Management of Side Effects and Drug Interactions of Anti-mycobacterial in Tuberculosis

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Article ID: WMC002749
Article Type: Review articles
Submitted on: 19-Dec-2011, 01:04:37 PM GMT    Published on: 19-Dec-2011, 03:32:03 PM GMT
Article URL: http://www.webmedcentral.com/article_view/2749
Subject Categories: INFECTIOUS DISEASES
Keywords: Tuberculosis, Infectious, Interactions, Side effects, Manage, Mycobacterial


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Abstract

Background: Tuberculosis is a communicative disease caused by Mycobacterium tuberculosis that may cause death if it is left untreated. The incidence of tuberculosis has decreased since the introduction of anti-tubercular drugs. Undesirable side effects and drug-drug interaction of anti-tubercular drugs will result in discontinuation or substitution of other drugs. This may influence patient’s response and compliance. It also may increase the risk of treatment failure.

Purpose: The purpose of this assignment is to study the side effects and drug interactions of anti-tubercular drugs as well as the way to manage them.

Literature Review: Journals related to anti-tubercular agents are referred to accomplish this assignment. Databases such as Science Direct and PubMed are used to search for these journals.

Discussion: Patients with tuberculosis are with treated anti-tubercular agents, either in monotherapy or in combination. The anti-tubercular drugs will bring adverse effects to the patients if not managed properly such as hepatotoxicity and rashes due to hypersensitivity. The anti-tubercular drugs will also interact with other medications such as antiretroviral drugs as well as among themselves. The negative effects from these interactions have to be managed.

Conclusion: Tuberculosis treatment will bring positive effects as well as negative effects due to side effects and drug interactions of the anti-tubercular drugs. Therefore, the side effects of as well as the interactions of the anti-tubercular drugs have to be managed to prevent treatment failure or even worse, death in the tuberculosis patient.

Introduction

Tuberculosis is a communicative disease which is caused by bacterial infection in the lungs. Tuberculosis is one of the oldest human diseases and is the main cause of death in many countries. Due to the introduction of several anti-mycobacterial drugs, tuberculosis disease and deaths have decreased steadily since the 1900s. In 1992, 13,000 tuberculosis cases were reported by Centers for Disease Control and Prevention. According to World Health Organization, 9.8 million of new tuberculosis cases were reported as well as 1.8 million deaths due to tuberculosis were reported in 2008. (National Institutes of Health, 2010)

There are 2 stages of tuberculosis treatment, which consists of the first line anti-tubercular drugs and second line anti-tubercular drugs. According to a research made in Rwanda, the cure rates of multi drug resistant tuberculosis (MDR-TB) are much higher following the inclusion of second line anti-tubercular drugs. According to the study, tuberculosis is treated with combinations of first line anti-tubercular drugs and second line anti-tubercular drugs. The drugs commonly used consist of rifampin, isoniazid, pyrazinamide, ethambutol, streptomycin, kanamycin, rifabutin, clarithromycin, para-aminosalicylic acid, ethionamide, oflaxacin and fluoroquinolones. (A. Umubyeyi et al., 2007)

No matter how efficient these drugs are towards tuberculosis, these drugs will interact with other drugs or medications as well as bring adverse reactions to the body. Examples of side effects caused by anti-tubercular drugs consist of drug-induced hepatotoxicity, nephrotoxicity, ototoxicity and rash. (Daphne Y et al., 2003) Hepatitis is one of the side effect that occurs commonly among anti-tubercular drugs. It is reported that pyrazinamide and rifampin (Jasmer RM et al, 2002) as well as isoniazid (Ferebee SH, 1969) can cause hepatitis. However, it is reported that the prevalence of serious hepatotoxicity has decreased 25 years later. (Nolan CM et al, 1999)
Since the drug interactions between anti-tubercular drugs and other medications as well as the side effects caused by the anti-tubercular drugs will cause negative effects to the body, they should be discontinued or substituted with another drug as soon as possible to avoid possible mortality especially due to hepatitis. In a study, it is reported that hepatotoxicity caused by isoniazid can cause patient morbidity and mortality. (Kopanoff DE, 1978) According to the study made by Daphne Y et al., there are six cases where severe hepatitis resulted in discontinuation of isoniazid and pyrazinamide and both of these drugs were not rechallenged. In that study, two cases of rash and one case of gastrointestinal intolerance also resulted in the stopping of usage of drugs rifampin and pyrazinamide and in one case of severe vomiting, isoniazid, rifampin and pyrazinamide are discontinued and were not administered again. (Daphne Y et al., 2003) The objectives of this review are to study the side effects and drug interactions of anti-tubercular drugs as well as the way to manage them.

**Literature Review**

Data for this review is were obtained from publications identified by systematically searching PubMed and Science Direct within the range of 1967 to 2010. But, we also obtain some information from a journal published in 1941. The keywords we used in order to search for these journals consist of tuberculosis, anti-mycobacterial, side effects, drug interactions, anti-tubercular.

**Discussion**

Anti-tubercular drugs are similar to a lot of other medications in terms of causing side effects to the patients who took them. The side effects of the anti-tubercular drugs may range from mild to fatal. Isoniazid, rifampin, pyrazinamide and ethambutanol are drugs which are frequently used in the treatment of tuberculosis (Janin, 2007). Isoniazid, rifampin and pyrazinamide are three of the anti-tubercular drugs which can induce hepatotoxicity in patients.(Schaberg, 1995).

Isoniazid can cause hepatotoxicity in the patients( Zaleskis, 2005) as its metabolic products such as monoacetyl hydrazine, hydrazine and isonicotinic acid have been suggested as being hepatotoxic. Rifampin is also another anti-tubercular drug which can cause hepatitis. But it only induces low intensity of hepatotoxicity compared to isoniazid and pyrazinamide. ( Thompson et al, 1995) However, it will increase the isoniazid toxicity when it is used in combination with isoniazid. (Zaleskis, 2005). Pyrazinamide is the most hepatotoxic compared to the other two. But, its hepatotoxicity depends on the its dose. The higher the dose of pyrazinamide, the higher the risk of inducing hepatotoxicity. (Wing and Chi, 2006) The prevalence of drug-induced hepatotoxicity in Malaysia is 9.7% (Marzuki OA et al, 2008) which is comparable to those reported in other Asian Countries. (Parthasarathy R et al,1986 , Turktas H et al, 1994) However, the incidence of drug-induced hepatotoxicity in developed countries are 3%-4%, which are comparatively lower. (Combs DL et al, 1990) Hepatotoxicity in patients can be detected by conducting a blood test. If the patients’ serum transaminase is more than 3 times of the normal level, it can be deduced that these patients have anti-tubercular drug induced hepatotoxicity (Wing and Chi 2006). In the case of severe hepatotoxicity, the serum transaminase of the patients will be 10 times higher than the normal level. ( Zaleskis, 2005)

Isoniazid, rifampin and pyrazinamide are hepatotoxic drugs can induce hepatotoxicity in the patients in 10 days. (Thompson et al, 1995) Therefore, liver functions tests (LFTs) which includes all the parameters should be carried out before the treatment is started to obtain the baseline for comparison between the normal condition and the hepatotoxic condition. (Wing and Chi, 2006). If the transaminase levels are less than three times of the normal level, the current treatment can be continued with the condition of having LFTs in a weekly basis. However, if the transaminase are more than 3 times of the normal level, current regimen should be discontinued immediately until the liver function returns to normal. Once the liver function returns to normal, rechallenge can be conducted. But if hepatotoxicity takes place again, the hepatotoxicity inducing drugs should be substituted with streptomycin or ethambutol. (Thompson et al, 1995)

Other than inducing hepatotoxicity, isoniazid may also induce peripheral neuropathy in patients. According to a study done by Jasmer et al, 2% of the patients experience peripheral neuropathy after taking isoniazid in the doses that are usually prescribed by physicians. Since this side effect is due to the interference of the metabolism of pyridoxine by isoniazid in patients (Jasmer et al, 2002), this side effect can be managed by the administration of 10-50mg of pyridoxine to patients receiving isoniazid to prevent peripheral neuropathy. (Vanhoof et al, 2003) Isoniazid may also cause hypersensitivity reactions
such as acneform skin rash or systemic lupus erythematosus. (Hershfield, 1999) Systemic lupus erythematosus is regarded as a disease which is accompanied by a widespread of tissue damage to segments of the vascular tissue and various surfaces. (Klemperer, 1941) According to a study made in Singapore, among the 660 patients who participated in the study, the overall prevalence of hypersensitivity reactions is 9.4% (Ng et al, 1971) Hypersensitivity reactions in patients can be managed by discontinuing isoniazid once hypersensitivity reactions occur.

Similarly, other than inducing hepatotoxicity, rifampin may also cause serious adverse effect like renal failure, hemolysis and thrombocytopenia (Hershfield, 1999). Thrombocytopenia is caused by the platelets absorbing anti-rifampin antibodies and eventually resulting in platelet damage (Addington, 1979). Thrombocytopenia occurs in 1-8% of the patients who took rifampin. Thrombocytopenia can be detected by conducting a blood test which includes platelet count. Patients with thrombocytopenia tend to experience a lower platelet count as compared to normal individuals. Therefore, it can be deduced that the particular patient developed thrombocytopenia if they have a platelet count much lower than the normal level. (Koju D et al, 2005) In order to prevent thrombocytopenia from worsening (Addington, 1979), the rifampin use should be discontinued as prolonged thrombocytopenia might be fatal to patients.

Besides causing hepatotoxicity, Pyrazinamide can also cause arthralgias which will cause the patient to experience pain, tenderness or swelling of joints. (Hershfield 1999) According to a study conducted in India, arthralgias occur in 22% of the patients under the pyrazinamide treatment. (Qureshi et al, 2007) However, management of arthralgias doesn’t require discontinuation of pyrazinamide as low doses of nonsteroidal anti-inflammatory agents (NSAIDS) can be used for pain relief when necessary. Besides that, arthralgias may also be reduced by intermittent administration of pyrazinamide. (Migliori et al, 1999)

The most significant side effect of ethambutanol is retrobulbar neuritis (Hershfield, 1999), whereby the patients will experience symptoms like blurred vision, decreased visual acuity, central scotoma and colour blindness. Administration of high dose of ethambutanol will increase the ocular toxicity. The occurrence of optic neuritis is around 6% when the dosage administered is 25mg/kg (Addington, 1997). Therefore, in order to manage this side effect, the visual acuity of the patient should be monitored before the administration of ethambutanol. However, ethambutanol should be discontinued if the initial symptoms of retrobulbar neuritis appear. (Migliori et al, 1999) Besides that, red green discrimination test is also required to be carried out but it is not required for further monitoring if there is no occurrence of eye symptoms. (Addington, 1979). Other than that, patients taking ethambutanol must check their visual acuity and colour vision in a monthly basis. (Hershfield, 1999)

Streptomycin is an aminoglycoside antibiotic and the first anti-tubercular agent that is effective in treating TB. The most severe side effect of streptomycin is otoxicity. This ototoxicity occurs due to the vestibular or cochlear damage to cranial nerve VIII. (Marcos et al, 2010) The risk of getting ototoxicity will be increased if the patient has a history of hearing impairment. It is estimated that 17-33% of patients taking streptomycin will develop ototoxicity. (Doughias and Hirose, 2007). To manage ototoxicity, streptomycin should be discontinued. (Migliori et al, 1999) Therapeutic drug monitoring should also be done to maintain the Cmax of streptomycin at 15–40mg/ml and Ctough at less than 5mg/ml as the human body can only tolerate the streptomycin toxicity within this range. (Coyne et al, 2009) However, if headache, vomiting, vertigo and tinnitus occurs, the dose of streptomycin should be reduced (Migliori et al, 1999).

Sometimes, streptomycin administration can also cause nephrotoxicity. (Hershfield, 1999). Accumulation of streptomycin in the renal tubules produces renal toxic effects (Marcos et al, 2010). Oliguria, urinary casts, proteinuria, and decreased creatinine clearance, as well as increased serum levels of urea and creatinine shows a clinical and laboratory manifestation of nephrotoxicity (Arbex et al, 2010). To detect nephrotoxicity in patients, the creatinine test can be conducted. If the level of the serum creatinine is normal before and after the treatment with streptomycin, (Koju D et al, 2005) it can be deduced that the patient is experiencing nephrotoxicity. This is because patients who are currently experiencing renal failure will not be able to excrete creatinine out of their body efficiently.

Cycloserine cause neuropsychotic side effect such as depression, seizures, psychosis, suicidal ideation and paranoia. In response to psychosis and depression, patients will have a high tendency to commit suicide. These effects can be worsened through renal impairment due to the decrease in cycloserine excretion. Those patients who are taking cycloserine for more than 500mg daily might experience renal dysfunction. As a result, cycloserine-induced toxicity might occur which will lead to the side effects mentioned above. Therefore, the plasma
concentration of cycloserine must be monitored at below 30 mg/ml as the concentration above that might induce toxicity in the body. (Coyne et al, 2009).

The side effects of cycloserine can be managed through several ways. For example, pyridoxine can be introduced to prevent the occurrence of neurotoxic effects. (Arbex et al, 2010). Besides that, in the case of occurrence of psychotic symptoms, antipsychotic drugs should be administered and cycloserine should be discontinued in immediate basis to relieve the psychotic effects of cycloserine. (Migliori et al, 1999). Other than that, cycloserine usage should be avoided for patients with a history of seizures or psychologic problems. (Arbex et al, 2010).

In some tuberculosis patients, the treatment using a single anti-tubercular drug can be less efficient in treating tuberculosis than the usage of a combination of anti-tubercular drugs. However, these combinations can bring positive effects as well as negative effects to the health of the patients. Therefore, the drug interactions between the anti-tubercular drugs are considered before the drugs are prescribed to the patients as the drug interactions might influence the effectiveness of the tuberculosis treatment. According to a study done by Palmero, the results showed that combined therapy was more effective than monotherapy. When isoniazid was added to the therapy involving streptomycin and paraaminosalicylic acid, the effectiveness of the treatment increased. In 1960, a study has been done by substituting paraaminosalicylic acid with ethambutol so that the tuberculosis treatment involved isoniazid, ethambutol and streptomycin. As a result, the treatment course was reduced from 18-24 months to 18 months. The treatment course was shortened again through the addition of rifampin into the treatment. Lastly, the addition of pyrazinamide in the therapy reduced the duration of the treatment even further. (Palmero DJ, 2007)

Other than interacting among each other, anti-tubercular drugs will also interact with anti-retroviral drugs, also known as anti-HIV drugs. HIV is a virus which can cause AIDS in individuals. Nowadays, there are AIDS patients who are tuberculosis patients as well. However, there is difficulty in treating tuberculosis concomitantly with HIV. This is because there is drug interactions between these two classes of drugs. An example of antiretroviral drugs is the HIV protease inhibitors. Rifamycins which are a group of anti-tubercular drugs and it consist of rifabutin, rifapentine and rifampin. The presence of these anti-tubercular drugs in the serum of HIV patients with tuberculosis will lower the serum concentrations of HIV protease inhibitors. According to a study conducted, rifampin reacts with HIV protease inhibitors in such a way that it decreases the serum concentration of the HIV protease inhibitors by 35% to 92% whereas rifabutin reduces the serum concentration of HIV protease inhibitors by 15% to 45%. (Cato A et al, 1998, Kerr B et al, 1997, Sahai J et al, 1996 & Polk RE, 1998.) The reduction of HIV protease inhibitor is so high that this condition cannot be overcome by the addition of HIV protease inhibitors. (Burman WJ et al, 1999.) The serum concentration of HIV protease inhibitors cannot be increased even by administering rifamycins intermittently. (Ellard GA et al, 1986) Some studies reported that the increase in rifabutin from the interaction between rifabutin and HIV protease inhibitors is caused by the inhibition of the metabolism of rifabutin by the liver by HIV protease inhibitors. (Iatsimirskaia E et al, 1997) Other than rifamycins, non-rifamycin anti-tubercular drugs can also interact with antiretroviral drugs. A study shows that co-administration of ethionamide with protease inhibitors can actually result in the increase in the serum concentrations of ethionamide and therefore, the toxicity increases. (Jenner PJ et al, 1981)

To overcome these negative effects, standard doses of HIV protease inhibitors cannot be given with rifamycins and ethionamide stated above. Therefore, an anti-tubercular drug, ritonavir can be given as an alternative to rifamycins and ethionamide. However, low doses of ritonavir that is 100-200mg per dose of HIV protease inhibitors are not sufficient enough to overcome the side effects brought by HIV protease inhibitors. As a result, high doses of ritonavir which is about 400mg per dose of HIV protease inhibitors are given with HIV protease inhibitors. (CDC, 2007)

Another example of an antiretroviral drug is HIV nucleoside reverse transcriptase inhibitors. An example of a drug from this class is zidovudine. Zidovudine is metabolised through the glucoronidation process which is carried out by glucuronosyl-transferase enzymes. (Haumont M et al, 1990) These enzymes are induced by rifamycins. (Oesch F et al, 1996) This will result in the decrease in the plasma concentration of zidovudine. According to studies done, rifampin decreases the plasma concentration of zidovudine by 47% (Gallicano K et al, 1997) whereas rifabutin decreases it by lesser than 15%. (Gallicano K et al, 1995, Narang P et al, 1993)

Besides that, HIV non-nucleoside reverse transcriptase inhibitors are also another class of antiretroviral drugs. Delavirdine is example of non-nucleoside reverse transcriptase inhibitors. Co-administration of delavirdine with rifampin almost
completely abolishes the plasma concentration of delavirdine while the concentration of rifampin remains unchanged. If it is co-administered with rifabutin, the plasma concentration of delavirdine will decrease by 80% (Borin MT et al, 1997) while the rifabutin concentrations increases by three times. This will result in rifabutin toxicity in our body. (Cox SR et al, 1998) Nevirapine is another drug from this class. According to related studies, rifampin and rifabutin decreases the serum concentration of nevirapine by 37% and 16% respectively. (Roxane Laboratories, 1997) Therefore, it is not recommended to co-administer nevirapine and delavirdine with rifamycins.

To avoid negative effects from arising due to these drug interactions, first of all, delavirdine and rifamycins are not recommended to be administered together. Non-rifamycins are more recommended in these cases. In the case of nevirapine, nevirapine-based therapies are avoided for patients with high CD4 cell counts. Standard doses of nevirapine which is 200mg daily for 2 weeks long which is followed by 200mg twice daily should be administered for patients taking rifamycins. (CDC, 2007)

**Conclusion**

In conclusion, the anti-tubercular drugs used might bring side effects such as hepatitis, hypersensitivity reaction, peripheral neuropathy, renal failure, hemolysis and thrombocytopenia, arthalgias, retrobulbar neuritis, ototoxicity, nephrotoxicity and neuropsychotic side effects. In order to manage the side effects, patients have to go for liver tests periodically, discontinue the drugs for a particular period, substitute the drugs with less potent drugs, or by reducing the dose of drug given to the patients.

Besides that, tubercular drugs can interact with each other as well as other medications, for example, antiretroviral drugs. These interactions may be positive or negative. In order to manage these drug interactions, those drugs cannot be given together, or just substituted with another anti-tuberculosis drug. Therefore, it is important to manage the side effects and drug interactions of the anti-tubercular drugs to prevent treatment failure or even death.

**Acknowledgement**

We would like to thank Dr. Amin from Discipline of Pharmacology of School of Pharmaceutical Sciences, Universiti Sains Malaysia for giving us this opportunity to accomplish this assignment as we are able to learn a lot of things regarding anti-tuberculosis therapy through this assignment. Besides that, we would like to our coursemates who has given us some ideas as well as advices concerning our assignment so that we can produce a better written review.

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