

## ADVERSE DRUG REACTION

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

U K Misra, J Kalita, C Rathore

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Cross reactivity between phenytoin, carbamazepine, and oxcarbazepine is reported. An 8 year old boy with partial seizures developed maculopapular rashes 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 aromatic anticonvulsants (phenytoin, carbamazepine, and oxcarbazepine), valproate or newer anticonvulsants should be used if a patient has sensitivity to these drugs.

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 haemopoietic 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.<sup>1,2</sup> An overlap between phenytoin and carbamazepine toxicity has also been reported,<sup>3</sup> 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  $5.3 \times 10^9/l$  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  $6.4 \times 10^9/l$  with 58% polymorphs, 31% lymphocytes, and 1% eosinophils. Urinalysis was normal. Serum bilirubin was 3.4  $\mu\text{mol/l}$ , 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  $\mu\text{g/l}$ .

Phenytoin was discontinued abruptly and the patient was prescribed sodium valproate 200 mg three times a day instead with 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, purpura, urticaria, erythroderma, exfoliative dermatitis, erythema multiforme, and toxic epidermal necrolysis. Photosensitivity and

mucosal involvement can also occur.<sup>1</sup> Besides a skin reaction, carbamazepine can also produce fever, lymphadenopathy pseudolymphoma syndrome,<sup>4</sup> serum sickness, systemic lupus erythematosus-like syndrome,<sup>5</sup> and hypersensitivity vasculitis.<sup>6</sup> 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.<sup>7</sup> 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, phenytoin was most commonly implicated (40 cases) followed by a combination of phenytoin and phenobarbitone (seven cases) and mesentoin (four cases).<sup>2</sup> Although cervical lymphadenopathy has been reported to be common after phenytoin exposure, generalised lymphadenopathy seems to occur more often.<sup>8–9</sup> In a study of 25 lymph nodes that had been collected from patients taking phenytoin from 1965 to 1991, the timing of development of lymphadenopathy after phenytoin exposure ranged from one week to 30 years. The histology was benign in 15 and consistent with non-Hodgkin's lymphoma in seven and Hodgkin's lymphoma in three patients. Sequential biopsy was available in five patients; in two of these patients there was progression from paracortical hyperplasia to malignant lymphoma. This study highlights heterogeneity and the non-specific nature of histological changes in lymphadenopathy associated with phenytoin.<sup>2</sup> However reports of true lymphoma with phenytoin should be regarded as an association rather than causative.

An overlap in the toxicity of phenytoin, phenobarbitone, and carbamazepine has been described under the rubric of anticonvulsant hypersensitivity syndrome.<sup>3</sup> There is clinical<sup>10</sup> and in vitro<sup>11</sup> evidence of cross reactivity between carbamazepine and phenytoin, although cross reaction in patients switched from one drug to the other does not always occur.<sup>10</sup> In our patient, however, there was significant cross reactivity between phenytoin and carbamazepine and oxcarbazepine. The basis of cross reactivity can be explained by their mechanism of action. The aromatic anticonvulsants are metabolised to hydroxylated aromatic compound—for example, epoxic metabolites formed by cytochrome P450<sup>12–13</sup> or other metabolites formed by myeloperoxidase.<sup>14</sup> These molecules are bound to tissue macromolecules causing cell damage or act as haptan to elicit an immune response.<sup>11–15</sup> Oxcarbazepine is a 10 keto derivative of carbamazepine and has similar antiepileptic efficacy and fewer unwanted side effects than carbamazepine as it is a prodrug for the monohydroxyderivative. A cross reactivity of one in four has been reported between oxcarbazepine and carbamazepine.<sup>16</sup> In another study, however, all the three patients who had skin rashes with oxcarbazepine were sensitive to carbamazepine.<sup>17</sup>

To prove the role of hypersensitivity, patch test and in vitro lymphocyte transformation tests have been done. These tests,

though useful in establishing the diagnosis, are reliable only after the signs of toxicity have subsided.<sup>1</sup> As soon as the diagnosis of hypersensitivity to aromatic antiepileptic drugs is suspected, the offending drug should be discontinued. The laboratory tests should include blood count, serum transaminase, urinalysis, and creatine kinase. Corticosteroids are usually administered if symptoms are severe. These seizures are best managed by valproate, benzodiazepine, and newer anticonvulsants. Drugs of same group (aromatic antiepileptic drugs) should be avoided if there is toxicity to any one of them.

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## Authors' affiliations

U K Misra, J Kalita, C Rathore, Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Correspondence to: Professor U K Misra, Department of Neurology, Sanjay Gandhi PGIMS, Raebareilly Road, Lucknow 226014, India; ukmisra@saggi.ac.in, ukmisra@indiatimes.com

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