Pyrazinamide-Induced Hyperuricemia

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INTRODUCTION

Although often asymptomatic, elevated levels of uric acid can cause crystal deposition and potentially lead to three major disorders: gout, urolithiasis, and urate nephropathy.[1] Hyperuricemia can result from overproduction or underexcretion of uric acid in the body. It can also be induced by certain medications. Xanthine oxidase inhibitors, such as allopurinol (Zyloprim, Prometheus Labs) or febuxostat (Uloric, Takeda), are commonly used to lower the body's uric acid production. Rasburicase (Elitek, Sanofi-Aventis), a urate-oxidase approved for tumor lysis syndrome, has been used off-label to lower uric acid levels quickly in situations of severe nephropathy. We report a case of suspected pyrazinamide-induced hyperuricemia in a kidney transplant patient resulting in acute renal injury.

PATHOPHYSIOLOGY

Hyperuricemia is normally defined as a serum uric acid (SUA) level greater than 7.0 mg/dL, the approximate level at which urate is supersaturated in plasma.[2] Uric acid is produced by purine metabolism in humans. In contrast to most other mammals, humans lack the enzyme uricase that metabolizes uric acid into allantoin, a more water-soluble compound that can be excreted easily by the kidney. As a result, high SUA levels can exceed the solubility threshold and precipitate in the form of sodium urate crystals, ultimately leading to gout and urolithiasis.[3] Extremely high uric acid levels can overwhelm the kidneys and cause acute renal failure. Approximately 70% of uric acid is excreted from the kidneys; the remainder passes into the gastrointestinal tract, where it is oxidized to allantoin, allantoic acid, urea, and carbon dioxide. Uricase and other enzymes present in intestinal bacteria metabolize these compounds.[4]

Hyperuricemia may be caused by increased urate production (overproducers) or decreased renal urate excretion (underexcreters), with the dominating contributing factor being the underexcretion of urate.[5] Common causes of hyperuricemia can be found in Table 1.

Many medications have been associated with elevated uric acid levels. Pyrazinamide and ethambutol are two antituberculous drugs that have been reported to induce hyperuricemia.[6-7] Pyrazinamide is a strong urate retention agent, causing a greater than 80% reduction in renal clearance of uric acid at a 300-mg therapeutic daily dose.[8] The metabolite pyrazinoic acid is oxidized by xanthine oxidase and is likely responsible for the hyperuricemic effect. Hyperuricemia has been reported in 43% to 100% of patients treated with pyrazinamide (alone or in combination).[6,9] Furthermore, gouty attacks have been associated with patients taking pyrazinamide.[4] Ethambutol can also cause hyperuricemia by decreasing renal uric acid clearance, but it does so less consistently and to a lesser degree than pyrazinamide. Calcineurin inhibitors have also been shown to raise uric acid levels.[10] Cyclosporine has a greater association with causing hyperuricemia than tacrolimus, which may be related to renal function impairment.

Table 1 Common Acquired Causes of Hyperuricemia[2]

Cause	Increased Urate Production	Decreased Renal Excretion of Urate
Metabolic/ endrocrine	• Excess purine from diet • Ethanol • Fructose consumption	• Dehydration • Lactic acidosis • Ketosis • Hypothyroidism • Hyperparathyroidism
Hematological/ renal	• Myeloproliferative disorders • Polycythemia • Lymphoproliferative disorders	• Hypertension • Polycystic kidney disease • Chronic renal failure
Drugs	• Ethanol • Cytotoxic drugs • Vitamin B_{12} (treatment of pernicious anemia)	• Ethanol • Cyclosporine (Sandimmune) • Thiazide diuretics • Loop diuretics • Ethambutol (Myambutol) • Pyrazinamide • Aspirin (low-dose) • Levodopa (Larodopa) • Nicotinic acid (Niacin)
Miscellaneous	• Obesity • Psoriasis • Hypertriglyceridemia	• Obesity • Sarcoidosis • Toxemia of pregnancy • Chronic lead intoxication

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Table 2 Gout Management Agents[2]

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

TREATMENT

Asymptomatic hyperuricemia is common and treatment is generally unnecessary. The diagnosis of gout requires confirmation of the presence of monosodium urate crystals in synovial fluid.[2] Gout can be further classified into the clinical phases of acute gouty arthritis, intercritical gout (interval between attacks), and chronic tophaceous gout. Table 2 summarizes agents used to prevent and treat gout. Acute gouty attacks are treated with indomethacin or other nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and/or intra-articular corticosteroids.[2] Oral NSAIDs are generally prescribed for a seven- to 10-day course or until a few days after inflammatory symptoms have diminished. Colchicine (Colcrys, Takeda) is used to manage intercritical gout. Treatment doses are 1.2 mg orally for the first dose, followed by 0.6 mg orally one hour later (a total of 1.8 mg per attack). Gout prophylaxis is managed with 0.6 mg orally daily of colchicine or 0.6 mg twice daily of colchicine. The dose should be decreased when administering with P-glycoprotein inhibitors or CYP3A4 inhibitors, and in patients with renal impairment. Urate-lowering drugs may be used for prevention in patients with recurrent gout. Probenecid and sulfinpyrazone are uricosuric agents used for patients who undersecrete uric acid.[2] Probenecid inhibits tubular reabsorption of secreted and filtered urate, increasing its excretion. The starting dose of probenecid is 250 mg orally twice daily, which can be increased gradually to 3 g daily. Allopurinol and febuxostat decrease uric acid synthesis by inhibiting xanthine oxidase and are commonly used for treating hyperuricemia. The usual adult daily maintenance dose is 200 to 300 mg and 40 to 80 mg orally for allopurinol and febuxostat, respectively. Pyrazinamide and ethambutol-induced hyperuricemia can normally be controlled by xanthine oxidase inhibitors.[4]

Rasburicase is a recombinant urate-oxidase indicated for initial management of plasma uric acid levels in cancer patients receiving chemotherapy likely to result in tumor lysis syndrome and subsequent elevation of plasma uric acid.[11] Rasburicase is indicated only for a single course of treatment for up to five days. Based on the Red Book Online average wholesale price at the time of this writing, the cost of one dose of rasburicase for a 70-kg person at 0.2 mg/kg intravenous (IV) was $7,460.[12] Off-label use of rasburicase has been shown to be effective in the long-term treatment of patients with tophaceous gout.[3] Richette et al demonstrated reduced uricemia and tophi with 0.2 mg/kg monthly rasburicase injections over six months in 10 patients intolerant to allopurinol with moderate-to-severe renal failure and tophaceous gout.[13] Garay et al reviewed three additional cases using rasburicase in tophaceous gout.[14] Patients ranged in age from 33 to 57 years of age and were treated for six to 16 months. All reported normalization of tophi.

Case Report

A 34-year-old Filipino male presented to the New York Harbor Healthcare System Department of Veterans Affairs–Manhattan Campus Renal Clinic for routine follow-up. He had a history of gout and tuberculosis (TB) with dissemination to neurological and pleural sites. The TB dissemination was likely caused by reactivation due to immunosuppression from a renal transplant in 2006. His past medical history also included inflammatory bowel disease (IBD). He had been admitted less than one month earlier to the same institution, where he had initiated a TB regimen including daily, oral administration of rifabutin (Mycobutin, Pfizer) 300 mg, isoniazid 300 mg with pyridoxine 25 mg supplementation, pyrazinamide 1,500 mg, and ethambutol (Myambutol, X-Gen Pharma) 1,200 mg.

Upon presentation at the clinic, the patient reported a recent gout attack with severe diffuse polyarticular arthritis over the previous seven days. This attack affected his hands, elbows, knees, and feet, bilaterally. He denied flank pain, abdominal pain, dysuria, nausea, or vomiting, but stated he had a transient fever on the day prior to presentation. Laboratory assessment revealed serum uric acid (SUA) equal to 26.7 mg/dL (normal, 4.4–7.6 mg/dL), serum creatinine (SCr) elevated to 2.6 mg/dL (baseline, 1.5 mg/dL), serum CO_2 reduced to 20 mmol/L (normal,

24–32 mmol/L), and urine pH equal to 5.5 (normal, 4.5–8.0). Repeat measurements confirmed these results. This supported a strong suspicion for uric acid nephropathy secondary to his profound hyperuricemia.

Prior to admission, his medication regimen included iron polysaccharide 150 mg orally twice daily and allopurinol 100 mg orally twice daily, in addition to his TB therapy. Immunosuppression for kidney transplantation included tacrolimus (Prograf, Astellas) 3 mg orally every morning and 4 mg orally every evening, and mycophenolate mofetil (Cellcept, Genentech) 1,000 mg orally twice daily, which was discontinued when he was diagnosed with TB. He had received his transplant medications consistently for seven years prior to admission. IBD was managed with monthly IV infusions of 300 mg of infliximab (Remicade, Janssen Biotech) for the six months prior to his TB diagnosis. Only tacrolimus was maintained after the TB diagnosis, within the prior month. The patient reported strict adherence to his prescribed therapy and reported no dietary indiscretions that may have precipitated hyperuricemia.

He was immediately treated for hyperuricemia with a single IV dose of 7.5 mg rasburicase (0.1 mg/kg; his weight was 75 kg). Alkalinization was initiated with an IV infusion of sodium bicarbonate 150 mEq in dextrose 5% in water (D5W) at 75 mL/hr, and oral citric acid/sodium citrate (334 mg/500 mg per 5-mL solution, 15 mL orally twice a day). Alkalinization was titrated to a serum CO_2 of 22–29 mmol/L (normal, 24–32 mmol/L) and a urine pH of 6–6.5 (normal, 4.5–8.0). Allopurinol was discontinued due to suspicion of a paradoxical increase in uric acid when used in combination with pyrazinamide.[6]

Pain was initially managed with acetaminophen/codeine (Tylenol #3, Janssen) 300/30 mg orally every six hours as needed; he received 10 doses. However, insufficient pain control warranted intramuscular (IM) morphine sulfate at 4 mg every six hours as needed. He received six doses of morphine sulfate. For management of the gout attack, colchicine 0.3 mg orally every other day was initiated, due to his diminished renal function. Previous colchicine use was not reported by the patient or the hospital record. Tacrolimus was continued for immunosuppression maintenance. All anti-TB agents were initially maintained, though ethambutol and pyrazinamide were carefully evaluated for their potential for inducing hyperuricemia. On the fourth day of admission, pyrazinamide was discontinued and substituted with moxifloxacin (Avelox, Bayer Healthcare) 400 mg orally per day. The Naranjo algorithm (a method of estimating the probability of adverse drug reactions [ADRs]) was performed, and pyrazinamide garnered a score of 5 (probable ADR).[15] The change from pyrazinamide to moxifloxacin was expected to promote a more favorable balance between TB management and risk for recurrent hyperuricemia. The intent was to resolve the hyperuricemia while maintaining TB management.

The single rasburicase dose yielded a reduction of SUA from 26.7 to 0.0 mg/dL on the day after administration (day 3 of hospitalization). At discharge, the SUA gradually increased to 6.0 mg/dL (normal, 4.4–7.6 mg/dL); the SCr was 1.6 mg/dL.

Alkalinization of the serum and urine led to conditions less likely to result in urate crystallization. This occurred by day 2 of admission (see Table 3).

After a nine-day hospital course, the patient recovered and was stabilized. Febuxostat (Uloric, Takeda) 40 mg orally per day was initiated. A recommendation for starting pegloticase (Krystexxa, Savient Pharmaceuticals) was to be considered if the uric acid level exceeded 7 mg/dL. Colchicine was continued at 0.3 mg every other day in accordance with recommendations from a rheumatology consult. The patient was continued on a daily oral regimen of moxifloxacin (400 mg), ethambutol (1,200 mg), rifampin (300 mg), isoniazid (300 mg), and pyridoxine (25 mg) for TB treatment. Tacrolimus (3 mg orally every morning and 4 mg orally every evening) was maintained for renal transplant management. The patient was discharged and scheduled for follow-up in the renal clinic.

PREVENTION APPROACHES

Approximately two out of three patients with drug-induced hyperuricemia will remain asymptomatic.[3] Patients on medications that are associated with inducing hyperuricemia should be encouraged to maintain adequate hydration and routinely have their uric acid levels monitored. Elevated levels warrant further evaluation, estimating the risk for each individual in developing gout, urolithiasis, and/or acute nephropathy. There are no published guidelines on how to prevent drug-induced hyperuricemia. Xanthine oxidase inhibitors can be considered to lower uric acid levels in high-risk patients where the benefits outweigh the risks. Rasburicase may be an option, since it has been used off-label in severe cases of hyperuricemia to prevent acute kidney injury.

CONCLUSION

Antituberculosis medications such as pyrazinamide and ethambutol have been associated with increasing uric acid levels. Although often considered asymptomatic, severe hyperuricemia can ultimately lead to renal failure. Numerous treatments and prevention strategies exist for managing hyperuricemia. Some of these include NSAIDs, intra-articular glucocorticoids, colchicine, probenecid, allopurinol, urinary alkalinization, and hydration. Rasburicase treatment has been used in a small number of patients, in an off-label manner, to rapidly treat severe hyperuricemia. Quick treatment reduces uric acid levels to alleviate the burden on the kidneys and further decrease the chance of renal injury.

Table 3 Laboratory Values of the Case Patient

Laboratory Values	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Serum uric acid (mg/dL)	26.7*	1.2	0.0	0.7	1.0	1.8	3.0	4.5	6.0
Serum creatinine (mg/dL)	2.6	2.1	2.0	2.4	2.3	2.2	1.9	1.8	1.6
Serum carbon dioxide (mmol/L)	20.0	25.0	32.0	31.0	31.0	30.0	26.0	29.0	24.0
Urine pH	5.5	6.0	7.0	8.0	7.5	8.0	7.5	—	—

* Rasburicase 0.2 mg/kg intravenous administered once

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REFERENCES

1. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med* 1987;82(3):421.
2. Harris A, Siegel L, Alloway J. Gout and hyperuricemia. *Am Fam Phys* 1999;59(4):925–934.
3. Becker MA. Asymptomatic hyperuricemia. UpToDate. April 2013. Available at: http://www.uptodate.com/contents/asymptomatic-hyperuricemia. Accessed May 2014.
4. Scott JT. Drug-induced gout. *Baillieres Clin Rheumatol* 1991;5(1):39–60.
5. Gustafsson D, Unwin R. The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality. *BMC Nephrology* 2013;14**:**164.
6. Gerdan G, Nurullah A, Ucan ES, et al. Paradoxical increase in uric acid level with allopurinol use in pyrazinamide-induced hyperuricemia. *Singapore Med J* 2013;54(6) e125–128.
7. Postlethwaite AE, Bartel AG, Kelley WN. Hyperuricemia due to ethambutol. *N Engl J Med* 1972;286(14):761–762.
8. Gutman AB, Yu TF, Berger L. Renal function in gout. III. Estimation of tubular secretion and reabsorption of uric acid by use of pyrazinamide (pyrazinoic acid). *Am J Med* 1969;47(4):575–592.
9. Sharma TN, Jain NK, Mathur BB, et al. Hyperuricemia and arthralgia during pyrazinamide therapy. *Ind J Tub* 28(2).
10. Tumgor G, Arikan C, Kilic M, Aydogdu S. Frequency of hyperuricemia and effect of calcineurin inhibitors on serum uric acid levels in liver transplanted children. *Pediatr Transplant* 2006;10(6):665–668.
11. Food and Drug Administration website. Elitek (rasburicase) label. October 16, 2006. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103946s5083lbl.pdf. Accessed September 10, 2014.
12. Red Book Online. Ann Arbor, Michigan: Truven Health Analytics. Accessed September 9, 2014.
13. Richette P, Briere C, Hoenen-Clavert V, et al. Rasburicase for tophaceous gout not treatable with allopurinol: an exploratory study. *J Rheumatol* 2007;34(10):2093–2098.
14. Garay RP, El-Gewely MR, Labaune J-P, Richette P. Therapeutic perspectives on uricases in gout. *Joint Bone Spine* 2012;79(3):237–242.
15. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239–245. ■