Epilepsy & Behavior 142 (2023) 109158

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Brief Communication

Intravenous topiramate for seizure emergencies – First in human case report

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ARTICLE INFO

Article history:
Revised 31 January 2023
Accepted 23 February 2023

Keywords:
Intravenous
Topiramate
Antiseizure medication
Pregnancy
New drug
Epilepsy

ABSTRACT

Topiramate (TPM) is widely used in focal and generalized epilepsies. It is commercially available as tablets and sprinkles capsules for oral treatment. Previous studies comparing intravenous (IV) to oral TPM in healthy adults showed more rapid pharmacodynamic effects in cases of IV administration. Despite promising findings, no clinical application in humans followed. We present a case of a pregnant woman with idiopathic generalized epilepsy who experienced a generalized tonic-clonic seizure in the third trimenon due to low TPM levels attributed to pregnancy followed by repeated prolonged absences. We applied a new meglumine-based solution (1%) of TPM (10 mg/ml) in two IV infusions of 200 mg each under EEG monitoring over a total duration of 1 hour. The infusion was well tolerated and led to a rapid increase in plasma TPM levels. A clinical as well as electroencephalographic improvement was documented within the first hours. To the best available knowledge, this is the first reported case where IV TPM was used therapeutically for seizure treatment in humans. It is also the first time that the new meglumine-based solution was used in a human with epilepsy. The advantages of IV route delivery and the solution's quick preparation, high tolerability, and low toxicity make it ideal for use in many clinical settings and high-care patients. IV TPM seems to be a reasonable adjunctive option for adults with seizures, previously stabilized on oral TPM, who need rapid plasma concentration boosting. Although our experience was successful in using injectable TPM in seizure emergencies, randomized controlled clinical trials are required to make recommendations for the use of IV TPM on patients with epilepsy.

This paper was presented at the 8th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures held in September 2022 in Salzburg, Austria.

1. Introduction

Topiramate (TPM) is used broadly for treating epilepsy and is commercially available as tablets and sprinkler capsules for oral treatment. Topiramate is a sulfamate-substituted derivative of D-fructose with multiple mechanisms of action such as modulation of voltage-dependent sodium channels, an increase of GABAergic inhibition, and blocking of glutamate-mediated neuroexcitation via kainate and AMPA receptors without apparent effect on NMDA receptors. In addition, TPM acts as a weak inhibitor of carbonic anhydrase in the central nervous system [1,2,3]. It is effective as a broad-spectrum anti-seizure medication (ASM) and is used for other medical conditions too such as migraine prophylaxis and in the treatment of idiopathic intracranial hypertension. Intravenous (IV) medications have many advantages as they offer rapid drug delivery and are necessary when oral administration is not possible [3]. Parenteral formulations of many other ASMs are used in seizure emergencies. A commercial formulation of IV infusions of TPM is however not available. Bioequivalence studies comparing

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https://doi.org/10.1016/j.yebeh.2023.109158
1525-5050/

IV to oral TPM in healthy adults showed more rapid pharmacodynamic effects in cases of IV administration when sulfobutylether-β-cyclodextrin (Captisol®) was used for dissolving TPM [4]. Despite promising findings concerning the potential use of injectable TPM in seizure emergencies, no further clinical application in humans followed. To the best available knowledge, this is the first reported case of IV TPM infusion in a patient with epilepsy for the treatment of seizure recurrence due to low medication levels. This is also the first time a novel meglumine-based solution was used in a human with epilepsy.

2. Case report

We present a 42-year-old woman in her 36th week of pregnancy, with a previous medical history of idiopathic generalized epilepsy (IGE). The patient started having absences when she was 8 years old, and she had been seizure-free over the last 25 years of her life. The patient also had generalized tonic-clonic seizures (GTCS) since the age of 17 years, and she had been seizure-free over the last 3 years. Six years prior to the current admission, the patient experienced a non-convulsive status epilepticus (NCSE) because of malabsorption of ASM due to gastroenteritis. Previous medical history ruled out other causes of epilepsy and febrile seizures. Past medical history included a suicide attempt by drug intoxication 15 years ago and a penicillin allergy. Previous medications of valproic acid and levetiracetam had been discontinued because of intolerance. Lamotrigine (LTG) and TPM, which comprise her current treatment, had been used for more than 10 years.

A few hours before the current admission, the patient suffered a GTCS which lasted about 2 minutes. A second GTCS occurred after the admission so an IV infusion of lorazepam (1000 mg) and levetiracetam (2000 mg) was administered. The patient reported adherence to ASM treatment consisting of oral TPM (50 mg; 1.43 mg/kg) and LTG (200 mg; 7.71 mg/kg) twice daily. Therapeutic drug monitoring (TDM) and clinical evaluation during pregnancy were not performed as the patient did not have follow-up visits either at our outpatient clinic or in private practice over the previous two years. On admission, TDM showed low levels of TPM, at 2.1 mg/l (normal values: 5.0–25.0 mg/l) and levels of LTG slightly above the lower limit of the therapeutic range, (2.2 mg/l; normal values: 2.0–12.0). Routine blood biochemistry was normal. No brain imaging was performed. EEG revealed frequent paroxysms of generalized spike-slow-wave complexes of 4–5 Hz with a maximal duration of 5 sec and no clinical correlation as well as prompt reactivity during the epileptiform discharges (Fig. 1a). A detailed neurologic examination was unremarkable except for some delayed responsiveness, which was interpreted as a postictal state. The remainder of the physical examination was normal. Oral TPM (200 mg) was administered as a single dose and the oral dosage of TPM was adjusted to 100 mg twice daily. Another seizure occurred and an emergent cesarean section was performed later that day due to fetal distress. The following day, EEG showed abundant paroxysms of generalized spike-/polyspike-slow-wave complexes of 3,5 Hz with a shorter duration of up to 2 seconds. The TDM of TPM assessed 3 hours prior to EEG was in a therapeutic range of 5.0 mg/L. A new meglumine-based solution (1%) of TPM (10 mg TPM per ml of an aqueous solution of 1% meglumine), developed by PrevEp Inc (Bethesda, MD; patents filed) was used. The IV formulation of TPM was a physician-directed magistral preparation. TPM is licensed for focal and generalized seizures and the IV formulation was administered in line with the compassionate use regulations of the European Medicines Agency (EMA) and the Austrian Medicinal Act. (https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=10010441)

The IV solution was freshly prepared as an individual formulation for the specific patient by the institutional/hospital pharmacy within 24 hours before use.

Meglumine is included in the FDA Inactive Ingredients Database, as an excipient for injection and oral tablets, and in parenteral medicines licensed in the UK and other European countries. Meglumine is widely used in parenteral pharmaceutical formulations and is generally regarded as a nontoxic material at the levels usually employed as an excipient, including pregnancy [5].

Two intravenous infusions of TPM (200 mg) were administered under continuous EEG monitoring over a total duration of 1 hour (5.63 mg/kg at a 6.67 mg/min infusion rate). This led to a significant reduction of epileptiform potentials (Fig. 1b). The meglumine-based IV solution of TPM was well tolerated. Vital signs and electrocardiography were normal. TDM after 16 hours showed increased levels of TPM (7.5 mg/l) and LTG (3.7 mg/l). We quantified and compared the presence of polyspike-slow-wave activity between the first EEG recording and the EEG recording after TPM IV infusion. Of note, the EEGs were recorded in the late morning of each day. A clear reduction of polyspike-slow-wave activity was documented from 85% before treatment to 12% after treatment, based on a 20 min recording time. EEG improvement was in line with clinical improvement as the patient remained seizure-free during hospitalization and at a 7-month follow-up. Regular follow-up visits and TDM at regular intervals were suggested.

3. Discussion

To the best available knowledge, this is the first reported case where IV TPM was used therapeutically, for acute seizure treatment, in humans. The serum concentration of TPM declines gradually throughout pregnancy due to still unknown pathophysiological mechanisms [6,7]. Despite a pronounced intra-individual variability [8] it has been reported that drug serum levels may drop up to 30–40% during the last trimester of pregnancy. Also,

TPM serum drug levels have been reported to decrease during pregnancy compared with postpartum values, by around 50% [9], thus suggesting TDM during pregnancy and post-partum [10]. Previous studies have compared the pharmacokinetic-pharmacodynamic profile of IV to oral TPM in healthy adults [4,10]. A sulfobutylether-β-cyclodextrin (Captisol®)-based solution (10%) of TPM (10 mg/ml) had been used [11]. Clark et al described a comparable adverse-event-profile between oral and IV administration of TPM, with more rapid and severe CNS symptoms in the latter, suggesting more rapid pharmacodynamic effects [4]. This pattern of adverse events between oral and IV TPM is observed using other ASMs too [12]. Despite the promising findings with regard to the potential use of injectable TPM in seizure emergencies, no further clinical application in humans followed. In the case presented here, a new meglumine-based 1% solution of TPM was used in a human with epilepsy for the first time. Meglumine is an FDA/EMA-approved excipient with high tolerability and low toxicity. It does not pose limitations in daily or IV exposure and is safe to use in high-care patients including patients with renal impairment and children. Experimental data show rapid brain entry of IV-administered TPM in rats, as measured in extracellular fluid [13].

The advantages of IV route delivery and the meglumine-based solution's quick preparation, high tolerability, and low toxicity make it ideal for use in many clinical settings with wide application. IV TPM seems to be a reasonable adjunctive option for adults

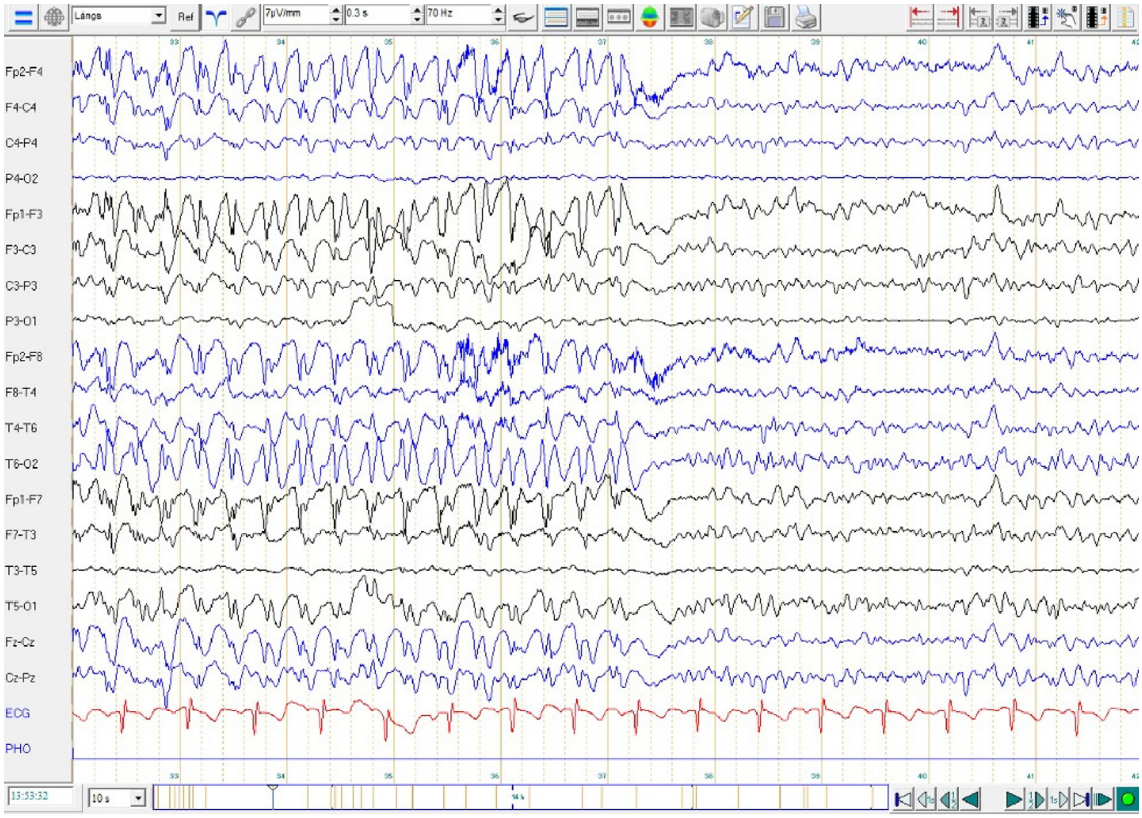

Fig. 1a. EEG before treatment with IV topiramate: Interictal EEG with generalized spike-slow-wave complexes of 4–5 Hz, with duration of 5 seconds.

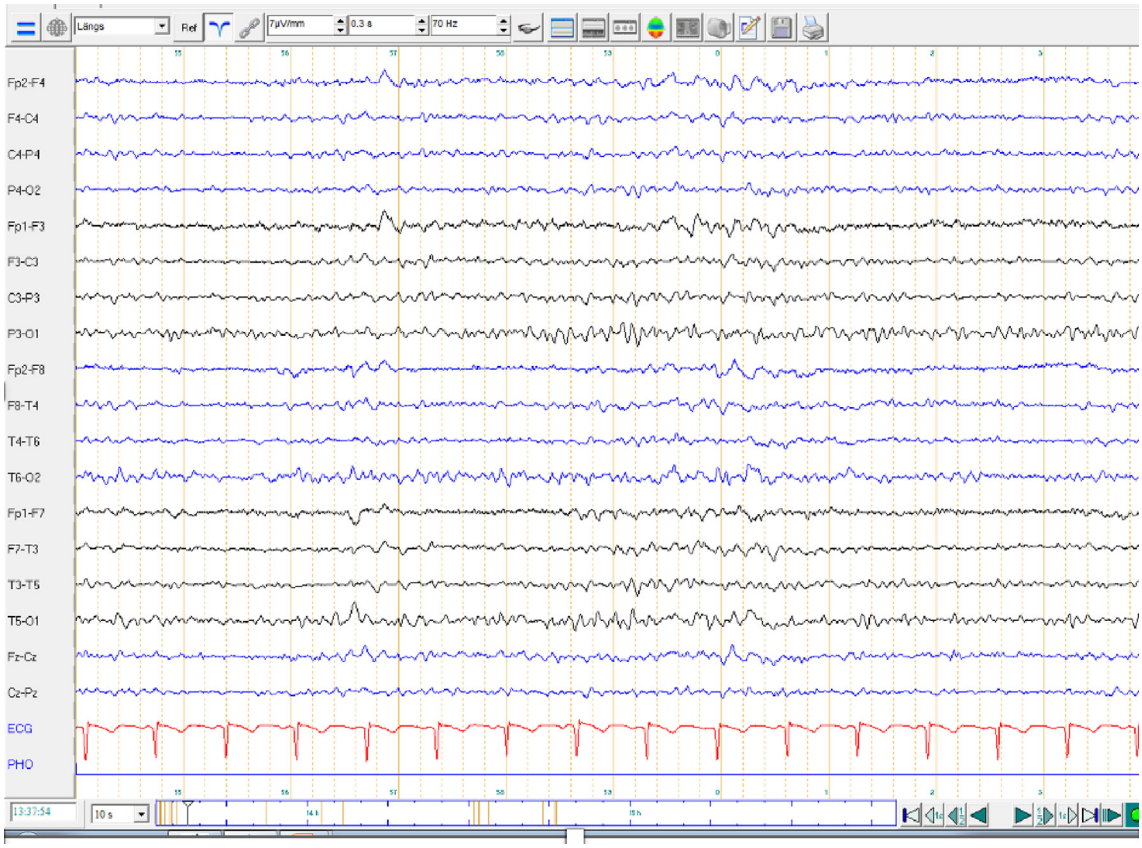

Fig. 1b. EEG after loading with IV topiramate: Interictal EEG with significant reduction of the epileptiform potentials.

with seizures, previously stabilized on oral TPM, who need rapid plasma concentration boosting.

In our case, IV application was chosen for rapid loading to achieve sufficient serum levels in a short time. The oral bioavailability of TPM is about 80%, t_{max} 2 hours to 4 hours, and time to steady state with oral tablets is 4–5 days [14]. This was deemed to be inappropriate to the potential harms of an additional seizure in the last trimenon and the threat of impending status epilepticus. In our patient, IV administration of TPM was the most suitable option. Considering her previous history of NCSE due to insufficient ASM she needed rapid anti-seizure coverage. She also reported intolerance to other IV ASMs, which could have been considered as potential treatment options. Adjusting the dosage of her other medication, LTG, would require a longer time and be therefore not appropriate for use in an emergency setting. Lastly, an IV administration of TPM gave us the possibility to quickly readjust the dosage in the postpartum phase. Although our experience was successful in using injectable TPM in seizure emergencies, randomized controlled clinical trials are required to make recommendations for the use of IV TPM on patients with epilepsy. Further potential therapeutic applications would be refractory and super refractory status epilepticus [15].

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: L.A. does not report any conflict of interest. P.B.V. does not report any conflict of interest. F.R. does not report any conflict of interest. C.O.S. does not report any conflict of interest. W.L. is cofounder and CSO of PrevEp Inc. (Bethesda, MD), which is developing the meglumine-based solution of TPM. G.K. does not report any conflict of interest. E.T. has received personal fees from Arvelle Therapeutics, Inc., Argenx, Bial, Biogen, Biocodex, Böhringer Ingelheim, Eisai, Epilog, Everpharma, GlaxoSmithKline, GW Pharma, Jazz Pharmaceuticals, LivaNova PLC, Marinus Pharmaceuticals, Inc., Medtronic, NewBridge Pharmaceuticals, Novartis, Sandoz, Sanofi, Sunovion Pharmaceuticals, Inc., Takeda, UCB Pharma, and Xenon; grants from Austrian Science Fund (FWF), Bayer, Biogen, Eisai, European Union, GlaxoSmithKline, Novartis, Österreichische Nationalbank, Red Bull, and UCB Pharma; He is CEO of NeuroConsult GmbH.; and has been a trial investigator for Eisai, GlaxoSmithKline, Marinus, Pfizer, and UCB Pharma.

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