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Research Article

Hypokalaemia a Risk for Morbidity and Mortality among DR-TB Patients on CAT 1V-SLD Intensive Treatment Phase in a Tertiary Hospital in Nigeria

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Abstract

Background: Hypokalaemia is one of the recognizable adverse effects from second line drugs used in Multi drug resistant Tuberculosis (MDRTB) treatment; this may cause poor treatment tolerability, response, and disease progression with grave consequence if quick recognition and intervention is not available. This article aims to highlight the occurrence of morbidity and mortality related to hypokalaemia among patient on treatment with Second Line Drugs (SLD) for MDR-TB in Nigeria, with the objective of promoting adequate evaluation and quick response and treatment to this important Adverse drug reaction (ADR).

Method: This is a retrospective cohort study of patients enrolled for treatment at a MDR-TB treatment center in ATBU Teaching Hospital, Bauchi, Nigeria. And a review of the existing case note. Data was categorized based on sex, age, and case definitions at diagnosis, laboratory values for serum potassium, urea, createnine and other electrolytes was obtained from the routine baseline and monthly follow up register at the center.

Results: The study enrolled 120 subjects, of whom 76 (63%) were males and 44 (37%) were females. Sixty-seven patients (56%) were found to have hypokalemia based on French Agency for Research on AIDS and Viral Hepatitis (ANRS) Adverse Drug Reaction Grading Scale. An association was observed between aminoglycoside use and development of hypokalemia..

Five of the 120 patients studied (4.2%) died of hypokalemia, four of whom were males. There were more cases between the ages of 16 to 45yrs, however, hypokalaemia related mortality was observed more among 60 yrs of age (60%) compared to other age groups, there were also more mortality among patients with previous treatment failure (60%) compared to new cases (40%). Capreomycin based regimen and co-morbidity was associated with increase incidence of hypokalaemia 62% and 32% respectively.

Conclusion: Patients with MDR-TB on aminoglycoside-containing SLD regimen with co-morbidity and elderly should be monitored closely for hypokalemia-associated side effects. A high index of suspicion, early diagnosis and prompt treatment at MDR-TB treatment centers may help reduce the associated morbidity and mortality.

Keywords: *Aminoglycoside; Multi-Drug Resistant Tuberculosis; Adverse Drug Reactions; Hypokalaemia; Morbidity; Mortality; Nigeria*

Abbreviations

ATBUTH: Abubakar Tafawa Balewa University Teaching Hospital; ADR: Adverse Drug Reaction; ANRS: National Agency for Research on AIDS and Viral Hepatitis France; Bdq: Bedaquiline; CAT IV: Category 1V Drug Regimen; CFz: Clofazimine; DM: Diabetes Mellitus; DR-TB: Drug Resistant Tuberculosis; MDR-TB: Multidrug Resistant Tuberculosis; DST: Drug Sensitivity Testing; E: Ethambutol; Eto: Ethionamide; ECG: Electrocardiogram; E/U/Cr: Electrolyte Urea and Creatinine; HBC: High Burden Countries; I: Isoniazid; K: Potassium; Na^{2+}-K^{+}: Sodium-Potassium Pump; PAS: Para Amino Salicylic Acid; PR: ECG Interval; Pto: Prothionamide; QRS: ECG Interval; R: Rifampicin; US DOD: United State Department of Defense; Z: pyrazinamide

Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to isoniazid (H) and rifampicin (R) the two most powerful antituberculous (Tb) drugs is a major concern in global TB control [1] as it is thought that more than half a million MDR-TB cases emerge per year [2]. MDR-TB is also a serious public health problem in Nigeria as it is estimated that 4.3% of new TB cases have MDR-TB while 25% of retreatment cases have MDR TB, with Nigeria listed as a high burden country (HBC) for TB, DR TB and TB-HIV [2].

Adverse drug reaction (ADR) has been recognized as an important factor in drug resistance Tb through poor drug adherence and high rate of treatment default among patients, there is also increase morbidity and mortality among both drug susceptible (DST) and drug resistant Tuberculosis (DRTB) when ADR is common. The drug regimens used in the treatment of DST are associated with multisystem mild, moderate and severe side effects, these include drug induced nausea, vomiting, diarrhea, hepatitis, optic neuritis and peripheral neuropathy among others [3]. It is also known that the adverse effect profile reported for the second line drugs used in MDR-TB treatment are more severe than that of the first line drugs [3-7].

The multisystem spectrum of adverse drug reaction (ADR) from second line drugs used in MDRTB treatment include hypokalemia which are usually very significant and is responsible for morbidity and mortality among patient particularly elderly ones during the intensive phase with aminoglycosides based category 1V treatment regimen [4-8].

Nephrotoxicity induced by aminoglycosides manifests clinically as non-oligouric renal failure, characterize by a slow rise in serum creatinine and a hypo-osmolar urinary output developing after several days to week of commencement of treatment. Aminoglycosides are nephrotoxic because a small but sizable proportion of the administered dose (≈5%) is retained in the epithelial cells lining the S1 and S2 segments of the proximal tubules, after glomerular filtration Aminoglycosides accumulated by these cells are mainly localized with endosomal and lysosomal vacuoles and are also localized with the Golgi complex [9]. The basic chemical structure required for both potency and the spectrum of antimicrobial activity of aminoglycosides is that of one or several aminated sugars joined in glycosidic linkages to a dibasic cyclitol. In most clinically used aminoglycosides the latter is 2-deoxystreptamine, and it is streptidine in streptomycin and derivatives of fortamine in the fortimicin series. Aminoglycosides act primarily by impairing bacterial protein synthesis through binding to prokaryotic ribosome [10].

They elicit an array of morphological and functional alterations with increasing severity [11]. Hypokalemia is one of the major complications of aminoglycoside treatment, hence it is necessary to obtain baseline serum K+ level before commencing patients on treatment [12].

In Nigeria, the introduction of Kanamycin (Kn), Amikacin (Am) and Capreomycin (Cn) as part of WHO CAT IV Second Line Drugs for the treatment of MDR-TB in 2010 raises the possibility of aminoglycoside-related toxicity among MDR-TB patients [5, 9].

In the setting of MDR-TB, hypokalemia, defined as serum potassium (K+) levels below the normal range of 3.5 to 5.0 mmol/L, likely results from several factors. Aminoglycosides cause acute tubular necrosis with tubular salt wasting and loss of potassium. At risk patients

include the elderly, those with congenital disorders like Liddle syndrome, Giteleman syndrome and Fanconi syndrome, which are all associated with poor renal handling of potassium. This results in poor re-absorption of K+ in the distal convoluted tubules due to impairment of H+- K+ pump [13, 14].

Drug induced gastritis is also implicated: Vomiting and diarrhea are both common side effects of anti-TB drugs, especially prothionamide (Pto), ethionamide (Eto), para-aminosalicylic acid (PAS) isoniazid (H), ethambutol (E), pyrazinamide (Z), clofazimine (Cfz), bedaquiline (Bdq).

Other causes of renal potassium loss include comorbid conditions, such as diabetic mellitus (DM).

Patients with hypokalaemia can present with, nausea, vomiting, muscle weakness, dyspnea, confusion, fatigue, arrhythmias and sudden death. ECG features include flattened or inverted T wave, prominent U wave, ST segment depression, prolonged PR interval and widened QRS interval [15].

Despite wide spread use of Aminoglycosides in the management of MDRTB in Nigeria there has been no study carried out to look into possible adverse effect of such drugs as it affect morbidity and mortality among patients.

This research is aimed to highlight the relationship between hypokalaemia, morbidity, mortality and the use of aminoglycoside in SLD regimen of MDR-TB treatment, this will prompt early detection and reduction morbidity and mortality among patients.

Methodology

This study is a retrospective cohort design study conducted at DR-TB treatment center of Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH). Bauchi our target populations are all MDR-TB patients enrolled for intensive phase of treatment from January 2014 to June 2019.

Any MDR-TB patients registered for intensive phase of treatment between June 2014 to May 2019 who lacks laboratory chemistry results for electrolyte urea and creatinine (E/U/Cr) at base line and at least monthly for 4 months during the intensive phase or evidence of chronic kidney disease at base line was excluded from this study.

A proforma was used to collect data, a 'Standardized' MDR-TB treatment laboratory registers and patient laboratory results was used as the primary data source documents.

This retrospective cohort design study which was carried out through the laboratory monitor of serum potassium on aminoglycoside during the intensive phase of MDR-TB treatment at a tertiary hospitals in Nigeria, the laboratory analysis for E/U/Cr was carried out on enrolment as baseline and then subsequently monthly or as indicated throughout the intensive phase of the treatment.

Serum potassium as part of the electrolyte was analyzed by auto analyzer (Model: Chem well. Awareness technology inc. YSTE180C) at the chemical pathology laboratory of ATBUTH Bauchi.

Results

TThere were 120 MDR-TB cases reviewed for this study and each case was profiled based on age, sex, case definition, serum potassium and treatment outcome. The mean age of the patients was 35.5 years. there were more cases between the age of 16 to 45 and few cases among the extremes of age 1- 15 and >60yrs fig1. We found more male cases of hypokalaemia 76 (63%) than female cases 44 (37%)

figure 2.

Hypokalaemia was observed among the age group 16 to 30 yrs 31 (46.2%) and 31 to 45 yrs 27 (40.3%) of age (See table 1).

Out of the 120 patients studied 67 (56%) were found to have Hypokalaemia based on French Agency for research on AIDS and viral hepatitis (ANRS) adverse drug reaction grading scale. There were 42.2% of cases with serum potassium value within a normal range of 3.5 - 6.0 mmol/l, there were 29.2% cases of mild grade 1 disease, 11.7% grade 2 moderate diseases, 4.2% grade 3 severe disease and 10.8 grade 4 severe disease among the studied patients (See table 2).

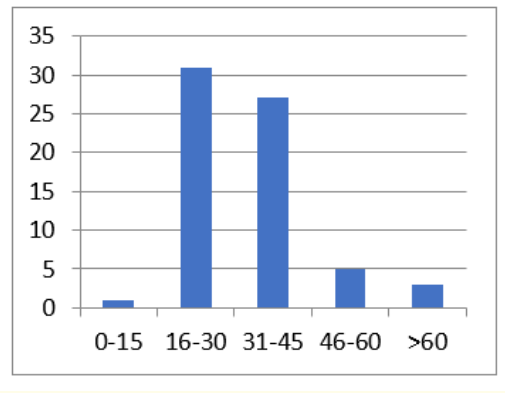

Figure 1: *Age groups of the study subjects.*

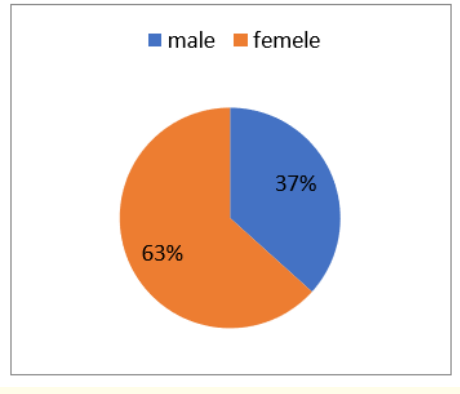

Figure 2: *Male to female ratio of the study subjects.*

However, mortality related to hypokalemia was 100% among elderly patients compared to young and middle-aged patients (p< 0.00001). Males had higher mortality 80% than females 20%, there were more mortality cases among patients above 60 yrs of age (3) compared to other age groups (2) among patients with hypokalaemia, there were also more mortality among patients with treatment failure (3) compared to new cases (2) among the mortality group (p< 0.00001) Table 3.

There were 62% of cases of hypokalaemia among Capreomycin based regimen (Figure 3). And there were about 32% of cases with

Age group (Yrs)	Frequency	Percentages (%)
1 - 15	1	1.5
16 - 30	31	46.2
31 - 45	27	40.3
46 - 60	5	7.5
> 60	3	4.5

Table 1: *Age related hypokalaemia.*

Grading	Value mmol/l	Freq among pat.	Percentage (%)
Normal value	3.5 - 5.0	53	44.2
Grade 1 mild	3.2 - 3.4	35	29.2
Grade 2 moderate	2.8 - 3.1	14	11.7
Grade 3 severe	2.5 - 2.7	5	4.2
Grade 4 v severe	< 2.5	13	10.8
Total		120	100

Table 2: *Mean serum potassium levels among subjects.*

one or more co-morbidity among all the cases studied out of which 60% had hypokalaemia and 90% of mortality had resulted from this group of patients

Discussion

Age	Sex	Serum K	Co-morbidity	Registration Group
40	F	2.7	RVS	Treatment failure
70	M	2.9	HTN	New case
65	M	2.2	DM. HTN	New case
42	M	3.1	-	Treatment failure
70	M	2.1	DM, HTN	Treatment failure

Table 3: *Age, sex, co-morbidity and registration group mortality.*

Hypokalaemia is decrease in the serum level of k in the blood (normal level 3.5 to 5.0 mmol/l). Hypokalaemia occurs when serum level of K is < 3.5 mol/l. Hypokalaemia and Hyperkalaemia are common electrolyte disorders caused by changes in potassium intake, altered excretion, or transcellular shifts. Diuretic use and gastrointestinal losses are common causes of hypokalaemia, whereas kidney disease,

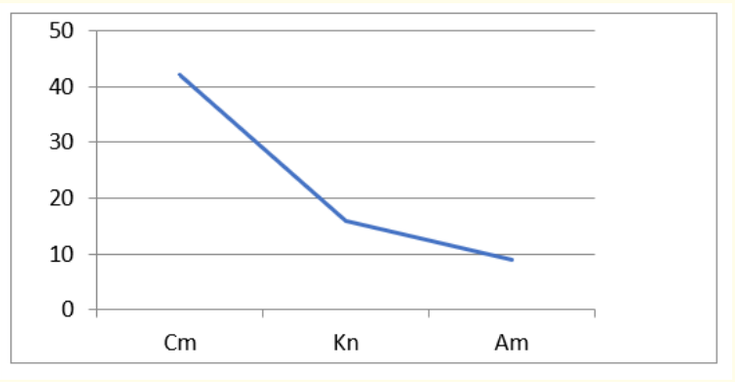

Figure 3: *Aminoglycoside use among patients with Hypokalaemia.*

hyperglycemia, and medication use are common causes of Hyperkalaemia. When severe, potassium disorders can lead to life-threatening cardiac conduction disturbances and neuromuscular dysfunction [16]. Hypokalaemia is a common feature in the management of multi drug resistance tuberculosis, it is one of the major complication resulting to death in MDR-TB patients if not manages properly hence it is important to do baseline serum K^+ level before commencement of patients on treatment for MDR-TB and hence the need for adequate follow up serum K^+ level during the course of treatment [17].

The treatment of MDR-TB is associated with a significant adverse effect profile which may impair the completion of treatment and patient adherence [4-6]. Though all adverse reactions are serious; Nephrotoxicity, CNS toxicity and neuropsychiatric effects tend to be a more significant risk to the treatment of MDR-TB as it is associated with increased morbidity, mortality and poor prognosis. This is similar to findings by other studies [8,16,17].

In his study we observed significant cases of hypokalaemia, with a mean of 3.33025 mmol/l and confidence interval of 0.139 and a p-value of 0.0008. Of the 120 patients studied 67 (56%) were found to have Hypokalaemia based on ANRS adverse drug reaction grading scale. There were 42.2% of cases with serum potassium value within a normal range of 3.5 - 6.0 mmol/l, there were 29.2% cases of mild grade 1 disease, 11.7% grade 2 moderate diseases, 4.2% grade 3 severe disease and 10.8 grade 4 severe disease among the studied patients Hypokalaemia was observed among the age group 16 to 30 yrs 31 (46.2%) and 31 to 45 yrs 27 (40.3%) of age. The frequency of hypokalaemia was higher than those found in Lima, Republic of Peru [18]. A lots of factors might have contributed to this high level electrolyte derangement in our study this is because most of our patient about 60% were cases of retreatment failure and had received on the average of 2 anti Tb treatment in the past and were diagnosed late and about 50% had low body mass index average of < 18 kg/m^2. In addition, administration of parenteral therapy in our cohort tended to be prolonged, usually lasting at least 8 months intensive phase in most patients before the introduction of the 4 months intensive shorter regimen.

IIn this study the use of Capreomycin was associated with hypokalaemia with 62% of patients who had low serum potassium had used Capreomycin, this is probably because most of our patients were re-treatment cases and this has shown that previous exposure to anti Tb medications and co-morbidity, were associated with an increased likelihood of acquiring hypokalaemia. In a similar study Hypokalemia was found in 38 of 86 (44%) patients while they were being treated with an injectable agent: 23 of 38 (61%) were treated with capreomycin and 15 of 38 (39%) were treated with amikacin. Eighteen of 38 cases resolved alone, without potassium replacement. Seventeen required replacement with oral potassium (13 of these 17 patients were treated with capreomycin) [17-19].

There were 5 cases of mortality recorded among the 120 patient studied representing 4.2% mortality and 6% among patient that had hypokalaemia. Males had higher mortality 80% than females 20%, there were more mortality above 60 yrs of age (60%) compared to other age group among patients with hypokalaemia this was probably as a result of higher level of co- morbid conditions among elderly patients. There were more mortality among patients with treatment failure (3) compared to new cases (2) among the mortality group , this is similar to the study conducted in south Africa which also show increase incidence of hypokalaemia related mortality among MDR/XDR- TB patients [20].

While monthly monitoring of patients on injectable is advocated, individuals with low body weight at presentation, co-morbid conditions and history of previous treatment with anti Tb medications need to be screened and monitored for electrolyte as well.

Conclusion

With the silent and subtle features and increase in morbidity and mortality associated with hypokalaemia among these patients, close monitoring and prompt management of such patient is key for effective and efficient treatment outcome. Key component in the manage-

ment of all adverse effects associated with MDR-TB therapy has been the utilization of simple algorithms to guide in the early diagnosis and treatment.

Our limitation were limited sample size as larger sample size will be required to adequately characterize effect of electrolytes and other risk factors among these patients, also analysis of toxic serum levels of the individual Aminoglycoside could throw more light on the toxicity profile of these drugs.

This study has opened our eyes to the ADR associated with some SLD in our temperate environment. Its relevance in other setting utilizing individualized treatment may vary.

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