Review paper

Treatment of cutaneous infections caused by *Mycobacterium tuberculosis*

Nina Wyrzykowska[1], Michał Wyrzykowski[2], Ryszard Żaba[1], Wojciech Silny[1]

[1]Department of Dermatology, Poznan University of Medical Sciences, Poland
Head: Prof. Wojciech Silny MD, PhD
[2]Dermatology Student Scientific Association, Poznan University of Medical Sciences, Poland
Head: Agnieszka Osmola-Mańkowska MD, PhD

Postep Derm Alergol 2012; XXIX, 4: 293-298
DOI: 10.5114/pdia.2012.30470

Abstract

Tuberculosis is still a very common global problem and it is responsible for more than 4,500 deaths every day. The risk of tubercular infection has been estimated to vary from 1% to 2% in developing countries. In the last years, an increased incidence of tuberculosis has been observed, which in countries with a high socio-economic status may be related to the HIV infection prevalence and population migration. The most frequent form of *Mycobacterium tuberculosis* infection is tuberculosis of the respiratory system which in Poland accounts for 91.6% of cases. Extra-pulmonary tuberculosis, which includes cutaneous tuberculosis, is rarely observed and its incidence is about 8.4%. With regard to the immunoreactivity or the PPD test and the presence of bacilli, three forms of cutaneous tuberculosis can be distinguished: anergic, reactive and hyperergic. The World Health Organization recommends isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin as the first-line anti-tuberculosis drugs. This paper is a review of the available present knowledge concerning selected medications, their mechanisms of action and potential adverse effects. Moreover, therapeutic schemes for new tuberculosis patients are also presented.

Key words: cutaneous tuberculosis, anti-tuberculosis drugs, treatment.

Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. The bacterium is a member of the family *Mycobacteriaceae* (fungi and bacteria) and for the first time was isolated by a German scientist Robert Koch, who was awarded with the Nobel Prize in 1905 for this discovery and his research on tuberculosis [1-3]. *Mycobacterium tuberculosis* is acid-fast in the Ziehl-Neelsen stain and weakly Gram-positive. It is aerobic (microaerophilic), straight or slightly curved rod-shaped, motionless, unencapsulated, 1-8 µm long by 0.3-0.6 µm wide and does not produce spores or toxins. Its reproduction is strictly subject to oxygen pressure, therefore unlimited *M. tuberculosis* multiplication is observed in the tuberculous cavities, while the multiplication under low oxygen pressure, e.g. in caseous lesions, is reduced [2, 3].

Since tuberculosis is responsible for more than 4,500 deaths every day, i.e. 1.7 million deaths per year, the disease still remains a significant global problem [4]. Tuberculosis accounts for 7% of all death causes [4, 5]. Currently 8 million new cases per year are noted [5] and it is estimated that 20-40% of the world population is infected by *M. tuberculosis* [6]. Over 90% of new tuberculosis cases occur in poorly developed countries, which is related to the prevalence of the infection with human immunodeficiency virus (HIV), poverty, low socio-economic status, development of *Mycobacterium* resistance to the drugs used and lack of an effective programme to combat tuberculosis [7]. On the other hand, the incidence of tuberculosis in developing countries results mainly from prevalent HIV infections and from increased migratory movement [4]. The risk of tuberculosis amounts to 1-2% in the countries with a high standard of living [8, 9].

In Poland in 2004, 9,493 cases of all forms of tuberculosis were noted, while the prevalence rate amounted to 24.9/100,000 inhabitants. Tuberculosis of the respiratory system accounted for 91.6% of all tuberculosis cases. The other 8.4% were the cases of extra-pulmonary tuberculosis. When compared to other European countries, the percentage is low, which probably proves that the epidemiological data are incomplete [10]. Three quarters of all tuberculosis patients are 15-50 years old, and

Address for correspondence: Nina Wyrzykowska MD, Department of Dermatology, Poznan University of Medical Sciences, 49 Przybyszewskiego, 60-355 Poznan, Poland, e-mail: nina.wyrzykowska@gmail.com

a greater tuberculosis incidence is observed in men than in women and in a rural than urban population [1, 10].

Mycobacterium tuberculosis infections usually occur by the respiratory route (droplet infection), and a source of infection is usually an active sputum-positive patient. In the case of extra-pulmonary tuberculosis, other routes of infection are also important. One of them is spread of the infection via blood or lymph vessels, which is relatively rare. Contact infection is also possible when micro-organisms penetrate an organism through damaged skin or mucous membrane and cause symptoms of cutaneous or mucous membrane tuberculosis [11]. With regard to the immunoreactivity or the PPD test (purified protein derivative test, tuberculin test) and the presence of bacilli in skin lesions, three forms of cutaneous tuberculosis can be distinguished: anergic, reactive and hyperergic [1]. The anergic form is characterized by its occurrence in patients with no earlier contact with *M. tuberculosis* and without immunity to it. The PPD test in these patients is negative, while numerous bacteria can be observed in skin or mucous membrane lesions, which stands for their high infectivity. The tuberculosis anergic form includes the following clinical types: primary ulcerous tuberculosis, also known as the primary complex, disseminated miliary cutaneous tuberculosis, cutaneous tuberculosis around the natural openings and serpiginous fungous tuberculosis [1]. The reactive form of tuberculosis occurs in patients without immunity disorders, after development of the primary complex, and a small number of bacilli is found in lesions, which determines low infectivity of the lesions. The lesions include verrucous cutaneous tuberculosis, lupus tuberculosis (with its numerous variants) and colliquative cutaneous tuberculosis [1]. Formation of tuberculids is a result of excessive immunological response to the contact with *M. tuberculosis.* They result in strongly positive results of the PPD test in the absence of or few *M. tuberculosis* cells in lesions. Tuberculids include lichen scrofulosorum that results from the administration of a tuberculosis vaccine (BCG – Bacillus, Calmette, Buérin) or conducting the PPD test, papular necrotic tuberculid, Bazin's disease, disseminated miliary lupus of the face, acne-like tuberculid and rosacea-like tuberculid [1, 12].

History of selected anti-tuberculosis drugs

The history of currently used anti-tuberculosis drugs goes back to 1943, when Waksman with his research team from the Rutgers University isolated streptomycin from *Actinomycetes – Streptomyces griseus.* Streptomycin turned out to be the first drug that decreased mortality due to tuberculosis [13]. For this discovery, Waksman was awarded with the Nobel Prize in physiology or medicine in 1952. The next, not less important step was introduction of isoniazid in 1952 – a drug that, similarly to streptomycin, significantly reduced mortality from tuberculosis [4]. Another stage in the development of anti-tuberculosis medications was the discovery of the fungus *Streptomyces mediterranei* in 1959, from which rifamycin B was isolated. During further studies, a semi-synthetic derivative of the ansamycin antibiotic was synthesized – rifampicin that was permanently included in the standards of tuberculosis treatment. Together with the discovery of rifampicin, the increasing problem of drug resistance was observed, when some patients did not respond to the pharmaceutical agents successfully used so far [4]. As a result of this disturbing phenomenon, works on creating new drugs – an alternative to the drugs available at that time, were initiated. The research brought about the synthesis of pyrazinamide in 1963 and ethambutol in 1967 – drugs that are used in anti-tuberculosis therapy to this day [4].

It is also worth mentioning attempts at local tuberculosis treatment in the 1960s by scientists Bolszakowa and Tichonow from the Scientific Research Institute for Skin and Venereal Diseases in Gorki [14]. They were interested in propolis, i.e. bee glue, rich in resin, plant wax, beeswax, essential oils, proteins, numerous micro-elements (Cu, S, Mg, Mn, Zn) and vitamins E, H, P. Bolszakowa and Tichonow used plant oil ointment and balm made of propolis and 96% ethyl alcohol mixture on 50 verrucous and colliquative tuberculosis patients [14]. The preparation was placed under occlusive dressing changed every second day in the verrucous tuberculosis patients and every day in the colliquative tuberculosis patients. The therapy lasted from 1 to 2 months. In the published study, the authors state that clinical recovery occurred in 38 patients from the study group, while in 12 other patients a significant health state improvement was observed. The researchers noted that propolis enabled pain-free treatment of tuberculosis skin lesions and considerably sped up the process of wound healing and the remaining scar was cosmetically satisfactory [14]. In spite of the promising results, the medical world was quite sceptical about the research results obtained in the Institute in Gorki. Further research conducted by Bolszakowa only (among other things with a preparation – a mixture of propolis, vaseline oil and 30% phtivazide), despite even more optimistic results, once again did not convince the medical world, and therefore nowadays the use of propolis-based preparations seems to be unfounded [14].

Selected anti-tuberculosis drugs

The World Health Organization (WHO) divided anti-tuberculosis drugs into 5 groups. The division was based on the usefulness of a given drug and its therapeutic effect. Group 1, the most important in tuberculosis treatment, includes: isoniazid, rifampicin, ethambutol and pyrazinamide. These drugs together with streptomycin from group 2 of pharmaceutical agents according to WHO, are considered as first-line anti-tuberculosis drugs [15, 16].

Isoniazid (isonicotinic acid hydrazide) is a pro-drug that only after its activation by bacterial catalyses begins to exhibit bactericidal activity, which consists in the inhibition of synthesis of mycolic acid – one of the main components of the *M. tuberculosis* cell wall. The inhibition of mycolic acid synthesis results from the drug interaction with nicotinamide adenine dinucleotide (NADH), when the inactive NADH form is produced, which impairs many functions essential for maintaining the life processes of *M. tuberculosis*, including the synthesis of mycolic acid. A bacterium deprived of such an important component of its cell wall dies. The drug is very well absorbed from the digestive tract and reaches its maximum concentration in 2 h after administration. Isoniazid very well penetrates into organism tissues and fluids, including the cerebrospinal fluid, where it reaches 90% concentration in serum after 3-6 h [17]. In addition, isoniazid very well penetrates through the placental barrier and is secreted in mother's milk, however, this fact should not cause a change in the treatment proceedings of pregnant women since isoniazid teratogenicity has not been proved [18, 19]. The described drug is metabolised in the liver by N-acetyltransferase. Depending on the enzyme and its activity, patients can be divided into slow and fast metabolizers. Isoniazid belongs to the group of drugs excreted by the kidneys, hence in the case of renal failure, the dose of the used drug should be decreased. During treatment with isoniazid, complications in many organs may occur. The cases of drug-induced lupus with the presence of antinuclear antibodies in patients undergoing treatment with this drug are commonly known [15]. Another equally severe complication is liver inflammation, at risk of which are especially the patients using isoniazid together with another anti-tuberculosis drug, such as rifampicin. A separate problem is neurotoxicity of isoniazid. Among all the drugs used in anti-tuberculosis therapy, isoniazid exhibits the greatest toxicity towards both the central and peripheral nervous system. During treatment with isoniazid, such nervous system complications were observed as polyneuritises, psychoses and peripheral paraesthesias [20].

The second drug successfully used in tuberculosis treatment is rifampicin, whose mechanism of action consists in the inhibition of DNA-dependent RNA polymerase, and thus generation of RNA and protein synthesis in a *M. tuberculosis* cell is prevented [21]. Similarly to isoniazid, also rifampicin has a high coefficient of absorption from the digestive tract and an equally high degree of penetration into tissues. Rifampicin also causes characteristic orange colouring of tears and urine. The described drug is metabolised in the liver and eliminated via the bile ducts, therefore particular caution in the treatment of patients with impaired bile secretion is advised. The most frequent adverse effects include gastro-intestinal disturbances like nausea, vomiting and stomach ache. Another definitely less frequent adverse effect is toxic influence on the liver. Rifampicin hepatotoxicity significantly increases when it is used together with isoniazid [22]. A study conducted by a research team from the Birmingham Heartlands Hospital revealed that hepatological complications due to the combined use of these two anti-tuberculosis drugs occur in 1.8% of patients and the problem more frequently affects patients after 35 years of age [22].

Another effective drug used successfully for years in tuberculosis treatment is ethambutol. The drug results in the inhibition of mycolic acid transport to the cell wall and is well absorbed from the digestive tract and excreted by the kidneys in the unchanged form. The most important problem observed during the administration of ethambutol is its toxic influence on the organ of vision. Some cases of ethambutol degenerative influence on the optic nerve have been reported, which may result in visual acuity or visual field disturbances, and even in complete irreversible blindness in the advanced stages. Hence, patients undergoing treatment with ethambutol should undergo frequent and regular ophthalmologic follow-up examinations, since early discontinuation of the drug administration may cause full recovery of the eye function [23].

Another drug from group 1 is pyrazinamide. The compound is a pro-drug that is transformed to its active form by bacterial pyrazinamidases. The active metabolite of this drug impairs the function of the bacterial type 1 fatty acid synthase, which results in the death of the bacterium [24]. The most significant adverse effect in the course of treatment with pyrazinamide is hepatotoxicity [25]. A research conducted in 2008 and commissioned by the Hong Kong Department of Health shows that the risk of hepatological complications in patients undergoing treatment with isoniazid and rifampicin only amounts to 0.8%, whereas the combined treatment with these drugs with pyrazinamide increases the risk to as much as 2.6%. It stands for a significantly increased risk of development of hepatological complications in the case of introducing pyrazinamide into anti-tuberculosis therapy [25]. Another adverse effect of treatment with pyrazinamide is an increase in blood serum uric acid, which may cause joint pain, joint inflammation, and in some cases, gout [26].

The history of modern tuberculosis treatment goes back to the discovery of streptomycin in 1943. The first treatments with streptomycin lasted for three months and resulted in a considerable clinical, radiological and bacteriological improvement of *M. tuberculosis* infections. WHO classifies the drug into group 2 of anti-tuberculosis drugs, however, since streptomycin was the first drug to significantly reduce mortality due to tuberculosis, it deserves an extended discussion [14, 15]. Streptomycin belongs to the group of aminoglycoside antibiotics. Similarly to other representatives of this drug group, it irreversibly binds to the 30S subunit of the bacterial ribosome, thus preventing the synthesis of proteins crucial for the bacterium existence. As opposed to the other described anti-tuberculosis drugs, streptomycin is not absorbed from the digestive tract and therefore it must

be administered by the parenteral route – in the form of intramuscular injections. The most frequent complication in the course of treatment with this aminoglycoside antibiotic is ototoxicity, which may be manifested as vertigo and balance or hearing disturbances. In the case of complications in the organ of hearing, it is recommended to perform the audiometric test. Other adverse effects observed during treatment with streptomycin is nephrotoxicity and neurotoxicity. Streptomycin is the only first-line anti-tuberculosis drug that cannot be used by pregnant women and breastfeeding mothers [18].

Apart from streptomycin, group 2 of anti-tuberculosis drugs includes also kanamycin, amikacin, capreomycin and viomycin [15]. Group 3 of anti-tuberculosis drugs comprises fluoroquinolones, such as moxifloxacin, gatifloxacin, levofloxacin, ofloxacin and ciprofloxacin [15]. Group 4 includes ethionamide, cycloserine and para-salicylic acid [15]. Treatment with drugs from groups 2, 3 and 4 should be restricted to the cases of resistance or intolerance to group 1 drugs. Group 5 includes drugs like clofazimine, amoxicillin with clavulanic acid, capreomycin and linezolid. However, it should be mentioned that the anti-tuberculosis effectiveness of these drugs is unclear [15].

Treatment of cutaneous tuberculosis

Treatment of cutaneous tuberculosis is based on the administration of anti-tuberculosis drugs that are individually selected depending on the results of bacteriological examination and tests of *Mycobacterium* sensitivity to particular drugs [2]. The effectiveness of individual drugs depends on the pathogen site of infection and metabolism intensity. The greatest group includes bacilli in the tuberculous cavities, where under favourable conditions they multiply extracellularly and are sensitive to all the basic anti-tuberculosis drugs, such as rifampicin, isoniazid, ethambutol and streptomycin [15]. The second group comprises bacilli that multiply the most intensely under intracellular conditions and are the most active in the first stage of the disease. Treatment with rifampicin and isoniazid is the most effective [15]. Another group of bacilli includes latent bacilli and bacilli with decreased metabolism. Anti-tuberculosis drugs have an effect on them only in the phases of metabolism activation and bacillus multiplication. This fact explains the administration of anti-tuberculosis drugs for many months, such as rifampicin and isoniazid, which offers an opportunity to sterilize the lesions and altogether prevent the disease recurrence in the future [15]. A special characteristic of *M. tuberculosis* is creating drug resistance. It is highly probable that each lesion contains drug-resistant bacilli. Drug resistance is created due to irregular drug intake by a patient and inadequate treatment, which concerns both inadequate drugs and their doses and results in too low therapeutic concentrations. Tables 1 and 2 present the recommended first-line drug doses depending on the frequency of their administration [16]. Due to the necessity of avoiding drug resistance, it is essential to administer simultaneously several anti-tuberculosis drugs.

The above knowledge made it possible to formulate basic principles of anti-tuberculosis therapy. The treatment must always be combined (with many drugs), regular and adequately long.

In the case of newly diagnosed and bacteriologically confirmed pulmonary tuberculosis with severe course and of extra-pulmonary tuberculosis with severe course, a two-phase therapeutic scheme is adopted. It is divided into the active phase and the maintenance phase. The first phase is the phase of intensive treatment, when four drugs are simultaneously administered for 2 months – at that time the number of bacilli is quickly decreasing. The subsequent 4 months of therapy is the sterilizing phase, when from two to three drugs are administered simultaneously. The phase is aimed at decreasing the risk of the disease recurrence. The treatment in total lasts 6 months. The scheme of the above treatment is presented in Table 3. Patients, in whom resistance to isoniazid in the maintenance phase is suspected, additionally receive treatment with ethambutol, which is shown in Table 4.

In the case of a risk of creating drug resistance to previously used drugs, i.e. in the case of tuberculosis recurrence, therapy failure or continuation of therapy after an interval longer than 1 month, it is recommended to

Table 1. Doses of first-line anti-tuberculosis drugs recommended by WHO in the case of everyday drug administration [4, 16]

Drug	Recommended dose [mg/kg body weight]	Maximum dose [mg]
Isoniazid	4-6	300
Rifampicin	8-12	600
Ethambutol	20-30	–
Pyrazinamide	15-20	–
Streptomycin	12-18	–

Table 2. Doses of first-line anti-tuberculosis drugs recommended by WHO in the case of drug administration every 3 days [4, 16]

Drug	Recommended dose [mg/kg body weight]	Maximum dose [mg]
Isoniazid	8-12	900
Rifampicin	8-12	600
Ethambutol	30-40	–
Pyrazinamide	25-35	–
Streptomycin	12-18	1000

Table 3. Therapeutic scheme in new tuberculosis patients with suspected sensitivity to the first-line anti-tuberculosis drugs, recommended by WHO [4, 16]

Drug	Intensive phase (administered for 2 months)	Maintenance phase (administered for 4 months)
Isoniazid	+	+
Rifampicin	+	+
Ethambutol	+	–
Pyrazinamide	+	–

Table 4. Therapeutic scheme in new tuberculosis patients with suspected resistance to isoniazid, recommended by WHO [4, 16]

Drug	Intensive phase (administered for 2 months)	Maintenance phase (administered for 4 months)
Isoniazid	+	+
Rifampicin	+	+
Ethambutol	+	+
Pyrazinamide	+	–

administer treatment with rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin for 2 months, then rifampicin, isoniazid, pyrazinamide and ethambutol for 1 month and then rifampicin, isoniazid and ethambutol for 5 months. The whole treatment lasts for 8 months [16].

In the case of newly diagnosed tuberculosis that is not confirmed bacteriologically, and in the case of extrapulmonary tuberculosis with a milder course, it is recommended to administer treatment with rifampicin, isoniazid and pyrazinamide for 2 months and then rifampicin and isoniazid for 4 months. The whole treatment lasts for 6 months [16].

The tuberculosis treatment of patients with chronic sputum positivity in spite of previous adequate treatment, in whom drug resistance is often detected, is long-term. The intensive phase of treatment is not shorter than 3 months, and simultaneously even as many as 5 anti-tuberculosis drugs are administered. The sterilizing phase lasts for 1.5 years [16].

It should be emphasized that the above-described therapeutic schemes concern patients with no other diseases. Patients with renal failure, liver diseases, immunoincompetent persons and pregnant women require a choice of drugs according to special rules [16].

As a complementary therapy in tuberculosis treatment, immunomodulators are used, which include corticosteroids, vaccines and other drugs, including biological drugs [4]. They aim at shortening the time of anti-tuberculosis therapy by modulation of the host immunological response and elimination of persistent micro-bacteria. Immunomodulators are a new attempt at shortening the disease treatment time. A research on mice showed a reduction in the inhibitory effect of Th2 lymphocytes on the protective response of Th1 lymphocytes by inhibiting interleukin-4 production or by down-regulating the Th2 response. However, these promising results require further investigation on human population [4].

Cutaneous tuberculosis treatment employs also methods that consist in a direct local effect on pathologically changed tissue. In the case of cutaneous tuberculosis located around the natural openings, apart from standard treatment with anti-tuberculosis drugs, 2% lactic acid and local anaesthetic agents are used. In many cases, and especially in patients with verrucous or colliquative tuberculosis, a complementary method is surgical excision of lesions or treatment with X-rays. Radiotherapy is administered for 3 weeks at a dose of 5 Gy per week [1].

Conclusions

In the last few years a significant increase in the incidence of tuberculosis, including cutaneous tuberculosis, was observed. According to WHO, basic anti-tuberculosis drugs include isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin. Anti-tuberculosis therapy should be long-term with combined administration of many drugs. Apart from the first-line anti-tuberculosis drugs, there is also a numerous group of pharmaceutical agents that have a proved effect on *M. tuberculosis*, however, their administration should be restricted only to the cases of resistance or intolerance to the basic agents. Also immunomodulators that enhance immunological response to *M. tuberculosis* are therapeutically used in tuberculosis treatment. Apart from systemic drug administration, methods that have a local effect on pathologically changed skin are also used.

References

1. Braun-Falco O, Plewig G, Wolff H, et al. Dermatology [Polish]. Czelej, Lublin 2002.
2. Rogozińska-Zawiślak A, Wiankowska-Śmiecińska E. Tuberculosis in children and adolescents – actual and important problem [Polish]. Prz Pediatr 2006; 36: 301-6.
3. Jabłoński L. Basic medical microbiology [Polish]. PZWL, Warsaw 1979; 361-72.
4. Scientific Working Group on Tuberculosis. Meeting report. 3-6 October 2005. Genewa, Szwajcaria 2006.
5. Nalepa P, Pasowicz M, Strączek C. Ulcerative tuberculosis of the skin around the anus or fissure accompanied by pulmonary tuberculosis [Polish]. Pol Merkuriusz Lek 2006; 21: 477.
6. Broughton WA, Morales RE, Bass JB Jr. Tuberculosis and disease caused by atypical mycobacteria. In: Clinical respiratory medicine. Albert RK, Spiro SG, Jett JR (eds.) 2004; 321-38.

7. Kumar B, Rai R, Kaur I, et al. Childhood cutaneous tuberculosis: a study over 25 years from northern India. Int J Dermatol 2001; 40: 26-32.
8. Teresiak E, Czarnecka-Operacz M, Bowszyc-Dmochowska M. Tuberculosis luposa – a case report and literature review. Post Dermatol Alergol 2006; 23: 192-7.
9. Pandhi D, Reddy BSN, Chowdhary S, et al. Cutaneous tuberculosis in Indian children: the importance of screening for involvement of internal organs. Eur Acad Dermatol Venereol 2004; 18: 546-51.
10. Szczuka I. Tuberculosis in Poland in 2004 [Polish]. Przegl Epidemiol 2006; 60: 529-36.
11. Jabłońska S, Chorzelski T. Skin diseases [Polish]. PZWL, Warsaw 2001; 61-70.
12. Misterska M, Walkowiak H, Szulczyńska-Gabor J, et al. An unusual location and progress of vasculitis nodosa – case report. Post Dermatol Alergol 2010; 27: 126-30.
13. Kostowski W, Herman Z. Pharmacology. Basic pharmacotherapy [Polish]. PZWL, Warsaw 2003.
14. Kędzia B, Hołderna-Kędzia E. Propolis treatment of some skin diseases [Polish]. Postępy Fitoterapii 2007; 1: 23-30.
15. Michałowska-Mitczuk D. Michałowska-Mitczuk D. Pharmacotherapy of tuberculosis. Postępy Farmakoterapii 2009; 65: 51-8.
16. WHO: Treatment of Tuberculosis: guidelines for national programmes. 4th Edition. Genewa, Szwajcaria 2010.
17. Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev 2010; 23: 858-83.
18. Keskin N, Yilmaz S. Pregnancy and tuberculosis: to assess tuberculosis cases in pregnancy in a developing region retrospectively and two case reports. Arch Gynecol Obstet 2008; 278: 451-5.
19. API Consensus Expert Committee. API TB Consensus Guidelines 2006: Management of pulmonary tuberculosis, extrapulmonary tuberculosis and tuberculosis in special situations. J Assoc Physicians India 2006; 54: 219-34.
20. Kass JS, Shandera WX. Nervous system effects of antituberculosis therapy. CNS Drugs 2010; 24: 655-67.
21. Shan L. ^{11}C-Labeled rifampicin. Molecular Imaging and Contrast Agent Database (MICAD) [Inernet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2010. 2010 updated 2010 Sep 01.
22. Kunst H, Khan KS. Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review. Int J Tuberc Lung Dis 2010; 14: 1374-81.
23. Li J, Tripathi RC, Tripathi BJ. Drug-induced ocular disorders. Drug Saf 2008; 31: 127-41.
24. Shan L. ^{11}C-Labeled pyrazynamide. Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2010. 2010 updated 2010 Oct 01.
25. Chang KC, Leung CC, Yew WW, et al. Hepatotoxicity of pyrazinamide: cohort and case-control analyses. Am J Respir Crit Care Med 2008; 177: 1391-6.
26. Gupta S, Gupta V, Kapoor B, Kapoor V. Pyrazinamide induced hyperuricaemia presenting as severe bilateral leg cramps. J Indian Med Assoc 2007; 105: 341-2.