

## Pyrexia Due to Isoniazid

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## Abstract

Isoniazid is one of the commonest drugs used for treatment and prophylaxis of tuberculosis especially in developing countries. The commonest adverse effects of isoniazid are mild increased liver transaminases (10-20%), peripheral neuropathy (dose-related incidence, 10-20% incidence with 10 mg/kg/d), loss of appetite, nausea, vomiting, abdominal pain and weakness. Adverse effects also include fever with rash but only fever without any other adverse effects or rash is uncommonly reported. We report a patient with pulmonary tuberculosis developing isoniazid induced pyrexia without rash with first dose of treatment. It can occur within 8 hours of starting the first dose. Patients may have drug allergies even though they might not report. High index of clinical suspicion is required for diagnosis as serology and other investigations have limited value.

## Introduction

Isoniazid, also known as Isonicotinylhydrazine (INH), is an organic compound used as first-line drug in treatment and prevention of tuberculosis. It was first synthesized around 1910 [1]. Isoniazid (Figure 1) is manufactured from isonicotinic acid, which is produced from 4-methylpyridine [2] and its first anti tuberculosis activity was found in 1950's. It is included in WHO list of essential medicines [3].

Isoniazid is bactericidal to rapidly multiplying mycobacteria [4], but 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 commonest adverse effects of isoniazid are mild increased liver transaminases (10-20%), peripheral neuropathy (dose-related incidence, 10-20% incidence with 10 mg/kg/d), loss of appetite, nausea, vomiting, abdominal pain and weakness. Adverse effects also include fever with rash but only fever without any other adverse effects or rash is uncommonly reported. This case report is regarding a patient with pulmonary koch's who developed isoniazid induced fever and drug had to be withdrawn.

## Case Presentation

In september 2014 a 50 year-old man was brought to emergency room with breathlessness, hemoptysis and altered sensorium. As GCS (Glasgow coma scale) was 7/15, patient was admitted in intensive care unit and was given BIPAP (Bi-level positive airway pressure) ventilation. History from relatives revealed fever with night sweats, cough with expectoration and shortness of breath from 2 months. Patient is an ex-smoker and alcoholic with consuming about 12 grams (whisky) per day from 15 years.

Systemic examination showed hyper-resonant note on percussion on left hemithorax and right infra scapular, interscapular, axillary and infra axillary areas. Right supra and infraclavicular area percussion revealed impaired note. Chest radiography showed features of tuberculosis which is common throughout Indian sub-continent (Figure 2). Samples of blood culture and sputum for acid fast bacilli were sent.

Investigations revealed total white blood cell count of 14,100/mm<sup>3</sup> (neutrophils 24%, lymphocytes 70%, eosinophils 3%, monocytes 3%) ESR 82mm/hr, hemoglobin of 8.4mg/dl and platelet count was 176,000. Renal function test and liver function test were normal. ECG showed tachycardia and RBBB (Right Bundle branch block) with first degree AV block (Figure 3). Echocardiography was normal with ejection fraction of 60%. Ziehl-Neelsen staining of sputum showed acid fast bacilli (Figure 4).

Patient improved over 2 days and was shifted to male chest ward after becoming asymptomatic. Patient was started on category I Antituberculosis Treatment (ATT) as per RNTCP (Revised national tuberculosis control program) guidelines in India (Table 1). Patient was a febrile before starting ATT. After 4 hours of starting ATT, patient developed high grade fever of 41°C. Clinical

**Table 1:** RNTCP categories.

New*	Previously treated**
New sputum smear-positive	Sputum smear-positive relapse
New sputum smear-negative	Sputum smear-positive failure
New extra pulmonary tuberculosis	Sputum smear-positive treatment after default
Others	Others#
<b>2H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>E<sub>3</sub> + 4H<sub>3</sub>R<sub>3</sub></b>	<b>2H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>E<sub>3</sub>S<sub>3</sub> + 1H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>E<sub>3</sub> + 5H<sub>3</sub>R<sub>3</sub>E<sub>3</sub></b>
2 months Intensive phase + 4 months continuation phase	3 months Intensive phase + 5 months continuation phase
Four drugs at Thrice-weekly Schedule for 2 months Intensive phase & Two drugs at Thrice-Weekly Schedule for remaining 4 months continuation phase.	Five drugs at Thrice-weekly Schedule for initial 2 months followed by Four drugs for next 1 month Intensive phase. Three drugs at Thrice-weekly Schedule for remaining 5 months continuation phase.

**H:** Isoniazid (300 mg), **R:** Rifampicin (450 mg), **Z:** Pyrazinamide (1500 mg), **E:** Ethambutol (1200 mg),

**S:** Streptomycin (750 mg)

Patients who weigh 60kg or more receive additional Rifampicin 150mg.

Patients who are more than 50 years old receive Streptomycin 500mg.

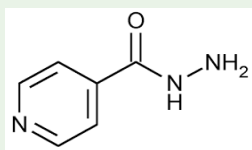
Patients who weigh less than 30kg receive drugs as per Pediatric weight band boxes according to body weight.

**Notes**

\*New categories includes former Categories I & III

\*\*Previously treated is former Category II

# Others include patients who are Sputum Smear-Negative or who have Extra-pulmonary disease who can have recurrence or resonance.



**Figure 1:** Chemical structure of INH.



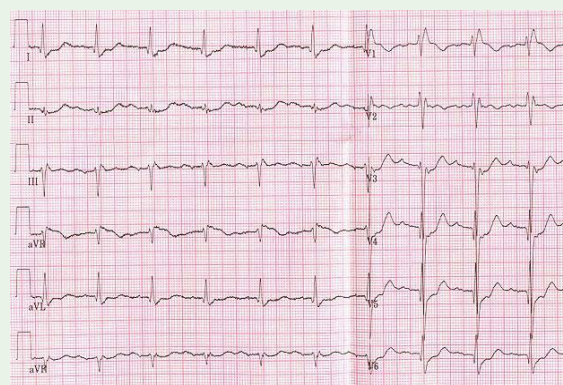
**Figure 2:** Chest radiograph showing pulmonary Koch's in June 2014.

examination and investigations revealed no secondary infection. Blood cultures, urine culture, serology for influenza, HIV, HBV, HAV, HCV (Hepatitis A, B and C) and sputum examination were negative for other infections. Patient was continued with ceftriaxone and azithromycin.

On 5th day, patient developed jaundice. Liver function tests revealed alanine and aspartate aminotransferase levels increased to 402 U/L and 990 U/L, respectively. ATT (Antituberculosis treatment) and antibiotics were discontinued. Blood and urine cultures were found to be again negative. Peripheral smear revealed that ratio of eosinophils was 7% and Immunoglobulin E (IgE) level were raised to 221 IU/mL (normal range: <100 IU/ mL).

**Table 2:** Naranjo adverse drug reaction probability scale.

1. Are there previous conclusive reports on this reaction?	Yes (+1) No (0) Do not know or not done (0)
2. Did the adverse events appear after the suspected drug was given?	Yes (+2) No (-1) Do not know or not done (0)
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes (+1) No (0) Do not know or not done (0)
4. Did the adverse reaction appear when the drug was readministered?	Yes (+2) No (-1) Do not know or not done (0)
5. Are there alternative causes that could have caused the reaction?	Yes (-1) No (+2) Do not know or not done (0)
6. Did the reaction reappear when a placebo was given?	Yes (-1) No (+1) Do not know or not done (0)
7. Was the drug detected in any body fluid in toxic concentrations?	Yes (+1) No (0) Do not know or not done (0)
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Yes (+1) No (0) Do not know or not done (0)
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes (+1) No (0) Do not know or not done (0)
10. Was the adverse event confirmed by any objective evidence?	Yes (+1) No (0) Do not know or not done (0)
Scoring	
≥ 9 = definite ADR	
5-8 = probable ADR	
1-4 = possible ADR	
0 = doubtful ADR	



**Figure 3:** Electrocardiogram showing RBBB with first degree AV block.

N-acetylcysteine infusion was started on preliminary diagnosis of toxic hepatitis as viral hepatitis serology was negative and abdomen ultrasound scan was normal. Patient was restarted on ATT with Ethambutol and Rifampicin at doses of 1250 mg and 300 mg per day and dose of rifampicin was increased to 600 mg 5 days later. Isoniazid 100 mg/day was added to treatment while his liver function test results remained normal but developed high grade fever of 40°C 5 hours after starting. Isoniazid challenge confirmed that the drug was the cause of fever. Pyrazinamide 500 mg/day was added to regimen and dose was increased to 1500 mg/day without any adverse effect.

The Naranjo adverse drug reaction probability scale is used to establish the cause and effect relationship between a drug and its adverse effect (Table 2). Our case with score of 10 definitely establishes



**Figure 4:** Ziehl-Neelsen staining of sputum showing Acid fast bacilli.



**Figure 5:** Chest radiography on January 2015 showing regression of tuberculous lesion.

the fact that fever was due to isoniazid. Patient was asymptomatic in follow up period and became sputum negative after 2 months and was declared free of Tuberculosis after 6 months. Chest radiograph done in January 2015 showed COPD changes and regression of lesion in right upper zone (Figure 5).

## Discussion

Krasnitz in 1953 first identified high fever due to INH [8]. Christianson CS et al. in a series of 1744 patients observed that 22 patients could not tolerate INH treatment and the most common side effect was fever (59%) [9]. Dutt et al., in a series of 814 cases reported that rate of fever was 1 percent [9]. High fever was observed during multi-drug therapy. One case who received INH chemoprophylaxis was reported to develop fever.

The mechanism is may be related to an immunopathological process associated with antibody formation. On borne, RK et al., study showed that high fever related to INH was more frequent in people allergic to Para amino salicylic acid, streptomycin and penicillin [10]. Eventhough patient did not give history of drug allergy he was found to be allergic to penicillin on skin testing.

Our patient developed high grade fever of 41°C within 8 hours after starting antituberculosis drugs, including INH. Considering study of Dutt et al., fever reaction developed between Day 10 and Day 20 of treatment. When the drug was stopped and started again, fever recurrence was observed in the first 2 -10 hours. In 1977 two case reports by Davis RS et al., observed that fever and myalgia occurred within 8 - 14 days, and when the treatment was withheld and started again, fever (40 C) was seen within two and three hours [11]. Antibody to INH was not done due to unavailability of test and unaffordability of patient.

Rifampicin is the commonest drug to among anti- tuberculosis drugs to cause flu-like syndrome that typically begins 2-3 hours after drug ingestion and lasts up to 8 hours [12]. It often occurs with intermittent high dose of rifampicin or when the drug has been restarted after a gap of days to months. The precise steps in the mechanism of rifampicin-induced antibody are not clearly known. One theory is that drug acts as a hapten binding to macromolecules in plasma acting as antigen and stimulating antibody formation. Hapten-antibody complexes bind complements and cause different hypersensitivity reactions [13]. Ethambutol also can cause flu-like illness [14].

Peripheral eosinophilia and high levels of IgE are commonly observed in drug-induced high fever [15]. Our patient's investigations showed eosinophilia (7%) and increased IgE levels. We put forward

the following observations based on our case report. Fever without rash can occur with isoniazid treatment. It can occur within 8 hours of starting the first dose. Patients may have drug allergies eventhough they might not report. First consideration should be infectious diseases to prevent significant morbidity and mortality in Tuberculosis. High index of clinical suspicion is important to diagnose this condition as serology and other investigations have a limited role.

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