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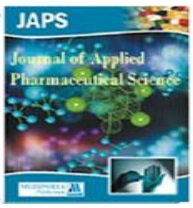

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Pharmacokinetic concerns in the management of drug induced vomiting in co-morbid tuberculosis patient: A case report from Malaysia

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ABSTRACT

A 46 years old patient with history of type II diabetes mellitus (DM) approached chest clinic with complaints of productive cough, low grade fever and night sweating. Positive sputum smear and cavities in upper lobe of left lung confirmed him as a pulmonary tuberculosis patient (PTB). He was prescribed World Health Organization recommended six months therapy for tuberculosis (TB). During treatment, patient suffered from persistent vomiting for which he was prescribed metoclopramide tablet (10mg). Total duration of TB treatment was prolonged up to 10 months which was attributed to frequent vomiting and uncontrolled blood sugar level throughout therapy. Appropriate glycaemic control is cornerstone in management of PTB patients with type II DM. According to United State Pharmacopoeia, dissolution time specification for rifampicin in fixed dose combination (FDC) is 45 minutes. This indicates that anti TB drugs must remain in gastrointestinal tract for at least 45 minutes. Administration of metoclopramide at least one hour before taking anti TB drugs can trim down episodes of vomiting.

Key words: Pulmonary tuberculosis; diabetes mellitus; vomiting; glycaemic control; metoclopramide; rifampicin.

INTRODUCTION

Tuberculosis (TB) is public health tragedy with an annual incidence rate of around 9 million cases. With an estimated 2 million deaths every year, it remains one of the major causes of adult mortality. Management of TB is quite difficult for patient and providers because of its longer duration which often results in low adherence to medication. Directly observed treatment short course (DOTS) strategy was adopted as basis of tuberculosis control in mid 1990s to overcome this problem. In this strategy isoniazid (H), pyrazinamide (Z), rifampicin (R), ethambutol (E) and streptomycin (S) are recommended as first line treatment (WHO, 2009). Outcome of treatment is reported on the basis of categories (table 1) developed and recommended by working group of WHO and International Union against Tuberculosis and Lung disease (IUATLD) (Espinal et al., 2000, Veen et al., 1998, WHO, 2009). These categories are developed for uniform reporting of treatment outcome in tuberculosis patients. Treatment success is defined as sum of cure and treatment completed (WHO, 2009). Unsuccessful outcome is calculated as sum of failure, default, transferred out (Romanus et al., 2000) and death.

Side effects associated with anti TB drugs have significant impact on duration of treatment. Abdominal and joint pain, nausea, vomiting, burning sensation in feet, itchiness and orange/red urine are minor side effects associated with essential anti TB drugs. Joint pain can be treated by giving aspirin, whereas burning sensation can be managed by administering 100mg pyridoxine daily (WHO, 2009). Nausea and vomiting can be reduced by counseling patient to take medication with small meals. Itchiness can be managed by giving anti-histamines. Skin rashes, deafness, dizziness, jaundice, confusion, visual impairment, shock and purpura are major side effects associated with anti TB drugs. In such case, either anti TB treatment should be stopped for

management of side effects or causative drug should be replaced or dropped off from treatment regimen (WHO, 2009).

Diabetes is one of major risk factors for tuberculosis and might decrease response to anti TB treatment. Additionally, tuberculosis might negatively affect glycaemic control by inducing glucose intolerance (Dooley and Chaisson, 2009).

We would like to discuss a case of pulmonary tuberculosis patient with uncontrolled type II diabetes mellitus (DM). During treatment, patient experienced persistent vomiting associated with anti TB drugs. Total duration of TB treatment was ten months.

CASE DESCRIPTION

A 46 years old Chinese male patient (54kg) came to chest clinic with history of productive cough for more than 6 months, low grade fever (on/off) for 3 weeks, night sweats, loss of weight & appetite for last 15 days. He was diagnosed as sputum smear confirmed patient of PTB (S +1, 1-9 acid fast bacilli/100 fields) with type II DM as co-morbidity. Chest radiograph showed cavities in upper lobe of left lung. Erythrocyte sedimentation rate (ESR) was elevated to 45 mm per hour. Fasting blood glucose (FBS) was 9.6 mmol/L. No record of anti-diabetic drugs was found from patient file. Drugs prescribed for intensive phase (IP) of TB treatment were isoniazid (225mg), rifampicin (450mg), pyrazinamide (1200mg) and ethambutol (825mg) (in fixed dose combination- film coated tablets), to be taken daily at primacy health care unit. After two weeks of treatment, patient complained persistent vomiting for which, he was prescribed metoclopramide tablet (10mg) to be taken with anti-TB drugs. After two weeks, patient again complained frequent episodes of vomiting. At this moment, he was advised to continue metoclopramide and anti TB drugs.

After two months of anti TB therapy (56 doses), patient's therapy was changed to continuation phase (CP). At this stage patient sputum smear became negative for acid fast bacilli (AFB). Cough and other symptoms were also improved. Culture and sensitivity results confirmed absence of resistant Mycobacterium strains to standard quadruple chemotherapy. FBS was 10.1mmol/L. During CP, patient was advised to take isoniazid (250mg) and rifampicin (600mg) (in fixed dose combination- film coated tablets) daily for 4 months at primary health care unit. After one week of CP, patient again reported at chest clinic with complaint of vomiting. At this moment, patient's therapy was stopped and he was advised to take metoclopramide (10mg) and ranitidine (150mg) tablets, 12 hourly. Once vomiting was completely resolved (7 days), patient was again advised to start CP of TB treatment. Patient was now counseled to take metoclopramide tablet (10mg) thirty minutes before taking anti-TB drugs. This strategy partially worked resulting in decreased frequency of vomiting. After two months of CP, patient showed clinical improvement although sign and symptoms were not completely resolved. He also complained occasional vomiting. He was advised to see chest physician after two months. Surprisingly on appointment date (after 4 months of CP), patient again complained persistent cough, shortness of breath, sore throat and lethargy. With this situation, chest physician decided to extend patient's therapy. After two months (first extension of CP) patients did not show significant improvement in sign and symptoms. As a result, his therapy was further extended. Finally after another two months, cough and fever was resolved. Chest X- ray showed static granuloma in upper lobe of left lung. ESR and other biochemical tests were normal. FBS was 9.9 mmol/L. Duration of IP and CP was 2 and 8 months, respectively. He was classified as "treatment completed" (table 1).

Table 1: Tuberculosis treatment outcome categories according to WHO and IUATLD recommendations

Outcome	Definition
Cure	A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.
Treatment failure	A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbor a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.
Died	A patient who dies for any reason during the course of treatment.
Default	A patient whose treatment was interrupted for 2 consecutive months or more.
Transfer out	A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.

DISCUSSION

By using WHO recommended anti TB regimen, treatment duration for PTB patient is 6 months (WHO, 2009). In this case, total duration of treatment was 10 months that was attributed to uncontrolled DM and side effects associated with anti TB drugs. DM is known risk factor for TB and can significantly affect immune system especially by altering bactericidal and phagocytic activity of polymorphonucler leucocytes (Marvisi et al., 1996). Wang et al (1999) reported that in diabetics, alveolar macrophages have less H_2O_2 (hydrogen peroxide) and are less activated. Diabetes also affects chemotaxis of monocytes and antigen presentation by phagocytes in response to *Mycobacterium tuberculosis* (Dooley and Chaisson, 2009). In current situation, patient's fasting blood glucose was uncontrolled throughout therapy. Recurrence of signs and symptoms of TB in 6^{th} month of therapy might be consequence of weakened immune system.

Rifampicin is inducer of cytochrome p450 enzyme system and therefore can decrease effective serum concentrations of sulfonyl ureas (Niemi et al., 2003). Rifampicin can also cause early-phase hyperglycemia with associated hyperinsulinaemia

(Takasu et al., 1982, Waterhouse et al., 2005). These effects of rifampicin on glycaemic control require careful monitoring with appropriate dose adjustment of anti diabetic agents necessary in diabetic patients with TB. Recurrence of sign and symptoms like cough and shortness of breath after six months of anti TB treatment might be due to poor glycaemic control.

Another important consideration in management of this patient was persistent vomiting associated with anti TB drugs. Most of times especially during IP, patient vomited within 30 minutes of drug intake. Vomiting was not resolved even after taking 10mg of metoclopramide with anti TB drugs. Furthermore, vomiting was partially resolved when administered thirty minutes before intake of anti TB drugs. For drug absorption, tablets must disintegrate in our gastrointestinal system followed by dissolution. According to United State Pharmacopoeia, dissolution time specification for rifampicin in fixed dose combination is 45 minutes (USP 26-NF 21, 2003). This indicates that anti TB drugs must remain in gastrointestinal tract for at least 45 minutes to attain minimum effective concentration. Orally administered metoclopramide achieves peak plasma concentration 1 to 2 hrs (Lacy et al., 2009) therefore it must be administered at least 45-60 minutes before intake of anti TB drugs.

CONCLUSION

Appropriate glycaemic control is among the most important issue in management of tuberculosis with diabetes. It is strongly recommended that such patients should be co-managed by chest physician and endocrinologist. Patient's compliance to anti diabetic drugs should be strictly observed. Establishment of TB-diabetes clinic can give more promising results. Moreover, proper management of side effects like vomiting can also trim down duration of tuberculosis treatment.

ETHICAL APPROVAL

Ethical approval was taken from Ministry of Health, Malaysia (ref. dim. KKM/NIHSEC/08/08/04P10-69).

COMPETING INTEREST

Authors declare that they have no competing interest.

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REFERENCES

Dooley KE & Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *The Lancet infectious diseases* 2009; 9: 737-746.

Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, Baéz J, Kochi A, Dye C & Raviglione MC. Standard short-course chemotherapy for drug-resistant tuberculosis. *JAMA: The Journal of the American Medical Association* 2000; 283: 2537-2545.

Lacy CAL, Armstrong LL, Goldman MP. & Lance LL. Drug information handbook. International ed. Lexi-Comp. USA (2009), 1119-1120.

Marvisi M, Marani,G, Brianti M & Della Porta,R. Pulmonary complications in diabetes mellitus. *Recenti progressi in medicina* 1996; 87: 623-627.

Niemi M, Backman JT, Fromm MF, Neuvonen PJ & Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. *Clinical pharmacokinetics* 2003: 42: 819-850.

Romanus V, Julander I, Blom-Bülow B, Larsson LO, Normann B & Boman G. (2000) Shortages in Swedish tuberculosis care. Good results only in 71 percent of cases after 12-month treatment as shown in a current study. *Läkartidningen* 2000; 97: 5613-5616.

Takasu N, Yamada T, Miura H, Sakamoto S, Korenaga M, Nakajima K & Kanayama M. (1982) Rifampicin-induced early phase hyperglycemia in humans. *The American review of respiratory disease* 1982; 125: 23-27.

USP 26-NF 21. United States Pharmacopeial Convention, Rockville, MD (2003), 1643-1646.

Veen J, Raviglione,M, Rieder HL, Migliori GB, Graf P, Grzemska M & Zalesky R. Standardized tuberculosis treatment outcome monitoring in Europe. Recommendations of a Working Group of the World Health Organization (WHO) and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting by cohort analysis of treatment outcome in tuberculosis patients. *European Respiratory Journal* 1998; 12: 505-510.

Wang CH, Yu CT, Lin HC, Liu CY & Kuo HP. Hypodense alveolar macrophages in patients with diabetes mellitus and active pulmonary tuberculosis. *Tubercle and Lung Disease* 1999; 79: 235-242.

Waterhouse M, Wilson C, White VLC & Chowdhury TA. Resolution of insulin-requiring diabetes after cessation of chemotherapy for tuberculosis. *Journal of the Royal Society of Medicine* 2005; 98: 270-271.

World Health Organization. Treatment of Tuberculosis: Guidelines 2009; WHO/HTM/TB/2009.420.