Egyptian Journal of Chest Diseases and Tuberculosis (2015) 64, 449–451

HOSTED BY

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

www.elsevier.com/locate/ejcdt
www.sciencedirect.com

CASE REPORT

Cycloserine induced delirium during treatment of multi-drug resistant tuberculosis (MDR-TB)

Gayatri Saraf [a], J.S. Akshata [b], Seby Kuruthukulangara [a], Harish Thippeswamy [a,*], Senthil Kumar Reddy [a], Shashidhar Buggi [c], Santosh K. Chaturvedi [a]

[a] *Department of Psychiatry, National Institute of Mental Health and Neuro Sciences, Bangalore 560029, India*
[b] *Department of Pulmonary Medicine, Rajeev Gandhi Institute of Chest Diseases, Bangalore 560029, India*
[c] *Department of Cardiovascular and Thoracic Surgery, Rajeev Gandhi Institute of Chest Diseases, Bangalore 560029, India*

Received 7 November 2014; accepted 30 November 2014
Available online 24 January 2015

KEYWORDS

Cycloserine;
Multi-drug resistant tuberculosis;
Delirium

Abstract *Objective:* To report about delirium related to Cycloserine.
Method: Systematic assessment and management of a patient who developed delirium during the course of treatment for MDR-TB.
Results: An association was found with the use of Cycloserine and development of delirium. The management of this case is described.
Conclusion: Patients with MDR-TB receiving Cycloserine should be closely monitored for neuropsychiatric side effects for early recognition and treatment.

Introduction

Regimens used for MDR-TB have been reported to cause more adverse effects than the first-line agents, with treatment discontinuation rates of 19–55% [1–5]. 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. Cycloserine does not share cross resistance with other anti-mycobacterial agents and hence is used for drug-resistant cases. Adverse effects of Cycloserine are mainly dose-related [6]. Psychiatric adverse events such as anxiety, hallucinations, depression, euphoria, behavioural changes and suicidality have been reported in 9.7–50% of individuals while on Cycloserine [7]. These side effects are most likely to occur during the first 3 months of treatment.

Report

A 72 year old lady, diagnosed as MDR-TB, admitted in the inpatient services of a regional chest institute was referred by the chest physician to the consultation liaison psychiatry team, with symptoms of being withdrawn and apathetic. These

* Corresponding author. Tel.: +91 080 26995279, +91 9480829486.
E-mail addresses: gayatri224@yahoo.co.in (G. Saraf), jsakshata@gmail.com (J.S. Akshata), seby.kuru@gmail.com (S. Kuruthukulangara), docharisht@gmail.com, ht.nimhans@nic.in (H. Thippeswamy), senthilreddi@gmail.com (S.K. Reddy), director.rgicd@gmail.com (S. Buggi), skchatur@gmail.com (S.K. Chaturvedi).
Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

http://dx.doi.org/10.1016/j.ejcdt.2014.11.032

symptoms were noted around 7 days following the intake of Cycloserine 500 mg OD. Subsequently, Cycloserine was stopped for a week due to these side effects, and the symptoms improved. A re-challenge of Cycloserine with the same dosage was attempted after a gap of a week that resulted in patient again developing similar psychiatric symptoms. On detailed evaluation, patient's relatives reported history of confusion, disturbed sleep, disorientation to time, calling out people's names and not recognising relatives which would worsen in the night in addition to the above symptoms. She had also shaved off her hair in the night on one occasion and did not provide any explanation for the same.

She did not have any past history of a psychiatric illness and her baseline investigations at admission to the hospital including electrolytes, complete blood count and ECG were within normal limits.

On examination, she was noticed to be disoriented to place and time, with fluctuating orientation for person and reported of perceptual disturbances in the form of visual hallucinations. Review of drug chart revealed that the MDR-TB regimen consisted of Kanamycin, Ofloxacin, Levofloxacin, Cycloserine, Ethionamide, Pyrazinamide, Ethambutol and Pyridoxine.

A clinical diagnosis of Cycloserine induced delirium was considered and Cycloserine was replaced with Para amino salicylic acid by the Chest Physician. The delirium was treated with Quetiapine 25 mg BD along with behavioural measures and suitable environmental modifications. A significant improvement in orientation and sleep was noted within 3 days. Subsequently, she had an episode of diarrhoea, which led to a worsening of delirium. Serum electrolytes were deranged (Sodium-128 mEq/L, Potassium-3.1 mEq/L, Chloride-105 mEq/L) and suitable correction was started by the physician. However, the delirium continued to worsen despite receiving Quetiapine, hence Risperidone 0.5 mg at night was added. She developed slurring of speech with the same and hence Risperidone was stopped. In view of worsening delirium, Quetiapine was stopped and Olanzapine 2.5 mg BD was started. Her repeat electrolytes continued to be deranged. Olanzapine was increased to 2.5 mg in the morning and 5 mg in the night, with which sleep and oral intake slightly got better. A week after this, patient started becoming withdrawn, unresponsive, refused to take orally. Resuscitation failed and patient succumbed to hypovolemic shock 4 days later.

Discussion

Drug regimens for MDR-TB use agents in combination that are more toxic than the first-line drugs. Further, some anti-tuberculosis drugs used in second-line regimens for drug resistant tuberculosis also potentiate the toxicity of other agents used in the regimen [1]. Psychiatric adverse effects are known in the treatment of tuberculosis and are associated with increased mortality and unfavourable prognosis [8]. There have been case reports of Cycloserine induced mania [9] and psychosis [10], however to the best of our knowledge, none reported on delirium so far.

In this patient, the score on Naranjo ADR probability scale was 5 which suggests probable association [9]. She also was on a combination of drugs which are known to cause psychiatric side effects such as Fluoroquinolones. The recurrence of symptoms after a rechallenge with Cycloserine further goes in favour of Cycloserine induced mental state changes. However, the patient deteriorated again due to the development of diarrhoea and electrolyte disturbances.

Cycloserine has been implicated to cause elevation of GABA due to inhibition of GABA transferase in studies on mice [11]. GABA has been implicated in delirium [12], with studies suggesting that GABA activity is increased in delirium due to hepatic encephalopathy and decreased in that caused by hypnotic/sedative withdrawal [13]. Glutamate is another neurotransmitter that has been researched in the pathogenesis of delirium [14,15]. Cycloserine also has effects on glutamatergic transmission through its actions on AMPA/Kainate and NMDA receptors [16]. Thus it can be hypothesised that Cycloserine could have caused delirium due to its actions on the GABA and glutamate neurotransmitter system. However, other factors that might have exacerbated/precipitated delirium are elderly age, diarrhoea, electrolyte imbalance and concurrent medications such as Fluoroquinolones. This mechanism is a possible cause of Cycloserine induced delirium in the current case; however, this could not be confirmed biochemically. There could be other unknown mechanisms, which are difficult to speculate.

This case illustrates the need for close monitoring of psychiatric adverse events in patients receiving regimens for MDR TB. This must also be followed by 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 addressal of these adverse events as delirium is associated with high mortality [17].

Conflict of interest

None declared.

References

[1] M.W. Carroll, M. Lee, Y. Cai, C.W. Hallahan, P.A. Shaw, J.H. Min, Frequency of adverse reactions to first- and second-line anti-tuberculosis chemotherapy in a Korean cohort, Int. J. Tuberc. Lung Dis. 16 (2012) 961–966.
[2] S.S. Shin, A.D. Pasechnikov, I.Y. Gelmanova, G.G. Peremitin, A.K. Strelis, S. Mishustin, Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia, Int. J. Tuberc. Lung Dis. 11 (2007) 1314–1320.
[3] T. Torun, G. Gungor, I. Ozmen, Side effects associated with the treatment of multidrug-resistant tuberculosis, Int. J. Tuberc. Lung Dis. 9 (2005) 1373–1377.
[4] D. Yee, C. Valiquette, M. Pelletier, I. Parisien, I. Rocher, D. Menzies, Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis, Am. J. Respir. Crit. Care Med. 167 (2003) 1472–1477.
[5] L.P. Ormerod, N. Horsfield, Frequency and type of reactions to antituberculosis drugs: observations in routine treatment, Tuber. Lung Dis. 77 (1996) 37–42.
[6] D.J. Girling, Adverse effects of antituberculosis drugs, Drugs 23 (1982) 56–74.
[7] A. Pachi, D. Bratis, G. Moussas, A. Tselebis, Psychiatric morbidity and other factors affecting treatment adherence in pulmonary tuberculosis patients, Tuberc. Res. Treat. Epub 2013, Apr 15.
[8] P. Baghaei, P. Tabarsi, D. Dorriz, M. Marjani, M. Shamaei, M.V. Pooramiri, Adverse effects of multidrug-resistant

tuberculosis treatment with a standardized regimen: a report from Iran, Am. J. Ther. 18 (2011) 29–34.
[9] C.A. Naranjo, U. Busto, E.M. Sellers, P. Sandor, I. Ruiz, E.A. Roberts, A method for estimating the probability of adverse drug reactions, Clin. Pharmacol. Ther. 30 (1981) 239–245.
[10] R.G. Bankier, Psychosis associated with Cycloserine, Can. Med. Assoc. J. 93 (1965) 35–37.
[11] J.D. Wood, Effect of L-Cycloserine on brain GABA metabolism, Can. J. Physiol. Pharmacol. 56 (1978) 62–68.
[12] J.R. Maldonado, Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment, Crit. Care Clin. 24 (2008) 789–856.
[13] R.F. Butterworth, Neurotransmitter dysfunction in hepatic encephalopathy: new approaches and new findings, Metab. Brain Dis. 16 (2001) 55–65.
[14] M.L. Gunther, A. Morandi, E.W. Ely, Pathophysiology of delirium in the intensive care unit, Crit. Care Clin. 24 (2008) 45–65.
[15] S. Ali, M. Patel, S. Jabeen, R.K. Bailey, T. Patel, M. Shahid, Insight into delirium, Innov. Clin. Neurosci. 8 (2011) 25–34.
[16] E. Rouaud, J.M. Billard, D-Cycloserine facilitates synaptic plasticity but impairs glutamatergic neurotransmission in rat hippocampal slices, Br. J. Pharmacol. 140 (2003) 1051–1056.
[17] A. Sharma, S. Malhotra, S. Grover, S.K. Jindal, Incidence, prevalence, risk factor and outcome of delirium in intensive care unit: a study from India, Gen. Hosp. Psychiatry 34 (2012) 639–646.