Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis

Research

Recherche

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Abstract

Background: The current Canadian and US guidelines for the treatment of multidrug-resistant latent tuberculosis infection advocate the use of pyrazinamide and a fluoroquinolone as a first-line treatment option. However, there is very little information in the literature that describes the use of these agents together. This case series describes the probable association between multiple adverse events and the use of pyrazinamide and levofloxacin in the treatment of individuals with suspected latent multidrug-resistant tuberculosis infection.

Methods: We studied a case series of 17 individuals with suspected latent multidrug-resistant tuberculosis infection in Hamilton, Ont., who were being treated with pyrazinamide and levofloxacin. The Naranjo scale was used to assess patients for musculoskeletal, central nervous system, gastrointestinal and dermatological adverse events. Hepatocellular events were assessed and defined using criteria established by the Council for International Organizations of Medical Sciences. Laboratory abnormalities and adverse events that were documented during combination drug therapy were evaluated to determine the likelihood of an association.

Results: Fourteen individuals developed musculoskeletal adverse effects (11 were deemed to be probably related to combination therapy). There were 8 reports of central nervous system effects (5 of which were assessed as being probably associated with therapy). Hyperuricemia and gastrointestinal and dermatological effects were also common; the use of pyrazinamide and levofloxacin was believed to be probably responsible for the emergence of these adverse effects. There were 5 cases of hepatocellular injury. Therapy was discontinued in all individuals.

Interpretation: The combination of pyrazinamide and levofloxacin appears to be a poorly tolerated regimen. The mechanism of a possible interaction is not yet understood. Given the severity of some of the adverse events, a better understanding of dosing and clearer guidelines for monitoring therapy are imperative if these drugs are to be prescribed together.

Tuberculosis (TB) has re-emerged as a major health concern throughout the world. In 1997, the World Health Organization estimated that there were 7.96 million new cases of TB globally and that 1.87 million people had died of this illness.[1] Adding to the burden of this disease is the emergence of drug-resistant strains. Multidrug-resistant TB, which is defined as resistance of *Mycobacterium tuberculosis* to at least isoniazid and rifampin, has emerged as an increasing concern in Canada and around the world.[2] A 1998 Canadian national surveillance report on the susceptibility of TB to drug therapy revealed that 1.2% of the 1423 TB isolates tested were resistant to isoniazid and rifampin.[3] Alarmingly, the incidence of multidrug resistant cases had doubled since 1993/94.[2]

Patients with latent TB infection do not have evidence of active disease but have a 10% cumulative lifetime risk of developing active illness.[2] Furthermore, it is believed that in most immunocompetent individuals in industrialized countries, newly

diagnosed active disease is generally a result of latent disease reactivation. Effective and targeted treatment of the latent infection is, therefore, imperative to reduce the risk of dissemination of TB in the population.[4,5] Guidelines for the treatment of multidrug-resistant latent TB infection were recently published by the Canadian Thoracic Society and in a joint publication by the American Thoracic Society and the US Centers for Disease Control and Prevention.[2,4] Both these guidelines recommend a 2-drug regimen for those thought to be infected with multidrug-resistant TB, especially if there are risk factors for reactivation. A 6–12-month course of pyrazinamide plus either a fluoroquinolone or ethambutol is suggested for such individuals. These recommendations are supported by expert opinion but not by controlled trials. It should be recognized that evidence for the efficacy of the aforementioned drug combinations in the prevention of reactivation does not exist, whereas such evidence does exist for the use of isoniazid in the treatment of latent TB infection in drug-sensitive TB. Thus far, the only information available about the efficacy and safety of pyrazinamide and fluoroquinolone in multidrug-resistant latent TB infection is in the form of a decision analysis and 2 case series that reported the intolerance of patients to this drug combination.[6–8]

Recently, 2 patients with active multidrug-resistant pulmonary TB infection were identified in Hamilton, Ont. Drug susceptibility testing of sputum in both cases revealed the growth of *Mycobacterium tuberculosis* that was resistant to isoniazid, rifampin, ethambutol, streptomycin and ethionamide, but susceptible to pyrazinamide, ofloxacin, rifabutin, amikacin, capreomycin and clofazimine. The individual with the index case had immigrated to Canada 9 months before the time of diagnosis and probably had had active disease since his arrival. A household contact also developed active multidrug-resistant disease. Both cases were diagnosed in 2000. Following this, 1500 contacts were identified and screened. This case series describes the use of pyrazinamide and levofloxacin in the treatment of 17 contacts with suspected multidrug-resistant latent TB infection and includes an assessment of the probable association of multiple adverse events.

Table 1: Characteristics of patients prescribed pyrazinamide and levofloxacin (continued on facing page)

Patient	Lab abnormality (baseline→peak)	Adverse event	Comorbidity	Medication	Comments (onset)*
1	↑Uric acid (362→587) ↑ALT (42→49) ↑GGT (31→49)	Headache, joint pain, pruritis	Pyelonephritis		↑Uric acid 9 d ↑ALT 44 d Sx 3–15 d
2	ALT (48→ ↓41) ↑CK (180→354)				↑CK 22 d
3	↑Uric acid (273→588) ↑ALT (14→203)	LRQ pain, fatigue, loss of appetite and weight loss, headache, pain (stiff fingers), pruritis	Cholecystectomy, mitral valve prolapse, family history of gout and kidney stones		↑Uric acid 32 d ↑ALT 32 d Sx 33 d
4	↑GGT (23→52)	Pain in knees, pain/ tightness in lower back	Ovarian cyst, pregnancy (previous yr)		↑GGT 52 d Pain 21 d Pruritis 1 d
5	↑Uric acid (286→504)	Joint stiffness, fatigue, altered sense of smell	Chronic headache, LRQ abdominal/pelvic pain, constipation		↑Uric acid 26 d Joint stiffness 24 d Altered sense of smell 23 d
6	↑ALT (47→502) ↑GGT (NA→57) ↑CK (116→786)	Aching joints, fatigue, diarrhea	Appendectomy, tubal ligation		↑ALT 30 d ↑CK 58 d Sx 1–14 d
7	↑Uric acid (276→563) ↑ALT (35→68) ↑GGT (43→61)				↑Uric acid 29 d ↑ALT 29 d ↑GGT 53 d
8	Baseline NA, No lab abnormality	URQ pain and aching	Myocardial infarction, osteoarthritis, tingling fingertips, HTN, ↑lipids	Pravastatin, ASA, acebutolol	Sx 34 d
9	↑CK (145→181) ↑ALT (12→110)	Pain in joints (knees, toes, elbows), pruritis, nausea, dizziness/ vertigo, vaginal spotting	Basal cell cancer, occasional peripheral neuropathy in fingertips		↑CK 52 d ↑ALT 38 d

Table 1 continued

Patient	Lab abnormality (baseline→peak)	Adverse event	Comorbidity	Medication	Comments (onset)*
10	↑ALP (152→161)	Joint pain, diarrhea, lower back pain	Myocardial infarction, ↑lipids		Sx 14 d
11	No lab abnormality	"Hyper"† in morning, chest acne	Pruritis, back pain		Sx 11 d
12	↑CK (NA→413)	↑Appetite			↑CK 42 d
13	↑Uric acid (217→489) Bili (NA→31) GGT (NA→175)	Nausea, fatigue, headache, ↑ankle pain, RLQ pain, LLQ pain	Diabetes mellitus, asthma, osteoarthritis, hypertension	Glyburide, indapamide, estrogen, ASA, tetracycline prn	↑Uric acid 25 d GGT 32 d Bili 32 d Sx 24 d
14	↑Uric acid (NA→598) ↑ALT (NA→165)				↑Uric acid 39 d ↑ALT 39 d
15	↑Urate (249→416) (measured by other lab)	Aching joints	Hypertension	Enalapril	↑Urate 19 d Sx 6 d
16	ALT (71→↓49) ?↑AST (NA→48)	Joint pain, stiffness, ↓concentration, leg cramps, eye pain, photosensitivity, ↓appetite, nausea, dizziness	Diabetes mellitus, depressions, obesity, CO_2 retention	Nefazodone, metformin, glyburide, ranitidine, prochloperazine prn, Centrum	Sx 23 d
17	↑Uric acid (184→429) ↑ALT (12→89)	↓Appetite, nausea, loose stools, aching hip, weight loss		Acetaminophen prn	↑Uric acid 33 d ↑ALT 33 d Sx 30 d

Note: ALT = alanine transaminase, GGT = gamma-glutamyl-transferase, Sx = symptoms, CK = creatine kinase, LRQ = lower right quadrant, NA = not available, URQ = upper right quadrant, HTN = hypertension, ALP = alkaline phosphatase, bili = bilirubin, RLQ = right lower quadrant, LLQ = left lower quadrant, prn = as occasion requires, AST = aspartate aminotransferase.
*Onset refers to onset of symptoms however many days after the patient started taking the combined medication (e.g., patient no. 1 experienced an increased ALT on day 44 after starting the combined medication).
†Term used by patient to describe feeling overstimulated.

Methods

A local multidrug-resistant TB assessment team was formed; it was led by public health officials, a respirologist expert in TB and a physician who was also an infectious disease epidemiologist, and was advised by Health Canada. The assessment team undertook a contact identification and surveillance program. Seventeen individuals who had a postexposure tuberculin skin test reaction that was greater than or equal to 5 mm and definite contact with at least one of the 2 cases were stratified according to their conversion status. Guidelines for the classification of tuberculin skin test reactions in relation to contact tracing were formulated in consultation with Health Canada. Because baseline tuberculin skin test reaction results were either not available or were more than 3 years old for all but 2 of the 17 individuals, it was necessary to consider other variables such as risk factors for earlier TB infection. Nine of the 17 individuals concerned were foreign born, and 11 were heath care workers; thus, previous infection was possible for many of them. Of the 17 cases, one was classified as a probable converter, 4 as possible converters and 12 as infected, with converter status as likely to be from recent contact as not. Exposure assessment was also critical in determining the likelihood of infection. A detailed exposure history was taken for all contacts. The infectiousness of the cases was also considered. The individual with the index case had multiple pulmonary cavities, a positive sputum smear showing many acid-fast bacilli and a harsh cough. The secondary case did not have cavities, but her sputum smear was positive. The decision to treat the 17 individuals with pyrazinamide and levofloxacin was made several months before guidelines for tuberculin skin test conversion (whereby an individual has an induration of 10 mm or more and an earlier test resulted in an induration of less than 5 mm)[2] and exposure definitions were adapted for use in this outbreak.

The median age of the contacts was 36 (range 18–58) years and 8 (47%) were female. No contacts had a history of substance abuse or dependence, and hepatitis B, C and HIV screens were negative in all patients. A baseline assessment was performed, including a complete blood cell count and uric acid, renal and liver function testing. Therapy for latent TB infection with pyrazinamide (15–17 mg/kg per day) and levofloxacin (500–750 mg/d) was based on body size and weight, as recommended in the published guidelines. This regimen was initiated in every individual between Nov. 13, 2000, and Dec. 13, 2000.

By Dec. 19, 2000, 7 patients had developed arthralgias and joint stiffness. Eight had abdominal pain or fatigue. At this point, the Division of Clinical Pharmacology was consulted and began an adverse medication events assessment (including both clinical evaluation and laboratory testing).

The Naranjo scale, a scale for measuring the probability of an adverse drug reaction, was then employed to subjectively assess the likelihood that the observed events were a result of the prescribed regimen. The Naranjo criteria, which have been validated for the assessment of drug-induced adverse events, consider the onset, course of reaction, and possible disease and drug alternatives.[9]

Results

The results of the clinical evaluation and laboratory testing are summarized in Tables 1 and 2. In summary, 14 of 17 individuals experienced at least one of a constellation of adverse hepatocellular, musculoskeletal, central nervous system, gastrointestinal and dermatological events. Fifteen individuals had elevated values for liver enzymes, uric acid or creatinine kinase. Because of the high frequency of adverse events (all patients experienced at least one abnormal symptom or sign), both drugs were discontinued in all patients (Tables 1 and 2). The median length of therapy was 32 (range 20–39) days.

Using the Naranjo scale, it was concluded that 11 of the 14 cases of musculoskeletal adverse effects were probably induced by the regimen prescribed. The remaining 3 cases were rated as possibly being a result of drug therapy. The drug regimen was believed to be probably responsible for 5 of 8 cases of central nervous system effects, and possibly responsible in 3 of 8 cases reported. The combination of pyrazinamide and levofloxacin was believed to be probably responsible for all reported gastrointestinal and dermatological manifestations.

Mild hyperuricemia occurred in 8 individuals. Although one individual was taking indapamide when prescribed her course of therapy for latent TB infection, her dose had been stable throughout the treatment period and, therefore, was not believed to have contributed to the elevation in uric acid levels. Five patients' uric acid levels returned to normal after the cessation of therapy. Follow-up results were unavailable for the remaining 3 patients.

Criteria established by the Council for International Organizations of Medical Sciences (CIOMS) were used both to assess the likelihood of drug-induced adverse hepatic events and to specifically define these events.[10] Five individuals with liver enzyme abnormalities experienced a rise in their liver enzymes that was greater than twice the upper limit of normal and were accordingly classified as having hepatocellular injury (alanine transaminase [ALT] 80–502 U). Baseline ALT values were unavailable for one of the 5 patients. However, the combination of pyrazinamide and levofloxacin was still considered to be responsible for her abnormal liver enzymes. This individual's initial ALT value was 47 U/L, climbed steadily while she was on the medication and peaked at 502 U/L 15 days after the medication was discontinued. The patient's ALT value returned to baseline 34 days after the medication was discontinued. A continued rise in ALT after discontinuation of medication occurred in one other individual whose ALT rose from 12 U/L and peaked at 89 U/L 15 days after the medication had been stopped. The ALT eventually declined in 4 of 5 patients with hepatocellular injuries. Follow-up values were not available for the fifth patient. Three other individuals only had mild elevations of their ALT that were not deemed clinically important. No new drug therapy, dose, toxin or concurrent illness could otherwise account for the observed abnormalities in transaminases.

Drug therapy was discontinued in all these individuals. Due to drug resistance, no other drug regimens were available for treatment.

Interpretation

The regimen of pyrazinamide combined with levofloxacin appears to be associated with adverse events in patients with latent multidrug-resistant TB infection. These findings have important clinical implications.[2,4] Two other reports have described poor tolerance to the combination of ofloxacin (a racemic compound that in vivo is converted to its L-enantiomer, levofloxacin)[11] and

Table 2: Adverse event profiles of patients taking pyrazinamide and levofloxacin

Nature of adverse event	Signs and symptoms	No. of patients	Onset, d*
Musculoskeletal	Joint pain or muscle stiffness	4	6–58
	Joint pain or muscle stiffness + elevated uric acid	6	
	Joint pain or muscle stiffness + elevated CK	2	
	Elevated CK	2	
Central nervous system	Dizziness, vertigo, headache, fatigue, difficulties concentrating, hyperactivity	8	11–33
Gastrointestinal	Nausea, weight loss, changes in appetite, diarrhea, other	9	1–34
Dermatological	Pruritis, photosensitivity, acne	5	1–34
Hyperuricemia	Uric acid and urate levels greater than the upper limit of normal	8	9–39
Elevated liver enzymes	ALT or ALP or AST or bilirubin (total)	8	29–44

*Onset, d refers to onset of signs and symptoms however many days after the patient started taking the combined medication.

pyrazinamide.[7,8] Discontinuation rates were high in both series, in which about 60% and 87% of patients respectively were unable to finish the full course of therapy. Similar to our findings, the effects described comprised musculoskeletal, gastrointestinal, dermatological and hepatocellular adverse events.

Levofloxacin is bactericidal, and peak concentrations of the drug must reach high levels to ensure optimal bactericidal activity.[12] It is generally considered to be one of the better tolerated fluoroquinolones;[13] the incidence of adverse effects deemed related to its use is estimated to be 6%.[14] Gastrointestinal intolerance (e.g., nausea, diarrhea) is the most frequently reported side effect, with an incidence of up to 5.1%.[13] Adverse events including those that affect the central nervous system, skin and musculoskeletal systems, as well as elevated liver enzymes, all occurred in less that 2% of patients prescribed levofloxacin during clinical trials.[12–14] The incidence of adverse effects observed in our patients (100%) greatly exceeded that expected. This high incidence could not be accounted for by any other disease process or change in concurrent drug therapy. Furthermore, the resolution of adverse effects that corresponded with the cessation of therapy further supports the belief that these occurrences were drug induced.

Pyrazinamide's antibacterial activity is limited to *M. tuberculosis* and is dependent on its conversion to the active metabolite, pyrazinoic acid, by the bacterial enzyme, pyrazinamidase.[14] Two of the most problematic adverse effects associated with its use include hepatotoxicity and polyarthralgia. Hepatotoxicity has traditionally been the most commonly reported adverse effect. It is believed to be dose related and is usually a result of direct liver toxicity. Previously, when doses greater than 3 g per day were prescribed, elevations in liver enzymes and symptomatic hepatitis occurred in about 15% of patients.[14,15] Current regimens employ doses of 15–30 mg/kg per day. Although the incidence of liver injury with this dosage range is unclear, severe toxic hepatitis has been reported with the lower doses.[16,17] It is believed that higher doses and prolonged duration of use may increase the risk of liver toxicity. The onset of the most severe hepatotoxic cases usually occurs after the first month of therapy. We observed both mild and clinically important hepatocellular injury in 47% of our patients, far above the expected rate of pyrazinamide hepatotoxicity. No new drug therapy or dose was initiated in any patients that could otherwise account for the observed abnormalities in transaminases. Elevations of liver enzymes in our patients generally occurred after one month of treatment had elapsed; this is consistent with pyrazinamide-induced hepatotoxicity.[14,15] The pyrazinamide doses prescribed were relatively low (15–17 mg/kg per day); however, a pharmacokinetic interaction between pyrazinamide and levofloxacin may have potentially existed and elevated the levels of both drugs. Higher serum drug levels could then be responsible for the increased incidence of adverse events.

Because pyrazinamide inhibits the tubular secretion of uric acid, hyperuricemia and attendant polyarthralgias occur in up to 40% of patients.[18] We observed elevated uric acid levels in 47% of our patients. The onset and course of the abnormal laboratory values were consistent with pyrazinamide-induced hyperuricemia; however, gouty arthritis did not occur in any of our patients.

No studies have been published that investigate a possible interaction between pyrazinamide and levofloxacin. However, the renal clearance of both these agents exceeds the rate of renal filtration.[12,19] This indicates that tubular secretion plays a prominent role in the excretion of both medications. It is plausible that both drugs may compete for the same transport mechanism. Eventual saturation of this mechanism would inhibit the excretion of both drugs. The resultant higher drug serum levels could then lead to an increased incidence of drug toxicity. Alternatively, inhibition of an enzyme such as xanthine oxidase, which is involved in the metabolism of pyrazinamide, could also contribute to the high incidence of side effects. This would appear to be the less likely phenomenon. Unfortunately, there were no assays available commercially to readily test this hypothesis when our patients were manifesting the adverse effects.

Despite the fact that documented evidence exists for such adverse effects[7,8] and that the onset and course of the events documented here clearly support a drug-induced origin, we can only conclude that the drug combination of levofloxacin and pyrazinamide was *probably* responsible for the effects that manifested in the majority of the patients. A definite conclusion supporting cause and effect was precluded because this would have entailed a rechallenge,[9,10] in which the medications could have been administered separately and then concurrently to healthy controls, documenting the nature and incidence of adverse events with each course. A comparison between the adverse events that occurred when each drug was given separately versus concurrently would have shed some light on the likelihood that a drug interaction was responsible for the elevated incidence of adverse events that we observed in our patients. However, given the inflated incidence and potentially serious consequences of some of these adverse effects, the risks of a rechallenge would have outweighed the benefits. The feasibility of such a trial is also questionable given the urgency of the situation and the ethical issues surrounding such a design.

This case series clearly illustrates a need for further work on effective and safe regimens with which to treat multidrug-resistant TB. Basic pharmacological research is needed to shed light on the mechanisms of any interaction, so that therapy can be prescribed in doses that will render effective drug levels, yet minimize toxicity. Clinical trials of drug therapy for multidrug-resistant latent TB infection are also needed. Clinicians should be selective in offering potentially toxic prophylactic drug regimens of unproven efficacy only to individuals at high risk of reactivating their multidrug-resistant TB. In the meantime, clearer guidelines for the monitoring of liver, uric acid and musculoskeletal parameters in patients prescribed pyrazinamide

and a fluoroquinolone are required. Current Canadian and US guidelines do not advocate regular follow-up liver function tests in all patients prescribed this drug regimen. Considering the high incidence of adverse events that can occur, physicians need to exercise extreme caution when prescribing pyrazinamide and levofloxacin together.

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