Original Article

EPIDEMIOLOGICAL SURVEY OF HYPERURICEMIA AS AN ADVERSE REACTION TO ANTITUBERCULOUS THERAPY WITH PYRAZINAMIDE

[1]Hisashi TAKI, [2]Kenji OGAWA, [3]Tatsuya MURAKAMI, and [3]Toshiaki NIKAI

Abstract [Purpose] Pyrazinamide is an antituberculous drug that is administered as a two-month course during treatment of pulmonary tuberculosis. Adverse reactions to pyrazinamide have been reported to include hyperuricemia. We performed a retrospective multicenter epidemiological survey to assess the relationship between various patient characteristics and the uric acid level, the changes of uric acid during pyrazinamide administration, and the use of medications for uric acid control as well as attacks of gout or arthralgia at the onset of hyperuricemia. A total of 226 patients who were admitted to four hospitals with pulmonary tuberculosis between January and December 2006 and received short-term intensive pyrazinamide therapy were studied. [Results] There were 172 men and 54 women with an average age of 59.5 years and an average body mass index of 19.8 kg/m^2. The average serum uric acid concentration before pyrazinamide treatment was 4.73±1.78 mg/dl, while the average uric acid level after pyrazinamide treatment was 10.63±2.67 mg/dl, which was significantly higher than the pretreatment level ($p<0.0001$). During treatment, hyperuricemia (Serum uric acid ≧8 mg/dl) was reported in 84.5% of patients and arthralgia developed in 4.42%. Although the therapy instituted in 51 patients (22.57%) had to be interrupted or discontinued due to liver dysfunction and skin rashes, which were probably caused by isoniazid and rifampicin, no patient ceased taking pyrazinamide due to an increase of uric acid. Drugs for uric acid control were administered to 21 patients (9.29%). Pyrazinamide is an important agent for intensive short-term antituberculous therapy. Hyperuricemia due to this drug can be managed by observation and does not require interruption of administration.

Key words: Pyrazinamide, Pulmonary tuberculosis, Hyperuricemia, Short-term intensive therapy, Gout

Introduction

When the recommendations for management of tuberculosis were revised in April 1996, pyrazinamide (PZA) was adopted for intensive short-term therapy as part of the initial standard treatment for pulmonary tuberculosis [i.e., 2 months of isoniazid (INH) + rifampicin (RFP) + PZA + streptomycin (SM) or ethambutol (EB) /4 months of INH+RFP+SM (or EB)].[1] Various studies were performed before PZA was adopted as part of standard antituberculous therapy in Japan. PZA was discovered in the 1950s, and initially attracted attention for its antituberculous activity in Europe and the U.S.A. The U.S. Centers for Disease Control (CDC) performed a study of combined therapy with PZA plus INH and RFP in 1986[2], and the World Health Organization (WHO) recommended PZA as a standard drug in 1991[3] In Japan, approval of PZA was delayed compared with Europe and the U.S.A. due to adverse reactions such as serious liver dysfunction. With the revision of medical care standards in April 1996, antituberculous therapy was reviewed, and 6-month therapy with 2-month INH+RFP+PZA+SM (or EB) /4-month INH+RFP+SM (or EB) was recommended, in which PZA is concomitantly administered for the first 2 months, and was approved. The therapeutic strategy for tuberculosis has involved seeking shorter and more powerful regimens, but it is necessary to also pay attention to the adverse reactions caused by antituberculous drugs while taking into account their other properties.

[1]Pharmacy Department, [2]Department of Pulmonary Medicine, National Hospital Organization (NHO) Higashi Nagoya National Hospital, [3]Department of Microbiology, Pharmacy Faculty, Meijo University
[1]独立行政法人国立病院機構東名古屋病院薬剤科, [2]同呼吸器科, [3]名城大学薬学部微生物学研究室

Correspondence to: Hisashi Taki, NHO Higashi Nagoya National Hospital, 5-101, Umemorizaka, Meito-ku, Nagoya-shi, Aichi 465-8620 Japan. (E-mail: takih@toumei.hosp.go.jp)
連絡先：滝　久司, 独立行政法人国立病院機構東名古屋病院臨床研究部/薬剤科, 〒465-8620 愛知県名古屋市名東区梅森坂5-101

(Received 7 Feb. 2008/Accepted 24 Mar. 2008)

Among the major adverse reactions caused by PZA, we focused on hyperuricemia associated with a 2-month course of PZA therapy as reported by Inoue et al.[4], and performed a retrospective epidemiological survey of patients receiving PZA for the initial 2 months of a 6-month course of intensive therapy.

Subjects and Methods

(1) Subjects

Three hundred and thirty-four patients who were admitted to four national hospitals (Higashi Nagoya National Hospital, Mie Chuo Medical Center, Toyama National Hospital, and Tenryu National Hospital) for treatment of pulmonary tuberculosis between January and December 2006 and received PZA for the initial 2 months of short-term intensive therapy were studied. A total of 108 patients (60 without data on serum uric acid levels before and after PZA administration and 48 with insufficient other data) were excluded, so eventually 226 patients were included in the survey.

The Ethical Review Boards of each institution approved this study.

(2) Methods

The following data were obtained on the 226 patients participating in this study: age, sex, height, body weight, BMI, serum creatinine level, alcohol intake, past history of gout, daily dose of PZA, serum uric acid level before PZA therapy (baseline uric acid level), maximum serum uric acid level during PZA therapy (peak uric acid level), interruption of PZA at the onset of hyperuricemia, use of uricosuric agents (benzbromarone) and uric acid inhibitors (allopurinol), attacks of gout or arthralgia, and use of concomitant drugs that could influence the uric acid level. For convenience sake, we defined hyperuricemia as a serum uric acid level greater than 8 mg/dl[4]. Statistical analysis was performed by using the paired t-test and Welch's t-test as appropriate.

Results

(1) Patient characteristics

There were 143 patients from NHO Higashi Nagoya National Hospital, 24 from NHO Mie Chuo Medical Center, 5 from NHO Toyama National Hospital, and 54 from NHO Tenryu National Hospital. Table shows the mean age, sex, height, body weight, BMI, serum creatinine, daily dose of PZA, baseline uric acid level, peak uric acid level, alcohol intake, history of gout, incidence of arthralgia, medications for hyperuricemia, interruption of PZA therapy, and use of concomitant drugs at each institution, as well as the overall mean values.

(2) Daily dose of PZA

The average daily dose (mean±SD) of PZA was 1.20±0.17 g (23.30±3.77 mg/kg) at NHO Higashi Nagoya National Hospital, 1.25±0.20 g (24.00±4.53 mg/kg) at NHO Mie Chuo Medical Center, 0.76±0.15 g (24.27±0.76 mg/kg) at NHO Toyama National Hospital, and 1.10±0.14 g (15.11±2.94 mg/kg) at NHO Tenryu National Hospital. The overall average dose was 1.18±0.19 g (23.33±4.34 mg/kg).

(3) Baseline and peak serum uric acid levels

The baseline serum uric acid level on admission before PZA administration was 4.73±1.78 mg/dl (mean±SD) and the peak uric acid level during PZA administration was 10.63±2.67 mg/dl, which was significantly higher than the baseline level ($p<0.0001$) as shown in Fig. 1. The daily dose of PZA is shown in relation to the peak uric acid level in Fig. 2, while the average daily dose per kilogram of body weight and peak

Table Clinical characteristics of the patients at each institution

	Higashi Nagoya	Mie Chuo	Toyama	Tenryu	All
	n=143	n=24	n=5	n=54	n=226
Age (years)	55.4±16.4	58.6±15.8	63.0±21.2	70.3±19.7	59.5±18.4
Sex					
Male	114	20	3	35	172
Female	29	4	2	19	54
Height (cm)	163.7	164.2	163.6	157.2	162.2
Body weight (kg)	53.2±10.9	53.6±11.3	51.6±11.9	47.9±13.1	52.0±11.7
BMI (kg/m^2)	19.7±2.95	19.8±3.20	19.3±4.22	19.4±4.40	19.8±3.39
Cr (mg/dl)	0.68	0.75	0.63	0.71	0.69
Dose of PZA (g) (mean±SD)	1.20±0.17	1.25±0.20	0.76±0.15	1.10±0.14	1.18±0.19
Serum uric acid before PZA treatment (mg/dl) (mean±SD)	4.69±1.73	5.72±2.16	4.66±2.01	4.42±1.55	4.73±1.78
Serum uric acid after PZA treatment (mg/dl) (mean±SD)	10.32±2.37	12.35±2.23	8.68±2.25	10.85±3.20	10.63±2.67
Daily alcohol drinker (%)	41.96	29.17	20.00	25.93	36.28
Medical history of gout (%)	2.80	4.17	0.00	0.00	2.21
Arthralgia (%)	2.10	4.17	0.00	11.11	4.42
Anti-hyperuricemic drug (%)	6.99	33.33	0.00	5.56	9.29
Stopping PZA (%)	20.28	20.28	20.00	29.63	22.57
Combined medicine (%)	4.20	8.33	0.00	18.52	7.96

uric acid level are plotted in Fig. 3.

(4) Incidence of hyperuricemia

The serum uric acid level increased in all of the patients after the start of treatment with PZA and the incidence of hyperuricemia was 84.51%.

As shown in Fig. 4, hyperuricemia occured at a similar incidence in men and women; however, the serum uric acid level was higher in men than in women.

The incidence of hyperuricemia among patients with a history of alcohol intake and a history of gout was 90.24% and 100%, respectively. The average baseline serum uric acid level was 5.59±1.59 mg/dl in patients with a BMI ≧25 (n=16), which was about 1.19 times higher than that of the 199 patients who had a BMI <25 (4.65±1.72 mg/dl).

Likewise, the peak serum uric acid level of patients those with a BMI ≧25 was 11.89±1.70 mg/dl, which was about 1.13 times higher than that of patients with a BMI <25 (10.45 ±2.59 mg/dl). The incidence of hyperuricemia was 100% among patients who had a BMI ≧25.

Fig. 5 shows the BMI in relation to the peak serum uric acid level.

(5) Events at the onset of hyperuricemia

At the onset of hyperuricemia, uricosuric agents and uric acid inhibitors were administered to 21 patients (9.29%), and arthralgia was reported by 10 patients (4.42%).

(6) Interruption of PZA therapy due to adverse reactions

PZA administration was interrupted due to adverse reactions in 51 patients (22.57%). The most common reason for interruption of PZA administration were liver dysfunction and skin rashes in 17 cases each, followed by dysphagia in 4 cases, aggravation of systemic symptoms and pyrexia in 2 cases each, and gastrointestinal disorder, arthralgia, petechiase, thrombocytopenia, aggravation of cardiac insufficiency, and death in 1 case each. The reason was unknown in 3 cases. There were no cases of interruption due to an increase of uric acid as an adverse reaction.

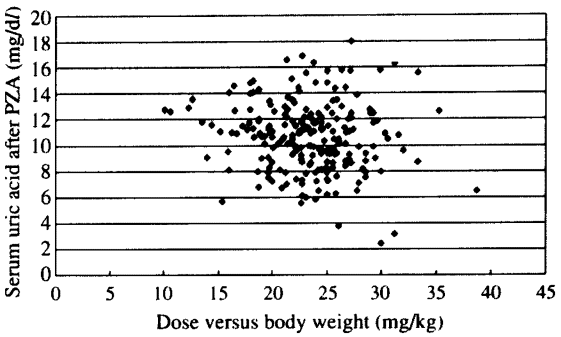

Fig. 3 Average PZA dose (mg/kg) versus the peak serum uric acid level

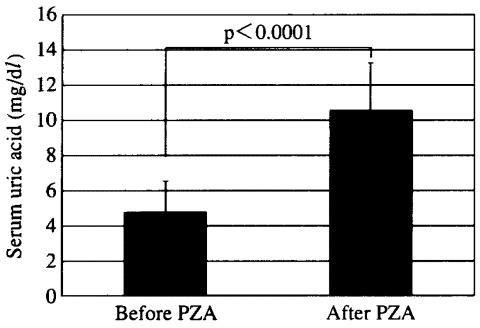

Fig. 1 Serum uric acid level before PZA administration and the peak level during administration

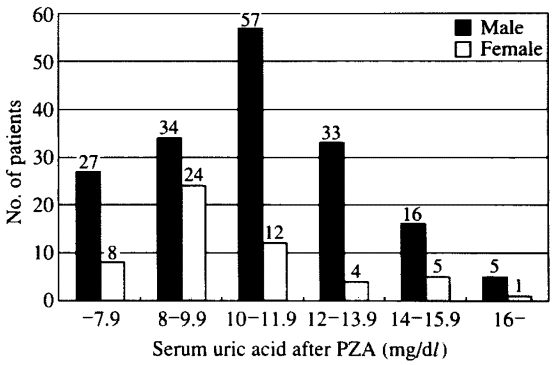

Fig. 4 Peak serum uric acid level in each sex

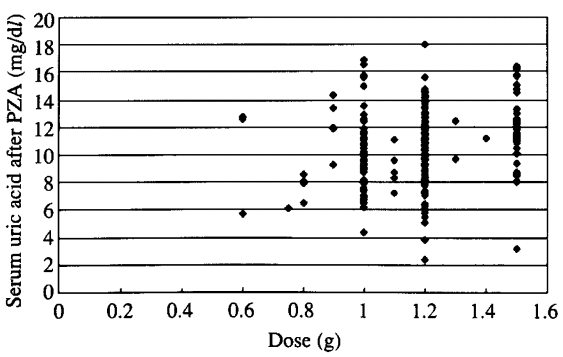

Fig. 2 Serum uric acid level versus the daily dose PZA

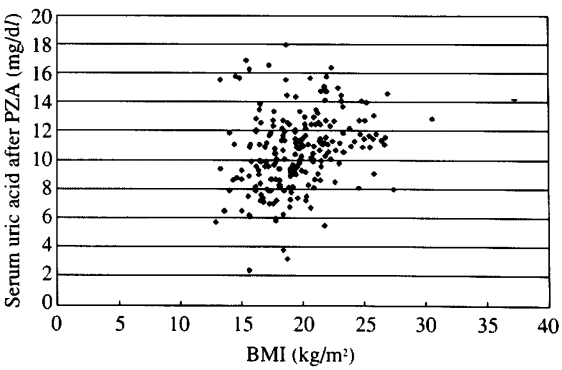

Fig. 5 BMI and the peak serum uric acid level

(7) Concomitant drugs influencing the uric acid level

The baseline serum uric acid level of 18 patients who concomitantly used trichlormethiazide, furosemide, torasemide, and theophylline (drugs with a potential influence on the serum uric acid level) was 5.36±1.98 mg/dl, which was slightly higher than the level of 4.68±1.76 mg/dl in 208 patients not taking any of the above-mentioned drugs. Similarly, the peak serum uric acid level was 12.09±3.24 mg/dl in the group using the above drugs, which was also slightly higher than the level of 10.50±2.58 mg/dl in the group without such concomitant drugs.

Discussion

Despite various attempts to make therapy shorter and more potent, the treatment of tuberculosis usually requires 6 months or longer, and it is necessary to undertake it while constantly paying attention to adverse reactions caused by antituberculous drugs. Among the major adverse reactions to PZA, we focused on hyperuricemia[4], which has been reported during a 2-month course of this drug. We conducted a retrospective epidemiological survey to assess the relationship between patient characteristics (including the dose of PZA used for short-term intensive treatment of pulmonary tuberculosis) and the serum uric acid level. As a result, we found that the daily dose of PZA was 1.18 g (22.59 mg/kg), which was slightly lower than the range of 1.5-2.0 g described in the package insert and the dose of 25 (20-30) mg/kg recommended by the WHO[5] This may be attributable to the fact that the average age of our subjects was as high as 59.5 years. Hyperuricemia is a major adverse reaction to PZA that is considered to occur because a major metabolite of PZA (pyrazinoic acid) suppresses uric acid secretion into the renal tubules and thus inhibits uric acid excretion, resulting in decreased uric acid clearance[6]. Hyperuricemia has been reported at a high incidence of 50-90% among adverse reactions to PZA[7][8], and occurred in 84.51% of patients (defined as 8 mg/dl or higher) in this study, suggesting that a very high incidence of hyperuricemia is caused by PZA administration. As for the normal value of serum uric acid used in this hospital, male is 3.6-7.0 mg/dl and female is 2.3-7.0 mg/dl. When the peak serum uric acid level was compared between men and women (Fig. 4), the most common peak range was 10-11.9 and 8-9.9 mg/dl for men and women, respectively, indicating that the serum uric acid level tended to be higher in men during PZA administration. With regard to the relationship between BMI and the uric acid level, the baseline and peak serum uric acid levels of obese patients with (BMI $\geqq$25 kg/m^2) were respectively 1.19 and 1.13 times higher than those of non-obese patients (BMI $<$25 kg/m^2). Notably, the incidence of hyperuricemia was 100% among patients with a BMI $\geqq$25 kg/m^2, so hyperuricemia occurred at an extremely high incidence in obese patients although there was no direct correlation between BMI and the peak serum uric acid level. At the onset of hyperuricemia, treatment to control the uric acid level was being given to 21 patients (9%). This percentage was far lower than that reported by Inoue et al. in 1999[4], who stated that hyperuricemia was treated in 12 out of 51 patients (24%). This is possibly because physicians involved in this study decided not to use such drugs for the following reasons: 1) concern about potential liver dysfunction based on a report of fulminant hepatitis due to benzbromarone, a uricusuric, in 2000, and 2) the risk of causing acute gout. When hyperuricemic patients, who have not suffered from gout for a long time, start treatment to control the serum uric acid level, the increase in the uric acid pool resulting from a decrease of uric acid in the synovial fluid is considered to cause the release of monosodium urate dehydrate (MSU) crystals deposited in the cartilage and synovial lining of joints[7], thus inducing acute attacks of gout. Also, it has been reported that acute gout rarely occurs in hyperuricemic patients on PZA therapy[8][9]. In the present survey, arthralgia was reported by 4.42% of the patients, but no attacks of gout occurred. Because PZA therapy is completed after a short period, it is generally considered that the increase of uric acid can be managed by observation without specific drug therapy. INH and RFP are most likely to cause liver dysfunction and skin rashes, so PZA was judged to have no role in the interruption of treatment by such reactions. The uric acid level was slightly increased by the use of concomitant drugs that could influence uric acid, but the effect was not statistically significant ($p=0.1353$). This suggested that such drugs can be continued until the completion of PZA therapy.

PZA is an important component of short-term intensive therapy, and interruption of administration results in a decrease of efficacy that may require extension of the treatment period. This survey showed that PZA administration was interrupted in 22.57% of patients, mainly due to liver dysfunction and skin rashes, and no cases of interruption attributable to hyperuricemia were reported. In addition, in a previous report, we pointed out that gout and arthralgia due to hyperuricemia occurring at a high rate by PZA administration were the problems[8]

Furthermore, it has been commented that allopurinol and probenecid were effective, though it was assumed that serum urate concentration returned to normal value immediately after stopping dosage of PZA[10]. However, although hyperuricemia was developed by PZA in our study, it was considered to be an adverse reaction that can be followed up. Thus, hyperuricemia is a very common, adverse reaction due to PZA that can be managed by simple observation.

Acknowledgments

The authors wish to thank the following institutions and responsible person for cooperating with Tokai Hokuriku National Hospital Pharmacist Association Survey. NHO Higashi Nagoya National Hospital (Hiromu Funaki and Chiharu Horibe), NHO Mie Chuo Medical Center (Hiroki Mase and Takeshi Noro), NHO Tenryu National Hospital

(Sanji Sato and Kiyosei Noaki), and NHO Toyama National Hospital (Katsunori Tabuchi).

References

1) Wada M: Pyrazinamide-containing initial intensive short course chemotherapy of pulmonary tuberculosis. Kekkaku. 1997 ; 72 : 587-595.
2) American Thoracic Society/Centers for Disease Control: Treatment of tuberculosis and tuberculosis infection in adults and children. Am Rev Respir Dis. 1986 ; 134 : 355-363.
3) WHO: Guidelines for tuberculosis treatment in adults and children in National Tuberculosis Programme. WHO/TUB. 1991 ; 91 : 161.
4) Inoue T, Ikeda N, Kurasawa T, et al.: Hyperuricemia and arthralgia during pyrazinamide treatment. Nihon Kokyuki Gakkai Zasshi. 1999 ; 37 : 115-118.
5) American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med. 2003 ; 167 : 603-662.
6) Higashino K, Moriwaki Y: Pharmacological agents affecting uric acid metabolism. Nippon Rinsho. 1996 ; 54 : 3364-3368.
7) Ishiguro S: Arthralgia and uricemia produced by Pyrazinamide. Kekkaku. 1982 ; 57 : 483-490.
8) The Japanese Society for Tuberculosis treatment committee: First-time standard setting for therapy of pulmonary tuberculosis after revision of the Medical Treatment Standard—special reference to results of questionnaire survey on reality of early stage short-term PZA therapy and occurrence of the adverse effects. Kekkaku. 1997 ; 72 : 639-642.
9) Terkeltaub RA: Arthritis and Allied Conditions (12th ed.). Lea & Febiger, Philadelphia. 1993, 1819-1833.
10) Ono H, Kouno S: Antituberculous side effect and measures. Rinshou and Kenkyu. 1998 ; 75 : 778-782.

肺結核短期強化療法に用いるPyrazinamideの副作用である高尿酸血症の疫学調査

[1]滝　久司, [2]小川　賢二, [3]村上　達也, [3]二改　俊章

要旨：〔目的〕Pyrazinamide (PZA) は肺結核治療の短期強化療法のなかで初期2カ月間に投与される抗結核薬である。抗結核薬の副作用はさまざまであるが，このうちPZAが原因と考えられる高尿酸血症に注目し，その患者背景と尿酸値との関係，さらにPZA投与による尿酸値の変動，また高尿酸血症出現時の尿酸コントロール薬使用および痛風・関節痛症状の有無など多施設共同によるレトロスペクティブな疫学調査を実施した。〔方法〕2006年1月から2006年12月までの期間に肺結核として入院し，短期強化療法にPZAを投与した国立病院機構4施設226例を対象に検討を行った。〔結果と考察〕男172例，女54例，平均年齢59.5歳。平均BMI 19.8 kg/m^2。PZA投与前の血清尿酸値は平均4.73±1.78 mg/dl，PZA投与後の血清尿酸最高値の平均は10.63±2.67 mg/dlとなり両者には$p<0.0001$と統計学的有意差が認められた。またPZA投与による8 mg/dl以上の高尿酸血症は84.5%に見られたが関節痛は4.42%の出現であった。さらに投与中断または中止例は51例 (22.57%) に見られたが，その理由はIsoniazid (INH)，Rifampicin (RFP) が原因として起こる可能性が高い肝機能障害と発疹であり，尿酸値上昇によるPZA中断例は見られなかった。また，高尿酸血症に対する尿酸コントロール薬の使用例は21例 (9.29%) であった。〔結論〕短期強化療法においてPZAの投与は重要であり，その副作用として特有な高尿酸血症は出現しても経過観察は可能であり投与中断には至らないことが分かった。

キーワーズ：ピラジナミド，肺結核，高尿酸血症，短期強化療法，痛風