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Isoniazid. With a word of caution in geriatric population

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Introduction

Isoniazid, a hydrazide of is nicotinic acid is one of the primary drugs used in Tuberculosis, which is highly bactericidal agent against the dividing tubercle bacilli. Most common adverse effects of this agent are Hepatitis, peripheral neuropathy and psychosis being rare one. Isoniazid-induced psychosis, though is rare, has been reported in patients with and without a psychiatric history both in isoniazid monotherapy or when used in combination with other antitubercular drugs.

Case series

Case 1: 84-year-old female, ex-chullah worker was admitted with complaints of productive cough and breathlessness of 1 month duration, along with a history of low-grade fever, night sweats for 1 month. No history of any paroxysmal nocturnal dysnea or orthopnea were present. On chest auscultation, bilateral fine crepts were present in intrascapular and infra-axillary areas of chest. The investigations revealed ESR of 100 mm for the first hour, rest all investigations were within normal limits. Chest Xray showed Bilateral minimal pleural effusion. The sputum analysis of the patient was positive for Acid fast bacilli . The patient was started on Antitubercular therapy as per DOTS Category 1 regimen. The patient remained admitted in the hospital under observation. Within 7 days of starting treatment, the patient started to have auditory hallucinations, occasional violent behavior was noted along with irrelevant talking and confusion. She was evaluated and no signs of any focal neurological deficit except the altered higher mental functions were found. Computed Tomography of Head, electrolytes, Kidney and liver function tests were normal. A decision to stop Antitubercular drugs was taken. Six days after stopping the antitubercular drugs, she improved completely. Antitubercular therapy was started again with Tab Rifampicin 300 mg, Tab Ethambutol 850 mg once a day, given for 3 days. On day 4 Tab Pyrazinamide 750 mg was also added. The patient was observed for 2 days. The patient maintained his normal sensorium on this new regimen. The patient was discharged with this regimen of drugs without Isoniazid. On follow up the patient was doing well.

Case 2: 75-year-old female, homemaker by profession, belonging to middle socioeconomic strata in rural area with no history of any psychiatric illness was brought to hospital with chief complaints of incoherent speech, listening of voices that don't exist, frequent episodes of crying along with episodes of shouting in the last 2 days. Patient started to experience these symptoms within 2 weeks of starting Antitubercular drugs including Isoniazid, Rifampicin, Ethambutol and Pyrazinamide for Pulmonary Tuberculosis. The patient is a known diabetic and was on tablet metformin 500 mg once a day. The physical examination and vitals of the patient were normal and tests including Complete blood count, Kidney function tests, liver function tests and serum electrolytes were normal. Chest Xray revealed fibrotic band in right middle lobe. Computed tomography Brain of the patient was normal. So due to absence of any other cause, diagnosis of Drug induced psychosis by Isoniazid was contemplated.

A decision to stop all antitubercular drugs was taken. Within a week of stopping the Antitubercular drugs, the psychotic symptoms of the patient resolved completely. Antitubercular therapy was started again with Tab Rifampicin 300 mg, Tab Ethambutol 850 mg once a day, given for 3 days. On day 4 Tab Pyrazinamide 750 mg was also added. The patient was observed for 2 days. The patient maintained his normal sensorium on this new regimen. The patient was discharged with this regimen of drugs without Isoniazid. On follow up the patient was doing well.

Case 3: A 78-year-old female, presented to hospital with chief complaints of Shortness of breath since a week. On examination saturation was 78 percent off oxygen, other vitals were within normal range. Patients Chest X ray was suggestive of Right sided massive pleural effusion. Pleural fluid tapping done and fluid analysis revealed the fluid to be exudative with lymphocytic predominance. Patient was started on empirical antitubercular therapy with the drugs Isoniazid, Ethambutol, Rifampicin and Pyrazinamide. Patient was kept under observation and liver function tests along with kidney function tests were monitored. Within 10 days of starting the antitubercular therapy patient started to become violent, talking irrelevant, insomniac and had visual hallucinations. Computed Tomography of brain was normal along with electrolytes, kidney function tests and liver function tests which were also in the normal range. A decision to stop Antitubercular drugs was taken. It was observed that patient began to show improvement in the psychotic symptoms within 3 days of stopping the treatment. Antitubercular therapy was started again with Tab Rifampicin 300 mg, Tab Ethambutol 850 mg once a day, given for 3 days. On day 4 Tab Pyrazinamide 750 mg was also added. Patient developed sudden cardiac arrest during the hospital stay and was declared dead after all the resuscitative efforts.

Table 1: Investigations.

Investigations	Case 1	Case 2	Case 3
1. S. Creatinine	0.8 mg/dl	1.0 mg/dl	0.9 mg/dl
2. S. Urea	22 mg/dl	43 mg/dl	37 mg/dl
3. S. Uric Acid	4 mg/dl	3.6 mg/dl	4.2 mg/dl
4. S. Total Protein	6.8 g/dl	6.4 g/dl	7 g/dl
5. S. Albumin	3.8 g/dl	4 g/dl	3.9 g/dl
6. S. Bilirubin	0.8 mg/dl	1 mg/dl	0.7 mg/dl
7. SGOT	20 U/L	35 U/L	28 U/L
8. SGPT	35 U/L	38 U/L	20 U/L
9. S. Sodium	140 meq/l	139 meq/l	148 meq/l
10. S. Potassium	3.8 meq/l	4.0 meq/l	4.8 meq/l
11. Hb	10 g/dl	9.6 g/dl	11 g/dl
12. ESR	80 mm	66 mm	89 mm
13. Total leukocyte count	10,000/mm3	8800/mm3	6400/mm3
14. Platelet count	1.5 lac	1.8 lac	2.8 lac
15. Ultrasonography Abdomen and Pelvis	Grade 1 fatty liver	GB Sludge present	No significant abnormality
16. Chest Xray	Bilateral CP angle blunting	Fibrotic band right middle zone	Right sided massive pleural effusion
17. Computed Tomography Head	No significant abnormality	No significant abnormality	No significant abnormality

Table 2: Investigations.

	Case 1	Case 2	Case 3
1. Time duration between medication initiation and start of psychotic symptoms	7 days	14 days	10 days
2. Time duration between stoppage of medication and resolution of symptoms	6 days	7 days	3 days
3. Psychiatric symptoms manifested	Auditory hallucinations Occasional violent behavior Irrelevant talking and confusion	Incoherent speech Listening of voices that didn't exist Episodes of crying Episodes of shouting	Violent behavior Talking irrelevant Insomnia Visual hallucinations
4. Drugs and their doses given for treatment initiation	Isoniazid 300 mg/day Rifampicin 600 mg/day Ethambutol 800 mg/day Pyrazinamide 1,500 mg/day	Isoniazid 300 mg/day Rifampicin 600 mg/day Ethambutol 800 mg/day Pyrazinamide 1,500 mg/day	Isoniazid 300 mg/day Rifampicin 600 mg/day Ethambutol 800 mg/day Pyrazinamide 1,500 mg/day
5. Modified drug regimen given	Tab Rifampicin 300 mg Tab Ethambutol 850 mg given for 3 days once daily On day 4 Tab Pyrazinamide 750 mg was also added	Tab Rifampicin 300 mg Tab Ethambutol 850 mg given for 3 days once daily On day 4 Tab Pyrazinamide 750 mg was added	Tab Rifampicin 300 mg Tab Ethambutol 850 mg given for 3 days once daily On day 4 Tab Pyrazinamide 750 mg was added

Discussion

An adverse drug reaction is an untoward reaction to a medication which constitutes a significant healthcare burden. India is the country with highest prevalence of TB in the world [1]. Psychosis refers to a disorder characterized by delusions, hallucinations, and confusion. Substance-induced psychosis, refers to any psychotic episode that is related to the consumption of an offending medicine [2].

Tuberculosis remains a top infectious disease globally and Antitubercular therapy has proven to be effective in improving cure rates. But keeping in view the high doses of drugs used, adverse drug reactions, tolerance and compliance is a concern.

Most cases of Antitubercular agent associated psychosis were caused by Isoniazid, with Ethambutol induced psychosis being rare [3].

Isoniazid related psychiatric disorders reported in literature include psychosis, obsessive compulsive neurosis and mania.

The mechanism of Isoniazid induced toxicity involves INH acting as a nonselective monoamine-oxidase inhibitor, that prevents the degradation of monoamines, including epinephrine, norepinephrine, serotonin, and also dopamine, leading to a raised concentration of these neurotransmitters; mainly dopamine and serotonin at the synapse which act on the dopaminergic receptors, leading to psychotic symptoms [4].

Another mechanism suggests that the use of INH leads to a pyridoxine deficiency, that leads to a reduction in the concentration of the neurotransmitters. Isoniazid combines with pyridoxine 5'-phosphate and pyridoxal 5'-phosphate to form a complex that inhibits the action of pyridoxal kinase. The action of pyridoxal kinase is to convert pyridoxal to pyridoxal phosphate, which is an important coenzyme in the metabolism of amino acids, including tyrosine and tryptophan. Pyridoxal 5'-phosphate is an active form of vitamin-B6, which acts as a cofactor in the synthesis of Gamma Amino Butyric Acid (GABA); this leads to depletion in the levels of GABA. Decrease in the levels of GABA has been implicated in many disorders including psychosis [5].

The timing of the administration of antitubercular therapy and the subsequent onset of psychotic symptoms, in the absence of any prior psychiatric history, strongly pointed to a diagnosis of drug-induced psychosis. Among all antitubercular medications, Isoniazid (INH) is the most commonly associated with acute psychosis triggered by treatment. Therefore, INH was initially suspected as the likely cause of the psychotic episode in this case [6].

The patients discussed in the cases developed psychotic symptoms within 2 weeks of initiating the Antitubercular Therapy which improved within 10 days of stopping the therapy and reintroduction of Antitubercular drugs except for Isoniazid was done gradually.

Conclusion

Isoniazid induced psychosis has variable presentations. No other cause, than the offending drug could be attributed to the psychotic symptoms of the patients. The symptoms of the patients improved within a week of stopping Isoniazid and antitubercular therapy was restarted excluding isoniazid.

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