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LETTER TO THE EDITORS

Gamma-hydroxybutyrate (GHB) and topiramate—clinically relevant drug interaction suggested by a case of coma and increased plasma GHB concentration

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To the Editor:

A 52-year-old woman was hospitalized for worsening chronic cluster headache refractory to all guideline-based medical and invasive treatments. Based on class IV evidence [1] she had regularly taken high-dose gamma-hydroxybutyrate GHB = sodium oxybate (Xyrem®; UCB-Pharma AG, Bulle, Switzerland) 4.5 g twice-nightly at 2300 and 0300 hours for the last 6 years. This was the only drug that markedly improved her nocturnal headache episodes and insomnia. As an additional therapeutic effort, topiramate (Topamax®; Janssen-Cilag AG, Baar, Switzerland) was added to the therapeutic regime, with the patient taking a single dose of topiramate 25 mg at 1800 hours, followed by the usual two daily doses of GHB. The next morning the patient had developed confusion, followed by intermittent myoclonic jerks, miosis, and a rapid onset of coma [Glasgow Coma Scale (GCS) score was 3 at 0800 hours]. Pulse, blood pressure, respiratory rate, pulse oximetry, electrocardiogram, and laboratory values, including electrolytes and blood glucose, were unremarkable. The plasma GHB concentration, determined by gas chromatography–mass spectrometry (GC-MS) of a blood sample collected at 0800 hours, was 259 mg/L. One hour later electroencephalography (EEG) showed intermittent bifrontal theta activity, a pattern described during sedation with GHB [2]. At 1300 hours the patient awoke from coma and rapidly recovered within a few hours. Topiramate was stopped, but GHB was continued as before. Two days later the plasma GHB concentration was 91 mg/L based on GC-MS analysis of a blood sample collected at 0800 hours.

In this patient, who was given topiramate concomitant with GHB, the GHB concentration 5 h after the second daily dose of GHB was 2.8-fold higher than without topiramate, and 1.8-fold higher than the peak concentration of 142 mg/L that would be expected 0.5–2 h after the daily second dose according to Xyrem®'s product information. The patient had taken topiramate without concomitant GHB in the past without problems. Based on the rapid onset but short duration of the otherwise unexplained coma and the EEG findings, we suggest that the coma was drug induced due to a pharmacokinetic interaction between GHB and topiramate. GHB has a short half-life of about 30 min [3], and metabolism via GHB-dehydrogenase is its main route of elimination [4]. In vitro studies have demonstrated that GHB-dehydrogenase is inhibited by the antiepileptic drugs valproate and ethosuximide [4], but according to Xyrem®'s product information no interaction studies with antiepileptics have been performed in humans. Alternatively, changes in the bioavailability of GHB or other unknown mechanisms of interaction are theoretically possible. In addition, topiramate increases GABA activity at its neuroreceptors, and an additional pharmacodynamic interaction must therefore also be considered.

In light of the increasing therapeutic as well as illicit use of GHB, as well as of newer antiepileptic drugs, possible interactions should be evaluated in formal pharmacokinetic studies. In the mean time, we suggest using such combinations only with great care.

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Conflicts of Interest None.

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