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A Case of Suspected Drug Interaction Between Topiramate and Co-administered Clarithromycin/Pranlukast

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Abstract

Case description: A 4-year-old boy presented with tuberous sclerosis and symptomatic partial epilepsy of the upper right extremity. Topiramate was prescribed for the treatment of epilepsy, and seizure behavior was well controlled. However, the patient experienced a significantly increased seizure frequency immediately after the administration of clarithromycin and pranlukast treatment during topiramate treatment. Topiramate is metabolized by CYP3A4, which is inhibited by clarithromycin and pranlukast. Thus, pharmacokinetic interactions may have occurred. This is the first report of a possible drug interaction between topiramate, clarithromycin, and pranlukast.

Keywords: Topiramate; Clarithromycin; Pranlukast; Interactions

Case Description

The patient was a 4-year-old boy with a 2-year history of symptomatic partial epilepsy with seizures in the upper right extremity. He had histories of tuberous sclerosis and infantile spasms, and his mother also had tuberous sclerosis. Following a worsening of status epilepticus, the patient was transferred and admitted to the Department of Pediatrics, Ehime University Hospital, where he had been receiving treatment for seizures. During a 2-week hospitalization period, he frequently experienced partial seizures in the upper right extremity, sometimes >10 times/day, which continued until discharge from hospital. The patient had been taking lamotrigine and vigabatrin for seizure control, and topiramate (5 mg) twice daily was added to the existing treatment. When topiramate was increased to 10 mg twice daily, the patient's mother reported that he became drowsy, and that this was improved by a dose reduction to 7.5 mg twice daily.

The course after discharge is shown in Figure 1. The frequency of partial seizures decreased in concurrence with increased doses of lamotrigine. The patient began to experience seizure-free days approximately 3 months after discharge. Seizure control was achieved, although daytime sleepiness increased. The patient's mother reported after the treatment of acute bronchitis and otitis media that he was "yawning in the morning" and "sleeping on the way to the nursery".

After achieving seizure control, the patient's condition suddenly deteriorated. His mother reported that seizures increased from 112 days after discharge and the patient developed nocturnal insomnia, although his daytime sleepiness disappeared. At that time, pranlukast (70 mg, twice daily), carbocisteine (200 mg, thrice daily), tipepidine (13.3 mg, thrice daily), and clarithromycin (150 mg thrice daily; later changed to 150 mg once daily) were prescribed for the treatment of acute bronchitis and otitis media. These drugs were discontinued 112 days after discharge. On the same day, vigabatrin was decreased from 900 mg twice daily to 750 mg twice daily. There was no significant improvement in the increased frequency of seizures, and the patient's nocturnal insomnia continued.

What is New and Discussion

It is well known that clarithromycin, a macrolide antibiotic, can produce drug interactions via inhibition of CYP3A4 [1]. In addition, topiramate and pranlukast, which is an anti-allergic agent, are primarily metabolized by CYP3A4. Therefore, the concurrent use of clarithromycin and topiramate to piramate may inhibit to piramate metabolism, leading to increased blood concentration of topiramate. Conversely, competitive metabolism may occur with the concurrent use of topiramate and pranlukast, as they are both metabolized by CYP3A4, thereby producing increased blood concentrations of both drugs. Thus, concurrent use of pranlukast and topiramate may also increase blood concentration of topiramate.

Higher doses of topiramate are more effective than lower-dose regimens, although side effects are dose-dependent. In the present case, the side effects during hospitalization were dose-dependent. Therefore, we suggest that the blood level of topiramate was increased by concurrent use with clarithromycin/pranlukast, and decreased when these drugs were discontinued. This may have caused a subsequent decrease in the anti-epileptic effect and ameliorated the side effect of somnolence, there by producing nocturnal insomnia.

In terms of the potential effects of other drugs administered to the patient, lamotrigine had no effect on the change in seizure frequency, as the dose was unchanged at 3 months after discharge. Furthermore, lamotrigine is metabolized by glucuronosyl transferase, and is therefore unlikely to have caused a drug interaction in the present case. With regard to vigabatrin, dose reduction and the increased frequency of seizures occurred at approximately the same time. However, it is unlikely that the dose reduction produced an increase in seizure frequency, as elevated levels of gamma-amino butyric acid

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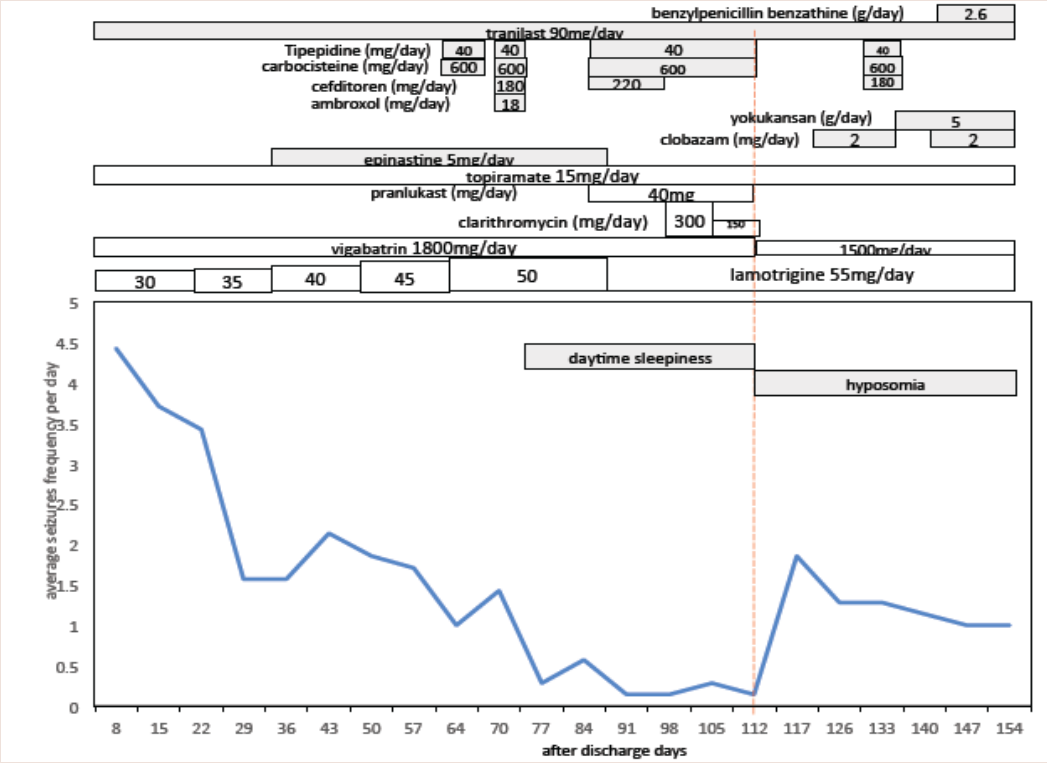

Figure 1: The course after discharge.

in the brain following a single dose of vigabatrin are maintained for at least 1 week [2,3].

In the present case, we observed a causal relationship between topiramate and adverse clinical events. The Naranjo scores for clarithromycin and pranlukast were as low as ≤2 [4]. In contrast, scores on the Drug Interaction Probability Scale (DIPS), which is a new tool to evaluate drug interactions, were 5 for both drugs, indicating that drug interactions may have contributed to the adverse events despite the low Naranjo scores [5]. Furthermore, clarithromycin, topiramate and pranlukast are primarily metabolized by CYP3A4. Therefore, the concurrent use of clarithromycin and topiramate may inhibit topiramate metabolism.

The Naranjo score is a much simpler probability scale designed to sensitively monitor adverse drug reactions (ADRs) and to improve inter-rater reliability. This scale enables categorical classification of ADRs as "definite", "probable", "possible", or "doubtful" based on the answers to 10 questions. The Naranjo scale is useful for assessing the causality of adverse reactions. However, the criteria of the Naranjo scale were not intended for evaluation of adverse events resulting from the interaction of 2 drugs, and thus the validity of the scale is limited to evaluations of single-drug adverse drug reactions. The DIPS was designed to assess the probability of a causal relationship between a potential drug interaction and an observed adverse drug reaction. The DIPS add or subtracts points based on the answers to a series of questions specific to the assessment of a potential drug interaction. We therefore suggest that DIPS scores be used in conjunction with Naranjo scores when assessing the potential causality of adverse events.

Conclusion

In conclusion, pharmacokinetic interactions may have occurred in this case because topiramate is metabolized by CYP3A4, which is inhibited by clarithromycin and pranlukast. This is the first report of a possible drug interaction between topiramate, clarithromycin, and pranlukast.

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