Phenytoin and carbamazepine cross reactivity: report of a case and review of literature

U K Misra, J Kalita, C Rathore

Cross reactivity between phenytoin, carbamazepine, and oxcarbazepine is reported. An 8 year old boy with partial seizures developed maculopapular rash with itching on day 15 of carbamazepine therapy. After stopping carbamazepine, phenytoin 100 mg daily was prescribed two days later. On the 12th day of phenytoin therapy he developed cervical and axillary lymphadenopathy with fever. Lymph nodes revealed reactive hyperplasia. Oxcarbazepine 75 mg twice daily also resulted in oral and mucosa ulceration. The seizures were controlled without any side effects with sodium valproate 200 mg three times a day and gabapentin 300 mg twice a day. Due to the cross reactivity of oxicontivulsants (phenytoin, carbamazepine, and oxcarbazepine), valproate or newer anticonvulsants should be used if a patient has sensitivity to these drugs.

ADVERSE DRUG REACTION

Phenytoin, phenobarbitone, and carbamazepine are first line antiepileptic drugs. Despite the availability of newer antiepileptic drugs, these first line drugs are commonly used because of their efficacy and low cost. These drugs have the limitation of a high toxicity, which involves the skin, liver, brain, kidney, and the gastrointestinal and haemopoetic systems, and these drugs result in both dose related toxicity and hypersensitivity reactions. The clinical spectrum of first line antiepileptic drugs is quite wide, ranging from a subtle skin rash to life threatening systemic toxicity and from benign lymphadenopathy to an association with malignant lymphoma.1,2 An overlap between phenytoin and carbamazepine toxicity has also been reported,3 which is not commonly appreciated by treating physicians. We recently managed a patient who had a skin reaction after carbamazepine and oxcarbazepine and lymphadenopathy after phenytoin treatment. We report this patient and highlight the problem of cross reactivity among first line antiepileptic drugs.

CASE REPORT

An 8 year old boy presented having had a right partial motor seizure one month previously. The first seizure involved his right face, arm and leg, was associated with tonic-clonic convulsions lasting for 1–2 min, and was followed by postictal confusion for 30–45 min. The second seizures occurred 20 days later. After the last attack, the patient developed right sided facial weakness. There was no history of associated fever, headache, or vomiting. The patient was a well nourished boy; his weight was 22 kg and general physical examination was normal. He had a right sided upper motor neurone type of facial weakness.

His blood counts, urinalysis, and a plain radiograph of his chest were normal. Cranial computed tomography revealed a ring enhancing lesion with an eccentric nodule in the left parietal cortex consistent with cysticercal granuloma. The patient was prescribed carbamazepine 100 mg three times a day. After 15 days of carbamazepine treatment he developed generalised itching and a maculopapular rash on his trunk, limbs, face, palms, and soles. There was no fever or jaundice. His haemoglobin was 116 g/l and leucocyte count 5.3 × 10^9/l with 3% eosinophils. Erythrocyte sedimentation rate was 30 mm in the first hour. His liver and kidney function tests and serum electrolytes were normal. Carbamazepine was discontinued immediately and phenytoin 100 mg daily was prescribed two days later once his rash started regressing. Twelve days after phenytoin therapy, the patient developed a low grade fever and painful cervical and axillary lymphadenopathy with recurrence of right partial seizure. There was no accompanying arthralgia, skin rash, or oedema this time. On examination, the patient was febrile with a temperature of 37.5°C, pulse 110 beats/min, and blood pressure 100/70 mm Hg. He had bilateral cervical and axillary lymphadenopathy which was discrete, firm, and 5–10 mm in size. The patient also had gaze-evoked nystagmus.

His total leucocyte count was 6.4 × 10^9/l with 58% polymorphs, 31% lymphocytes, and 1% eosinophils. Urinalysis was normal. Serum bilirubin was 3.4 μmol/l, aspartate aminotransferase 37 U/l, and alanine aminotransferase 52 U/l. Blood urea, serum creatinine, radiography of the chest, and ultrasonography of the abdomen were normal. IgM antibody to cytomegalovirus was negative. Fine needle aspiration of the right cervical lymph node revealed reactive hyperplasia. The serum phenytoin level was 22.4 μg/l.

Phenytoin was discontinued abruptly and the patient was prescribed sodium valproate 200 mg three times a day instead of monitoring of his liver function. His fever subsided within a week and the neck gland regressed 15 days later. After one month of sodium valproate therapy, he again started having partial motor seizures, which were restricted to the right side of his face. He was advised to take oxcarbazepine 75 mg twice daily in addition to valproate. Four days after the addition of oxcarbazepine he developed multiple oral mucocutaneous ulceration and oxcarbazepine was discontinued abruptly and gabapentin 300 mg twice daily was prescribed. His seizures have been controlled for the last eight months on sodium valproate 200 mg three times a day and gabapentin 300 mg twice a day without any side effects.

DISCUSSION

Our patient developed a maculopapular skin rash on carbamazepine, mucocutaneous ulceration on oxcarbazepine, and lymphadenopathy and fever on phenytoin treatment soon after starting the respective drugs. The temporal relationship of these side effects soon after starting antiepileptic drugs is consistent with drug toxicity. The dermatological side effects of carbamazepine include macular, maculopapular rash, eczematoid dermatitis, purpuria, urticaria, erythoderma, exfoliative dermatitis, erythema multiforme, and toxic epidermal necrolysis. Photosensitivity and
mucosal involvement can also occur.1 Besides a skin reaction, carbamazepine can also produce fever, lymphadenopathy, pseudolymphoma syndrome,2 serum sickness, systemic lupus erythematosus-like syndrome,3 and hypersensitivity vasculitis.4 The side effects of carbamazepine were restricted to a mild maculopapular rash in our patient but these may be quite variable. Generally these appear after 1–8 weeks of exposure. In our patient the rash was noted on the 15th day.

Our patient developed fever and cervical and axillary lymphadenopathy on the 12th day after starting phenytoin. An association between lymphadenopathy and phenytoin was reported soon after its introduction in 1938.5 An association between lymphadenopathy, pseudolymphoma, and even malignant lymphoma has been reported in several case reports and small series. In a large study, out of 58 patients with lymphadenopathy receiving antiepileptic drugs, 2 although cervical followed by a combination of phenytoin and phenobarbitone patients with lymphadenopathy receiving antiepileptic drugs, case reports and small series. In a large study, out of 58

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