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Cycloserine Induced Psychosis, Insomnia and Suicidal Attempts in a Young Female Patient with Pre-Extensively Drug Resistant Tuberculosis

Priyanka Pravinbhai Hotha, Shubhima Grover, Rachna Gupta*

Department of Pharmacology, University College of Medical Sciences, Delhi, India.

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ABSTRACT

The World Health Organization classifies cycloserine as a group four second line anti tubercular drug for the treatment of drug resistant tuberculosis. Neuropsychiatric adverse drug reactions associated with cycloserine need more attention as they may compromise treatment success. Here, we report a case of cycloserine induced psychosis, insomnia and suicidal attempts in a young female patient with pre-extensively drug resistant tuberculosis (pre-XDR-TB). A 20-year-old female patient was prescribed longer oral XDR-TB regimen (high dose of moxifloxacin, cycloserine, linezolid, clofazimine, bedaquiline and pyridoxine). After fifteen days of treatment, patient developed changes in behaviour with frequent episodes of spontaneous and excessive laughing or crying. She also developed insomnia, started to hear voices and made two attempts of suicide. Following this, cycloserine was discontinued. Clonazepam and clomipramine were prescribed to her. Patient gradually recovered over a period of one month. Extreme caution with regular and close monitoring should be exercised while administering cycloserine because psychiatric adverse drug reactions could be associated with increased risk of poor drug adherence in drug resistant tuberculosis.

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Introduction

SThe World Health Organization (WHO) has defined Pre-extensively drug resistant tuberculosis (pre-XDR-TB) as TB that fulfils the definition of multidrug resistant and rifampicin resistant TB along with resistance to any fluoroquinolone (FQ) (1). Drug resistant TB is recognised by line probe assay (LPA) and liquid culture and drug susceptibility test (LC & DST) (1). First line LPA (FL LPA) detects resistance for rifampicin and isoniazid whereas second line LPA (SL LPA) detects resistance for FQ. For the effective management of tuberculosis, early identification of drug resistance is extremely important. This helps the clinician to modify the treatment regimen accordingly and thus in controlling transmission of multidrug-resistant TB (2). WHO classified cycloserine as a group IV second line anti tubercular drug used for the treatment of drug resistant TB (3). Neurological adverse drug reactions (ADRs) such as headaches, drowsiness, depression, confusion, psychosis, convulsions and tremors are frequently associated with cycloserine (4). Here, we describe a case of cycloserine induced psychosis, insomnia and suicidal attempts in a young female patient with pre-extensively drug resistant tuberculosis, which was reported to pharmcovigilance centre, University College of Medical Sciences, Delhi.

Case report

A 20-year-old female (weighing 35 kg) was diagnosed as a case of sputum positive pulmonary tuberculosis. Her first line LPA result indicated resistance to both first line anti TB drugs, rifampicin and isoniazid. In second line LPA, fluoroquinolone resistance was also detected in the patient. LC & DST report detected sensitivity towards moxifloxacin (1.0), linezolid and clofazimine. Hence based on these reports, the patient was diagnosed as a case of pre-XDR-TB. She was started moxifloxacin (600 mg/day), cycloserine (500 mg/day), linezolid (600 mg/day), clofazimine (100 mg/day),

*Corresponding Author: Dr Rachna Gupta
Address: Department of Pharmacology, University College of Medical Sciences, Delhi, India.
Email: drrachna1@rediffmail.com

bedaquiline (400 mg once daily for initial 14 days, followed by 200 mg three times a week for 22 weeks) and pyridoxine (100 mg/day). After fifteen days of therapy, the patient developed changes in her behaviour and mood imbalance with frequent episodes of spontaneous and excessive laughing or crying, insomnia, irritability and inability to concentrate in her study. The patient also started to hear voices and felt that somebody was conspiring against her. She had seen strange and scary faces. She also had complaint of suicide ideation and made two attempts of suicide. All these symptoms progressively worsened over a period of one month. Following this, she came to Guru Teg Bahadur hospital TB centre. Her laboratory investigations including full blood count with differentials, serum electrolytes, liver, kidney and thyroid function tests were all within normal range. Her systemic examination including central nervous system, cardiovascular, abdominal and respiratory examinations were normal. Her personal and family history was negative for any psychiatric illness. No history of pre-existing comorbidities, smoking, and alcohol intake were present.

Clinician suspected it as a case of cycloserine induced psychosis and replaced cycloserine with ethambutol (800 mg/day). Other drugs were continued as same. A psychiatric consultation was obtained and she was prescribed clonazepam 0.5 mg twice daily and clomipramine 25 mg/day in addition to pre-XDR-TB treatment. Patient gradually recovered over a period of one month with complete resolution of above psychiatric symptoms.

Discussion

In the present case report, patient received high dose of moxifloxacin, bedaquiline, linezolid, clofazimine and cycloserine. Cycloserine induced neurological ADRs are a cause of concern because it can increase the mortality, significantly lower the quality of life, contribute to a poor prognosis and compromise the treatment success (5).

In general, 9.7% to 50% of the patients develop cycloserine related neurological ADRs within twelve weeks of therapy. However, psychosis with cycloserine is seen within the first two weeks of therapy (4, 5). Patients develop early and severe symptoms of psychosis if they have additional possible risk factors such as a higher initial dose of medication, hepatic and renal insufficiency, or a family history of psychosis (6). In the present case report, patient was a young female without any history of impaired liver or kidney functions. Also, there was no personal or family history of psychiatric illness. She developed psychiatric ADRs after 15 days of starting pre-XDR-TB treatment. Clinician anticipated cycloserine as a suspected drug for these ADRs.

Pharmacokinetic properties of cycloserine may be favourable for the manifestations of psychiatric ADRs. As cycloserine is completely absorbed and well distributed throughout the body. It crosses the blood brain barrier and reaches a cerebrospinal fluid concentration that is equivalent to its plasma concentration. In the first 12 hours, only half of the cycloserine is excreted unchanged in urine (4).

Cycloserine may cause severe psychosis which can lead to suicidal tendencies (1). However, cycloserine is not absolutely contraindicated even in psychiatric patients receiving anti TB treatment because it has no cross resistance to other anti TB drugs and has a good gastrointestinal tolerability (1). Previously, Sharma et al., (7) reported psychosis along with delusions, insomnia and hallucinations with cycloserine in a MDR-TB patient. Nkporbu AK et al., (4) have also found psychosis as the main ADR along with insomnia, hallucinations and irritability in MDR-TB patient. In addition, Jangra et al., (8) also reported suicidal ideation with cycloserine in MDR- TB male patient. In the present case report, patient was on pre-XDR-TB therapy and developed changes in behaviour with frequent episodes of spontaneous and excessive laughing or crying, insomnia, started to hear voices and made two attempts of suicide.

The exact mechanism of cycloserine induced neurological ADRs is unknown (9). It can be due to a decrease in the central nervous system production of gamma aminobutyric acid as a result of inhibition of glutamic decarboxylase (9). Psychotic action of cycloserine is mediated through N-Methyl-D-Aspartate receptor pathway and cycloserine has partial NMDA agonist action which may be responsible for neurological ADRs (6). Another possible mechanism could be due to hyperdopaminergic state which is achieved at more than 100mg dose (10).

In various case reports, clinicians prescribed antipsychotic drugs, benzodiazepines and vitamin B complex if patients develop cycloserine induced neuropsychiatric ADRs with an occasional requirement to stop cycloserine (5). In contrast, some studies have shown that cycloserine induced psychiatric side effects disappear completely when cycloserine is withdrawn (4). Yadav et al., (9) found in a case series that out of two patients, one patient did not require any treatment for cycloserine induced psychosis. Psychiatric symptoms recovered completely on the third day of ceasing cycloserine alone. Intini et al., (11) reported that a female patient developed cyloserine induced neuropsychiatric ADRs after three months and was prescribed antipsychotic drugs. After three months, she recovered completely. In the present case report, patient was prescribed benzodiazepine (clonazepam) and antidepressant drug (clomipramine) for neuropsychiatric ADRs and symptoms were normalised within one month. Causality assessment was done based on the World Health Organization Uppsala Monitoring Centre criteria and it was found to be probable/likely.

Conclusion

Our case report highlights the importance of awareness regarding psychiatric adverse drug reactions associated with

cycloserine in the patients on drug resistant tuberculosis therapy. Clinician should prescribe cycloserine with extreme caution and patient should be regularly monitored for such adverse drug reactions, since psychosis/ psychiatric ADRs could be associated with increased morbidity and poor drug adherence causing antitubercular treatment failure with higher risk of multidrug-resistance.

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