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Pyrazinamide induced hyperuricemia

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Abstract

Pyrazinamide and Ethambutol are antitubercular drugs that raise Uric acid levels by lowering excretion and increasing uric acid reabsorption and cause life-threatening renal impairment such as Acute Nephropathy, Urolithiasis, and other. Hyperuricemia is reported by 82.3 percent of antitubercular treatment patients. In this paper, I present the case of a 20-year-old male patient who developed hyperuricemia after using the antitubercular medicine Pyrazinamide, as well as the pathophysiology, treatment, and prevention of hyperuricemia.

Keywords

hyperuricemia; pyrazinamide; uric acid; gout; urolithiasis.

Introduction

In underdeveloped countries like India, tuberculosis is a frequent disease. Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide are the four medications that make up standard Antitubercular Therapy (ATT). Pyrazinamide is a significant ATT medication, however it has possible urate retention side effects, such as an 80 percent reduction in renal uric acid clearance at 300 mg/day [4], that put's stress on the renal function & causes the Urolithiasis, Acute nephropathy & acute gout attacks. This case report focuses on the alternative and safer usage of Pyrazinamide and Anti-gout medicines in hyperuricemia prevention and therapy.

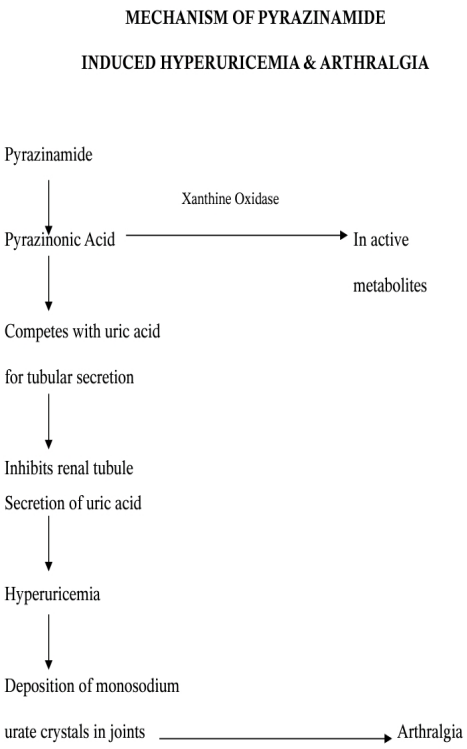
Pathogenesis

Hyperuricemia is a condition in which the level of uric acid in the blood is unusually high. Hyperuricemia is characterized as a high level of uric acid in the blood. Females have a uric acid concentration larger than 6 mg/dl, males have a uric acid concentration greater than 7 mg/dl, and youth (<18 years old) have a uric acid concentration greater than 5.5 mg/dl. The amount of uric acid in the blood depend on the balance between the amount of purines eaten in food, the amount of urate synthesized within the body &

the amount of urate that is excreted through the urine or through the Gastrointestinal track [5]. Uric acid is synthesized as the end product of an exogenous pool of purines in the colon, liver, and vascular endothelium, as well as endogenously from damaged, dying, and dead cells [6], whereas nucleic acid, adenine, and guanine are degraded into purines. As a result, it's critical that the purine production and excretion balances are kept in check. Humans, unlike other mammals, are unable to convert uric acid to the more soluble molecule allantoin due to a lack of the uricase enzyme. Uric acid is converted to highly soluble uric acid. The enzyme uricase converts 5-Hydroxyisourate to 5-Hydroxyisourate, which is then converted to 5-Hydroxyisourate. 5-Hydroxyisourate is broken down into allantoic acid and ammonia, which the kidney eliminates [6]. However, the enzyme uricase has lost its functional activity in humans. Uricase mRNA can be found in human liver, but it has two premature stop codons and encoding genes, making it a pseudo gene [7].

Mechanism of hyperuricemia and arthralgia

The exact mechanism of pyrazinamide induced hyperuricemia remains to be elucidated. The sequence of events in the causation of hyperuricemia and arthralgia in patients on pyrazinamide is depicted below. Pyrazinamide is converted to pyrazinoic acid by hepatic deaminase which is further hydroxylated to 5–hydroxy pyrazinoic acid by xanthine oxidase [6]. Pyrazinoic acid is supposed to be the active metabolism in man. Urate, the end product of purine metabolism is excreted by glomerular filtration and subsequent reabsorption in proximal tubule. The serum uric acid concentration greatly depends on the rate of renal clearance of uric acid which is dependent upon the distal tubular secretion of uric acid that is almost totally inhibited by pyrazinoic acid. Pyrazinoic acid may also increase proximal reabsorption of filtered uric acid. As a result, serum uric acid concentration increases leading to deposition of monosodium urate crystals in the joints. This being the probable mechanism of action of pyrazinamide, allopurinol is not advised in the management of arthralgia since it being a xanthine oxidase inhibitor will increase the concentration of pyrazinoic acid.



Clinical Presentation

Hyperuricemia is characterized by the increase serum uric acid concentration that can cause the monosodium urate crystal deposition in the joints & cartilage, thus lead to the major disorders like Urolithiasis, Gout Arthritis and Urate nephropathy [3]. Acute gout Arthritis lead to the sudden severe attacks of pain, swelling, redness & tenderness in one or more joints. It most often affect the joints include elbows, knees, wrist, ankles and fingers. It is speculated that lower body temperature, night time dehydration or a nocturnal dip of cortisol levels may contribute to the risk of gout attacks at night time [8].

Treatment

Treatment of the Hyperuricemia depends on the condition & stage of the patient. If the patient is asymptomatic it generally rarely requires any treatment intervention. The presence of Monosodium urate crystal on the synovial fluid of the joints confirm the diagnosis of hyperuricemia [9]. Acute gouty arthritis, intercritical gout (Interval between attacks) & chronic tophaceous gout are the clinical phases of gout. The two major causes of Hyperuricemia is overproduction & under excretion of uric acid [10], so the treatment focuses on this aspect & also to provide symptomatic relief. It is speculated that lower body temperature, night time dehydration or a nocturnal dip of cortisol level may contribute to the risk of gout attack at night time [8]. Oral NSAID's are prescribed for the symptomatic relief of the pain & inflammation. Indomethacin is the drug of choice as analgesic at 25-50 mg orally QID (Four times a day). It is generally used for 7-10 days / till the symptoms persist. Acute gout is managed by Colchicine, first loading dose of 1.2 mg orally followed by the maintenance dose of 0.5 mg orally after one hour of the gout attack. The two major classes of Antigout drugs are Uricosurics & Xanthine oxidase synthesis inhibitors. Uricosurics drug decreases the tubular reabsorption of secreted & filtered urate, thus increasing the excretion of urate. Probenecid is the choice of Uricosurics at 250-500 mg twice a day. Probenecid should be administered with plenty of fluids to avoid urate crystallization in urinary tract. Uric acid synthesis inhibitors work by inhibiting the xanthine oxidase enzyme, thus inhibits the production of urate/uric acid. Allopurinol is used at 200-300 mg once a day (OD) in the secondary hyperuricemia because of cancer chemotherapy/ Radiation/ thiazide type diuretics.

Phase	Drug	Dose
Acute gout	Nonsteroidal anti-inflammatory drugs	• Indomethacin (Indocin): 25–50 mg four times daily • Naproxen (Naprosyn): 500 mg twice daily • Ibuprofen (Motrin): 800 mg four times daily • Sulindac (Clinoril): 200 mg twice daily
	Colchicine	1.2 mg orally initially, 0.6 mg orally one hour later
	Corticosteroids	• Prednisone: 0.5 mg/kg orally on day 1; taper by 5 mg each day thereafter • Triamcinolone acetonide (Kenalog): 60 mg intramuscularly; repeat in 24 hours if necessary
Intercritical gout	Colchicine	0.6 mg orally once or twice daily
Chronic tophaceous gout (prophylaxis)	Sulfinpyrazone	50 mg three times daily initially; gradually titrate up until serum urate is < 6 mg/dL; maximum 800 mg per day
	Probenecid	250 mg twice daily initially; gradually titrate up until serum urate is < 6 mg/dL; maximum 3 g per day
	Allopurinol	50–100 mg daily; gradually titrate up until serum urate is < 6 mg/dL; typical dosage 200–300 mg daily
	Febuxostat	40 mg daily initially, titrating up to 80 mg daily

Case Presentation

A 20 year old male Patients with the weight of 46 kg presented to the hospital with the chief complaints of high fever, night sweats & Chronic productive cough (since 1 month). On CT-scan it's show's "A large area of consolidation with cavitary changes are seen in the lower lobe of the left lung". On sputum analysis it confirms the infection of Mycobacterium Tuberculosis. In drug susceptibility testing, it shows the presence of Isoniazid resistant tuberculosis (Mono-Resistant TB). Then he is started with the TB - Regimen including daily oral administration of

Tab. Rifampicin 450 mg/day

Tab. Ethambutol 1000 mg/day

Tab. Pyrazinamide 1250 mg/day

Tab. Levofloxacin 750 mg/day for six months.

After the 8 Weeks of therapy patient develop the symptoms of redness, pain & swelling in the left knee. After examining the symptoms, physician advice to stop the Pyrazinamide for 5 days & prescribed Tab. Prednisolone 5 mg thrice a day. Tab. Pantoprazole 40 mg twice a day. Continue both the medicine for five days. Rest all medicine (Antitubercular medication) should be administered as prescribed. After the 5 days, since no improvement is seen in patient, On routine examination it is found that serum uric acid is raised (10.59 mg/dl) So the patient is prescribed with the Tab. Febuxostat 40 mg once a day for 7 days During this therapy, the dose of the Pyrazinamide was so adjusted that 500 mg once a day for 3 days 1000 mg once a day for next 3 days. After this continue 1250 mg once a day. Rest all medicine (Antitubercular) is administered as prescribed.

After 7 days, on routine examination there is no significant reduction in the serum uric acid (10.32 mg/dl). So again Tab. Febuxostat 40 mg once a day for another 12 days during this period the dose of the Pyrazinamide (PYZ) is again adjusted for 12 days as

Stop PYZ for 3 days

PYZ 250 mg for next 3 days

PYZ 500 mg for next 3 days

PYZ 750 mg for next 3 days.

During this period rest of all medicine (Antitubercular medication) should be administered as prescribed. After the 12 days of dose distribution therapy of Pyrazinamide the patient was re-examined, but the redness, pain & swelling still persist on the left knee. Concentration of serum uric acid is 10 mg/dl. So at this stage, the Pyrazinamide is stopped from the Antitubercular regimen & the alternative Linezolid is prescribed.

Tab. Rifampicin 450 mg/day

Tab. Ethambutol 1000 mg/day

Tab. Levofloxacin 750 mg/day

Tab Linezolid 600 mg/day

This regimen for another 3 month & after that only continue Tab. Linezolid 300 mg/day for next 3 months, with no other Antitubercular medication. After one month of therapy patient was re-examined & patient is normal with no redness, tenderness, swelling & pain, serum uric acid levels is also in the normal range (7.1 mg/dl)

Prevention approaches

Approximately 43-100% patient report Hyperuricemia with the Antitubercular regimen containing pyrazinamide [1,11]. So if the patient report Hyperuricemia due to Pyrazinamide it is of prime importance that patient should be well hydrated, with plenty of fluids & routinely have their Serum Uric acid levels monitored. Elevated uric acid can leads the the Acute gout attacks, urolithiasis & Acute nephropathy this leads to the renal dysfunction. As there are no published guidelines about how to manage the Pyrazinamide induced Hyperuricemia [5], so febuxostat is the drug of choice which inhibit the xanthine oxidase enzyme, since the Uric acid production is lowered.

Conclusion

Antitubercular drugs like Pyrazinamide and Ethambutol are known to cause hyperuricemia in patients. Because Ethambutol is less effective in causing Hyperuricemia, Pyrazinamide is the primary cause. So, it is recommended that desensitization therapy of Pyrazinamide should be started, if the tolerability of the patient is good enough then Pyrazinamide can be continued & if not then the Pyrazinamide should be discontinued & safer alternative to be prescribed. The serum uric acid content and renal function should be checked often in patients using antitubercular therapy. Elevated Uric acid should be treated with Xanthine oxidase inhibitors (Febuxostat 40 mg/day). An alternative should be suggested based on the patient's condition and it is recommended that the patient stay hydrated.

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