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APPRAISING THE PREPONDERANCE OF DRUG-INDUCED NEPHROTOXICITY IN HOSPITAL-BASED SETTING OF CENTRAL INDIA: A CROSS-SECTIONAL STUDY

Dr. Sonali Rode,[1] Dr. Amrita Umathe,[2] Dr Prasad Udhoji,[3] Dr. Shailesh Parate,[4*] Dr. Harsh Salankar[5]

[1]MBBS, MD, Professor, Department of Pharmacology, Shri Balaji Institute of Medical Sciences, Raipur, Chhattisgarh

[2]MBBS, MD, Assistant professor, Department of Pharmacology, Government Medical College, Akola, Maharashtra

[3]MBBS, MD, Assistant Professor, Department of Physiology, Dr. Rajendra Gode Medical College, Amravati, Maharashtra

[4*]MBBS, MD, Additional Professor, Forensic Medicine & Toxicology, AIIMS, Rishikesh, Uttarakhand

[5]MBBS, MD, Professor, Department of Pharmacology, NKP Salve Institute of Medical Sciences & Research Centre, Nagpur, Maharashtra

Corresponding Author: Dr. Shailesh Parate

Email id- shailesh.fmt@aiimsrishikesh.edu.in

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ABSTRACT

Background: Drug-induced renal disease is one of the most frequent etiological causes contributing to acute renal failure and chronic kidney disease in the current clinical setting. Different medicines cause certain typical renal responses by direct toxicity and immunologic mechanism virtue.

Aim: The purpose of this study was to evaluate the incidence and prevalence of drug-induced nephrotoxicity (DIN) among kidney disease patients in the central Indian population.

Methods: 500 participants within a predetermined age range were screened for the study, and anthropometric and demographic data were collected over a period of 2 years. A total of 120 patients with drug-induced nephrotoxicity were studied. Half of the study participants were female and ranged in age from 30 to 70 years. Serum creatinine was measured and protein was analyzed using the dipstick method. The 4-variable modification of diet in renal disease (MDRD) equation and the Cockcroft-Gault equation adjusted for body surface area (CG-BSA) were used to estimate the glomerular filtration rate (GFR). Detailed drug history was jotted down for the subjects who were included in the study

Results: Using MDRD to measure GFR, 2.8% of patients had proteinuria with DIN in 6.3% of subjects (n=120). Using the CG-BSA approach, it was discovered that the DIN prevalence was 24%. It was shown that there was a strong correlation between DIN and gender, advanced age, smoking, diabetes, hypertension, and abdominal obesity. The most common drugs causing nephrotoxicity were nonsteroidal anti-inflammatory drugs (NSAIDs) followed by aminoglycosides, diuretics, and, anticancer drugs.

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Conclusion: DIN is a major causative factor (24%) responsible for kidney diseases. The stark discrepancy in DIN prevalence between the MDRD and CG-BSA equations indicates the need for improved methods of evaluating renal function in the people of central India. Additionally, the CG-BSA equations point to a similar requirement for improved metrics to evaluate renal function. NSAIDS because of their widespread use are the most common drugs leading to nephrotoxicity.

Keywords: Body Mass Index (BMI), Cockcroft-Gault (CG), Drug-Induced Nephrotoxicity (DIN), Proteinuria, Glomerular Filtration Rate (GFR),

INTRODUCTION

Globally, chronic renal illness is rapidly spreading and becoming endemic. In India, a sizable population is also afflicted by chronic kidney disease (CKD). However, specific evidence and prevalence change depending on the region.[1] The rising prevalence of systemic illnesses including diabetes, hypertension, and ischemic heart disease may be to blame for this. Additionally, there is a dearth of knowledge about chronic renal disease in India, where almost 70% of the population lives in rural regions with limited access to healthcare, leading to advanced detection of chronic renal disorders that call for aggressive management.[2]

Research indicates that individuals with CKD should receive prompt attention and sufficient preparation along with preventive interventions. The risk factors for the prevalence of CKD can be changed, though. The incidence of drug-induced nephrotoxicity (DIN) is rising quickly due to increased drug use, easy access to medications, and the availability of over-the-counter medications, such as non-steroidal anti-inflammatory drugs (NSAIDs). The medications that are most frequently linked to acute renal failure and CKD are contrast agents, NSAIDs, ACEIs, and antibiotics.[3] Acute glomerulonephritis, which is infrequently associated with drugs such as rifampicin, is one of the syndromes linked to chronic kidney disease (CKD).[4] Vasopressin analogs, tricyclic antidepressants, vincristine, phenothiazines, and cyclophosphamide all cause inappropriate ADH release. It has been observed that amphotericin, aminoglycosides, lithium, and demeclocycline are related to nephrogenic diabetic insipidus.[5]

Risk factors for renal toxicity include aging, liver illness, renal ischemia, concurrent use of nephrotoxic drugs and diuretics, and depletion of Na+ and K+. Elevating trough values could be a sign of approaching nephrotoxicity. [6] Medications linked to long-term interstitial nephropathy are NSAIDs, aspirin, acetaminophen, female sex, age over 60, history of chronic pain, and cumulative analgesic usage > 1 gram per day for more than two years.[7]

DIN affects adults at a rate of 14–26% and children at a rate of 16%.1 A minimum of 24–48 hours of medication exposure and a rise in serum creatinine of 0.5 mg/dl or 50% over a 24-72 hour period are considered indicators of nephrotoxicity. A 50% rise in serum creatinine, however, is not a very specific marker of renal disease. DIN falls under two categories: Type B (idiosyncratic reactions) and Type A (dose-dependent reactions).[8] Dose-dependent reactions are predictable due to the drug's pharmacological characteristics, while idiosyncratic reactions are unpredictable since they depend on patient-related factors.

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The use of medications that result in crystals that are insoluble in urine can cause crystal nephropathy. These crystals form in the lumen of the distal tubule, blocking the flow of urine and causing the interstitial response. Examples include methotrexate, triamterene, ampicillin, ciprofloxacin, sulphonamides, and antivirals such as acyclovir, foscarnet, ganciclovir, and indinavir. DIN can be observed in any one of the four phenotypes.[9,10]

The purpose of this clinical investigation was to evaluate the frequency and prevalence of drug-induced nephrotoxicity among CKD patients.

MATERIAL AND METHODS

The study was conducted for 2 years, from November 2021 to October 2023, at a tertiary care hospital following approval from the ethics committee.

500 adults between the ages of 30 and 70 years were screened for renal illnesses using a kidney disease comprehensive questionnaire, an anthropometric assessment, blood pressure monitoring, and urine dipstick testing. Anthropometric and demographic information was collected for every research participant. Additionally, serum creatinine was assessed for each participant, and protein urine analysis was performed using a dipstick. The 4-variable modification of diet in renal disease (MDRD) equation and the Cockcroft-Gault equation adjusted for body surface area (CG-BSA) were used to estimate the glomerular filtration rate (GFR). 120 patients between the ages of 30 and 70 years who had drug-induced nephrotoxicity were included in the study. Detailed drug history was jotted down for the subjects who were included in the study.

Either renal damage or a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m2.8 are indicators of chronic kidney disease (CKD).

Proteinuria was defined as the presence of protein in the urine as detected by 1+ (0.3 g/l) or more on dipstick.[10]

Hematuria was also defined as 1+ (25 red blood cells/µl) and above. Kidney function was determined by the use of both CG corrected to the BSA and the 4-variable MDRD formula.

This estimated creatinine clearance (ml/min) was further corrected to BSA to obtain creatinine clearance (ml/min/1.73 m^2).[11]

Hypertension was defined as the presence of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, on examination or self-reported history of hypertension or use of antihypertensive medications.[12]

Diabetes mellitus was defined as a fasting blood sugar value more than or equal to 126 mg/dl or a self-reported history of diabetes or taking insulin or other medications for the control of diabetes.[13]

Obesity was defined using the Indian consensus definition: malnutrition < 18 kg/m^2, normal BMI: 18.0-22.9 kg/m^2, overweight: 23.0-24.9 kg/m^2, obesity: >25 kg/m^2. Abdominal obesity was defined as waist circumference in men > 90 cm, women > 80 cm.[14]

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RESULTS

The study comprised 120 patients, ranging in age from 30 to 70 years, with a mean age of 39.88 ± 15.87 years, who had experienced drug-induced nephrotoxicity. 54.16% of patients were female. The demographic characteristics of the study subjects are listed in Table 1. 21.66% (n=26) of the participants were found to be in the 30–40 year age group, 29.16% (n=35) to be in the 41–50 year age group, 28.33% (n=34) to be in the 51–60 year age group, and 20.83% (n=25) to be in the above 60 year age group. In the current study, there were 54.16% (n=65) females and 45.93% (n=55) males. In terms of occupation, 46.66% (n=56) of the subjects belonged to the labor class, 25% (n=30) were professionals in the workforce, and 28.33% (n=34) were not in the workforce.

After analyzing the population's stratification based on GFR, it was discovered that, for participants with GFRs of >90, the MDRD number was 60% (n = 72), the CG number was 23.33% (n = 28), and the CG-BSA number was 37.5% (n = 45). Using MDRD, CG, and CG-BSA, GFRs of 60–89 were seen in 33.33% (n = 40), 45.83% (n = 55), and 37.5% (n = 45) of the individuals, respectively.

With MDRD, CG, and CG-BSA, the GFR of 30-59 was observed in 5% (n = 6), 28.33% (n = 34), and 15% (n = 18) of cases, respectively. 1.66% (n=2), 1.66% (n=2), and 0.83% (n=1) of the subjects had a GFR of 15–29 utilizing the MDRD, CG, and CG-BSA techniques, respectively. Table 2 indicates that 0.83% (n=1) of the CG subjects had a GFR of less than 15.

Upon comparing the features of the patients with and without DIN, it was observed that in 120, 54.16% (n=65) of the subjects were female, and 29.16% (n=35) of the subjects with DIN were in the age range of 41 to 50 years. Of the subjects, only 14.16% (n=17) were vegetarians, while 28.33% (n=34) were either unemployed or did not work.

When it came to the habits of participants with DIN, 14.16% (n=17), 11.66% (n=14), and 26.66% (n=32) of the subjects had smoking, alcohol, and tobacco use, respectively. Of the participants with DIN, 26.66% (n = 32), 56.66% (n = 68), and 12.5% (n = 15) had diabetes, hypertension, and abdominal obesity, respectively. Table 3 demonstrates that participants with DIN had considerably higher rates of diabetes and hypertension ($p<0.001$).

We conducted a multivariate logistic regression analysis to see which of these factors would be most predictive of developing DIN. Table 4 illustrates how age, gender, diabetes, and hypertension emerged as significant risk factors for DIN with $P < 0.01$, 0.02, 0.001, and 0.001, respectively. NSAIDS (30.83 %) were the most common drugs causing nephrotoxicity followed by aminoglycosides, diuretics, anticancer drugs, ACE inhibitors, Vancomycin, and other drugs as shown in Table 5.

DISCUSSION

The study comprised 120 patients, ranging in age from 30 to 70 years, with a mean age of 39.88 ± 15.87 years, who had experienced drug-induced nephrotoxicity. Of the patients, 54.16% were female. 21.66% (n=26) of the participants were found to be in the 30–40 year age group, 29.16%

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(n=35) to be in the 41–50 year age group, 28.33% (n=34) to be in the 51–60 year age group, and 20.83% (n=25) to be in the above 60 year age group. In the current study, there were 54.16% (n=65) females and 45.93% (n=55) males. In terms of occupation, 46.66% (n=56) of the subjects belonged to the labor class, 25% (n=30) were professionals in the workforce, and 28.33% (n=34) were not in the workforce.

These attributes aligned with the research conducted by Earley A et al. (2012)[15] and Varma PP et al. (2016),[16] whose investigations evaluated similar populations and demography.

The population stratification based on GFR was also evaluated in this study. Using the MDRD number, it was shown that for GFR of >90, there were 60% (n = 72), 23.33% (n = 28), and 37.5% (n = 45) participants in the CG-BSA number. Using MDRD, CG, and CG-BSA, GFRs of 60–89 were seen in 33.33% (n = 40), 45.83% (n = 55), and 37.5% (n = 45) of the individuals, respectively. With MDRD, CG, and CG-BSA, the GFR of 30-59 was observed in 5% (n = 6), 28.33% (n = 34), and 15% (n = 18) of the cases, respectively. 1.66% (n = 2), 1.66% (n = 2), and 0.83% (n = 1) of the subjects had a GFR of 15-29 using the MDRD, CG, and CG-BSA technique, respectively.

GFR of less than 15 was seen in just 0.83% (n=1) of CG participants. These outcomes agreed with those of Bhardwaj R et al. (2017)[17] and Levey AS18 et al. (2009),[18] whose authors reported comparable GFR levels using the MDRD, CG, and CG-BSA approaches.

Comparing the characteristics of the individuals with and without DIN, the current study also found that, out of 120, 54.16% (n=65) were female, and the majority of subjects with DIN were between the ages of 41 and 50, accounting for 29.16% (n=35) of the subjects. Of the subjects, only 14.16% (n=17) were vegetarians, while 28.33% (n=34) were either unemployed or did not work. When it came to the habits of participants with DIN, 14.16% (n=17), 11.66% (n=14), and 26.66% (n=32) of the subjects had smoking, alcohol, and tobacco use, respectively.

Of the participants with DIN, 26.66% (n = 32), 56.66% (n = 68), and 12.5% (n = 15) had diabetes, hypertension, and abdominal obesity, respectively. Diabetes and hypertension were substantially more common in DIN individuals ($p<0.001$). These findings corroborated those of studies published in 2006 by Ma YC et al.[19] and in 2010 by Delanaye P et al.[20], who found a substantial correlation between age, diabetes, and hypertension with DIN.

A multiple logistic regression analysis was conducted in this study to determine which of these characteristics would be more likely to predict developing DIN. Variables related to age, gender, diabetes, and hypertension were found to be significant risk factors for DIN, with $P < 0.01$, 0.02, 0.001, and 0.001, respectively.

This was in agreement with Grootendorst DC et al[21] in 2009 showing a similar relationship between DIN with hypertension, age, and diabetes. The commonest drugs causing nephrotoxicity were NSAIDs followed by aminoglycosides, diuretics, anticancer drugs, ACE inhibitors, vancomycin, and other drugs similar to the study conducted by Ghane and Assadi.[22] NSAIDS being the most commonly prescribed medicines for routine ailments justifies the above finding.

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CONCLUSION

Within the bounds of its limitations, the current study finds that there is a growing trend in India towards a higher prevalence of DIN, particularly in rural areas. Additionally, age, diabetes, and hypertension were found to have a strong correlation with DIN and to be prognostic indications of DIN. A smaller sample size, geographic area biases, a shorter monitoring period, and the study's single-institution design were among its few drawbacks. Therefore, in order to draw a firm conclusion, more longitudinal studies involving a bigger sample size and a longer monitoring period are needed.

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TABLES

Table 1. Demographic characteristics of the studied population (n=120)

Characteristics	Number	Percentage (%)
Age group		
30-40	26	21.66
41-50	35	29.16
51-60	34	28.33
>61	25	20.83
Gender		
Male	55	45.83
Female	65	54.16

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Occupation		
Labour	56	46.66
Professional	30	25
Nonworking	34	28.33

Table 2. Stratification of the population according to the GFR (n=120)

GFR categories	MDRD n (%)	CG n(%)	CG-BSA n(%)
>90	72(60)	28(23.33)	45(37.5)
60-89	40(33.33)	55(45.83)	56(46.66)
30-59	6(5)	34(28.33)	18(15)
15-29	2(1.66)	2(1.66)	1(0.83)
<15	0(0)	1(0.83)	0(0)

GFR – Glomerular Filtration Rate, MDRD- Modification Of Diet In Renal Disease, CG-Cocktail-Gault, BSA- Body Surface Area

Table 3: Characteristics of the DIN versus non- DIN group

Characteristics	DIN absent (n=380) (%)	DIN present (n=120) (%)	p-value	Odds ratio
Age group				
30-40	137(36.05)	26 (21.66)	<0.01(S)	
41-50	96(25.26)	35 (29.16)		
51-60	119(31.31)	34 (28.33)		
>61	28(7.36)	25 (20.83)		
Gender				
Male	209(55)	55 (45.83)	0.02(S)	1.765
Female	171(45)	65 (54.16)		
Occupation				
Labour	143(37.63)	56 (46.66)	0.28(NS)	
Professional	62(16.31)	30 (25)		
Nonworking	175(46.05)	34 (28.33)		
Food habit				
Vegetarian	47(12.36)	17(14.16)	0.203(NS)	0.673
Non-vegetarian	333(87.63)	103(85.83)		
Habits				
Smoking	26(6.84)	17(14.16)	0.021(S)	1.896
Alcohol	39(10.26)	14(11.66)	0.115(NS)	
Tobacco	78(20.52)	32(26.66)	0.887(NS)	
Abdominal obesity	76(20)	32(26.66)	0.027(S)	1.115
Hypertension	123(32.36)	68(56.66)	<0.001(S)	3.151
Diabetes	10(2.63)	15(12.5)	<0.001(S)	3.113

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Table 4: Variables associated with CKD by logistic regression

Variable	Logistic regression			
	p-value	OR	95% CI for OR	
			Lower	Upper
Age	<0.001	1.040	1.029	1.052
Sex	0.010	1.693	1.135	2.527
Type of family	0.393	0.844	0.571	1.246
Hypertension	0.009	1.699	1.139	2.533
Diabetes	0.034	2.051	1.054	3.991
Abdominal obesity	0.312	0.799	0.517	1.235
Smoking	0.898	0.961	0.527	1.753

Table 5. Groupwise distribution of the drugs causing nephrotoxicity (n=120)

Sr. No.	Drugs	No of patients (n=120) (%)
1	**NSAIDS**	37 (30.83%)
2	**Aminoglycosides**	32 (26.7%)
3	**Diuretics**	27 (22.5%)
4	**Anticancer drugs**	25 (20.83%)
5	**ACE inhibitors**	20 (19.2%)
6	**Vancomycin**	13 (10.83%)
7	**Others**	11 (09.17%)