

Cycloserine Induced Psychosis among Patient's on Second Line Treatment for Drug Resistant Tuberculosis in Bauchi and Port Harcourt, Nigeria

Type of Article: **Case Report**

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ABSTRACT

BACKGROUND

Adverse effects from second line drugs used in MDRTB treatment include neuropsychiatric effects which are usually very significant as they may cause anxiety and lead to default and poor adherence by patients if quick recognition and intervention is not available. This case series aims highlight the occurrence of cycloserine related psychosis among patient on treatment for MDR-TB in Nigeria, with the objective of promoting adequate evaluation and quick response and treatment to this important ADR.

METHOD

he case records of 3 patients from two MDR-TB in-patient treatment centers in Nigeria and a review of the existing literature was utilized. Results

RESULTS

An association was found with the use of Cycloserine and development of Psychosis during the management of these patients with MDR-TB. Early recognition and quick treatment is required to ensure treatment continuation and resolution of the ADR.

CONCLUSION

Patients with MDR-TB on Cycloserine containing CAT IV regimen should be monitored closely for neuropsychiatric

side effects for early diagnosis, prevention and treatment.

KEYWORDS

Cycloserine; Multi-drug resistant tuberculosis; Adverse Drug Reactions; Psychosis; Nigeria

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to isoniazid (H) and rifampicin (R) 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 2.9% of new TB cases have MDR-TB while 14% of retreatment cases have MDR TB, with Nigeria listed as a high burden country (HBC) for TB, DR TB and TB-HIV.²

The drug regimens used in the treatment of drug susceptible Tuberculosis (TB) are associated with multisystem mild, moderate and severe side effects which include drug induced hepatitis, optic neuritis and peripheral neuropathy among others³. 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 MDR-TB treatment include neuropsychiatric effects which are usually very significant as they may cause anxiety and lead to default and poor adherence by patients if quick recognition and intervention is not available^{4,8}.

With the diagnosis of MDR-TB and subsequent WHO approval of CAT IV/2nd line treatment regimen⁵ for MDR-TB in Nigeria, it is expected that patients on MDR-TB treatment will present with these side effects. It is therefore evident that the management of MDR-TB in Nigeria with a treatment duration of 20 months⁹ will be confronted with challenges related to the increased adverse effect profile of 2nd line drugs.

Although drug induced encephalopathy is not exclusive to MDR-TB drugs; 2nd line TB drugs have been documented to cause encephalopathy and a spectrum of neuropsychiatry effects such as headaches, depression, seizures, sleep disorders, psychoses and other mental disturbances.^{5,6,10}

Levofloxacin, terizidone and Cycloserine are the MDR-TB second line drugs that have been the most implicated in CNS toxicity. Of all these, cycloserine has however been associated with a higher frequency of psychiatric and CNS related ADRs such as psychotic states with suicidal tendencies compared to other second line drugs.^{10,11} Many reports associating cycloserine with psychosis have therefore been published from various countries.^{12,13}

Cycloserine (4-amino-3-isoxazolidinone) is a tuberculostatic antibiotic effective against *Mycobacterium tuberculosis*. Cycloserine works as an antibiotic by inhibiting cell-wall biosynthesis in bacteria.^{14,15} As a cyclic analogue of D-alanine, cycloserine acts against two crucial enzymes important in the cytosolic stages of peptidoglycan synthesis: alanine racemase (Alr) and D-alanine:D-alanine ligase (Ddl).¹⁵ The first enzyme is a pyridoxal 5'-phosphate-dependent enzyme

which converts the L-alanine to the D-alanine form.¹⁵ The second enzyme is involved in joining two of these D-alanine residues together by catalyzing the formation of the ATP-dependent D-alanine-D-alanine dipeptide bond between the resulting D-alanine molecules.¹⁵ If both of these enzymes are inhibited, then D-alanine residues cannot form and previously formed D-alanine molecules cannot be joined together.¹⁵ This effectively leads to inhibition of peptidoglycan synthesis.¹⁵ Cycloserine is a broad spectrum antibiotic and has been classified by WHO as a second-line group IV oral bacteriostatic drug used in a dose of 250–500 mg twice daily.³ Cycloserine does not share cross resistance with other anti-mycobacterial agents and hence its choice for drug-resistant Tb (DR-TB). The adverse effects of Cycloserine are mainly dose-related and idiosyncratic¹⁶. Some Psychiatric symptoms such as anxiety, depression, paranoia, hallucinations, euphoria, behavioral changes and suicidality have been reported in 9.7–50% of individuals on Cycloserine¹⁷; with these side effects most likely to occur during the first 12 weeks of treatment.¹⁷

Cycloserine has been implicated to cause elevation of GABA due to inhibition of GABA transferase in studies on mice¹⁸. GABA has been implicated in delirium¹⁹, with studies suggesting that GABA activity is increased in delirium due to hepatic encephalopathy and decreased in delirium caused by hypnotic/sedative withdrawal.²⁰ Glutamate is another neurotransmitter that has been researched in the pathogenesis of delirium.^{21,22} Cycloserine also has effects on glutamatergic transmission through its actions on AMPA/Kainase and NMDA receptors.²³ It can therefore be hypothesized that Cycloserine can cause delirium due to its actions on the GABA and glutamate neurotransmitter system. However, other factors that may exacerbate or precipitate psychosis in patients are concurrent medications such as Fluoroquinolone and clinical states like diarrhea.²³

The neurotoxic actions of cycloserine have also been demonstrated from an RCT study²⁴ which showed that the psychotic effects of D-cycloserine which are mediated by the NMDA receptor pathway resulted in worsening of psychotic symptoms and general psychopathology in schizophrenic patients in which addition of 100 mg D-cycloserine, to typical antipsychotics.

In view of the negative perception of psychiatric diseases in Nigeria^{25,26} which results in stigmatization²⁵, resistance to medical treatment and the preference for spiritual healing.²⁶ It is important that healthcare providers have the knowledge and experience to manage cycloserine related psychosis.

It is expected that this reports will contribute to pharmacovigilance and provide the experience and knowledge on CNS toxicity of 2nd line drug among MDR-TB patients in Nigeria.

CASE SUMMARIES

Case 1

A 48 year old female with diabetes, diagnosed with MDR-TB, was admitted in the inpatient services of a MDR-Tb treatment center in ATBU Teaching Hospital, North Eastern Nigeria. She was categorized as a new case since there was no previous history of tuberculous treatment and contact was traceable to her daughter who was successfully treated for MDR-Tb. She was HIV negative and did not have any past history of a psychiatric illness or hypertension. Her baseline investigations on admission which included serum electrolytes, liver function test, renal function test, complete blood count, and audiometry were normal. Her glycemic control was poor with an RBS of 27mmol/l. She was thus rehydrated and switched from her OHAs to insulin with resulting good glycemic control. The patient was commenced on Cycloserine 500mg OD in addition to other CAT IV MDR-Tb drugs which included Kanamycin, Prothionamide, Levofloxacin, Pyrazinamide and Pyridoxine based on the

National guideline for DR-Tb treatment.⁹ Four days after commencement of treatment the patient was noticed to have become withdrawn, irrational and suspicious of the co-patients, accusing them of stealing her things and trying to poison her. A diagnosis of probable cycloserine induced psychosis was made and cycloserine was discontinued for 72 hours pending a Neuropsychiatric review. The patient's symptoms resolved with the withdrawal of cycloserine, but recommenced with the reintroduction of the drug with the patient becoming more violent, irrational, disruptive, hallucinating, insomniac and withdrawn. She was then commenced on initial 100mg dose of IM chlorpromazine followed by tabs Haloperidol 5mg BD and Benzhexol 5mg BD with a reduction in the dose of cycloserine to 250mg daily. The patient's mental state improved with resolution of hallucinations, confusion, and normalization of sleep within 3 days, the dose of cycloserine was then scaled up to 500mg after 2weeks without a reoccurrence of symptoms.

Case 2

23 year old male student, without diabetes or hypertension who had been diagnosed with MDR-TB, was admitted at the in-patient services of an MDR-Tb treatment center in the University of Port Harcourt Teaching Hospital, South-South, Nigeria. He had received 2 previous treatments for tuberculosis prior to diagnosis with category 1 and II regimens. He was HIV negative and did not have any past history of a psychiatric illness and his baseline investigations at admission including electrolytes, liver function test, renal function test, complete blood count, and audiometry were normal. He was commenced on Cycloserine 500mg OD in addition to other CAT IV MDR-Tb drugs which included Capreomycin, Prothionamide, Levofloxacin, Pyrazinamide and Pyridoxine based on the National guideline for DR-Tb treatment.⁹ Eight weeks after commencement of treatment the patient was noticed to have poor sleep, hyperactivity, agitation, irrelevant speech and unusual claims. There were no

hallucination and suicidal ideation. He was reviewed by the neuropsychiatrist who made a diagnosis of depressive psychosis probably induced by cycloserine. He was placed on 100mg dose of IM chlorpromazine BD stat, followed by tabs risperidone 5mg BD and Haloperidol 5mg BD. In spite of treatment for 1 week the patient still had irrelevant talk, hyperactivity and agitation. Cycloserine was then withdrawn for one week with a resolution of symptoms. Cycloserine was then reintroduced in a graded pattern beginning with 250mg daily for two weeks and then escalated to 500mg daily. The dose of pyridoxine was also increased to 200mg daily. The patient remained in stable state until discharge.

Case 3

A 52 year old male with diabetes diagnosed with MDR-TB, was admitted in the inpatient services of a MDR-Tb treatment center in University of Port Harcourt Teaching Hospital, South South Nigeria. He had received previous treatment for Tuberculosis prior to diagnosis. He was HIV negative and did not have any past history of a psychiatric illness or hypertension. His baseline investigations at admission to the hospital including electrolytes, renal function, liver function test, complete blood count were normal. His baseline audiometry indicated hearing impairment. His glycemic control was poor with an RBS of 14 mmol/l; he was then switched to insulin which improved the glycemic control. He was commenced on Cycloserine 500mg OD in addition to other 2nd line MDR-Tb drugs which included Capreomycin, Prothionamide, Levofloxacin, Pyrazinamide and Pyridoxine based on the National guideline for DR-Tb treatment.⁹ Three weeks after commencement of treatment the patient was noticed to refuse medications, became withdrawn and talked irrationally. He was also talkative with paranoid delusions, auditory and visual hallucination with destructive and violent behaviour. He was reviewed by the neuropsychiatrist who made a diagnosis of schizophrenia from probable cycloserine

induced psychosis. He was placed on 100mg dose of IM chlorpromazine BD stat, followed by tabs risperidone 5mg BD, Haloperidol 5mg BD. Cycloserine dose was reduced to 250mg daily for 1 week and increased back to 500mg daily as the patient became stable within 4 days of antipsychotic use. He continued his treatment and remained stable till his discharge.

DISCUSSION

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; 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.^{8,16,17} These risk of treatment interruption is more likely in Nigeria due to the negative perception of psychiatric diseases and the socio cultural attitudes that promote refusal of medical treatment.^{25,26} It is therefore imperative that CNS ADRs like psychosis be taken seriously, identified early and treated promptly in order to ensure adherence with treatment.

Cycloserine induced mania and psychosis has been reported in previous literatures.¹⁰⁻¹³ The prevalence of cycloserine psychiatric ADRs from a meta analysis of 27 studies with 2164 patient is estimated to be 5.7%¹⁰, while a South African study²⁷ estimated a prevalence of 8.3% for psychosis and confusion in patients on cycloserine. Cycloserine is associated with a higher frequency of psychiatric and CNS-related ADRs than other second-line drugs²⁷.

It is reported that the psychiatric ADRs of cycloserine usually occur on the average within 12 weeks of treatment. This is in line with the duration of onset the 3 cases reported which ranged from 4 days to 8 weeks. It is however difficult to explain the risk or predisposition for the varied duration of onset.

The spectrum of symptoms have also been found to vary among patients as seen from the

3 reported cases; as not all patients develop suicidal ideations, hallucinations, delusion and negative symptoms of schizophrenia. This variation seen among the cases may be explained by factors such as the premorbid state of the patients, as patients with schizophrenic psychotic predisposition make develop worsening of negative symptoms as a result of cycloserine use. . The exacerbation of schizophrenic symptoms may also be explained by the antagonistic effects of D-cycloserine at the glycine recognition site of the NMDA receptor due to competition with the endogenous agonist glycine as shown in a study by van Berckel et al²⁴. This makes the evaluation of the patient's premorbid psychiatric history an important part of the pretreatment assessment. Other possible factors are the interaction and neurotoxic effect of with other drugs like levofloxacin which has been shown to produce significant anxiety and insomnia as it also has effects on the NMDA and GABA systems.²⁸ Consequently patients with these effects may tend to manifest with anxiety and insomnia as seen in one of the cases. The effect of cycloserine are also dose related²⁷, therefore patients who receive effective higher doses will be more likely to present earlier and with more severe symptoms. This may occur in patients with better drug absorption and impaired liver function.

There is no documented age or gender predisposition to the development of cycloserine induced psychosis. It has however been documented that factors such as the HIV status may have a role Cycloserine ADRs was to be significantly more common in patients who were HIV positive than in patients who were HIV negative with regard to peripheral neuropathy, psychosis and confusion.²⁷ Though 2 of the reported patients were diabetic there is no documentation of diabetes as risk factor for CNS toxicity and ADR from cycloserine in patients with MDR-TB.

The cases presented in this series can be attributed to cycloserine based on the Naranjo ADR probability score of ≥ 6 for all the cases

which suggests a significant probable association²⁹. The resolution and recurrence of symptoms after withdrawal, dose reduction and reintroduction respectively are strong pointers in this regard. In addition none of the patients has any evidence of metabolic encephalopathy from either renal or hepatic impairment as their baseline tests were all within normal limits. It is thus important to note that baseline and monitoring for liver and renal function should be done in patient with the psychotic symptoms.³⁰

In spite of the significant manifestation of cycloserine psychosis in the 3 reported cases all the patients continued their treatment. This is in accordance with earlier reports that psychiatric morbidities are not a contraindication to the treatment of patients for MDR-TB.³¹ The cases presented in this report have shown the psychiatric complications can be managed and treated without the need for treatment discontinuation.

This case series illustrates the need for close monitoring of psychiatric adverse events in patients receiving regimens for MDR-TB in Nigeria. It is recommended that patients on 2nd line regimen for MDR-TB should have a proper psychiatric evaluation pretreatment in addition to a thorough evaluation of other confounding factors that might lead to a similar clinical picture. As multi-drug resistance becomes more prevalent, there is a need for close liaison between chest physicians and psychiatrists to ensure prompt and appropriate response and treatment of these adverse events as psychosis is associated with increased morbidity and the risk of poor drug adherence.³²

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