

# Erythromycin-induced Carbamazepine Toxicity: An Avoidable Problem

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## Abstract

Carbamazepine (CBZ) is frequently prescribed for the control of generalized and partial seizures in children. Erythromycin is a macrolide antibiotic often used in children with minor bacterial infections, especially in those with an allergy to penicillin. Multiple case reports and pharmacokinetic studies have established that erythromycin causes CBZ toxicity when the two drugs are given concurrently. Despite all the available evidence on the adverse interaction between these two drugs, doctors continue to prescribe both medications. We report yet another case of CBZ toxicity induced by the concurrent administration of erythromycin. Doctors need to be aware that this drug combination predictably causes adverse side effects and they should seek alternative therapy for patients receiving long-term CBZ therapy who need antibiotic coverage.

## Key words

Carbamazepine; Erythromycin; Drug interaction.

## Case Report

A 4-year-old girl being followed up in our neurology clinic for idiopathic epilepsy was on maintenance therapy with CBZ (300 mg/day in three divided doses, which was equivalent to 15 mg/kg/day). She had been on the same dose of CBZ for the past 12 months and the serum level had been found to be within the normal therapeutic range (34-51 umol/l). Her seizure disorder had been under good control. Two days prior to her presentation to our hospital, erythromycin had been started by a private practitioner at a dose of 250 mg four times a day, for acute tonsillitis. Within 48 hours she had developed an unsteady gait and slurring of speech. There was no history of any recent vaccination and the only medications she had been on were CBZ and erythromycin.

On admission, she was alert and afebrile. Vital signs were normal. Neurological examination revealed an ataxic gait, horizontal nystagmus and slurred speech. Examination of her other systems was unremarkable.

Investigations including complete blood count, plasma glucose, liver and renal function tests, cranial computerized tomography and examination of the cerebrospinal fluid were all normal. However, a CBZ level taken on admission was markedly elevated at 121 umol/l.

With the discontinuation of erythromycin and CBZ, the child's condition rapidly improved. All the neurological symptoms and signs disappeared by the third day of hospitalisation, when her serum CBZ level was also found to have fallen to 21 umol/L. Treatment with CBZ was then reinstated at her usual dosage of 15 mg/kg/day. She suffered no further side-effects and remained well when seen again 3 months after discharge from hospital.

## Discussion

CBZ is almost totally absorbed from the gastrointestinal tract and produces a peak serum concentration after 4-8 hours. It is 75%-80% protein bound. The major metabolic pathway starts in the hepatic mixed function oxidase (P450) system, producing carbamazepine-10,11-epoxide.<sup>1</sup> Erythromycin interferes with the metabolism of CBZ by competitive binding to cytochrome P-450, blocking the metabolism of CBZ to carbamazepine-epoxide.<sup>2</sup> Symptoms of intoxication usually appear within 24 hours of starting therapy with erythromycin and resolve 48 to 72 hours after discontinuation of either drug. In a retrospective study of 427 cases of acute CBZ poisoning,

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Schmidt et al<sup>3</sup> found that such overdoses follows a distinct four-stage sequence of clinical events with corresponding CBZ plasma levels. Stage 1 is characterized by coma and seizures with a CBZ level more than 107  $\mu\text{mol/L}$ . In stage 2, patients are combative, may hallucinate or display choreiform movements with a CBZ level of 64-107  $\mu\text{mol/L}$ . Drowsiness and ataxia are the dominant features of stage 3 when CBZ level is between 47 to 64  $\mu\text{mol/L}$ . During stage 4, unexpected deterioration may occur and late relapses have been documented. This is when the CBZ level has fallen to less than 47  $\mu\text{mol/L}$ . In their study, Schmidt et al. demonstrated a moderate association between CBZ dose and plasma levels but no significant association between plasma levels and mortality in acute CBZ poisoning. They also suggested that the course of intoxication is more benign in patients aged below 15 years. However, similar data on acute toxicity due to the interference of CBZ metabolism by other drugs in patients who are on regular therapeutic dose of CBZ is yet to be made available.

All well-documented drug interactions are essentially avoidable. Clearly, it is of utmost importance that prescribing doctors enquire about concurrent medications at all times and consider their potential interactions.

Nevertheless, this is sometimes not so easy in Hong Kong as a lot of patients (children and adult alike) may be taking medications from a few different doctors at the same time without the doctors' knowledge. Parents should be advised and educated to inform doctors of all the concurrent medications their children are on. Another way to avoid such mishap is for patients to have an obvious sticker or a warning chop placed on the front page of their epilepsy diaries, stating that they are on CBZ and should avoid drugs like erythromycin if possible. Pharmacists should also pay close attention to such potential interactions and question prescribers when appropriate. Finally, if it is absolutely necessary to prescribe erythromycin to patients already on CBZ, the CBZ dose should be reduced and the level closely monitored.

## References

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