CASE REPORT

Insomnia and Psychosis induced by Cycloserine

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Abstract

Cycloserine induced psychiatric disorders like delusions and hallucinations, mania and associated seizures have been well reported including from this centre. We failed to cite insomnia along with psychos reported with the use of cycloserine while reviewing the literature and thus, we present a case of psychosis and insomnia induced by cycloserine.

Key Words

Insomnia, Psychosis, Cycloserine, Multi-drug resistant tuberculosis

Introduction

Multi-drug resistant tuberculosis (MDR-TB) is not only a concern in developing countries like India but also in the developed countries globally. Currently, there is an armamentarium of drugs available for its management and cycloserine is one among them. Cycloserine (D-4-amino-3-isoxazolidine), discovered in 1954 by Harned and Kropp (1) is broad-spectrum antibiotic produced by Streptomyces orchidaceus and is used as a category IV / second line anti-tubercular treatment (ATT) in multidrug tuberculosis (MDR-TB). Cycloserine induced psychiatric disorders like delusions and hallucinations, mania and associated seizures have been well reported including from this centre. (2-5)

With the emergence of MDR-TB and extensively drug-resistant TB, second line drugs like the cycloserine are used more frequently. Although, it is an effective drug, but it is not without adverse effects. Neurological and/or psychiatric disturbances are most common. [2-5] We failed to cite insomnia along with psychos reported with the use of cycloserine and thus, we present a case of psychosis and insomnia induced by cycloserine.

Case Report

A 36 years old hypothyroid, normotensive, non-diabetic male patient weighing 47 kg was diagnosed as a case of MDR-TB on 4-07-2017 as per the Xpert MTB-RIF Assay in which resistance to Rifampicin was detected. He was admitted in the Chest Diseases Hospital, Government Medical College (GMC), Jammu on 14-7-17 and was started with Category IV DOTS treatment on 19-7-2017. It consisted of Inj. Kanamycin 750 mg intramuscular once daily, tablet Cycloserine 750 mg once daily, tablet Ethionamide 750 mg once daily, tablet Levofloxacin 1000 mg once daily, tablet Ethambutol 1200 mg once daily, tablet Pyrazinamide 1500 mg once daily and tablet Pyridoxine 100 mg once daily. Patient was discharged on 24-07-17 with the advice to continue anti-tubercular therapy (ATT). In November 2017, he started complaining of giddiness, frequent falling spells, inability to do routine work, decreased sleep at night and irrelevant talking. In January 2018, he reported to the emergency of the hospital with history of fall in which he sustained injuries to both the ankle joints was correlated due to deprived sleep at that time. He was again admitted in the Chest Diseases Hospital in January 2018 for complaints of cough and weakness. He was given Inj. Ceftriaxone + Sulbactam 1.5 g i.v. twice a day, Inj Etophylline + Theophylline 1 amp twice a day, nebulisation with Ipratropium bromide and budecort and syrup of herbal liver tonic. Here he also sought psychiatrist consultation for above mentioned complaints. His Hamilton Depression Rating Score (HAM-D) was 18, Hamilton Anxiety Rating Score (HAM-A) was 13. His overall quality of life (QoL) raw score on WHOQOL-BREF scale was 2 and overall health raw score was 2. The raw and transformed (0-100) scores of Physical health (Domain 1) of WHOQOL-BREF were 16 and 31, of psychological (Domain 2) were 15 and 38, of social relationship (Domain 3) were 6 and 25 and of environment (Domain 4) were 24 and 50. There was no evidence of any neurological deficit as such. As cycloserine was suspected to be the possible offending agent, the ATT was de-challenged on 18-1-2018. Thus, DOTS Category-IV regiment was stopped and the patient was put on tablet. levofloxacine 500 once daily, tablet macrozide 750 mg once daily and tablet pyridoxine 100

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mg once daily was started. Also, he was started on tablet olanzapine 2.5 mg at bed time and long with tab lorazepam 2mg bed time. The patient showed improvement few days after de-challenge only with the antipsychotic treatment and is still on follow up and recovering from the ADEs. .

The patient had history of smoking, he left one year back. There was no associated history of alcohol, drug abuse, any conflict with family, friends or at work place or any past problem of psychosis and insomnia. Also, there was no family history of mental disorders. There was evidence of irrelevant talking with inability to give proper history or answers to the questions.

Laboratory investigations revealed: Haemoglobin- 10.6g/dl, total leucocyte count- 14,000 / mm3, ESR- 30 mm/hr, Sr. urea- 34 mg/dl, Sr. createnine- 1.1 mg/dl, SGOT- 22 IU/ml, SGPT- 25 IU/ml, Sr. bilirubin (total)- 0.5 mg/dl, HIV- I & II- non reactive, T3- 1.02 ng/ml, T4- 5.6 ?g/dl, TSH- 25.61 ?IU/ml

The temporal relationship, the fact that brief de-challenge ameliorated the symptoms but only with help of treatment and re-challenge of cycloserine was not carried due to ethical constrains. Furthermore, the appearance of psychiatric manifestations and Insomnia could not be explained by any concurrent disease, drug or chemical. Adverse drug reaction (ADR) was probable as assessed by WHO uppasla monitoring the center causality scale and Naranjo's score (score = 6). (7),(8)

Severity of the reaction as assessed using Hartwig ADR severity assessment scale (9) classified the said ADR as potentially serious. Preventability assessment was done by using Schumock and Thornton scale (10) which classified the ADRs as preventable. The ADR was not studied for dose dependent response and in view of its uncertain mechanism it is difficult to comment on the type of ADR.

Discussion

Psychosis induced by cycloserine has been repoted various authors like Tandon VR et al [6], Sharma et al [2], Nkporbu et al [11], Bankier G [1]. Insomnia induced by cycloserine is also reported but is reported as associated manifestation well reported. [1, 11] In our case also, the temporal relationship between drug administration and start of both the adverse events and gradual recovery of the patient after de-challenge along with symptomatic treatment suggest that cycloserine was the offending drug. Also, the same could not have been caused by the disease itself or any concomitant medicine. Thus, the adverse drug reaction is classified as probable according to WHO-Uppsala Monitoring Centre causality assessment scale, with a score of 6 on the Naranjo scale.(7,8) The reaction was found to be serious in nature as per the Hartwig ADR severity assessment.(9) Also, it was found to be prventable according to the Schumock and Thornton preventability assessment scale.(10) It was difficult to classify the type of ADR and also no dose response relationship was studied.

The possible neurobiological basis of this reaction could be due to its binding and modulation of the N-methyl-D-aspartate (NMDA) receptor antagonists and partial agonistic activity at the NMDA receptor associated glycine site at doses above 500 mg/day.(12,13)

Nkporbu *et al* (11) reported that reactions to cycloserine are observed within 2 weeks of starting the drug. This could be attributed to its pharmacokinetic characteristics that it crosses the blood brain barrier and only 50% of the parenteral dose is metabolized after first 12 hours, which are responsible for rapid manifestations of ADRs.(11) However, in this was not the case in our patient in whom the ADRs were reported only after 3 months of treatment.

From the ongoing discussion it is evident that reports of psychiatric manifestations induced by cycloserine use are on the rise. Also, MDR-TB in itself is a rampant health concern across the globe. Thus, creating awareness among chest physicians, neurologists and psychiatrists about the varied neuropsychological manifestations of cycloserine is need of the hour.

References

1. Bankier RG. Psychosis associated with cycloserine. *Can Med Assoc J* 1965;3;93(1):35-37
2. Sharma B, Handa R, Nagpal K, Prakash S, Gupta PK, Agrawal R. Cycloserine-induced psychosis in a young female with drug-resistant tuberculosis. *Gen Hosp Psychiatry* 2014;36:451.e3-4.
3. Bakhla AK, Gore PS, Srivastava SL. Cycloserine induced mania. *Ind Psychiatry J* 2013;22:69-70.
4. Fujita J, Sunada K, Hayashi H, Hayashihara K, Saito T. A case of multi-drug resistant tuberculosis showing psychiatric adverse effect by cycloserine. *Kekkaku* 2008;83:21-5
5. Tandon VR, Rani N, Roshi, *et al*. Cycloserine induced psychosis with hepatic dysfunction. *Indian J Pharmacol* 2015; 47:230-1.
6. Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45
7. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *Lancet* 2000;356:1255-9
8. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm* 1992;49:2229-32
9. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm* 1992;27:538
10. Nkporbu A, Oluwaseun A, Alasia D, Chukwuemeka SP. Cycloserine Induced-Psychosis in a 22-Year Old Male Pharmacy Student: A Case Report. *American J Psychiatry and Neuroscience* 2016:4(1);1-4
11. Emmett MR, Mick SJ, Cler JA, Rao TS, Iyengar S, Wood PL. Actions of D-cycloserine at the N-methyl-Daspartate-associated glycine receptor site in vivo. *Neuropharmacology* 1991; 30:1167-71
12. Van Berckel BN, Lipsch C, Gispen-de Wied C, *et al*. The partial NMDA agonist D-cycloserine stimulates LH secretion in healthy volunteers. *Psychopharmacology* 1998;138:190-97