International Journal of Risk & Safety in Medicine 19 (2007) 175–178
IOS Press

Case Report

Serious adverse drug reactions in a case of neurotuberculosis

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Abstract. *Introduction*: Tuberculosis remains one of the most important infectious disease plaguing the developed and developing countries worldwide. Antitubercular drugs (ATD) are associated with a wide spectrum of adverse drug reactions (ADR), which often pose a significant problem. Vigilant ADR monitoring and close follow up is needed to ensure early detection and prompt management of such untoward events and minimize the morbidity associated with them. *Case summary*: We report a case of ATD induced hepatitis with bilateral optic neuritis along with corticosteroid induced proximal myopathy in a young male patient of 21 years with neurotuberculosis. Although ATD induced hepatitis and ethambutol induced optic neuritis are established clinical entities but the infrequent occurrence of such diverse ADRs in the same patient encouraged us to report it. A Medline search till December 2006 revealed that there are no such reported cases. Each suspected adverse reaction was assessed for causality using the Naranjo's ADR probability scale and it was found to be of *definite* association of INH induced hepatotoxicity and *probable* association of ethambutol induced optic neuritis and corticosteroid induced proximal myopathy. *Conclusion*: This case is being reported taking into consideration the rarity of simultaneous occurrence of a plethora of adverse drug reactions in the same patient and also to highlight the problem that clinicians face while treating patients of tuberculosis due to the occurrence of such ADRs.

Keywords: ADR, optic neuritis, drug induced myopathy, hepatotoxicity, INH, ethambutol, corticosteroid

Introduction

Tuberculosis remains one of the most important infectious disease plaguing the developed and developing countries worldwide. More than eight million people develop active TB annually, and approximately two million die from the disease each year. Global strategies are focused on minimizing the disease burden in the community. Early disease detection, pharmacotherapy and ensuring treatment compliance are the corner stones for achieving therapeutic success. Antitubercular drugs (ATD) are associated with a wide spectrum of adverse drug reactions, which often pose a significant problem. Therefore vigilant adverse drug reaction (ADR) monitoring and close follow up are needed not only to assess and treat such problems but also to ensure compliance to drug therapy.

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The first line antitubercular drugs commonly used are isoniazid (INH), rifampicin (RIF), ethambutol (EMB), pyrazinamide (PZA) and streptomycin (SM). The common adverse effects noted with these ATDs are nausea and vomiting, hepatotoxicity, skin rashes, hyperuricaemia, optic neuritis, vestibular and cochlear toxicity [11].

We report a case of suspected ATD induced hepatitis with optic neuritis along with steroid induced proximal myopathy. This case is being reported taking into consideration the rarity of concomitant occurrence of such reactions in the same patient and the infrequent occurrence of steroid induced proximal myopathy. These adverse effects had posed a significant morbidity to the patient, which resulted in prolongation of his hospital stay and subsequently readmission.

Case report

A 20-year-old healthy male patient was admitted to the hospital on 19 Feb 2005 with a history of low-grade fever and headache for four weeks and three episodes of focal seizures, neck stiffness and photophobia for two days. There was no past history of pulmonary or extra pulmonary TB, major medical or surgical ailments. He was non-diabetic and there was no history of addiction to tobacco or alcohol. A provisional diagnosis of neuro-tuberculosis was made on the basis of the CSF picture and the CT scan and MRI Brain. ATD therapy was started from 19 February 2005 with a daily dose of: INH 300 mg, RIF 450 mg, PZA 1250 mg and EMB 800 mg. He was also put on prednisolone (40 mg daily dose for 2 weeks and then reduced to 20 mg) and phenytoin (300 mg) due to meningial involvement and occurrence of seizures. The baseline liver function tests (LFT) were normal.

After about ten days of initiation of ATD therapy he developed nausea with vomiting but without icterus. LFT report revealed normal serum bilirubin level but raised serum aminotransferases – SGOT (132 U/l) and SGPT (118 U/l) levels (1 March 2005). Virological markers for hepatitis B and A were negative and upper abdominal ultrasonography was normal. INH, RIF and PZA were temporarily withdrawn. A clinical diagnosis of ATD induced hepatotoxicity was made based on temporal association with drug intake and improvement with dechallenge. ATD therapy was continued with ethambutol (EMB) and subsequent addition of ofloxacin and streptomycin (SM). SGPT levels normalized within 3 weeks of drug discontinuation. The suspect drugs were gradually reintroduced in phases.

After about four weeks of initiating therapy, patient complained of bilateral proximal muscle weakness of the upper limbs mainly without any history of muscle pain or any features of neuropathy. Drug history revealed that he was on prednisolone initially at 40 mg daily dose for 2 weeks and then 20 mg daily dose when he developed muscle weakness. Clinically there was diminished muscle power in both arms and investigations revealed normal serum creatine kinase level, the electromyography (EMG) report showed only mild reduction of myoelectrical activity while nerve conduction velocity report (NCV) was normal but muscle biopsy was not done. A clinical diagnosis of suspected corticosteroid induced proximal myopathy was made and prednisolone withdrawn. There was marked improvement of his complaints with dechallenge and he was discharged from the hospital on 28 March 2005 as he had improved clinically and his LFT report was normal. In the subsequent follow-up visits serial monitoring of SGPT levels showed normal levels at 39.6 and 42.8 U/l (27 April and 8 June 2005).

However he complained of bilateral visual problems which he noticed sometime from end April onwards and ophthalmologic check up revealed pale optic disc, normal intraocular pressure, normal visual fields and no abnormality in colour vision. Visual evoked potential (VEP) report showed bilateral optic

neuritis. The clinical diagnosis of ethambutol induced bilateral optic neuritis was made and the suspect drug was withdrawn and he was only on INH, RIF and ofloxacin. Streptomycin was stopped after 2 months of initiation of therapy with daily 0.75 mg injections.

Patient had to be readmitted to the hospital with jaundice on 30 August 2005 as he complained of intense nausea and vomiting. Serum bilirubin at the time of admission was 2.9 mg/dl and SGPT – 109.3 U/l, SGOT – 81 U/l. Suspect drugs INH and RIF were stopped and again he showed marked improvement with dechallenge. Subsequently the serum bilirubin and enzymes levels normalized (bilirubin 1.4 mg/dl; SGPT – 39.3 and SGOT – 41 U/l on 3 October 2005). Patient was discharged on 7 October 2005 with the advice to continue RIF, Ofloxacin. LFT was normal (25 October 2005). The reappearance of hepatotoxicity with re-challenge confirmed the diagnosis of ATD induced hepatotoxicity. As per the Naranjo's ADR probability score this was found to be a case of definite association [9].

The patient finally completed anti-tubercular therapy in February 2006 with a modified regimen of INH, RIF, PZA, EMB initially and subsequently SM, Ofloxacin and RIF. He has attended several follow up visits and repeat MRI of brain showed regression of the cortical lesions and CT scan brain report was also normal. A repeat VEP test even after a year showed partial improvement of bilateral optic neuritis but there was significant clinical improvement of the ocular complaints. This case highlights that impact of serious adverse drug reactions associated with anti-tubercular therapy and the difficulties faced in subsequent drug selection and therapy completion.

Discussion

This case of neurotuberculosis developed a series of ATD induced adverse effects for which the suspect drugs had to be withdrawn temporarily. Initially he developed symptomatic hepatotoxicity with only raised liver enzyme levels but subsequently had icteric hepatotoxicity. INH and PZA had to be omitted while ofloxacin, rifampicin and streptomycin were given instead. Investigations were conducted to rule out other causes like infective hepatitis and no gall bladder, hepatic or pancreatic pathology were detected on imaging studies. Clinical examination or past history did not reveal any evidence of pre-existent liver disease and there was also no history no of alcohol addiction. Therefore on the basis of exclusion of other common causes of raised liver enzymes and jaundice, improvement with dechallenge and development of jaundice with rechallenge we arrived at the diagnosis of INH and PZA induced hepatotoxicity and as per the Naranjo's Adverse Drug Reaction Probability Scale [9] it was found to be of a *definite* association.

Antitubercular drugs that are known to cause hepatotoxicity are INH, RIF and PZA. The bandwidth of such reactions include asymptomatic rise of only ALT and AST to clinical jaundice [8,10]. Criteria for diagnosis of drug induced liver injury are rise in more than thrice the upper limit of normal (ULN) level of ALT or conjugated bilirubin or a combined increase in the levels of AST, alkaline phosphatase and bilirubin provided that one of these was at least twice the ULN [2,4,11]. The clinical patterns of hepatotoxicity are often classified as hepatocellular, cholestatic or mixed types. Liver injury attributed to INH, RIF and PZA is usually of the hepatocellular type. The risk factors that have been identified to predispose to hepatotoxicity are preexisting liver disease, malnutrition, female sex and alcohol addiction [8,10].

Ethambutol induced optic neuritis has been well documented since its first use and it commonly manifests as retro bulbar neuritis. Ocular toxicity presents as difficulty in visual acuity, scotomas and inability to distinguish between green and red colour. Classically it is dose and duration dependent and reversible

on therapy discontinuation [3,5]. The maximum visual recovery occurred in first six to eight weeks after stopping ethambutol. The visual recovery was partial and VEP remained abnormal even after 6 months. The exact mechanism of ocular toxicity is however not known. This was a case of *probable* association as per the Naranjo's Adverse Drug Reaction Probability Scale [9]. Though it was diagnosed to be ethambutol induced optic neuritis but incomplete recovery after 6 months of drug discontinuation often reduces the strength of such association. However there are published reports of ethambutol induced optic neuritis that have lead to incomplete recovery possibly indicating that the extent of damage done prior to drug discontinuation was significant enough to cause permanent damage [3].

During hospital stay he also developed corticosteroid induced proximal myopathy. Literature search shows that steroid induced myopathy is usually characterized by painless myopathy without features of neuropathy and normal or mild elevation of (creatine kinase) CK levels [1,6,7]. Usually chronic administration of oral corticosteroids of daily doses more than 10 mg prednisone (or its equivalent) predisposes patients to muscle injury. The underlying pathogenesis of steroid-induced myopathy associated with chronic use is a non-necrotic atrophic myopathy resulting in proximal muscle weakness without muscle pain or tenderness.

Conclusion

This case has been reported taking into consideration the rarity of simultaneous occurrence of a plethora of adverse drug reactions in the same patient and also to highlight the problem that clinicians face while treating patients of tuberculosis due to the occurrence of such ADRs. The morbidity associated with such ADRs often adds on to the disease morbidity and poses difficulty in drug regimen selection.

Implicating drugs in the causation of hepatitis, optic neuritis and myopathy was indeed a very difficult task especially in this case as the patient was on multiple drugs and a number of drugs had to be temporarily discontinued and then again reinstituted. Despite available literature to support such association there still remain various uncertainties to arrive at a confirmed diagnosis.

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