rademaker M.. Do women have more adverse drug reactions? Am J Clin Dermatol 2001;2(6):349-351.
13. Martin RM. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. Br J Clin Pharmacol 1998;46:505-11.
14. Stewart RB. Polypharmacy in the aged. Practical solutions. Drugs Aging 1994;4:449–61.
15. Beijer HJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci 2002;24:46-54.
16. Fardet L. Incidence and risk factors for corticosteroid-induced lipodystrophy: a prospective study. J Am Acad Dermatol 2007;57:604–609.