Hyperglycaemia induced by isoniazid preventive therapy

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ABSTRACT

We report the case of a HIV-positive patient with type 2 diabetes mellitus who presented with uncontrolled blood sugars after the initiation of prophylactic isoniazid (INH) therapy. INH is widely used for prophylaxis and treatment of tuberculosis (TB) around the world and INH-induced hyperglycaemia could be overlooked.

Keywords: Hyperglycaemia, isoniazid, isoniazid prophylaxis therapy

Introduction

India has the largest burden of tuberculosis (TB), second largest burden of diabetes, and third largest HIV burden in the world.[³] To find patients with the presence of all three co-morbidities is not an uncommon occurrence globally. Isoniazid (INH) is a highly specific bactericidal drug used against TB.[⁴]

Since 2016, the National AIDS Control Organisation (NACO), India, recommends “All asymptomatic HIV patients and those, in whom active TB is ruled out, should be offered Isoniazid Preventive Therapy (IPT) for six months.”[⁵]

While clinicians maintain a high index of suspicion for INH-induced hepatitis and peripheral neuropathy, they may tend to overlook INH-induced hyperglycaemia. Here, we present a case report of worsening glycaemic control following the initiation of isoniazid preventive therapy (IPT) in a 48-year-old HIV-positive woman with previously well-controlled type 2 diabetes mellitus.

Case Report

A 48-year-old HIV-positive woman with previously well-controlled type 2 diabetes mellitus presented on May 2017 to her family physician with high blood glucose levels [fasting blood sugars (FBS) of 173 mg/dl and HbA1c of 9.6%] and elevated liver enzymes (direct and indirect bilirubin, ALT, AST, and GGTP were raised and were 287 U/L, 337 U/L, and 726 U/L, respectively).

She was diagnosed with type 2 diabetes mellitus 4 years back. Prior to this visit her blood sugars were well controlled (previous reports on February 2017: FBS: 111 mg/dl, HbA1c: 5.7%; ⁷th July 2016: FBS: 100 mg/dl, HbA1c: 6%). She was on metformin-sustained release 500 mg BD and atorvastatin 10 mg daily.

The patient also stated that she was started on IPT on February 2017 with a dose of 300 mg and for a planned duration of 6 months of which she had completed 3 months. She was given pyridoxine 40 mg daily to prevent INH-induced peripheral neuritis, a well-known side effect. Additionally, fenofibrate was started for high blood triglyceride levels on January 2017.

The patient gives no history of other changes in her medication, no gross change in weight, no significant change in her diet, or...
fever. The patient claims to be compliant with her medication. There was no history of any other co-morbidities such as hypertension, TB, obesity, coronary heart disease, stroke, previous surgeries, or recent trauma. No history of substance abuse.

She was diagnosed with HIV-1 infection 7 years back after her husband tested positive. Her initial CD4 count was 377/mm³ (September 2010) and was started on antiretroviral therapy (ART) (lamivudine 150 mg, nevirapine 200 mg, and zidovudine 300 mg) on May 2011 after her CD4 count had dropped to 264/mm³. She has been compliant with her ART. She has been responsive to treatment with her latest CD4 count of 504/mm³ (December 2016).

On examination, she was moderately built and nourished. Her body mass index (BMI) was 23.45 kg/m². Her vitals were within normal limits. No icterus was noted. Systemic examination was unremarkable.

Impression: The sudden worsening of her glycaemic control was a puzzle to her physician and was causing distress to the patient. Taking into account that the only recent change was the initiation of INH, we looked at the possibility of this being a result of drug-induced hyperglycaemia. Our literature review showed one other documented case of hyperglycaemia caused by INH, hyperglycaemia was also known as an uncommon side effect.

The hypothesis that hyperglycaemia was caused by INH, we stopped INH and found that after 6 weeks of stoppings her FBS was 140 mg/dl and AST 40 U/L. Three months after the treatment was stopped her HbA1c was 6.2%. This supported our hypothesis.

Discussion

This is among the very few cases that document the occurrence of hyperglycaemia with IPT. The literature review using the keywords “Isoniazid prophylaxis therapy and hyperglycaemia” showed no results. Broadening the search to “Isoniazid and hyperglycaemia” showed 11 results. The Food and Drug Administration (FDA) reports that between 2005 and 2018 there have been 10,749 patients that experienced side effects with isoniazid of these only 41 (0.38%) reported hyperglycaemia.[8,9] It should be noted that the proportion of people receiving INH who were also tested for hyperglycaemia is unknown. The true incidence of hyperglycaemia with INH might be under recognised and under reported.

INH impairs glucose metabolism in several ways. While it is known that INH antagonises the effect of sulphonylureas and worsens the glycaemic control of diabetics. The effect of INH on biguanides is not well documented.[9] INH also impairs the release and action of insulin leading to hyperglycaemia even in non-diabetics.[10] In a case of sudden deterioration of diabetic control, drug-induced hyperglycaemia should be ruled out.

| Questions                                                                 | Answers                                                                 |
|--------------------------------------------------------------------------|------------------------------------------------------------------------|
| Can INH cause loss of glycaemic control in diabetics?                     | Yes                                                                    |
| Can INH cause hyperglycaemia in non-diabetics?                           | Yes                                                                    |
| Mechanism of hyperglycaemia                                              | Impairs insulin release                                                |
| Should INH be stopped in view of better glycaemic control?               | Antagonizes sulphonylureas                                              |
| Should the dosage of oral hypoglycaemic drug be increased for better glycaemic control? | We do not recommend stopping INH in view of significant reduction of TB in patients with HIV who have taken INH prophylaxis for 6 months |
| Role of family medicine physicians                                       | We do not recommend this. We recommend the use of newer insulin analogues for the duration of the prophylaxis as they are more predictable |

INH: Isoniazid; TB: Tuberculosis

Diabetics have a three-fold increase risk of TB,[8,9] IPT reduces the risk of TB in HIV-positive patients by 30–35%.[10,11]

The occurrence of hyperglycaemia in a patient receiving INH poses a clinical dilemma. The treating clinician must weigh the risks and benefits of continuing INH especially in situations where it used for prophylaxis. The optimal approach should depend on clinical judgement and patient preference.

In pursuance of the benefit of IPT to HIV patients and even more so for HIV patients with diabetes, we recommend the use of newer insulin analogues (in view of their predictable action) to control hyperglycaemia in patients on IPT, who do not present with elevated liver enzymes.

Learning points: India is known as both the TB and diabetes capital of the world. As family medicine physicians whose role lies in the realms of primary care it is not uncommon to see cases that are an intersection of both the diseases. Therefore, it is necessary to identify and understand different presentations of common problems such as hyperglycaemia, to be able to rule out other diagnosis and treat the patient appropriately. The above case adds to that knowledge [Table 1].

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Table 1: Learning points

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Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. World Health Organisation. Tuberculosis Fact Sheet. Available from: http://www.who.int/mediacentre/factsheets/fs104/en/. [Last accessed on 2018 Oct 31].
2. Central Intelligence Agency. HIV/AIDS – People Living with HIV/AIDS. 2013-14. Washington, DC: The World Factbook; 2013. Available from: https://www.cia.gov/library/publications/resources/the-world-factbook/rankorder/2156rank.html. [Last accessed on 2018 Oct 31].
3. International Diabetes Foundation. Diabetes Estimates. IDF Diabetes Atlas. 7th ed. Available from: http://www.diabetesatlas.org/across-the-globe.html. [Last accessed on 2018 Oct 31].
4. National Center for Biotechnology Information. PubChem Compound Database; CID=3767. Available from: https://www.pubchem.ncbi.nlm.gov/compound/3767. [Last accessed on 2018 Oct 31].
5. National AIDS Control Organization, Ministry of Health and Family Welfare, Government of India. Operational Manual for Isoniazid Preventive Therapy. June, 2016. p. 15-21. Available from: http://www.naco.gov.in/sites/default/files/IPT%20Manual%2030%20%20June%202016.pdf. [Last accessed on 2018 Oct 31].
6. Will you Have Hyperglycemia with Isoniazid – From FDA Reports – eHealthMe; 2017. Available from: http://www.ehealthme.com/ds/isoniazid/hyperglycemia/#print. [Last accessed on 2018 Oct 31].
7. Niazi AK, Kalra S. Diabetes and tuberculosis: A review of the role of optimal glycemic control. J Diabetes Metab Disord 2012;11:28.
8. National AIDS Control Organization, Ministry of Health and Family Welfare, Government of India. Operational Manual for Isoniazid Preventive Therapy. June, 2016. p. 15-21. Available from: http://www.naco.gov.in/sites/default/files/IPT%20Manual%2030%20%20June%202016.pdf. [Last accessed on 2018 Oct 31].
9. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. PLoS Med 2008;5:e152.
10. Leonard CE, Bilker WB, Brensinger CM, Han X, Flory JH, Flockhart DA, et al. Severe hypoglycemia in users of sulfonylurea antidiabetic agents and antihyperlipidemics. Clin Pharmacol Ther 2016;99:538-47.
11. Ayele HT, Mourik MS, Debray TP, Bonten MJ. Isoniazid prophylactic therapy for the prevention of tuberculosis in HIV infected adults: A systematic review and meta-analysis of randomized trials. PLoS One 2015;10:e0142290.