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Clinical course of intoxication with the new anticonvulsant drug perampanel

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ABSTRACT – Perampanel has recently been approved as an anticonvulsant drug for focal epilepsies. Phase III trials have shown good tolerability, although data regarding effects of high doses of perampanel are not available. Here, we describe the first case of a 34-year-old patient with perampanel intoxication and attempted suicide, in which the recommended daily dose of perampanel was exceeded ten-fold. Clinical signs of the intoxication and possible psychotropic effects are described.

Key words: epilepsy, intoxication, perampanel, suicide attempt, antiepileptic drug, side effect

Perampanel (PER) was initially investigated as a drug for Parkinson's disease. Although PER was not shown to be effective for this indication based on several clinical trials (Eggert *et al*., 2010), the first data concerning the safety and tolerability of the drug was obtained. PER was then investigated as a potential drug in epilepsy models and later in phase II and phase III trials. In studies to determine appropriate dosage (Kraus *et al*., 2012a) and phase III trials (French *et al*., 2012; French *et al*., 2013), PER demonstrated dose-dependent CNS side effects. PER, at 2 mg/day, demonstrated effects similar to placebo, as well as side-effects (Kraus *et al*., 2012b). At doses of 4 mg/day, dizziness, somnolence, and irritability were reported as adverse events (AEs), with a similar frequency to that at 2 mg/day. Dizziness, somnolence, ataxia, and AEs in general were more often reported at doses of 8 or 12 mg/day (reviewed in Serratosa *et al*., 2013). In these studies, no effects were observed on basic laboratory findings, vital parameters or ECG. In a recent study (Gidal *et al*., 2013), increased plasma concentrations of PER correlated with seizure reduction and an increased likelihood to develop AEs. Overall, PER was considered to be safe up to a daily dose of 12 mg per day, however, to the best of our knowledge, no reports exist regarding intoxication with doses exceeding multiple daily doses.

Here, we describe clinical findings in a patient who ingested 25.5 times her prescribed daily dose of PER (204 mg).

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Case study

The patient was a 34-year-old female Caucasian with a symptomatic focal epilepsy due to tuberous sclerosis, with complex focal and generalised tonic-clonic seizures. Diagnosis of tuberous sclerosis was based on genetic testing, which had previously revealed a single base deletion in the *TSC-1* gene. The patient had developed epilepsy at the age of 15. Intelligence was not tested, but the patient gave the impression she had a normal IQ. Under a medication of levetiracetam at 1,000 mg BID, topiramate at 100 mg BID, and pregabalin at 150 mg BID, she still reported 1-2 seizures per week. After informed consent was obtained, the patient participated in a double-blinded, randomised phase III study with PER, and having successfully participated in the study, was included in the open-label follow-up study with the same drug. During the titration phase, the daily dose was reduced once in one step (2 mg) due to AEs; vertigo and a tic of the upper lid of the left eye. The patient reported no history of psychiatric conditions. Scheduled unblinding revealed that the patient had been on a dose of 8 mg of PER during the blinded phase. Medication was continued. Fourteen days later, the patient reported to the study team *via* telephone that she had just ingested all her remaining study medication. Initially, the dose was estimated to be higher (264 mg), but based on the patient's good adherence to the study protocol beforehand, the ingested dose was finally estimated to be 204 mg, which was 25.5 times her daily dose. Emergency medical service (EMS) units were sent to the patient. Before they arrived, a conversation was conducted, during which the patient developed a slurred speech (dysarthria) and mild tiredness. The patient was admitted to the emergency department and was then admitted to a hospital ward 75 minutes after having got in contact with the study team. Based on the pharmacokinetic data with a peak concentration of PER after 60 minutes, emergency gastric lavage was cancelled by the gastro-enterologist. The patient developed sopor and exhibited withdrawal in response to painful stimuli. Her Glasgow Coma Scale score was 8. When the patient was transferred to our intermediate care unit, pupils were described as PERRLA, reflexes were weak and equal on both sides, and the patient showed no paresis, when reacting to pain. There was no need for respiratory support at any time. Impairment of consciousness lasted for two days. During this time, symptoms changed from sopor to a qualitative impairment of consciousness, including disorientation and misjudging situations. The EEG showed general slowing, but no epileptiform discharges. Blood samples showed normal values for blood cells, electrolytes, liver and kidney function, creatine kinase, LDH, and C-reactive peptide. ECG showed no critical changes. Blood samples for pharmacokinetic studies had to be discarded as no appropriate vials had been provided. The patient was excluded from the study. The existing medication with levetiracetam at 1,000 mg BID, pregabalin at 150 mg BID, and topiramate at 100 mg BID was continued, while PER was stopped. Furthermore, lamotrigine therapy was initiated. The psychiatric syndrome leading to a suicide attempt was diagnosed as either substance-induced depressive syndrome or organic depressive syndrome. The patient was transferred to a district psychiatric hospital after two days. At a 27-month follow-up visit, the patient and her husband reported mood instability with impaired impulse control, which had initiated after the start of the treatment with the study drug and had ceased after discharge from the psychiatric hospital. The psychiatric history of the patient was revealed at the visit but no relevant psychiatric condition before or after the participation in the study was reported by the patient or her husband. Suicidal thoughts, as well as previous suicide attempts, were not reported. The treatment regime, as well as seizure semiology and frequency, was similar to that before study participation.

Discussion

To the best of our knowledge, this is the first report of intoxication with a very large dose of PER. Clinical signs were dysarthria, followed by impaired consciousness initially with sopor and later with intermittent agitation, misperception, and disorientation of the situation, which could be described in psychiatric terms as delirium. Significant changes in vital parameters such as blood pressure, heart rate, ECG, and oxygen saturation were not observed. PER is entirely absorbed gastrointestinally and reaches peak plasma concentration after approximately one hour. Plasma levels subsequently decrease rapidly, reflecting a distribution into the body tissues. The time course of the symptoms might reflect these pharmacokinetic properties, as somnolence and delirium lasted for less time than the half-life of approximately 70 hours and AEs were associated with a higher plasma concentration of PER (Gidal *et al*., 2013). The effects of levetiracetam on modulation of AMPA-receptors in hippocampal neurons (Carunchio *et al*., 2007) might have had additive or potentiating effects on the AMPA-antagonism of PER and thus have contributed to the development of psychiatric symptoms leading to the intoxication. Though this is highly speculative, SNPs of catechol-O-methyl-transferase, dopa-beta-carboxylase, and a subunit of D2-receptors were shown to be associated with loss of self-control, restlessness, sleep

problems, and reactive-impulsive aggressive behaviour in patients treated with levetiracetam in a recent study (Helmstaedter *et al*., 2013).

Although a single case is insufficient to provide a general recommendation for PER intoxication, we conclude, based on this case and the above-mentioned reports, that gastric lavage may not be necessary and suggest that supportive treatment in the case of somnolence and delirium might be a suitable and sufficient treatment. This is, to the best of our knowledge, the first report of intoxication with PER, which itself is the first reported AED with an AMPA-antagonistic mechanism of action. To further determine whether the symptoms in our case illustrate the toxicity of the new class of AMPA-receptor antagonists or are specifically characteristic of PER, a systematic approach is necessary. □

Disclosures.
Anselm C Hoppner and Susanne Fauser have no disclosures to declare. Frank Kerling received grants from Desitin, EISAI, Novartis, and UCB.

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