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Case Report

Isoniazid Induced Pyrexia: A Case Report

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Abstract

Isoniazid is the most common drug used for management and prophylaxis of tuberculosis especially in developing countries. The most common adverse effects associated with use of isoniazid is transaminitis, peripheral neuropathy, loss of appetite, nausea, vomiting and abdominal pain. More over adverse effects also include fever with rash. We present a patient with pulmonary tuberculosis who developed isoniazid associated pyrexia without rash with the first dose of treatment. The side effects can occur within 8 hours of administrating the first dose. Patients may have past history of drug allergies even though they might not report. High index of clinical suspicion should be kept in mind for diagnosis as serology and other investigations may have limited value.

Keywords: Isoniazid; Fever; ATT; Drug allergies

Introduction

As known isoniazid, also known as Isonicotinylhydrazine (INH) is an organic compound used as the first-line drug in management and prevention of tuberculosis. It was first synthesized in the year 1910 [1]. INH is developed from isonicotinic acid, which is produced from 4-methylpyridine [2] and its first anti tuberculosis activity was found in 1950's. WHO list has enrolled INH in the list of essential medications [3].

INH is a bactericidal against multiplying mycobacteria [4], and is bacteriostatic to slow- growing mycobacteria [5]. It induces the P450 system and acts as a source of free radicals [6]. Isoniazid metabolized in the liver via acetylation [7] after reaching therapeutic concentrations in serum, cerebrospinal fluid, and within caseous granulomas. The most common adverse effects of isoniazid are raised transaminases (hepatitis), peripheral neuropathy, loss of appetite, nausea, vomiting, vague abdominal pain and weakness. Other Adverse effects also include fever with or without rash. This case report is regarding a patient with pulmonary tuberculosis who developed isoniazid induced fever and drug had to be withdrawn.

Case Presentation

In March 2019 a 42 year-old man was bought to our hospital with complaints of shortness of breath, hemoptysis (scanty) and altered mental status. Patient's haemodynamics were blood pressure- 100/62 mmhg, pulse 112/min, febrile (101.8 F), oxygen saturation at room air was 90% . He was admitted under intensive care unit and was given BIPAP (Bi-level positive airway pressure) ventilation.There was history of fever with nocturnal sweating, cough with expectoration and shortness of breath from last 3 months. No co-morbidity or addiction was noted.

On percussion there was hyper-resonant on right hemithorax and right infra scapular, interscapular and infra axillary areas. Chest skiagram showed features of tuberculosis.

Routine investigations: haemoglobin of 8.8mg/dl, total white blood cell count of 16,000 /mm3 (neutrophils 28%, lymphocytes 76%, eosinophils 2.8%, monocytes 2%), platelets 192000, ESR was 102mm/hr. Liver and renal function tests were normal. Echocardiography was normal with ejection fraction of 60%. His blood culture and sputum for acid fast bacilli (AFB) was send and later Ziehl-Neelsen staining of sputum revealed acid fast bacilli.

Patient improved remarkably well in 4 days' time. Patient was kept on category I Antituberculosis regimen (ATT) as per RNTCP (Revised national tuberculosis control program) guidelines. Patient was noticeably febrile before initiating ATT. But after 8 hours of starting ATT, patient developed high grade fever with chills (103 F). Clinical examination and further investigations showed no features of secondary infection. His Blood cultures, urine culture, serology for influenza, HIV, HBV, HCV, HEV and HAV (Hepatitis A, B and C) were negative and repeat sputum examination were negative for other infections.

After 48 hours patient developed jaundice. His liver function tests revealed alanine and aspartate aminotransferase levels increased to 508U/L and 672U/L, respectively. His ultrasonography of abdomen was normal. In view of this his ATT was discontinued. Patient was restarted on modified ATT with Ethambutol and Rifampicin at doses of 1250mg and 300mg per day. Gradually on 10th day his LFT were in decreasing trend and INH 100mg/day was added to treatment but soon he developed high grade fever of 102^0F 4 hours after starting INH. This confirmed that the drug was the main cause of his fever. Pyrazinamide 500mg/day was then added to regimen and dose was increased to 1500mg/day without any adverse effect. Followed by which there were no noticeable spikes of fever.

Discussion

Krasnitz in 1953 first identified high grade fever due to INH [8]. Christianson CS et al. in a series of 1644 patients observed that 24 patients could not tolerate INH treatment and the most common side effect was fever (69%) [9]. Dutt et al., in a series of 809 cases reported that side effects of fever (5%) [9].

The mechanism is may be related to an immunopathological process connected with antibody formation. In the study by Osborne RK et al., there was high grade fever related to INH more frequently in patients allergic to Para amino salicylic acid, streptomycin and

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penicillin [10]. Eventhough they did not gave history of any drug allergy and was found to be allergic to penicillin on skin testing.

In our case high grade fever of 103^0F was noticed after 8 hours after starting ATT, including INH. Taking into consideration the study of Dutt et al., fever reaction developed between Day 10 and Day 20 of treatment. When the drug was stopped and restarted again, fever relapse was observed in the first 2 -10 hours. In the two reported cases by Davis RS et al., in 1977 it was observed that fever and myalgia occurred within 8 - 14 days, and when the treatment was withdrawn and restarted again, fever (103^0F) was seen within two to three hours [11].

Rifampicin is the commonest drug to cause flu-like syndrome that typically begins 3-4 hours after drug initiation and lasts up to 8 hours [12].It often even occurs with intermittent high dose of rifampicin. The particular mechanism of rifampicin-induced antibody are not clearly known. One hypothesis is that drug acts as a hapten binding to macromolecules in plasma acting as antigen and invigorating antibody formation. Hapten-antibody complexes bind to complements and may cause different hypersensitivity reactions [12]. Ethambutol may also can lead to flu-like illness [13].

Conclusion

We bring up the following observations based on our case report. Fever without rash can occur with isoniazid (INH) prescription. It can occur within 8 hours of initiating the first dose. Patients may have history of drug allergies although they might not report. First step to be considered should be infectious diseases so as to prevent significant morbidity and mortality in Tuberculosis. High index of clinical suspicion is important to diagnose such condition as serology and other investigations have a very limited role.

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