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ASSESSING THE PREVALENCE OF DRUG-INDUCED NEPHRITIS IN HOSPITAL BASED SETTING OF CENTRAL INDIA: A CLINICAL CROSS-SECTIONAL RETROSPECTIVE STUDY

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Abstract

Background: One of the most common etiological factors leading to chronic kidney disease and acute renal failure in the present clinical scenario is drug-induced renal disease. By direct toxicity and immunologic mechanism virtue, certain stereotyped renal responses are initiated by various drugs.

Objectives: The present study was conducted to retrospectively assess the prevalence and incidence of drug-induced nephrotoxicity at the Department of Pathology, Sri Shankaracharya Institute of Medical Sciences, Bhilai, and Chhattisgarh. The study was conducted for 6 months on 120 subjects having drug-induced nephritis. The study subjects were within the age range of 30-70 years and had 50% females.

Methods: The study screened 500 subjects of a defined age group where anthropometric and demographic records were obtained followed by serum creatinine measurement and protein analysis using the dipstick method. Glomerular filtration rate was estimated (eGFR) using the 4-variable modification of diet in renal disease (MDRD) equation and Cockcroft-Gault equation corrected to the body surface area (CG-BSA).

Results: In 2.8% of subjects proteinuria was seen with DIN in 6.3% (n=120) subjects using MDRD for GFR assessment. The DIN prevalence was found to be 24% using the CG-BSA method. DIN was found to be significantly associated with hypertension, diabetes, smoking, abdominal obesity, advanced age, and gender. The large difference in Din prevalence between CG-BSA equations and MDRD shows that there is a need for having better measures for assessing the kidney function in the population of central India. Also, CG-BSA equations suggest a similar need for having better measures for assessing the kidney function in the population of central India.

Keywords: Body mass index (BMI), Cockcroft-Gault (CG), chronic kidney disease (CKD), drug-induced nephrotoxicity (DIN), Proteinuria, Glomerular filtration rate (GFR),

Introduction

Chronic Renal Disease is a fast-growing disease worldwide achieving the endemic levels. CKD is also affecting a large population in India.[1,2,3] However, exact evidence and prevalence vary in different geographical locations.[4] This can be owned by the increasing incidence of systemic diseases such as ischemic heart diseases, hypertension, and diabetes. Also, there is a lack of awareness concerning chronic renal disease in India with nearly 70% population residing in rural areas and had limited reach to health care services causing the diagnosis of chronic renal diseases at an advanced stage warranting aggressive intervention. Literature data suggest immediate attention and adequate planning with preventive measures in chronic kidney disease (CKD) subjects. However, the risk factors related to CKD prevalence are modifiable.[2,3]

DIN (drug-induced nephrotoxicity) incidence is rapidly increasing owing to easy access to the available drugs, increase in drug use, and availability of over-the-counter drugs including NSAIDs (non-steroidal anti-inflammatory drugs). The drugs most commonly associated with CKD and acute renal failure are Antibiotics, NSAIDs, angiotensin-converting enzyme inhibitors (ACEI), and contrast agents.[5] Apart from drugs various syndromes are also linked to CKD including Acute glomerulonephritis (rarely seen with drugs like rifampicin)- Associated with generalized anasarca, hypertension, oliguria; blood urea nitrogen (BUN) and serum creatinine (SCr) elevated; urine microscopy reveals proteinuria (> 2 g/24 hr) and RBC casts with > 80% dysmorphic RBCs. To assess the inflammation severity and pathology, a renal biopsy may be warranted.[4]

Inappropriate ADH secretion is seen with vasopressin analogs, tricyclic antidepressants, cyclophosphamide, cyclophosphamide, vincristine, and phenothiazines. Nephrogenic diabetes insipidus is seen to be associated with amphotericin, aminoglycosides, and lithium demeclocycline. Subjects having nephrotoxicity increase in number during therapy to 50% with 14 days 2 or more of therapy.[5]

The common risk factors associated with DIN and increasing risk and side-effects are co-existing use of other nephrotoxins, pre-existing renal dysfunction, volume-depleted state, and old age. However, identifying all the drugs associated with renal disease is not possible, a few prototype drugs are well-identified. In subjects where underlying drugs are not identified in renal disease subjects, the treatment should focus on withdrawing the drug and supportive management to reverse dysfunction largely.[6.7]

Clinical features – This is typically presented as acute tubular necrosis milder than oliguric acute renal failure (ARF). Other features include hypomagnesemia, hypocalcemia, hypokalemia, glycosuria, proteinuria, enzymatic, proximal tubular dysfunction, and non-oliguric ARF. Following therapy completion, renal function decreases in more than 50% of subjects with slow recovery needing 4-6 weeks. Also, incomplete recovery is seen in subjects with pre-existing renal insufficiency with few subjects progressing to chronic interstitial nephritis.[7,8]

Concomitant use of nephrotoxic agents and diuretics, liver disease, increasing age, renal ischemia, and Na+ and K+ depletion are risk factors for renal toxicity. Rising trough levels may indicate impending nephrotoxicity. Relative toxicity of drugs decreases from Neomycin, Gentamycin, Tobramycin, Netilmicin, Amikacin, to Streptomycin.[1.9.10]

Drugs associated with chronic interstitial nephropathy [11,12,23]

NSAIDs, aspirin, Acetaminophen, cumulative consumption of analgesic > 1 gram per day for more than two years, female sex, age older than 60 years, and chronic pain history.

Drugs altering intraglomerular hemodynamics [10-12,13,14]

NSAIDs, ARBs, ACE inhibitors, cyclosporine (Neoral) or tacrolimus, NSAIDs, ARBs, age older than 60 years, intravascular volume depletion, and underlying renal insufficiency. The incidence of drug-induced nephrotoxicity is 14-26 % in adults and 16% in pediatric cases.[1] Nephrotoxicity is defined as 0.5mg/dl or 50% rise in serum creatinine over a 24-72 hour time frame and a minimum of 24-48h drug exposure.[2] However, serum creatinine increase by 50% is not highly specific for kidney disease. DIN can be categorized as Type A-Dose-dependent and Type B-Idiosyncratic reactions.

Idiosyncratic reactions are unpredictable as they are dependent on patient-related factors, whereas, dose-dependent reactions are predictable based on the drug's pharmacological properties. The Kidney Disease Improving Global Outcomes (KDIGO) classify DIN into acute (1-7 days), sub-acute (8-90 days), and chronic (>90 days).[3,4] etiological factors for nephrotoxicity can be owned to different drugs intake and is explained by various mechanisms as [5,6]

- Crystal Nephropathy: Use of drugs that produce crystals that are insoluble in urine. These crystals precipitate within the distal tubular lumen, obstructing the urine flow and eliciting the interstitial reaction. Examples: Antimicrobial agents (Ampicillin, Ciprofloxacin, Sulphonamides), Antivirals (Acyclovir, Foscarnet, Ganciclovir, Indinavir), Methotrexate, Triamterene. DIN presents in one of the four phenotypes.
- Due to inflammation in the glomerulus, renal tubular cells, and surrounding interstitium: a) Glomerulonephritis: Inflammatory condition due to immune mechanism associated with proteinuria in nephrotic range. a. Examples: Gold, Hydralazine, Interferon-alpha, Lithium, NSAIDs, Propylthiouracil, Pamidronate. b) Acute Interstitial Nephritis: due to non-dose dependent idiosyncratic response. a. Examples: Allopurinol, Antibiotics (Beta-lactam, Quinolones, Sulphonamides, and Vancomycin), Antivirals (Acyclovir, Indinavir), Diuretics (Loop and Thiazide), NSAID's, Phenytoin, Proton pump inhibitors (Omeprazole, Pantoprazole, Lansoprazole, and Ranitidine) c) Chronic interstitial nephritis: Due to hypersensitivity reactions. a. Examples: Calcineurin inhibitors (Tacrolimus, Cyclosporin), Lithium, Aspirin, Acetaminophen.
- Renal tubular toxicity: Interfere with the mitochondrial function by increasing oxidative stress and forming free radicals. Examples: Aminoglycosides, Amphotericin B, Antiretrovirals (Adefovir, Cidofovir), Cisplatin, Contrast dye, and Zoledronate.
- By altering the Intraglomerular hemodynamics: Interfere with the kidney's ability to auto-regulate glomerular pressure, decrease in pressure and cause dose-dependent vasoconstriction of afferent arterioles. Examples: NSAID's, ACE inhibitors, ARB's, Calcineurin inhibitors like Cyclosporine and Tacrolimus.

Methods

The present retrospective clinical study was conducted to retrospectively assess the prevalence and incidence of drug-induced nephrotoxicity. The study was carried out at the Department of Pathology, Sri Shankaracharya Institute of Medical Sciences, Bhilai, Chhattisgarh. The study included 120 patients with drug-induced nephrotoxicity between 20-70 years age group. 54.16% of patients were female.

Some definitions regarding the present study

- CKD is defined as the presence of either kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2.[8]
- 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 RBC/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 fasting blood sugar value more than or equal to 126 mg/dl or 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]

Screening of 500 people aged 30-70 years was carried out for kidney diseases using a detailed questionnaire, anthropometric examination, blood pressure measurement, and urine dipstick tests. For all the study subjects, demographic and anthropometric data were obtained retrospectively. Also, protein urine analysis was done by dipstick and serum creatinine was measured in all participants. Glomerular filtration rate was estimated (eGFR) using the 4-variable modification of diet in renal disease (MDRD) equation and Cockcroft-Gault equation corrected to the body surface area (CG-BSA).

Results

The present retrospective clinical study was conducted to retrospectively assess the prevalence and incidence of drug-induced nephrotoxicity. The study included 120 patients with drug-induced nephrotoxicity between 20-70 years age group and the mean age of 39.88 ± 15.87 years. 54.16% of patients were female. The demographic characteristics of the study subjects are listed in Table 1. It was seen that there were 21.66% (n=26) subjects from 30-40 years age group, 29.16% (n=35) from 41-50 years, 28.33% (n=34) from 51-60 years, and 20.83% (n=25) from above 60 years age group. There were 45.93% (n=55) males and 54.16% (n=65) females in the present study. Concerning occupation, 46.66% (n=56) subjects were from the labour class, 25% (n=30) were working professionals, and 28.33% (n=34) were non-working.

On assessing the Stratification of the population according to the GFR, it was seen that for GFR of >90 using MDRD number was 60% (n=72), CG 23.33% (n=28), and CG-BSA number as 37.5% (n=45) subjects. GFR of 60-89, using MDRD, CG, and CG-BSA was seen in 33.33% (n=40), 45.83% (n=55), and 37.5% (n=45) subjects respectively. The GFR of 30-59 was seen in 5% (n=6), 28.33% (n=34), and 15% (n=18) respectively with MDRD, CG, and CG-BSA. The GFR of 15-29 using MDRD, CG, and CG-BSA method was seen in 1.66% (n=2), 1.66% (n=2), and 0.83% (n=1) subject respectively. The GFR of <15 was seen only in 0.83% (n=1) subject of CG as shown in Table 2.

On comparing the characteristics of the subjects with and without DIN, it was seen that in 120, 54.16% (n=65) were females with the majority of subjects with DIN were in the age group of 41-50 years with 29.16% (n=35) subjects. Only 14.16% (n=17) subjects were vegetarian and 28.33% (n=34) subjects were non-working or unemployed. Concerning habits in subjects with DIN, smoking, alcohol, and tobacco was seen in 14.16% (n=17), 11.66% (n=14), and 26.66% (n=32) subjects respectively. Abdominal obesity, hypertension, and diabetes was seen in 26.66% (n=32), 56.66% (n=68), and 12.5% (n=15) subjects respectively with DIN. Prevalence of hypertension and diabetes was significantly higher in subjects with DIN with $p<0.001$ as shown in Table 3.

A multiple logistic regression analysis was performed to see which among these variables would predict higher chances of developing DIN. Age, gender, hypertension, and diabetes variables emerged as important risk factors for DIN with $P < 0.01$, 0.02, 0.001, and 0.001 respectively as shown in Table 4.

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
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 no. (%)	CG no. (%)	CG-BSA no. (%)
>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) no. (%)	DIN present (n=120) no. (%)	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

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

Discussion

The present retrospective clinical study was conducted to retrospectively assess the prevalence and incidence of drug-induced nephrotoxicity. The study included 120 patients with drug-induced nephrotoxicity between 20-70 years age group and the mean age of 39.88 ± 15.87 years. 54.16% of patients were female. It was seen that there were 21.66% (n=26) subjects from 30-40 years age group, 29.16% (n=35) from 41-50 years, 28.33% (n=34) from 51-60 years, and 20.83% (n=25) from above 60 years age group. There were 45.93% (n=55) males and 54.16% (n=65) females in the present study. Concerning occupation, 46.66% (n=56) subjects were from the labour class, 25% (n=30) were working professionals, and 28.33% (n=34) were non-working. These characteristics were comparable to the studies of Earley A et al[15] in 2012 and Varma PP et al[16] where authors assessed comparable population and demographics in their study.

The present study also assessed the Stratification of the population according to the GFR, it was seen that for GFR of >90 using MDRD number was 60% (n=72), CG 23.33% (n=28), and CG-BSA number as 37.5% (n=45) subjects. GFR of 60-89, using MDRD, CG, and CG-BSA was seen in 33.33% (n=40), 45.83% (n=55), and 37.5% (n=45) subjects respectively. The GFR of 30-59 was seen in 5% (n=6), 28.33% (n=34), and 15% (n=18) respectively with MDRD, CG, and CG-BSA. The GFR of 15-29 using MDRD, CG, and CG-BSA method was seen in 1.66% (n=2), 1.66% (n=2), and 0.83% (n=1) subject respectively. The GFR of <15 was seen only in 0.83% (n=1) subjects of CG. These results were consistent with the results of Bhardwaj R et al[17] in 2010 and Levey AS[18] et al in 2009 where authors reported similar GFR values MDRD, CG, and CG-BSA methods.

The present study also compared the characteristics of the subjects with and without DIN, it was seen that in 120, 54.16% (n=65) were females with the majority of subjects with DIN were in the age group of 41-50 years with 29.16% (n=35) subjects. Only 14.16% (n=17) subjects were vegetarian and 28.33% (n=34) subjects were non-working or unemployed. Concerning habits in subjects with DIN, smoking, alcohol, and tobacco was seen in 14.16% (n=17), 11.66% (n=14), and 26.66% (n=32) subjects respectively. Abdominal obesity, hypertension, and diabetes was seen in 26.66% (n=32), 56.66% (n=68), and 12.5% (n=15) subjects respectively with DIN. Prevalence of hypertension and diabetes was significantly higher in subjects with DIN with p<0.001. These results were similar to what was reported by Ma YC et al[19] in 2006 and Delanaye P et al[20] in 2010 where authors reported a significant association of diabetes, hypertension, and age with DIN.

In the present study, a multiple logistic regression analysis was performed to see which among these variables would predict higher chances of developing DIN. Age, gender, hypertension and diabetes variables emerged as important 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 the similar relationship of DIN with hypertension, age, and diabetes.

Conclusion

Within its limitations, the present study concludes that the prevalence of DIN is increasing in India with a large increase in rural areas with high prevalence. Also, a significant association of DIN was seen with age, diabetes, and hypertension, and these factors were found to be predictive indicators for DIN. However, the present study had few limitations including a smaller sample size, geographical area biases, shorter monitoring period, and single-institution nature. Hence, further longitudinal studies with a larger sample size and longer monitoring period are required to reach a definitive conclusion.

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