Letter to the Editors

The onset of acute oxcarbazepine toxicity related to prescription of clarithromycin in a child with refractory epilepsy

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In comparison with carbamazepine, oxcarbazepine (OXC) has fewer associated side-effects and a reduced number of reported drug–drug interactions. The only cases of serious toxicity have been documented after suicide attempts using multiple drugs [1], but OXC toxicity alone has never been noted to be the only cause of death [2]. The main drug–drug interactions reported (in particular with other antiepileptics such as carbamazepine, phenobarbital and sodium valproate) actually result in the lowering of plasma OXC concentrations [3, 4].

We report a case of severe OXC toxicity after starting clarithromycin in a patient with refractory epilepsy and discuss the mechanism of this potential interaction. We suggest that clarithromycin may inhibit the efflux proteins of the blood–brain barrier (BBB), which are thought to be overexpressed in drug-resistant patients [5]. This inhibition may result in increased cerebrospinal fluid (CSF) concentrations of OXC and explain the signs of toxicity observed.

A 10-year-old boy with known refractory epilepsy presented to our department with symptoms suggestive of acute OXC toxicity. His past medical history included a diagnosis of epilepsy at the age of 18 months when he presented with generalized tonic clonic seizures and associated global developmental delay. There were no other significant illnesses or dysmorphism and he had been born at term without complications. The first child of non-sanguineous North African parents, there was a family history of epilepsy in three paternal second cousins (one with developmental delay). Diagnostic investigations performed included normal brain magnetic resonance imaging and positron emission tomography scan, karyotyping, genetic screening for fragile X syndrome and a metabolic screen, all of which were unremarkable. His medications at the time of presentation included: OXC 540 mg am/510 mg nocte, lamotrigine 100 mg b.d., sodium valproate 100 mg am/300 mg and topiramate

100 mg b.d. Despite the treatment, between two and three epileptic fits were reported per month. A course of clarithromycin (250 mg b.d.) was started due to a mild respiratory tract infection 3 days after the onset of coryzal symptoms. An hour after he had taken the first dose, the parents noticed their son was unsteady on his feet (Figure 1) and had a brief episode where he appeared unresponsive. Twenty-four hours after starting the antibiotic, he was brought to our paediatric emergency department with an increase in symptoms including vomiting, drowsiness and dizzy spells. Clinical neurological examination revealed hyperkinesia, ataxia and nystagmus. At the time of presentation, the patient was already afebrile with no respiratory signs other than mild coryzal symptoms. The rest of the clinical examination was unremarkable. On admission, blood tests were essentially normal, including: plasma electrolytes, liver enzymes, renal function and inflammatory markers (sodium 142 mmol l⁻¹, potassium 3.5 mmol l⁻¹, C-reactive protein 57 mg l⁻¹). An initial electroencephalogram showed a decrease in paroxysmal activity. Plasma levels of sodium valproate were dosed as suboptimal (21.7 mg l⁻¹, ref 50–100 mg l⁻¹) and as an incidental finding, the patient was noted to be mildly hypocalcaemic (2.08 mg l⁻¹, ref 2.20–2.80 mg l⁻¹). Twelve hours after admission, the dose of OXC was reduced to 420 mg (80% of the original) and the clarithromycin was stopped. The other medications remained unchanged. After a further 12 h, the dose of OXC was increased back to 540 mg as the clinical symptoms were much improved. Following this increase, once again the patient developed drowsiness and ataxia. As a result, the OXC dose was halved for 24 h. No further symptoms were reported and the dose was then progressively increased back to the initial value over a period of 72 h. No further symptoms or seizures were reported during the rest of his hospital stay and the patient was discharged home after 5 days.

Figure 1

Clinical symptoms vs. time since starting clarithromycin

OXC is particularly recommended due to the minimal side-effects and drug interactions seen in comparison with carbamazepine. We report the first case of OXC toxicity likely to have been induced by a drug–drug interaction with clarithromycin (250 mg b.d.). After two doses of clarithromycin, the patient needed to be hospitalized as an emergency for suspected toxicity. Many of the symptoms observed in our patient are known to be linked to possible OXC toxicity, including drowsiness, dizziness, nausea, vomiting, hyperkinesia, ataxia and nystagmus. Once the clarithromycin was stopped, a clear improvement was seen ($t_{1/2} = 4$ h). However, the early re-introduction of OXC (back to the initial dose after 12 h) resulted in a further similar episode. The dose was then halved and progressively increased over a period of 72 h with no further problems. This shows there is a latent period in the mechanism of interaction between clarithromycin and OXC. Furthermore, halving the OXC dose did not lead to any seizures in our patient. In the absence of treatment with clarithromycin, the patient had not previously developed any signs of OXC toxicity (despite being on the medication at the same dose for several months).

To date, the only reported OXC interactions are due to modifications in liver metabolism. Ninety-five percent of OXC is metabolized to the active monohydroxy derivative

(DMH) and 4% to the inactive dihydroxy derivative (DDH). Pisani *et al.* have shown that an increase in levels of the active metabolite and a decrease in the inactive form occur when OXC is administered in conjunction with viloxazine (an antidepressant) [6]. This inhibition of the conversion of the active DMH to the inactive DDH form has never been linked to any adverse clinical effects. Studies carried out to research possible interactions between macrolides (erythromycin) and OXC have not shown any interactions [7]. However, such studies were conducted in healthy volunteers with no prior drug resistance, and the results were based on potential changes in plasma concentrations of OXC and DMH.

It has been shown that normal OXC or DMH serum levels do not exclude central nervous system (CNS) toxicity or the occurrence of serious neurological adverse effects [8]. The lack of correlation between serum OXC levels and neurological side-effects can be explained by the fact that serum levels do not give a reliable reflection of the actual levels in the CNS. Thus, passage across the BBB may be an important factor in the efficacy of OXC and DMH. Numerous studies have demonstrated the role played by efflux proteins present on the membranes of cells which make up the BBB [9]. Increased expression of efflux proteins such as the P-glycoproteins (multidrug resistance 1 and 2) and

the Multidrug Resistance Proteins 1–9 has been observed in some drug-resistant patients, which could be responsible for a decreased concentration of OXC in the CSF, resulting in decreased clinical effects [4, 9–11]. Macrolides are known to be potent inhibitors of P-glycoprotein (50% decrease in activity). Therefore, we propose that the toxic side-effects observed in our patient after starting clarithromycin (whilst already on OXC) may be explained by an increase in brain OXC concentrations due to the inhibition of the active BBB efflux proteins.

We recommend physicians consider adjusting the dose of OXC when using a macrolide in drug-resistant patients due to the potential risks of drug toxicity.

Competing interests

None to declare.

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