International Journal of Research in Medical Sciences
Sharma S et al. Int J Res Med Sci. 2020 Mar;8(3):985-988
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20200767

Original Research Article

Adverse drug reaction risk assessment with prescribed renal risk drugs among hospitalized patients attending a teaching hospital in South India

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Received: 18 December 2019
Revised: 23 December 2019
Accepted: 24 January 2020

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ABSTRACT

Background: Renal impairment is the primary cause of mortality and morbid conditions in patients. Inappropriate drug use in patients who are with risk of renal damage causes harmful and deleterious effects. Adjusting doses based on renal function is necessary for renal risk drugs, primarily to avoid adverse reactions of medications. Aim of the present study was to assess the risk of incidence on ADRs with drugs lowering the renal function.
Methods: This is a cross-sectional observational study conducted in General Medicine department. 230 Patients constituted the sample in the study. The study was conducted for a period of one year and prescriptions with renal risk drugs were evaluated. Changes in the renal functional tests were compared to the normal range and adverse drug responses were monitored.
Results: A total of 230 patients who fulfilled the inclusion criteria were included in the study. The meanage of the study subjects were 50.9±15.2 respectively. 56.39% patients were men and 43.6% were women. Renal risk drugs included in the study are anti-hypertensive, antibiotics, and analgesics. Paracetamol (24.77%) followed by telmisartan (20.85%) are the predominantly prescribed renal risk drugs with high incidence of adverse drug reactions. Causality assessment by Naranjo ADR probability scale showed out of 211 ADRs, 51.6% were possible, 25.59% were doubtful, 21.8% were probable and 0.94% was definite.
Conclusions: The current study signifies that patients under high risk of renal damage require continuous monitoring and optimized therapy for better disease management.

Keywords: Antibiotics, Analgesics, Anti-hypertensive agents, Renal risk drugs, Renal damage

INTRODUCTION

Kidneys function by receiving a quarter of blood from heart and play an important role in the elimination of waste metabolites and toxic products. The kidney is therefore exposed to high concentrations of drugs leading to toxicity. It is therefore analyzed that drug-induced renal injury accounts for 25% of acute renal failure.[1] Drug-induced renal toxicity is one of the common etiologies in clinical practice and the incidence of acute kidney injury may be above 60 percent.[2] The mechanism of drug-induced nephrotoxicity is complex and not yet clear but it may be mediated through changes in intra-glomerular hemodynamic properties, impaired tubular secretion, inflammation, uric acid deposition, rhabdomyolysis, and thrombotic microangiopathy.[3]

Nephrotoxic drugs (ND) are therapeutic agents which are responsible to cause adverse effects and decline kidney function by either direct toxicity or decreasing renal blood flow. Several studies proved that nephrotoxic drugs are responsible for 19% - 25% of AKI in patients and the classes of drugs included are non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACE inhibitors), antibiotics and radio contrast agents.[4]

Patients with underlying renal insufficiency, defined as glomerular filtration rate (GFR) less than 60 mL/minute/1.73m^2, heart failure, sepsis and intravascular depletion are particularly vulnerable to develop nephrotoxicity. Drugs can cause nephrotoxicity by altering intra-glomerular hemodynamics and decreasing GFR (ACEI, angiotensin-converting enzyme blockers (ARBs), NSAID, Cyclosporine, and Tacrolimus).[5]

Renal impairment due to drugs occurs at pre-renal, intrinsic or post-renal stages. Impairing of glomerular hemofiltration leads to pre-renal failure by pre-renal drugs. Renal blood perfusion is reduced by drugs upon modulating the vasomotor tone of the afferent (pre-glomerular) or efferent (post-glomerular) arterioles decreasing glomerular filtration rate followed by renal failure. Prostaglandin secretion dilates afferent arterial which is inhibited by Non-steroidal anti-inflammatory drugs (NSAIDs).[6] Chronic use of acetaminophen, aspirin and diuretics is associated with chronic interstitial nephritis causing fibrotic changes and renal scarring.[5]

METHODS

A hospital based cross-sectional study was conducted in a tertiary care teaching hospital, Guntur, Andhra Pradesh in the in-patient department of General Medicine from July 2018 to July 2019. A total of 230 patients constituted the sample for study. The study subjects were included by complete follow-up after getting informed consent from each of them.

Inclusion criteria

- Patients prescribed with antibiotics, analgesics and anti-hypertensives.
- Patients of either sex from 18-60 years of age admitted in general medicine
- Patients agreed with informed consent process

Exclusion criteria

- Pregnancy and lactating women.
- Out ward patients in the General medicine department.
- Patients with multiple co-morbidities and major illness.
- Patients who lost follow-up.
- Patients without adverse drug reactions.

This study was conducted after obtaining the approval from Institutional Human Ethical Committee of Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur. After obtaining consent from the study subjects who are willing to participate in the study; the following data were collected from patient medical record and entered in patient data collection form such as changes in the renal functional tests, adverse drug reactions due to renal risk drugs.

Statistical analysis

The mean and standard deviation was determined for sample size based on age wise distribution and the most prescribed renal risk drug was evaluated in percentage. The most commonly reported ADRs were identified and evaluated in percentage.

The adverse drug responses identified were subjected to WHO causality assessment scale and the Naranjo ADR probability scale for their probability and Hartwig severity scale to assess severity and were documented.

RESULTS

Total of 211 study subjects were included in the study and prescribed with renal risk drugs, majority of study subjects were males 119 (56.39%) and females constitute 92 (43.6%) of the total study subjects shown in (Table 1). The overall mean age of the study subjects was 50.9±15.2.

Table 1: Distribution of sample population based on gender.

Gender	N (%)
Male	119 (56.39)
Female	92(43.61)

Table 2: Renal risk drugs causing adverse drug reactions among in-patients.

Renal risk drugs	N (%)
Paracetamol	55 (27.22)
Tramadol	28 (13.86)
Mefenamic Acid	1 (0.49)
Aspirin	19 (9.4)
Doxycycline	4 (1.98)
Amoxicillin	3 (1.48)
Ofloxacin	8 (3.96)
Nitrofurantoin	1 (0.49)
Rifaximin	6 (2.97)
Furosemide	29 (14.35)
Telmisartan	44 (21.78)
Propranolol	1 (0.49)
Olmesartan	1 (0.49)
Amlodipine	1 (0.49)
Lisinopril	1 (0.49)

The details of the medications causing ADRs shown in (Table 2). The drugs causing the most frequent ADRs were non-steroidal anti-inflammatory drugs (NSAIDs) in 103 (50.99%), anti-hypertensive agents in 77 (38.11%), and antibiotics in 22 (10.89%). Furthermore, no fatal ADRs were observed during the study.

Regarding the pattern of distribution for adverse drug reactions among the respondents, a total number of 211 different adverse drug reactions were observed with the most frequent pedal edema (18.5%). Other frequently occurring adverse drug reactions were Shortness of breath (13.1%), urinary incontinence (13.1%), decreased urine output (10.8%), elevated serum creatinine (9.5%) and proteinuria (6.7%) as per (Table 3).

Table 3: Adverse drug responses identified after initiations of renal risk drugs.

ADR observed	N (%)
Shortness of breath	29 (13.1)
Pedal edema	41 (18.5)
Decreased urine output	24 (10.8)
Increased urine output	5 (2.2)
Urinary incontinence	29 (13.1)
Abdominal pain	9 (4.0)
Burning urination	15 (6.7)
Discoloured urine	3 (1.3)
Fever	7 (3.1)
Haematuria	14 (6.3)
Proteinuria	15 (6.7)
Elevated serum creatinine	21 (9.5)
Irregular heartbeat	1 (0.4)
Glycosuria	2 (0.9)
Hypokalemia	3 (1.3)
Serum urea	1 (0.4)
Hypertension	2 (0.9)

Table 4: Causality assessment by naranjo ADR probability scale.

WHO probability scale	Naranjo ADR probability scale
Certain 1 (0.47%)	Definite 2 (0.94%)
Probable 46 (21.8%)	Probable 46 (21.8%)
Possible 112 (53.08%)	Possible 109 (51.6%)
Unlikely 52 (24.64%)	Doubtful 54 (25.59%)
Conditional 0 (0%)	
Unassesable 0 (0%)	

The causality assessment for the observed adverse drug reactions was assessed using both the WHO causality assessment scale and the Naranjo ADR probability scale as shown in Table 4. Using the WHO causality assessment rating, certain cases were 01 (0.47%), probable cases were 46 (21.8%) and possible cases were 112 (53.08%). Using the Naranjo algorithm, definite cases were 2 (0.94%), probable cases were 46 (21.83%), possible cases were 109 (51.6%) and 54 (25.59%) were doubtful cases.

In addition Hartwig severity scale used to assess the severity of ADRs reported, showed that majority of the reports were of mild nature (85.30%) followed by moderate (14.70%) as shown in Table 5.

Table 5: Severity assessment of adverse response by Hartwig and Siegel scale.

Severity	N (%)
Mild	180 (85.30)
Moderate	31 (14.70)
Severe	0 (0.0)

DISCUSSION

The study was initiated on categorization of renal risk drugs, identifying the patients prescribed with renal risk drugs like antibiotics, analgesics and anti-hypertensive agents were included in the study, and these patients were followed and monitored for the incidence of adverse drug reactions. These adverse drug reactions were documented and assessed using Causality assessment scales.

Present study reported more number of men developing ADRs as compared to women (M:W 1.61:1) which is similar to other studies.[7,8] This can be probably because of the more admission of men as well as severe disease condition leading to polypharmacy. Age wise analysis revealed incidence of ADRs was highest in elderly, between 40-60 years of age (47.39%) followed by less than 20 years and more than 60 years. The present observation was similar to the study done by Dhar K et al in which proportion of ADRs were accounted for Elderly patients 46 (57.5%), followed by children 26 (32.5%) and geriatrics 8 (10%).[8]

Among the total sample population analysed, patients with renal complications (26.06%) were most effected followed by hepatic diseases (19.9%), ID (14.21%), Respiratory complications (10.9%), gastroenterology (8.05%), endocrinology (7.58%), cardiovascular (6.63%), neurology (5.68%) and orthopedics (0.94%).

Most prescribed renal risk drugs was paracetamol (24.77%), followed by telmisartan (16.81%), tramadol (14.37%), furosemide (12.23%), aspirin (9.78%), doxycycline (3.66%), nitrofurantoin (3.36%), rifaximin (2.75%), olmesartan (2.44%), ofloxacin (2.14%), spironolactone and propranolol (1.83%), amoxicillin (1.52%), naproxen (1.22%), mefanimic acid, amlodipine and lisinopril (0.3%). The study was in agreement with the study carried out by Chih-Cheng et al, mostly prescribed classes of drugs are NSAIDs.[7]

Major proportion of ADRs in sample population was observed with paracetamol (26.06%) followed by

telmisartan (20.85%), furosemide (13.74%), tramadol (13.27%), aspirin (9%), nitrofurantoin (4.73%), ofloxacin (3.79%), rifaximin (2.84%), doxycycline (1.89%), amoxicillin (1.42%) and mefanimic acid, propranolol, amlodipine, olmesartan, lisinopril with 0.47% and naproxen, spironolactone, amikacin were negligible. The study is in agreement with the study carried out by Chih-Cheng et al, with a slight variation i.e., inclusion criteria includes the subjects with hypertension.[7]

The most common ADRs were pedal edema (14.69%), shortness of breath and urinary incontinence (10.39%), decreased urine output (8.6%), elevated serum creatinine (7.52%), proteinuria (5.37%), hematuria (5.01%), increased urine output (1.79%), discoloured urine and hypokalemia (1.07%), increased blood pressure, glycosuria, hyperkalemia (0.71%), cloudy urine, irregular heartbeat, urge to urinate, oliguria, dehydration, elevated serum creatinine, vomiting, headache and diarrhea (0.35%). In this study, patients has low albumin level and this may be the reason for incidence of adverse drug response due to decrease binding of albumin bound drugs and accumulation of unbound fraction in plasma which is in agreement with a study by Corsonello and colleague.[9]

Causality assessment was carried for ADRs by WHO causality rating, and Naranjo algorithms, both the methods showed similar causality findings, which strengthen the endorsed causality evaluation. Using the WHO causality assessment rating, certain cases were 01 (0.47%), probable cases were 46 (21.8%), and possible cases were 112 (53.08%). However, in the study carried out by Kiguba R et al, shows 25% (66/269) of aa-ADRs were of probable/definitecausality.[10] In addition Hartwig severity assessment scale showed that majority of the reports were of mild nature (85.30%) followed by moderate (14.70%). However in the study carried out by Danial M et al, severity assessment using modified Hartwig and Siegel scale categorized 14 (13.6%) severe, 61 (59.2%) moderate and 28 (27.2%) mild ADRs.[11]

CONCLUSION

The current study signifies that patients under high risk of renal damage require continuous monitoring and optimized therapy for better disease management. Renal risk drugs include various classes of drugs like antibiotics, analgesics and anti - hypertensives which compromise major proportion of prescribed drugs in the hospitals. So, spontaneous detection of adverse drug reactions helps the health care professionals to provide better therapy to the patients with renal impairment. The analysis on patients demonstrated the value of drug experts as a part of multi-disciplinary team in general health care.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Sharma S, Ramineni HB, Shahitha KP, Mounika K, Ramyachandra P, Girija B. Adverse drug reaction risk assessment with prescribed renal risk drugs among hospitalized patients attending a teaching hospital in South India. Int J Res Med Sci 2020;8:985-8.