Journal of Tropical Pediatrics, 2015, 61, 351–356
doi: 10.1093/tropej/fmv042
Advance Access Publication Date: 1 July 2015
Original Paper

OXFORD

Is Hyperuricemia Overlooked when Treating Pediatric Tuberculosis Patients with Pyrazinamide?

by Tuğba Şişmanlar,[1] Ayşe T. Aslan,[1] and Irem Budakoğlu[2]

[1]Pediatric Pulmonology Department, Gazi University Hospital, 06500 Beşevler, Ankara, Turkey
[2]Medical Education Department, Gazi University Hospital, 06500 Beşevler, Ankara, Turkey
Correspondence: Tuğba Şişmanlar, Pediatric Pulmonology Department, Gazi University Hospital, 06500 Beşevler, Ankara, Turkey. Tel: +90 312 2027554. E-mail <tsismanlar@yahoo.com>.

ABSTRACT

The treatment of tuberculosis (TB) requires long-term multiple drug use. Hyperuricemia is frequently reported in adults, but there are few data for the pediatric population. This study aimed to review drug-related side effects in pediatric patients that received treatment for TB. Patients with active TB undergoing treatment were followed for drug-related side effects. During the 7 year period, 23 patients with a mean age of 7.9 ± 4.66 years were treated. Drug-related side effects were observed in 14 patients. Hyperuricemia occurred in 12 of the 14 patients, vs. hepatotoxicity in 2. In all, eight of the patients with hyperuricemia had $\geq$2 episodes during pyrazinamide (PZA) therapy. Based on these findings, we devised an algorithm that could be used for the management of hyperuricemia in patients receiving PZA because of TB, and recommend that hyperuricemia be closely monitored during PZA therapy.

INTRODUCTION

Tuberculosis (TB) is a common cause of morbidity and mortality in children, especially those living in endemic regions. Prompt diagnosis and early treatment are essential for effective disease management, even in drug-resistant cases [1]. The treatment of TB requires long-term multiple drug use, and rare drug-related side effects have been reported in children. Hepatotoxicity is the most commonly reported side effect of the treatment of TB in the pediatric population, occurring in approximately 3–10% of patients [2, 3]. Hyperuricemia is a frequently reported side effect in adult patients (40–86%) treated for TB with pyrazinamide (PZA) [4–6]. The rate of hyperuricemia in children treated for TB with PZA has not been reported and the literature includes just one study on hyperuricemia in children [7].

Uric acid (UA)—the end product of purine metabolism—is produced via a xanthine oxidase-catalyzed reaction [8]. Hyperuricemia in children is defined as a plasma UA level >7 mg/dl [9] and may result from overproduction or underexcretion of UA, or both. For instance, a major metabolite of PZA, pyrazinoic acid, can cause hyperuricemia via inhibiting renal tubular secretion of UA [10]. Nephrolithiasis and acute kidney injury in patients with tumor lysis syndrome are well known, whereas recent data suggest that UA might also be involved in the pathogenesis of acute and chronic kidney disease and hypertension [11].

© The Author [2015]. Published by Oxford University Press. All rights reserved. For Permissions, please email: journals.permissions@oup.com

Downloaded from https://academic.oup.com/tropej/article/61/5/351/1647698 by Main Library of Gazi University user on 10 December 2020

Hyperuricemia was reported to be a significant side effect of PZA in the European Respiratory Society (ERS) Task Force's report on the management of TB in Europe [12]. The ERS recommends routine UA monitoring only in patients receiving PZA therapy that have a documented history of hyperuricemia. Allopurinol, a drug that inhibits the xanthine oxidase enzyme responsible for the conversion of hypoxanthine to xanthine and UA, is recommended only if hyperuricemia is symptomatic [12, 13].

According to the latest data from the Turkey Ministry of Health, there were 15 697 cases of TB, of which 761 (4.9%) were children [14]. The present study aimed to review the occurrence of drug-related side effects in pediatric patients that received treatment for TB.

MATERIALS AND METHODS

The study included patients with active TB that presented between 2007 and 2014 to Gazi University Hospital, Pediatric Pulmonology Department, Ankara, Turkey (a tertiary and referral hospital for TB), and received TB treatment. Drug-related side effects were retrospectively reviewed. Demographic data, distribution of involved organs, treatment protocol, treatment duration, treatment season, drug-related side effects, the timing and recurrence of side effects and the number of recurrences were recorded.

All patients initially received first-line anti-TB treatment that included a combination of three or four drugs for 2 months; isoniazid (INH) 10–15 mg/kg/d, rifampin (RIF) 10–15 mg/kg/d, PZA 30–40 mg/kg/d and ethambutol (EMB) 15–25 mg/kg/d. Thereafter, INH and RIF 10–15 mg/kg/d were continued for an additional 4–8 months, depending on the organs involved. Treatment was administered according to WHO and Turkish TB diagnosis and treatment guidelines [15, 16].

Basal levels of transaminases, bilirubin, blood urea nitrogen (BUN), creatinine and UA and complete blood count were measured in all the TB patients before the start of anti-TB treatment. Then, serum transaminases, bilirubin, BUN, UA and creatinine levels were measured twice a week during the first 2 weeks of treatment, weekly during weeks 3 and 4, twice a month during the second month of initial therapy and then every 2 months until no side effects were observed. All side effects related to the administered anti-TB drugs, such as skin rash, pruritus, nausea, constipation, optic neuritis, hepatotoxicity and hyperuricemia, were observed during the treatment. A side effect was defined as any adverse reaction that required specific treatment or led to the interruption or discontinuation of ≥ 1 of the drugs included in the standard therapy.

Hepatotoxicity was defined as an aspartate transaminases (AST) level and/or alanine transaminases (ALT) level exceeding the upper limit of normal by >3-fold in the presence of such symptoms as anorexia, nausea, vomiting and abdominal pain, an AST level and/or ALT level exceeding the upper limit of normal by >5-fold without accompanying symptoms and/or a total bilirubin level >2 mg/dl [17].

Treatment was interrupted or changed, if necessary, in patients that developed hepatotoxicity.

While receiving anti-TB treatment, a >7 mg/dl increase in the basal UA level was accepted as hyperuricemia, which is a well-known side effect of PZA in adults [9, 17]. Patients with treatment-related hyperuricemia were investigated for renal disease and concomitant use of loop-inhibiting diuretics. Oral rehydration was administered to patients with hyperuricemia. Allopurinol therapy was initiated when hyperuricemia persisted despite rehydration. Other types of side effects were recorded when observed.

Statistical analysis was performed using SPSS v.16.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as mean $\pm$ SD. The chi-square and Mann–Whitney U-test were used for data analysis. The level of statistical significance was set at $p < 0.05$.

RESULTS

The study included 23 TB patients that were treated as outpatients; mean age was 7.9 ± 4.66 years and 14 (60.9%) were male. Patient age, distribution of involved organs, treatment protocols, drug-related side effects, timing and recurrence of side effects and the number of recurrences are presented in the Table 1. In all, 13 (56%) patients had pulmonary involvement. During the initial treatment period, 17 patients received a combination of INH, RIF and PZA, whereas 6 received INH, RIF, PZA and EMB. Among the patients, nine received treatment during spring, eight during summer, and six during winter.

Downloaded from https://academic.oup.com/tropej/article/61/5/351/1647698 by Main Library of Gazi University user on 10 December 2020

Table 1. Patient age, distribution of involved organs, drug-related side effects, timing of side effects, recurrence of side effects and the number of recurrences

Age	Involved organs	Side effects[a]	Timing	Recurrence	Recurrences (*n*)
0.25	Miliary	UA↑ (7.8)	2nd week	Yes	3
1	Lymph node	Transaminase↑	1st week	Yes	2
1.5	Lung	Transaminase↑	11th week	No	
3	Lung	–			
4	Endobronchial	–			
5	Lung	UA↑ (8.8)	2nd week	Yes	2
5	Urinary	UA↑ (7.4)	1st week	Yes	3
5	Pericardium	UA↑ (8.1)	1st week	Yes	2
5	Lung	UA↑ (8.8)	2nd week	No	
7	Joint	–			
7	Pericardium	–			
8	Joint	UA↑ (9)	1st week	No	
8	Lung	UA↑ (8.9)	1st week	Yes	4
8	Lung	UA↑ (8.9)	5th week	No	
10	Urinary	UA↑ (8.7)	1st week	Yes	4
10	Lung	UA↑ (7.5)	4th week	No	
11	Lung	UA↑ (8.2)	4th week	Yes	6
12	Lung	–			
12	Lung	–			
14	Lymph node	–			
15	Lung	–			
15	Lung	–			
16	Lung	UA↑ (7.5)	2nd week	No	

[a]Maximum UA level (mg/dl).

Overall, drug-related side effects were observed in 14 (60%) patients. In all, two patients had elevated transaminases, which resolved following interruption of treatment; this condition recurred in one of these two patients and resolved following an additional interruption of treatment. Hyperuricemia was observed in 12 (52%) patients while receiving PZA treatment. All 12 of these patients were given allopurinol because they did not improve with rehydration. Mean time to the development of hyperuricemia was 2.1 ± 1.4 weeks. In eight patients, hyperuricemia occurred more than once; one of these patients had hyperuricemia six times and two had it four times during the first 2 months of treatment. Hyperuricemia resolved in a mean 1.1 ± 0.35 weeks following allopurinol therapy. After the second month of the treatment, when PZA was withdrawn, hyperuricemia was not observed.

All of the patients completed the treatment and did not require a change in treatment because of side effects. Patients with drug-related side effects were evaluated for concomitant liver, kidney and other diseases, but none were observed. There were not be any significant differences in age ($p > 0.005$), gender ($p = 0.89$), treatment season ($p = 0.6692$) or involved organs ($p = 0.418$) between the patients that did and did not develop hyperuricemia.

No other side effects were identified.

DISCUSSION

The present findings show that hyperuricemia is a common side effect in children treated for TB. As reported in adult TB patients, hyperuricemia was observed in 52% of the present study's patients that received PZA therapy. Similar adult series reported

Downloaded from https://academic.oup.com/tropej/article/61/5/351/1647698 by Main Library of Gazi University user on 10 December 2020

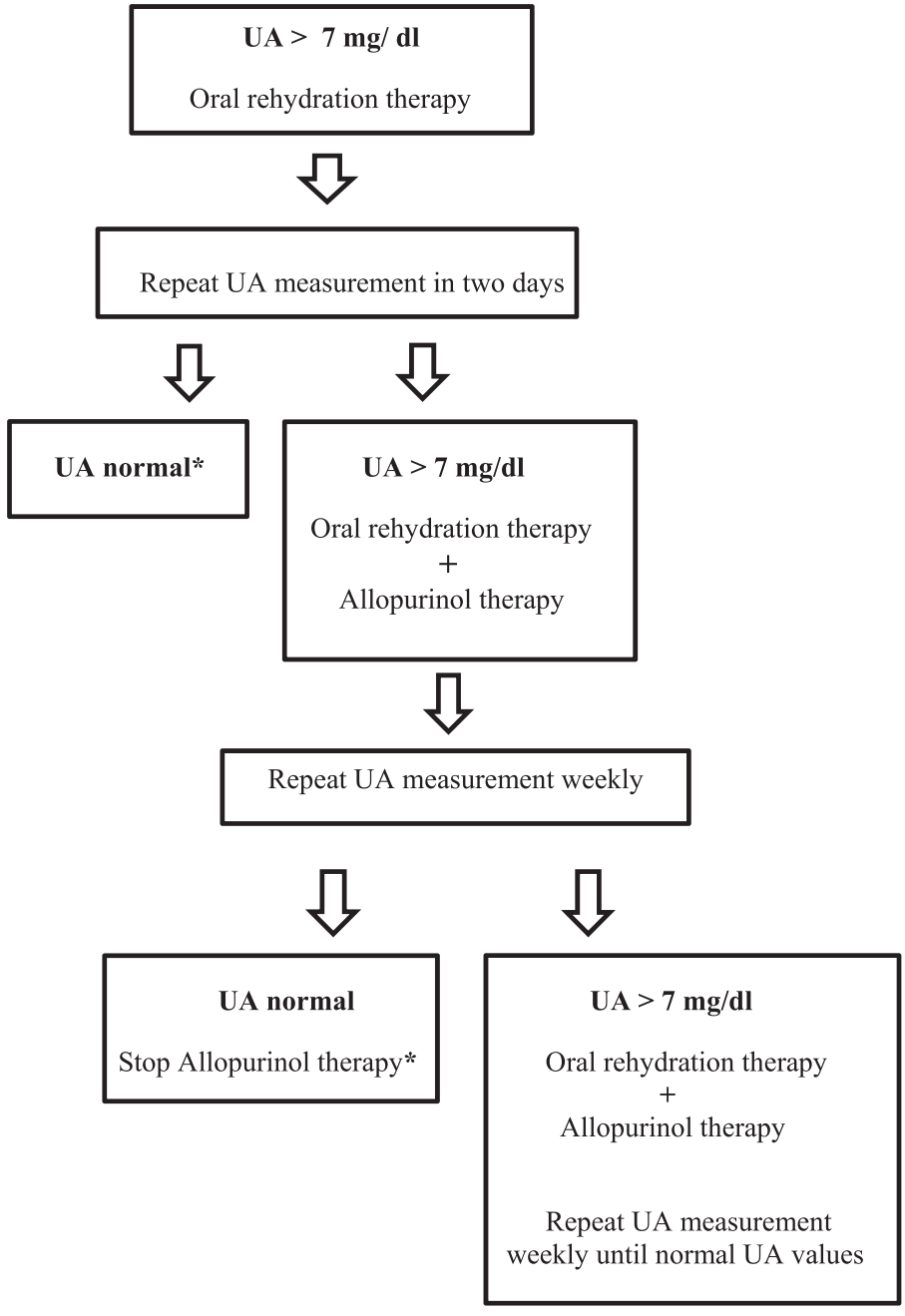


Fig. 1. Proposed algorithm for the management of hyperuricemia in pediatric TB patients treated with PZA. * Measure serum BUN, UA, and creatinine twice a week during the first 2 weeks of treatment, weekly during weeks 3 and 4, and twice a month during the second month of initial therapy, except when findings or symptoms related to side effects are not observed.

the occurrence of hyperuricemia in 40–47% of patients [4, 5]; in contrast, one adult study reported that the rate of hyperuricemia was 86% [6]. To the best of our knowledge, the present study is the first to report the rate of hyperuricemia in children treated for TB. Hepatotoxicity is the most frequent

Downloaded from https://academic.oup.com/tropej/article/61/5/351/1647698 by Main Library of Gazi University user on 10 December 2020

side effect of TB treatment, and the rate of hepatotoxicity in the present study was 8% (similar to earlier reports) and hyperuricemia was the most frequent side effect (52%).

Hyperuricemia plays an important role in the pathogenesis of numerous disorders, including acute kidney injury, chronic kidney disease, hypertension, gout, atherosclerosis, insulin resistance and metabolic syndrome [11, 18–21]. Furthermore, several recent observational studies reported that an elevated UA level was associated with an increased mortality rate [22–27], and that treatment of asymptomatic hyperuricemia with allopurinol prevented vascular events in adults [28]. Despite the lack of symptoms associated with hyperuricemia in patients, they were treated with PZA to avoid such complications.

Several algorithms exist for the management of hepatotoxicity, whereas there is no algorithm for the management of hyperuricemia. Based on the present findings, we propose an algorithm for the management of hyperuricemia in pediatric patients receiving PZA due to TB (Fig. 1). We recommend measurement of serum BUN, UA and creatinine twice a week during the first 2 weeks of treatment, weekly during weeks 3 and 4 and twice a month during the second month of initial therapy, except when findings or symptoms related to side effects are not observed.

In the present study, hyperuricemia improved rapidly with allopurinol therapy. During PZA therapy, hyperuricemia can occur more than once. Indeed, during the first 2 months of treatment, one of the present study's patients had hyperuricemia six times and two patients had it four times. None of these patients required interruption or cessation of PZA therapy. Furthermore, in the present study, there were not any correlations between hyperuricemia, and patient age, gender, treatment season or involved organs. In conclusion, we recommend measurement of UA during PZA therapy. Because of several systemic results, hyperuricemia should be closely monitored during PZA therapy in pediatric TB patients.

REFERENCES

1. Marais BJ. Tuberculosis in children. J Paediatr Child Health 2014;50:759–67.
2. Ohkawa K, Hashiguchi M, Ohno K, *et al*. Risk factors for antituberculous chemotherapy-induced hepatotoxicity in Japanese pediatric patients. Clin Pharmacol Ther 2002; 72:220–26.
3. Bhatia S, Tullu MS, Kannan S, *et al*. An unusual recurrence of antitubercular drug induced hepatotoxicity in a child. J Postgrad Med 2011;57:147–52.
4. Steele MA, Des Prez RM. The role of pyrazinamide in tuberculosis chemotherapy. Chest 1988;94:845–50.
5. Papastavros T, Dolovich LR, Holbrook A, *et al*. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. CMAJ 2002;167:131–6.
6. Inoue T, Ikeda N, Kurasawa T, *et al*. Hyperuricemia and arthralgia during pyrazinamide treatment. Nihon Kokyuki Gakkai Zasshi 1999;37:115–18.
7. Tsakalidis D, Pratsidou P, Hitoglou-Makedou A, *et al*. Intensive short course chemotherapy for treatment of Greek children with tuberculosis. Pediatr Infect Dis J 1992;11:1036–42.
8. Fenech G, Rajzbaum G, Mazighi M, *et al*. Serum uric acid and cardiovascular risk: State of the art and perspectives. Joint Bone Spine 2014; 81:392–7
9. Baldree LA, Stapleton. Uric acid metabolism in children. Pediatr Clin North Am 1990;37:391–418.
10. Gerdan V, Akkoc N, Ucan ES, *et al*. Paradoxical increase in uric acid level with allopurinol use in pyrazinamide-induced hyperuricaemia. Singapore Med J 2013;54: 125–6.
11. Fathallah-Shaykh SA, Cramer MT. Uric acid and the kidney. Pediatr Nephrol 2014; 29:999–1008.
12. Migliori GB, Raviglione MC, Schaberg T, *et al*. Tuberculosis management in Europe. Task Force of the European Respiratory Society (ERS), the World Health Organisation (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) Europe Region. Eur Respir J 1999;14:978–92.
13. Allopurinol: Pediatric drug information. http://www.uptodate.com/contents/allopurinol-pediatric-drug-information?source=search_result&search=allopurinol&selectedTitle=2~130 (29 April 2014, date last accessed).
14. Tuberculosis reports of Turkey 2013. Turkey Ministry of Health, Presidency of Public Health Institutions, 2014. http://tuberkuloz.thsk.saglik.gov.tr/Dosya/Dokumanlar/raporlar/turkiyede_verem_savasi_2013_raporu.pdf (10 April 2015, date last accessed).
15. World Health Organization. *Treatment of Tuberculosis: Guidelines for National Programmes*. World Health Organization, Geneva 2003. WHO/CDS/TB/2003.313.
16. Guideline for tuberculosis diagnosis and treatment, Turkey Ministry of Health. http://tuberkuloz.thsk.saglik.gov.tr/bilgi-dokumanlar/kitaplar/805-tuberkuloz-tani-ve-tedavi-rehberi.html(29 April 2015, date last accessed).

Downloaded from https://academic.oup.com/tropej/article/61/5/351/1647698 by Main Library of Gazi University user on 10 December 2020

17. Centers for Disease Control and Prevention. American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of tuberculosis. Morbidity Mortality Weekly Rep (MMWR) 2003;52:RR-111–77.
18. Zhu Y, Hu Y, Huang T, *et al*. High uric acid directly inhibits insulin signalling and induces insulin resistance. Biochem Biophys Res Commun 2014;447:707–14.
19. Li L, Yang C, Zhao Y, *et al*. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease? A systematic review and meta-analysis based on observational cohort studies. BMC Nephrol 2014;15: 122–34.
20. Billiet L, Doaty S, Katz JD, *et al*. Review of hyperuricemia as new marker for metabolic syndrome. ISRN Rheumatol 2014;2014:852954. eCollection 2014.
21. Mastriani S, Stella A, Pontremoli R, *et al*. Serum uric acid and blood pressure in children at cardiovascular risk. Pediatrics 2013;132:93–9.
22. Kim SY, De Vera MA, Choi HK. Gout and mortality. Clin Exp Rheumatol 2008;26:115–9.
23. Tomita M, Mizuno S, Yamanaka H, *et al*. Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. J Epidemiol 2000;10: 403–9.
24. Niskanen LK, Laaksonen DE, Nyyssönen K, *et al*. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med 2004;164:1546–51.
25. Levine W, Dyer AR, Shekelle RB, *et al*. Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. J Clin Epidemiol 1989;42:257–67.
26. Freedman DS, Williamson DF, Gunter EW, *et al*. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Followup Study. Am J Epidemiol 1995;141:637–44.
27. Juraschek SP, Tunstall-Pedoe H, Woodward M. Serum uric acid and the risk of mortality during 23 years follow-up in the Scottish Heart Health Extended Cohort Study. Atherosclerosis 2014;233:623–9.
28. Akkineni R, Tapp S, Tosteson AN, *et al*. Treatment of asymptomatic hyperuricemia and prevention of vascular disease: a decision analytic approach. J Rheumatol 2014; 41:739–48.

Downloaded from https://academic.oup.com/tropej/article/61/5/351/1647698 by Main Library of Gazi University user on 10 December 2020