ECRONICON OPEN ACCESS

EC PSYCHOLOGY AND PSYCHIATRY
Research Article

Renal Function Abnormalities in Patients on Treatment with Antipsychotics: A Comparison between Typical and Atypical Antipsychotics

Chukwujekwu DC[1]* and Ohiri JU[2]

[1]*Department of Neuropsychiatry, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria*

[2]*Department of Chemical Pathology, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria*

***Corresponding Author:** Chukwujekwu DC, Department of Neuropsychiatry, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria.

Received: April 19, 2019; **Published:** April 26, 2019

Abstract

Objective: The study was designed to study renal function abnormalities in patients on treatment with antipsychotics at the University of Port Harcourt Teaching Hospital (UPTH) in Rivers State Nigeria.

Materials and Methods: Two groups of forty consecutive patients in typical and atypical antipsychotics respectively who attended the Neuropsychiatry Department of UPTH from November 2018and March 2019 were studied. Their blood samples were taken, and the serum concentrations of Creatinine and Urea were derived by the Jaffe and Urease method.

Results: The mean age of the 80 subjects was 38.3 ± 9.8 yrs. The largest proportions were male (62.5%), Christian (97.5%), had secondary education (67.5%), unemployed (75.0%), single (75.0%), of Ibo ethnic nationality (42.5%), schizophrenic (32.5%) and had neither family history of kidney disease (87.5%) nor comorbid psychoactive substance use disorder (62.5%).

The mean GFR of the subjects on atypical antipsychotics is statistically significantly lower than those on typical antipsychotics (93.95 ± 18.95, 114.20 ± 35.80; P = 0.008) as well as that of the controls (93.95 ± 18.95, 125.50 ± 31.98; P = 0.000).

Conclusion: The differences in the mean GFR values of the subjects compared with the controls are a significant marker of the increased risk of renal deficiency posed by prolonged use of antipsychotics especially the atypical ones.

Keywords: *Antipsychotics; Typical; Atypical; Kidney Disease; Chronic*

Introduction

The kidney is an invaluable organ that plays a vital role in the excretion of waste products and toxins such as urea, creatinine and uric acid, regulation of extracellular fluid volume, serum osmolality and electrolyte concentration as well as the production of some hormones [1].

Antipsychotics (both typical and atypical) are often employed in the management of a wide range of psychiatric disorders characterized by psychotic symptoms among others. The atypical antipsychotics have been considered to be at least as effective as conventional antipsychotic agents such as haloperidol with a lower risk of most adverse effects [2]. Nevertheless, new safety issues including increased risks of cerebrovascular adverse effects and death have emerged with respect to the use of atypical antipsychotics and hence have complicated their use [3-6].

Inspite of the many documented adverse side effects of antipsychotics, especially, cerebrovascular and cardiovascular side effects, not much has been done to compare the renal side effect profiles of typical and atypical antipsychotics, more especially in the undeveloped

world. This is the reason for this study. The study becomes more imperative when one considers that there is a rising prevalence of chronic kidney disease in recent times [7-9] and that Negroes face a higher risk of kidney failure than Caucasians [10-12].

Methodology

This is a prospective cross-sectional study in which psychiatric patients treated with antipsychotics who presented at the outpatient clinic of the Neuropsychiatry Department of the University of Port Harcourt Teaching Hospital (UPTH) were enlisted in the study. The study took place between November 2018 and March 2019. Incident cases that had not been treated on antipsychotics before and those with co-morbid medical conditions were excluded. Only those who had been on antipsychotic medication for at least six months were included in the study. Forty consecutive patients each on typical and atypical antipsychotics who met the inclusion criteria were selected.

Before the commencement of the study, approval was obtained from the ethical committee of UPTH and informed consent obtained from the subjects involved in the research.

All subjects underwent a thorough clinical evaluation and psychiatric diagnosis was made using the ICD-10 criteria. The subjects were matched for sex and age with healthy controls drawn from among medical students and hospital staff.

All enlisted subjects had a socio-demographic questionnaire administered to them. Also, blood samples were obtained from them as well as from the controls for analysis of urea and creatinine to enable the calculation of the Glomerular Filtration Rate (GFR).

Blood urea concentration analysis was done using the Urease method [13] while blood creatinine concentration was analyzed using the Jaffe method [14]. The GFR was calculated using the eGFR calculator by the abbreviated MDRD equation: 186 X (Creatinine/88.4)$^{-1.154}$ X (Age)$^{-0.203}$ X (0.742 if Female) X (1.210 if Black) [15]. There tests were carried out by one of the authors who is a doctor and specialist in laboratory medicine, assisted by a medical laboratory scientist, at the chemical pathology department of UPTH.

Data analysis was carried out using the Statistical Package of the Social Sciences (SPSS, version 16) at 5% level of significance and 95% confidence interval. Frequency distributions tables were used to display the sociodemographic and clinical variables of the subjects. One way ANOVA was used to test for significant difference in GFR and urea values between groups. The Turkey Post Hoc Test was used to determine which group was specifically significantly different from the other. Pearson's correlation test was employed to test for the relationship between GFR and urea blood concentrations with age.

Results

The mean age of the 80 subjects studied was 38.3 ± 9.8 yrs. The minimum age was 18 yrs while the maximum was 58 yrs.

Table 1 shows the frequency of the sociodemographic and clinical variables of the subjects. The largest proportion of the subjects were male (62.5%), Christian (97.5%), had secondary education (67.5%), unemployed (75.0%), single (75.0%), of Ibo ethnic nationality, (42.5%); schizophrenic (32.5%), had no family history of kidney disease (87.5%) and had no history of comorbid psychoactive substance use disorder (62.5%).

Table 2 depicts the means of the GFR urea values of the subjects and the controls. The mean GFR of the subjects on atypical antipsychotics was (lesser (93.95 ml/min/1.73m^2), than that of typical (114.20 ml/min/1.73m^2) compared to the controls (125.50 ml/min/1.73m^2). Those on typical antipsychotics had a higher mean urea concentration (3.21 mmol/litre) than subjects on atypical (2.85 mmol/litre) compared to the mean urea concentration of the controls (2.75 mmol/litre).

		N = 80
Variables	**Frequency (n)**	**Prevalence (%)**
Gender		
Male	50	62.5
Female	30	37.5
Religion		
Christian	78	97.5
Islam	2	2.5
Education		
Primary	6	7.5
Secondary	54	67.5
Tertiary	20	25.0
Employment		
Employed	20	25.0
Unemployed	60	75.0
Marital Status		
Single	60	75.0
Married	18	22.5
Separated/Divorced	2	2.5
Ethnic nationality		
Ikwere	22	27.5
Ibo	34	42.5
Yoruba	6	7.5
Ogoni	2	2.5
Kalabari	8	10.0
Ijaw	4	5.0
others	4	5.0
Family History of mental Illness		
Yes	22	27.5
No	58	72.5
Diagnosis		
Schizophrenia	26	32.5
Depression	18	22.5
Bipolar Affective Disorder	20	25.0
Delusional Disorders	4	5.0
Others	12	15.0
Family History of kidney Diseases		
Yes	10	12.5
No	70	87.5
Comorbid Substance Use		
Yes	30	37.5
No	50	62.5

Table 1: *Frequency of the sociodemographic and clinical variables of the subjects.*

		N	Mean	Std. Deviation
GFR (ml/min/1.73m^2)	Typicals	40	114.20	35.80
	Atypicals	40	93.95	18.95
	Control	40	125.50	31.98
	Total	120	111.22	32.32
UREA (mmol/litre)	Typicals	40	3.21	1.51
	Atypicals	40	2.85	0.96
	Control	40	2.76	0.81
	Total	120	2.94	1.23

Table 2: *Means of the GFR and urea values of the subjects and control.*

Table 3 displays the table of ANOVA values. There was statistically significant difference in the mean GFR values between the various groups on antipsychotics compared with controls. The converse is true for the mean urea levels of the various groups.

		Sum of squares	df	Mean Square	F	Sig.
GFR (ml/min/1.73m^2)	Between Groups	20442.067	2	10221.033	11.512	.000*
	Within groups	103878.300	117	887.849		
	Total	124320.367	119			
UREA (mmol/litre)	Between Groups	151.848	2	79.924	4.463	0.627
	Within groups	1990.592	117	17.014		
	Total	2142.440	119			

Table 3: *Table of ANOVA values.*

**Significant at p < 0.05.*

Table 4 shows the results of the Post Hoc Test results for multiple comparisons. The mean GFR of patients on atypical antipsychotics was significantly lower than that of those on typical antipsychotics (93.95 ± 18.95, 114.20 ± 35.80; P = 0.008). Similarly there was statistically significant difference between the mean GFR scores of subjects on atypical, antipsychotics and the control group (93.95 ± 18.95,125.50 ± 31.98; P = 0.000). However, the difference in the mean GFR scores between those on typical antipsychotics and the control group is not statistically significant.

Turkey HSD					
Dependent Variable	**(I) Subject type**	**(J) Subject type**	**Mean Difference (I - J)**	**Std. Error**	**Sig.**
GFR (ml/min/1.73m^2	Typicals	Atypicals	20.25*	6.66	0.008
		Control	-11.30	5.49	0.211
	Atypicals	Typicals	-20.25*	6.66	0.008
		Control	-31.55*	6.46	0.000
	Control	Typicals	11.30	5.69	0.211
		Atypicals	31.55*	5.46	0.000
UREA (mmol/litre)	Typicals	Atypicals	0.36	.92	0.678
		Control	0.45	.92	0.739
	Atypicals	Typicals	-0.36	.92	0.678
		Control	0.09	.92	0.594
	Control	Typicals	-0.45	.92	0.739
		Atypicals	-0.09	.92	0.594

Table 4: *Post HOC test (multiple comparisons).*

**The mean difference is significant at the 0.05 level.*

Table 5 depicts the Pearson's correlations of GFR and Urea values with the age of the subjects. There was significant negative correlation between GFR and Age (-.345; p = 0.000).

		Age	GFR	Urea Conc.
Age	Pearson's Correlation	1	-.345**	.127
	Sig. (2 tailed)		.000	.168
	N	120	120	120
GFR	Pearson's Correlation	-.345**	1	-.126
(ml/min/1.73m^2	Sig. (2 tailed)	.000		.172
	N	120	120	120
Urea	Pearson's Correlation	.127	-.126	1
(mmol/litre)	Sig. (2 tailed)	.168	172	
	N	120	120	120

Table 5*: Pearson's correlations.*

***: Correlation is significant at the 0.05 level (2-tailed).*

Discussion

The pivotal role played by the kidneys in the excretion of waste products and toxins as well as in homeostasis via the control of extracellular fluid volume, serum osmolality, electrolyte concentration as well as the production of some hormones cannot be overemphasized [1]. Furthermore, renal disease is known to play a crucial role in altering the pharmacokinetics of medications especially in the elimination or clearance and plasma protein binding [16].

The largest percentages of the subjects were male and single. This is similar to reports from other studies [17,18].

Furthermore, the larger proportions of our study cohort were schizophrenic and unemployed. This is similar to the findings by Monmany., *et al.* in their study of the clinical and sociodemographic characteristics of a sample of outpatients on long acting injectable antipsychotic treatment [19].

However, while a greater percentage of our patients (67.5%) had at least a secondary education, San L., *et al.* reported the largest chunk of their subjects had a primary education [17]. A greater proportion of our subjects is of the Christian faith and belonged to the Ibo ethnic nationality. This is not surprising because the study was carried in the Niger Delta region of Nigeria that is predominantly Christian and has the Ibo ethnic group as one of the main resident ethnic nationalities.

The study reported that the mean GFR of the subjects on atypical antipsychotics was lesser than that of those on typical antipsychotics as well as that of the controls and these differences are statistically significant. Furthermore, even though the subjects on typical antipsychotics had lower mean GFR than those of the control group, the difference in their means was not statistically significant. This suggests that atypical antipsychotics have a greater tendency to cause renal impairments than the typical type. This result is in consonance with reports by some researchers [20,21]. While Wang., *et al.* reported that risks for chronic kidney disease were higher for those who had second generation (atypical) antipsychotics longer cumulatively than those who did not [2], Ann., *et al.* reported that clozapine the prototype of atypical antipsychotics caused acute renal failure of the interstitial type [21] while others have reported that the atypical antipsychotics have a higher risk for hospitalization with acute kidney injury [22,23].

Mauri., *et al.* further opined that compared to typical antipsychotics, even though it has been documented that atypical antipsychotics cause lower level of side effects such as extrapyramidal symptoms, tardier dyskinesia and narcoleptic malignant syndrome, their safety has been questioned recently judging by the rising incidence of metabolic syndrome [24].

Some studies have shown that African Americans (negroids) are at increased risk for cardiovascular and metabolic diseases including chronic kidney disease [10].

Underlying genetic mechanisms may be responsible for the increased frequency of high blood pressure and kidney disease and particular emphasis on the role of APOL I polymorphisms have been suggested [10].

Nevertheless, other researchers reported that neither typical nor atypical antipsychotics was associated with an increased risk of chronic kidney disease in schizophrenic patients treated with these medications [25].

This study shows a negative correlation between GFR values and age. This implies that with increasing age, the GFR values reduce [26] indicating declining renal functioning with age.

Conclusion

Normal GFR values are synonymous with healthy renal function and a value above 90 ml/min/1.73m^2 is considered normal [26]. From our study, the mean GFR of the subjects on both typical and atypical antipsychotics as well as the control are within the normal range. However, the differences in the mean GFR values are a significant marker of the increased risk of renal deficiency posed by the prolonged use of antipsychotics especially the atypical ones.

Limitation

This is a cross sectional study. A cause and effect is difficult to be concluded due to the small sample size and there's difficulty controlling for the wide range of confounders. Therefore, the application of the results of this study to the general population should be done with caution. The eGFR used to calculate the GFR is better suited for children than adults; as it can overestimate GFB by 20 - 30% [26].

Bibliography

1. Gounden V and Jialal I. "Renal Function Tests". StatPearls (2019).
2. Jeste DV., *et al*. "Lower Incidence of Tardive Dyskinesia with Risperidone Compared with Haloperidol in Older Patients". *Journal of the American Geriatrics Society* 47.6 (1999): 716-719.
3. Wooltorton E. "Risperidone (Risperdal): Increased Rate of Cerebrovascular Events in Dementia Trials". *Canadian Medical Association Journal* 167.11 (2002): 1269 -1270.
4. Wooltorton E. "Olanzapine (Zyprexa): Increased Incidence of Cerebrovascular events in Dementia Trials". *Canadian Medical Association Journal* 170.9 (2004): 1395-1396.
5. Schneider LS., *et al*. "Risk of Death with atypical Antipsychotic Drug Treatment for Dementia: Meta-analysis of Randomized Placebo-controlled Trials". *Journal of the American Medical Association* 294.15 (2005): 294-1943.
6. Centre for Drug Evaluation and Research. EDA Public Health advisory: Deaths will antipsychotics in Elderly patients with behavioural Disturbances (2006).
7. Coresh JM., *et al*. "Prevalence's of Chronic Kidney Disease in the United States". *Journal of the American Medical Association* 298.17 (2007): 2038-2047.

8. Coresh J., *et al*. "Chronic Kidney Disease. Awareness, prevalence and Trends Among US adults, 1999 to 2000". *Journal of the American Society of Nephrology* 16.1 (2005): 180-188.

9. Coresh J., *et al*. "Prevalence of Chronic Kidney Disease and decreased Kidney Function in the Adult US Population Third national health and nutritional Examination Survey". *American Journal of Kidney Diseases* 41.1 (2003): 1-12.

10. Saab KR., *et al*. "New Insights on the Risk for Cardiovascular Disease in African Americans: The Role of Added Sugars". *Journal of the American Society of Nephrology* 26.2 (2015): 247-257.

11. Saxena N and Guiterrez OM. "Fibro blast Growth Factor 23, Vitamin D and health Disparities Among African Americans with Chronic Kidney Disease". *Seminars in Nephrology* 33.5 (2013): 448-456.

12. Norris K and Nissenson AR. "Race, Gender and Socioeconomic Disparities in CKD in the United States". *Journal of the American Society of Nephrology* 19.7 (2008): 1261-1270.

13. Liu L., *et al*. "Quantitative Analysis of Urea in Human Urine and Serum by H Nuclear Magnetic Resonance". *Analyst* 137.3 (2012): 595-600.

14. Peake M and Whting M. "Measurement of serum Creatinine-Current Status and Future Goals". *Clinical Biochemist Reviews* 27.4 (2006): 173-184.

15. eGFR Caculator-U Kidney's nephrology Community.

16. Ward S., *et al*. "When to adjust the dosing of psychotropics in patients with renal impairment". *Current Psychiatry* 15.8 (2016): 60-66.

17. San L., *et al*. "Sociodemographic, Clinical and Treatment Characteristics of relapsing schizophrenic patients". *Nordic Journal of Psychiatry* 67.1 (2013): 22-29.

18. Lamargue I., *et al*. "Clinical and Sociodemographic profile of patients with schizophrenia according to the antipsychotics treatment prescribed". *Encephale* 32.3 (2006): 369-376.

19. Mommany JM., *et al*. "Clinical and Sociodemographic characteristics of sample of outpatients with long acting injectable antipsychotic treatment". *European Psychiatry* 33 (2016): S543.

20. Wang HY., *et al*. "Second generation antipsychotic medications and risk of chronic kidney disease in schizophrenia a population based nested case-control study". *BMJ Open* 8.5 (2018): e019868.

21. An NY., *et al*. "A Casey Clozapine Induced Acute Renal Failure". *Psychiatry Investigation* 10.1 (2013): 92-94.

22. Hwang YJ., *et al*. "Atypical antipsychotics drugs and the risk for acute kidney injury and other averse cufcemes in order adults a population based cohort study". *Annals of Internal Medicine* 161.4 (2014): 242-248.

23. Sarkar S and Gupta N. "Drug Information update Atypical antipsychotics and narcoleptic Malignant Syndrome: Nuances and pragmatics of the association". *BJPsych Bulletin* 41.4 (2017): 211-2016.

24. Mauri MC., *et al*. "Clinical Pharmacology of Atypical Antipsychotics: an Update". *EXCLI Journal* 13 (2014): 1163-1191.

25. Tzeng N., *et al*. "Is Schizophrenia associated with an increased risk of chronic kidney disease?: a Nationwide matched cohort study". *BMJ Open* 5.1 (2015): e006777.

26. National Kidney foundation. "K/DOQL Clinical Practice Guidelines for chronic kidney disease evaluation, classification and stratification". *American Journal of Kidney Diseases* 39.2 (2002): S1-S286.

Volume 8 Issue 5 May 2019