CMI Clinical Management Issues

Case report

Clinical management of carbamazepine intoxication during anti-tubercular treatment: a case report

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Abstract

We describe a 67-year-old man with medical history of focal post-stroke seizure and type 2 diabetes mellitus treated with carbamazepine, clobazam, gliclazide, insulin glargine, and omeprazole we visited for the onset in the last 7 days of asthenia, cough with mucus, breathing difficulty, chest pain, and weight loss. After clinical and laboratory tests, pulmonary tuberculosis was diagnosed, and a treatment with isoniazid, ethambutol, pyrazinamide rifampicin, and pyridoxine was started. Therapeutic drug monitoring of tuberculosis treatment documented that all drugs were in normal therapeutic range. Four days after the beginning of the treatment, we documented the improvement of fever, and three days later the patient showed sleepiness, visual disorder and asthenia. Clinical and pharmacological evaluation suggested a carbamazepine toxicity probably related to a drug interaction (Drug Interaction Probability Scale score = 6). The impossibility to switch carbamazepine for another antiepileptic drug, due to a resistant form of seizure, induced the discontinuation of tuberculosis treatment, resulting in the normalization of serum carbamazepine levels in one day (10 μg/ml) and in the worsening of fever, requiring a new clinical and pharmacological evaluation. The titration dosage of carbamazepine and its therapeutic drug monitoring allowed to continue the treatment with both antitubercular drugs and carbamazepine, without the development of adverse drug reactions. To date, tuberculosis treatment was stopped and clinical evaluation, radiology and microbiology assays documented the absence of tubercular infection and no seizures appeared (carbamazepine dosage 800 mg/bid; serum levels 9.5 μg/ml).

Keywords: Carbamazepine; Isoniazid; Rifampicin; Drug-drug interactions; Therapeutic drug monitoring

Gestione clinica di una intossicazione da carbamazepina durante un trattamento anti-tubercolare: un caso clinico

CMI 2015; 9(2): 41-44

http://dx.doi.org/10.7175/cmi.v9i2.1175

INTRODUCTION

Drug-drug interactions (DDIs) represent a common cause of adverse drug reactions (ADRs), particularly in patients using multiple drugs [1] inducing an impairment of quality of life and an increase in healthcare costs [2]. Therapeutic drug monitoring (TDM) is useful to improve drug safety reducing the development of ADRs, particu-

Why we describe this case

Drug-drug interactions are common in patients using multiple drugs. This case report suggests that, when a drug switch is not possible, the therapeutic drug monitoring may help physicians in the management of treatments that usually could not be administered together

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Disclosure
The authors declare they have no competing financial interests concerning the topics of this article

Blood tests	January 20th, 2014	Normal range
Glucose (mg/dl)	89	70-100
Creatinine clearance (ml/min)	87	85-130
Serum creatinine (mg/dl)	0.75	0.7-1.2
Potassium (mEq/l)	3.9	3.6-5
Total cholesterol (mg/dl)	165	< 220
LDL-cholesterol (mg/dl)	95	< 130
HDL-cholesterol (mg/dl)	40	35-39
Triglycerides (mg/dl)	72	50-150
Aspartate aminotransferase (IU/l)	26	8-48
Alanine aminotransferase (IU/l)	22	7-55
C-reactive protein (mg/l)	18	0.5-10
Erythrocyte sedimentation rate (mm/h)	62	0-22
White blood cells (cells/µl)	17,910	4,500-11,000

Table I. *Laboratory findings at admission*

larly during the treatment with drugs that have a narrow therapeutic index.

CASE REPORT

A 67-year-old man (weight = 65 kg, height = 1.68 m) was referred for evaluation on January the 20th, 2014 owing to the onset in the last 7 days of asthenia, cough with mucus, breathing difficulty, chest pain, and weight loss (1.8 kg). His medical history reported focal post-stroke seizure unresponsive to several antiepileptic drugs (i.e., oxcarbazepine, topiramate, levetiracetam, lamotrigine, valproic acid) and well-controlled type 2 diabetes mellitus (HbA1c < 7%).

Medications included carbamazepine (800 mg/bid), clobazam (100 mg/daily), gliclazide (30 mg/tid), insulin glargine (100 IU), and omeprazole (20 mg/daily). On physical examination, blood pressure was 108/70 mmHg, heart rate = 83 beats/min, respiratory rate = 20 breaths/min, temperature = 38.1°C, SpO_2 = 98% on room air; tuberculin skin test was performed.

Laboratory test revealed high levels of C-reactive protein (CRP = 18 mg/l), erythrocyte sedimentation rate (ESR = 62 mm/h) and white blood cells (WBC = 17,910 cells/µl). Other biochemical tests were in normal range (Table I).

Chest X-ray showed multifocal opacities in the right upper lobe with thickening and upward shift of the minor fissure, pleural effusion, and hilar lymphadenopathy. Three days later, tuberculin skin test proved positive, as confirmed by interferon-gamma release blood test, while microbiology of sputum documented the presence of *Mycobacterium tuberculosis*. Pulmonary tuberculosis was diagnosed and a treatment with a fixed-dose combination of isoniazid 75 mg/day, ethambutol 275 mg/day, pyrazinamide 400 mg/day and rifampicin 150 mg/day (Rimstar®) + pyridoxine (50 mg/day) was started. Two days later, the TDM of tuberculosis treatment, performed 2 hours after drug administration, documented that all drugs were in normal therapeutic range: isoniazid = 4.6 µg/ml (normal range = 3-6 µg/ml); ethambutol = 4 µg/ml (normal range = 2-6 µg/ml); pyrazinamide = 32.8 µg/ml (normal range = 20-50 µg/ml); rifampicin = 8.5 µg/ml (normal range = 8-24 µg/ml). Four days after the beginning of drug treatment, we documented the improvement of fever (36.8°C) but, three days later, the patient showed sleepiness, visual disorders, and asthenia. On physical examination, he was conscious and oriented in both time and space and presented somnolence, ataxia, and nystagmus; blood pressure was 97/68 mmHg with a pulse heart rate = 96 beats/min; electrocardiography revealed a cardiac block. Other causes of conscious disorders e.g. trauma, substance abuse, and infections were ruled out. Laboratory analysis and abdominal ultrasound examinations were negative; renal, liver, and heart failures were ruled out. Carbamazepine intoxication was postulated, and TDM confirmed it (serum carbamazepine levels = 16.60 µg/ml; normal range = 6-12 µg/ml). Pharmacological evaluation suggested a possible DDI between tuberculosis treatment and carbamazepine (Drug Interaction Probability Scale score = 6).

The impossibility to switch from carbamazepine to another antiepileptic drug, due to a resistant form of seizure, induced the discontinuation of tuberculosis treatment, resulting in the normalization of serum carbamazepine levels in one day (10 µg/ml). Two days later, we recorded a worsening of fever (37.9°C) that required a new clinical and pharmacological evaluation. Considering history, co-morbidity and drug treatment, tuberculosis treatment was re-administered and carbamazepine was titrated in 3 administrations/day (total = 400 mg/day), resulting in a good control of clinical symptoms. TDM of carbamazepine performed one day later was in normal range (10.1 µg/ml).

One- and two-month follow-up revealed a good control of tubercular disease, while

Time	Symptoms/laboratory tests	Treatment
Admission January 20th, 2014	Asthenia, cough with mucus, breathing difficulty, chest pain and weight loss	Carbamazepine (1,600 mg/day)
January 23rd, 2014	**Diagnosis of tuberculosis**	**Start** Rimstar® + pyridoxine
January 25th, 2014	TDM of tuberculosis treatment: normal range	
January 29th, 2014	Improvement of fever	
February 1st, 2014	Sleepiness, visual disorder, and asthenia; blood pressure = 97/68 mmHg, pulse heart rate = 96 beats/min; cardiac block Increase in plasma carbamazepine levels	**Stop** Rimstar® and pyridoxine
February 2nd, 2014	Normal plasma carbamazepine levels	
February 4th, 2014	Worsening of fever	**Start** Rimstar® + pyridoxine **Reduce** carbamazepine (total 400 mg/day)
February 5th, 2014	Normal plasma carbamazepine levels	
March, 2014	Normal plasma carbamazepine levels No seizures No adverse drug reactions	
April, 2014	Normal plasma carbamazepine levels No seizures No adverse drug reactions	Rimstar® switched to isoniazide + rifampicin
October, 2014	No tuberculosis	Stop isoniazide + rifampicin **Increase carbamazepine to 1,600 mg/day**

Table II. *Time course of drug treatment during the study*

TDM showed normal levels of both carbamazepine (10.0 µg/ml) and tuberculosis drugs (isoniazid = 4.7 µg/ml; ethambutol = l4.2 µg/ml; pyrazinamide = 34.5 µg/ml; rifampicin = 9.1 µg/ml), without the development of seizure or ADRs. Tuberculosis treatment was discontinued and switched to a fixed-dose combinations of isoniazide + rifampicin. In October, tuberculosis treatment was stopped and clinical evaluation, as well as radiology and microbiology assays, documented the absence of tubercular infection. No seizure or ADRs appeared (carbamazepine dosage = 800 mg/bid; serum levels = 9.5 µg/ml). Time course of drug treatment during the study is reported in Table II.

DISCUSSION

Here we report the case of a 67-year-old man with type 2 diabetes mellitus and resistant epilepsy responsive to carbamazepine and clobazam. Due to the development of tuberculosis, the patient was hospitalized and treated with isoniazid, ethambutol, pyrazinamide, and rifampicin, with a good control of tuberculosis.

It has been reported that in patients with tuberculosis, diabetes contributes to increase severity [3], reducing the response to tuberculosis treatment [4]. In our patient, clinical evaluation documented an improvement of tuberculosis symptoms, while TDM revealed that tuberculosis drugs were in normal range. However, 7 days after the beginning of tuberculosis treatment, the patient lamented sleepiness, visual disorder, and asthenia. Several papers showed that the administration of isoniazid in a patient treated with carbamazepine may induce the development of liver failure [5,6] able to induce conscious disorders.

Laboratory and clinical evaluation excluded secondary causes of conscious disorders (i.e. alcohol and substance abuse, encephalitis, hepatitis, neuroleptic malignant syndrome, drug toxicity).

Pharmacological evaluation hypothesized a carbamazepine intoxication related to a drug-drug interaction. In fact, carbamazepine is highly bound to plasma proteins (75-80%), with an half-life of 12-20 hours, and is metabolized in the liver by cytochrome P450 (CYP3A4) [7]; isoniazid and ethambutol are strong and weak CYP3A4 in-

Main questions a doctor should ask him/herself in this situation

- *Have I excluded other causes able to induce symptoms?*
- *Can I change the treatment?*
- *Can I evaluate the plasma levels of each drug?*

hibitors, respectively [8,9]. Therefore, these drugs probably slowed the elimination of carbamazepine in our patient.

In fact, TDM documented high serum carbamazepine levels, and the discontinuation of tuberculosis treatment induced a decrease in serum carbamazepine levels, with a worsening of tuberculosis.

In agreement with our previous papers [10,11], using the Drug Interaction Probability Scale (DIPS), we hypothesized an interaction between tuberculosis treatment and carbamazepine. The titration of carbamazepine dosage and its TDM allowed continuation of combined treatment with a good control both of seizure and tuberculosis and without the development of ADRs.

The Summary of Product Characteristics (SPCs) represents the primary source of information about DDIs for health care professionals. Unfortunately, DDIs cannot be listed exhaustively, consequently the information on potential DDIs may be insufficiently described, due to the limited space in the SPC.

In fact, in the present case, SPC suggests to evaluate carefully the co-administration of carbamazepine during the treatment with isoniazid, but when it is not possible to change the drugs, TDM is needed to optimize the therapeutic efficacy and safety of carbamazepine.

Key points

- *Drug-drug interactions (DDIs) may be common during a multiple therapy*
- *DDIs must be considered during a differential diagnosis*
- *Clinical conditions as well as therapeutic drug monitoring may be important during the clinical management*

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