The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics

Perampanel intoxication with impaired consciousness triggered by infection

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Received May 2, 2020 / Accepted May 24, 2020 / Published June 23, 2020.

To the Editor: Perampanel is a noncompetitive alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid receptor antagonist indicated for treating partial, secondary generalized, and tonic-clonic seizures. Therapeutic drug monitoring has been useful in determining its efficacy and adverse reactions [1]. Although perampanel has been reported to have no association with central nervous system (CNS) toxicity [2], actually, there are reports where perampanel overdose caused impaired consciousness [3] and severe aggression [4]. In this letter, we report a case of impaired consciousness due to perampanel intoxication which was due to not overdose but inflammation. We obtained signed informed consent from the patient for the publication of this report.

Case Report: A 74-year-old woman presented with a 65-year history of temporal epilepsy. Although seizure control was refractory to the combination of levetiracetam 2000 mg/day and carbamazepine 800 mg/day, carbamazepine was switched to perampanel 6 mg/day and lacosamide 300 mg/day. As a result, the frequency of seizures was reduced to several times per 4 weeks, leading to discharge. She was, however, re-hospitalized due to mental stress following the death of a relative on Day 1 as shown in Figure 1. She suffered from tremors which appeared to be different from previous epileptic seizures. The next day, she developed high fever (39℃), and ful and bronchitis was suspected based on the clinical symptoms despite of the negative influenza test. Thereafter, she was treated with an infusion of peramivir hydrate 300 mg. Concurrently, however, her perampanel concentration was increased from 524 (180-980) ng/ml at the time of previous discharge to 1490 ng/ml at this admission. The C-reactive protein (CRP) level was 6.5 mg/dl without leukocyte elevation. Her appetite was decreased but recovered after 3 days, again leading to discharge. On Day 292 as shown in Figure 1, she developed high fever (39℃). Her consciousness was reduced and she was referred to the medical department. She had a negative influenza test and an elevated CRP of 3.48 mg/dl without leukocyte elevation. She was treated with an infusion of an antimicrobial. Because of difficulty in standing and loss of consciousness, she was re-hospitalized to our hospital, again. The perampanel concentration reached a level of 2310 ng/ml, with a CRP of 4.80 mg/dl. Other abnormal findings included albumin, 3.3 (3.8-5.2) g/dl and potassium, 3.1 (3.5-5.0) mEq/l. Secondary bacterial bronchitis was diagnosed, and she received cephalexin, 750 mg/day for 5 days. Her consciousness gradually improved. At discharge (Day 343), the blood levels of levetiracetam and lacosamide were 37.7 (12-46) μg/ml and 13.1 (10-20) μg/ml, respectively. Perampanel levels were lowered to 1010 ng/ml.

These events may have been caused by a change in the equilibrium between the brain and blood due to changes in perampanel's protein binding rate. Of the three antiepileptic drugs, perampanel is the only drug with a high protein binding rate and is the only basic drug. Generally, basic drugs bind strongly to α1-acid glycoprotein (AGP). Most plasma proteins are occupied by albumin; AGP is small, and its levels increase 3-5 times during in-

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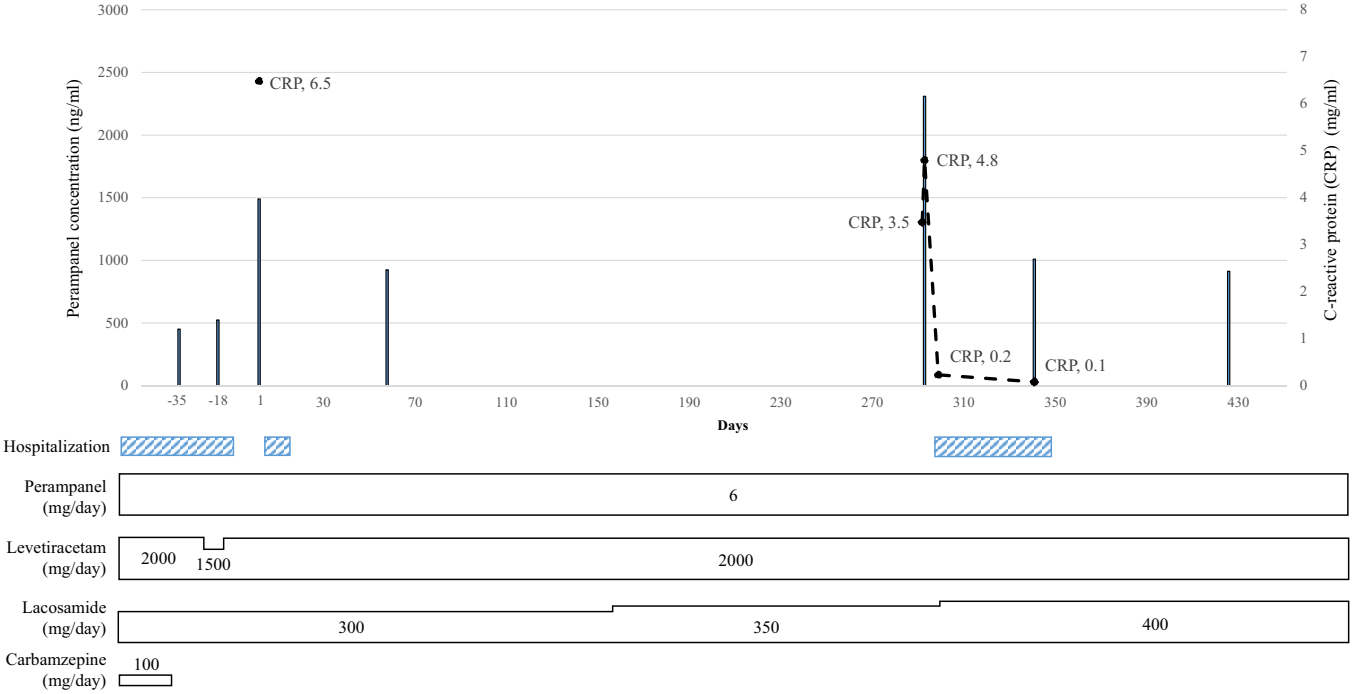

Figure 1. Time course of perampanel, CRP levels, and pharmacotherapy

flammation [2].Therefore, the total concentration of perampanel may have increased as a result of binding to the increased levels of AGP [2]. Furthermore, the proportion of drug bound to AGP tended to decrease at higher concentrations [1]. Hypoalbuminemia developed during the second episode of fever. Although perampanel has a low hepatic extraction rate (< 0.3) [1], the free concentration temporarily increased. The fat-soluble free perampanel moved into the brain. Consequently, elevated levels of perampanel in the brain caused impaired consciousness and reduced seizure occurrence. This plausible explanation is just a possibility because AGP's and free perampanel's concentrations were not measured. We also failed to measure levetiracetam and lacosamide concentrations. Therefore, potential lacosamide and levetiracetam toxicity cannot be ruled out. However, the pharmacokinetic interaction affecting the adverse effects of each of the three antiepileptic drugs has not been reported [1], [5]. Nonetheless, since it has been reported that perampanel and levetiracetam interacted with each other in fatigue [1] and psychiatric symptoms [4], there can be a synergistic effect [5]. Moreover, consciousness disturbance of this patient might have been associated with high fever as well as perampanel intoxication. In any case, this case shows the possibility of perampanel intoxication associated with inflammation.

CONFLICT OF INTEREST

T.M. has received speaking fees from Otsuka, Daiichisankyo, and MSD.

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