



## RESEARCH ARTICLE

# Preclinical pharmacokinetics and tolerability of a novel meglumine-based parenteral solution of topiramate and topiramate combinations for treatment of status epilepticus

Chris Rundfeldt<sup>1</sup> | Pavel Klein<sup>1,2</sup>  | Detlev Boison<sup>1,3</sup> | Alexander Rotenberg<sup>1,4,5</sup> | Raimondo D'Ambrosio<sup>6</sup> | Cliff Eastman<sup>6</sup> | Benton Purnell<sup>3</sup> | Madhuvika Murugan<sup>3</sup> | Howard P. Goodkin<sup>7</sup> | Wolfgang Löscher<sup>1,8,9</sup> 

<sup>1</sup>PrevEp Inc., Bethesda, Maryland, USA

<sup>2</sup>Mid-Atlantic Epilepsy and Sleep Center, Bethesda, Maryland, USA

<sup>3</sup>Department of Neurosurgery, Robert Wood Johnson & New Jersey Medical Schools, Rutgers University, Piscataway, New Jersey, USA

<sup>4</sup>Division of Epilepsy and Neurophysiology, Department of Neurology, Boston Children's Hospital, Boston, Massachusetts, USA

<sup>5</sup>FM Kirby Center for Neurobiology, Boston Children's Hospital, Boston, Massachusetts, USA

<sup>6</sup>Department of Neurological Surgery, University of Washington, Seattle, Washington, USA

<sup>7</sup>Department of Neurology, UVA Health, Charlottesville, Virginia, USA

<sup>8</sup>Translational Epilepsy Research Group, Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine, Hannover, Germany

<sup>9</sup>Center for Systems Neuroscience, Hannover, Germany

## Correspondence

Wolfgang Löscher, Translational Epilepsy Research Group, Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine, Bünteweg 17, Hannover D-30559, Germany.  
Email: [wolfgang.loescher@tiho-hannover.de](mailto:wolfgang.loescher@tiho-hannover.de)

## Abstract

**Objective:** For an antiseizure medication (ASM) to be effective in status epilepticus (SE), the drug should be administered intravenously (i.v.) to provide quick access to the brain. However, poor aqueous solubility is a major problem in the development of parenteral drug solutions. Given its multiple mechanisms of action, topiramate (TPM) is a promising candidate for the treatment of established or refractory SE, as supported by clinical studies using nasogastric tube TPM administration. However, TPM is not clinically available as a solution for i.v. administration, which hampers its use in the treatment of SE. Here, we describe a novel easy-to-use and easy-to-prepare i.v. TPM formulation using the U.S. Food and Drug Administration (FDA)-approved excipient meglumine.

**Methods:** During formulation development, we compared the solubility of TPM in bi-distilled water with vs without a range of meglumine concentrations. Furthermore, the solubility of combinations of TPM and levetiracetam and TPM, levetiracetam, and atorvastatin in aqueous meglumine concentrations was determined. Subsequently, the pharmacokinetics and tolerability of meglumine-based solutions of TPM and TPM combinations were evaluated in rats, including animals following fluid percussion injury or pilocarpine-induced SE.

**Results:** The amino sugar meglumine markedly enhances the aqueous solubility of TPM. A comparison with data on dissolving TPM using sulfobutylether- $\beta$ -cyclodextrin (Captisol) demonstrates that meglumine is much more effective for dissolving TPM. Furthermore, meglumine can be used to prepare drug cocktails where TPM is co-administered with another ASM for SE treatment. The tolerability studies of the meglumine-based TPM solution and meglumine-based TPM combinations in normal rats and the rat fluid percussion injury and pilocarpine-induced SE models demonstrate excellent tolerability of the novel drug solutions. Preclinical studies on antiseizure efficacy in the SE model are underway.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *Epilepsia* published by Wiley Periodicals LLC on behalf of International League Against Epilepsy.

**Significance:** In conclusion, the novel meglumine-based solution of TPM presented here may be well suited for clinical development.

#### KEYWORDS

atorvastatin, benzodiazepines, cyclodextrins, levetiracetam, status epilepticus

## 1 | INTRODUCTION

Topiramate (TPM; Figure 1) is a broad-spectrum antiseizure medication (ASM) with established efficacy as oral monotherapy or adjunctive therapy in the treatment of adult and pediatric patients with partial seizures (with or without generalized seizures), generalized tonic-clonic seizures, and seizures associated with Lennox–Gastaut syndrome.<sup>1,2</sup> In addition, TPM is used for the prevention of migraine,<sup>3</sup> and in combination with the amphetamine derivative phentermine, has been cleared by the U.S. Food and Drug Administration (FDA) for appetite suppression.<sup>4</sup> TPM has activity at multiple molecular targets,<sup>5,6</sup> which may account for why it is effective in both epilepsy and migraine.

Based on its multiple mechanisms of action, TPM is a promising candidate for the treatment of benzodiazepine (BDZ)–resistant (established) status epilepticus (SE) and SE that fails to respond to BDZ and at least one other ASM, a condition termed refractory SE (RSE). Indeed, several clinical studies indicate that oral and nasogastric tube TPM administration may ameliorate RSE.<sup>7–10</sup> However, TPM is not clinically available as a solution for intravenous (i.v.) administration, which hampers its use in the treatment of SE.

Topiramate's water solubility (~6–10 mg/mL) is too limited to allow the development of its aqueous solution for i.v. administration. By using sulfobutylether- $\beta$ -cyclodextrin (SBE- $\beta$ -CD; Captisol) as an excipient, an i.v. TPM solution was developed and patented,<sup>11</sup> but it has not been approved by the FDA and, to our knowledge, it is not in clinical development for treatment of SE. The high concentrations of SBE- $\beta$ -CD needed to dissolve TPM in water may limit its clinical use (see Discussion).

We developed a novel, easy-to-use and easy-to-prepare, intellectual property (IP)–protected i.v. TPM formulation using the FDA-approved excipient meglumine, which provides excellent i.v. tolerability and compatibility with multiple pharmaceuticals and lacks the limitations of SBE- $\beta$ -CD.<sup>12</sup> This can allow the i.v. use of TPM in SE and RSE and potentially improve treatment of RSE.

Meglumine (*N*-methyl-D-glucamine; Figure 1) is a derivative of sorbitol that has regulatory acceptance as a well-tolerated excipient for drug formulations. It has a high water solubility (240 mg/mL), increases the aqueous

### Key Points

- Status epilepticus is a medical emergency and more effective treatments are urgently needed.
- Given its multiple mechanisms of action, topiramate is a promising candidate but not clinically available for parenteral injection.
- Here we describe the development of a novel aqueous solution of topiramate by using the U.S. Food and Drug Administration (FDA)–approved excipient meglumine.
- Meglumine is much more effective for dissolving topiramate than sulfobutylether- $\beta$ -cyclodextrin (Captisol).
- Pharmacokinetic and tolerability studies in rats demonstrate excellent tolerability of the novel drug solution, which is thus well suited for clinical development.

solubility of lipophilic drugs, and improves their absorption.<sup>12,13</sup> Meglumine is applied either as a counterion to form a salt with the active pharmaceutical ingredients (used for instance in contrast media) or as a functional excipient. In addition to enhancing drug solubility, meglumine is used to improve drug stability and adjust pH values. For instance, oxcarbazepine film-coated tablets contain meglumine. To our knowledge, meglumine has not been used previously to dissolve ASMs for parenteral use.

Here, we describe the novel meglumine-based i.v. formulation of TPM and compare the solubility of TPM in meglumine with its solubility in SBE- $\beta$ -CD (Captisol). Furthermore, we report that meglumine can be used to prepare drug cocktails, for example, TPM and the ASM levetiracetam (LEV; Figure 1) in one solution, which may enhance the antiseizure capacity of an injectable agent in SE and RSE treatment. As recently reported,<sup>14</sup> such cocktails with TPM may also be promising candidates for the prevention or modification of epilepsy after brain injury. The pharmacokinetics and tolerability of parenteral administration of meglumine-based solutions of TPM and TPM cocktails were evaluated in rats.

## 2 | MATERIALS AND METHODS

The novel TPM formulation using meglumine as the primary excipient (PrevEp004) as well as combinations of TPM and other drugs in the same formulation is described in a provisional US patent application no. 62/926130, which was submitted recently for worldwide protection under WO 2020/214960 A1. For animal experiments on the parenteral TPM formulation, adolescent or adult male Sprague–Dawley rats (body weight range ~100–170 g for the experiments in naive rats and rats with traumatic brain injury [TBI] and ~350–400 g for the experiments with pilocarpine) were used. All animal procedures were conducted in accordance with protocols approved by the local Institutional Animal Care and Use Committee (IACUC) and the principles outlined in the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

### 2.1 | TPM solution in meglumine

The maximum solubility of TPM in bi-distilled water with vs without a range of meglumine concentrations was determined under stirring at room temperature. Before adding TPM, meglumine (available as a powder) was dissolved in water to yield meglumine concentrations of 0.5%, 1%, 2.5%, or 3.5%. The meglumine solutions were prepared fresh daily and stability was determined over 20 h at room temperature. The pH of the solutions was measured and, if needed, adjusted using dilute HCl.

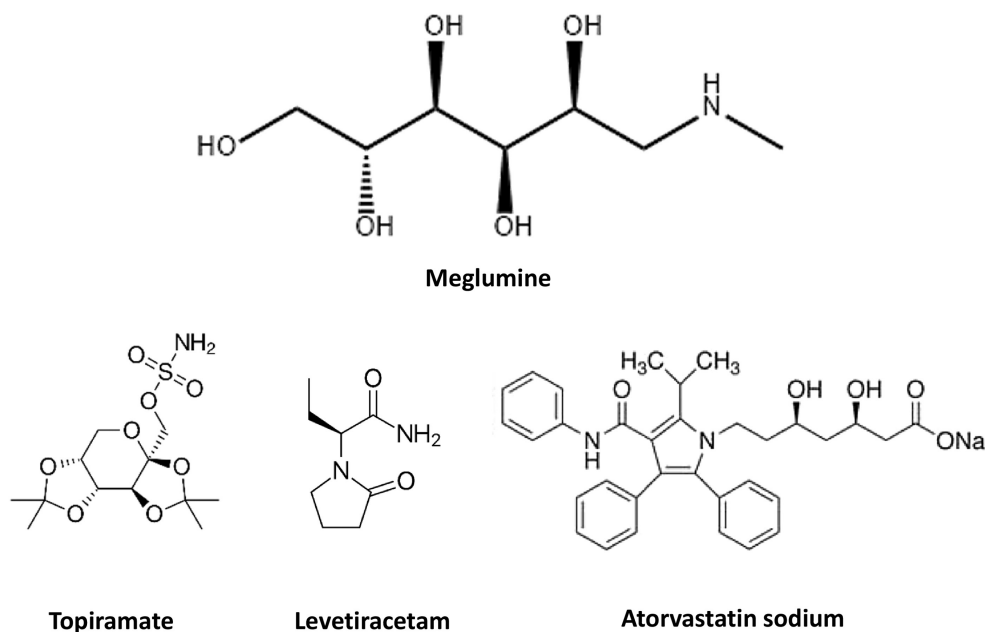
Based on general recommendations for i.v. solutions,<sup>15,16</sup> a pH <9 was used as a goal pH. Each experiment was performed at least twice to determine the maximum solubility of TPM.

### 2.2 | Solutions of TPM combinations in meglumine

In additional experiments, we dissolved TPM together with LEV in meglumine solutions (PrevEp005). We further determined whether a combination of TPM, LEV, and atorvastatin sodium (ATV; Figure 1) can be dissolved in the same meglumine solution because PrevEp, Inc is evaluating this combination (PrevEp001) for the prevention of posttraumatic epilepsy. In some of these experiments, we also used the FDA-approved amphipathic, nonionic surfactant Tween 80 (polysorbate 80) together with meglumine to inhibit the recrystallization of drugs in solutions.<sup>17</sup>

For comparison with meglumine, we used the hydroxypropyl derivative of  $\beta$ -cyclodextrin (HP- $\beta$ -CD; Kleptose). Furthermore, we used the solubility data of TPM in SBE- $\beta$ -CD (Captisol) from the patent<sup>11</sup> for comparison with meglumine.

TPM and LEV were purchased from Chemenu (Mount Laurel, NJ), ATV (as sodium salt) from abcr (Karlsruhe, Germany), and meglumine from Merck (Darmstadt, Germany). HP- $\beta$ -CD (Kleptose) was kindly provided by Roquette-Pharma (Frankfurt, Germany). Tween 80 was purchased from AppliChem (Darmstadt, Germany).



**FIGURE 1** Structures of the compounds used in this study.

## 2.3 | Pharmacokinetics of meglumine-based solutions of TPM and TPM combinations in rats

In a group of four, naive young male Sprague–Dawley rats, a cocktail of TPM, LEV, and ATV was administered i.p. 3 times a day (every 8 h) for 1 week. The three drugs were dissolved freshly each day in an aqueous solution of 0.3% meglumine (pH 8.9) and administered at the following doses t.i.d.: TPM, 30 mg/kg; LEV, 200 mg/kg; and ATV sodium, 10 mg/kg, respectively. These doses were based on previous preclinical experiments with these drugs.<sup>14,18</sup> Blood was withdrawn at 0.5 h and 8 h following the first administration on day 1 and 8 h after the last administration on day 7.

Drug levels in plasma were determined by ultra-performance liquid chromatography (UPLC) mass spectrometry (MS) by the Chemical Analytical Facility Core (Environmental and Occupational Health Sciences Institute) of Rutgers University (Piscataway, NJ). Details of the analytical conditions including UPLC, ESI (electrospray ionization), and MS mode have been described in detail previously.<sup>19–21</sup>

## 2.4 | Tolerability of meglumine-based solutions of TPM and TPM combinations in rats following fluid percussion injury

We previously showed that the tolerability of ASMs and other drugs may be lower in rodents with brain insults than in uninjured rodents.<sup>22</sup> Thus the tolerability of a cocktail of TPM, LEV, and ATV was examined in young male Sprague–Dawley rats following fluid percussion injury (FPI), using a model of rostral parasagittal FPI (rpFPI) as described in detail previously.<sup>23,24</sup> The rpFPI model of TBI has a historical mortality rate of about 10% by 1-week post-injury. A group of 14 FPI rats was treated intraperitoneally (i.p.) t.i.d. with a cocktail of TPM, LEV, and ATV in 0.3% meglumine, using the dosing protocol described previously for the pharmacokinetic experiments. Treatment was started at 1 h after FPI. Mortality, body weight, and general behavior (such as locomotor activity, posture, and grooming) of the rats were examined during treatment. A group of 15 vehicle-treated FPI rats was used as a control.

## 2.5 | Tolerability of a meglumine-based solution of TPM injected i.v. after diazepam in rats following SE

The pilocarpine (or lithium-pilocarpine) model in rats is widely used as a model of established SE and RSE.<sup>25–27</sup>

Here, we used it to test the tolerability of TPM when administered i.v. after diazepam. For induction of SE, rats received lithium chloride 3 mEq/kg, i.p., followed 24 h later by an i.p. injection of 50 mg/kg pilocarpine. Methylscopolamine (1 mg/kg, i.p.) was administered 1 h before pilocarpine to block the peripheral cholinergic effects of the convulsant. Following pilocarpine, each animal was monitored continuously for the occurrence of behavioral and electrographic seizures. SE was defined by continuous behavioral limbic seizures, interrupted by generalized convulsive seizures, or by intermittent generalized convulsive seizures (with inter-seizure intervals of less than 3 min) without normalization of the animal's behavior (i.e., exploring the cage, eating, responding to external stimuli) between seizures. On electroencephalography (EEG), continuous spiking >2 Hz and amplitude >2 times the background were defined as the start of SE (time = 0). TPM (at doses ranging from 15 to 120 mg/kg, i.v.) was administered at different intervals after diazepam (1–10 mg/kg) (see Results for details). Following i.v. administration of TPM, the animals were observed closely for behavioral adverse effects and mortality over a period of at least 4 h.

## 2.6 | Statistics

Student's paired *t* test was used to analyze the pharmacokinetic data. Statistical tests and correlation analyses were performed by GraphPad Prism version 9 (La Jolla, CA, USA).

# 3 | RESULTS

The main outcome of the experiments is summarized in Table 1.

## 3.1 | TPM solution in meglumine

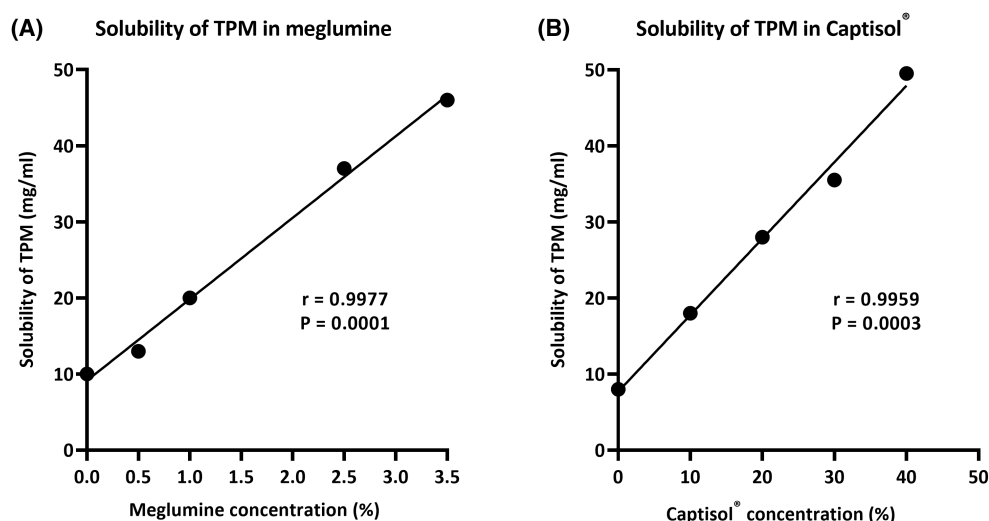
In water without meglumine, a maximum of 10 mg TPM could be dissolved in 1 mL by stirring and moderate heating, but it took ~30 min before TPM was completely dissolved. When meglumine was dissolved in water at different concentrations (ranging from 0.5% to 3.5%), TPM was dissolved immediately in these solutions without heating. A linear correlation between the concentration of meglumine and the maximum solubility of TPM was obtained (Figure 2A). At 3.5% meglumine, 46 mg TPM could be dissolved per milliliter, thus increasing the solubility of TPM about 5-fold compared to water without meglumine. Because meglumine is basic ( $pK_a = 9.5$  at 20°C), the pH of the solution increased with increasing concentrations of meglumine,



**TABLE 1** Summary of the main outcome of the study

Experiments	Outcome
1. Solubility of TPM in water with meglumine (0.5%–3.5%)	Up to ~5-fold increase in solubility compared to water without meglumine
2. Solubility of TPM combinations in water with meglumine (0.5%–2.5%)	Either double (TPM + LEV) or triple (TPM + LEV + ATV sodium) combinations are easily dissolved
3. Pharmacokinetics of meglumine-based solutions of TPM and TPM combinations in rats	Elimination half-lives of ~2 h (TPM, LEV) and 1.7 h (ATV); no accumulation during i.p. treatment for 1 week with TPM (30 mg/kg t.i.d.), LEV (200 mg/kg t.i.d.), and ATV (10 mg/kg t.i.d.)
4. Tolerability of meglumine-based solutions of TPM and TPM combinations following FPI in rats	No increased mortality or distress during i.p. treatment for 1 week with TPM (30 mg/kg t.i.d.), LEV (200 mg/kg t.i.d.), and ATV (10 mg/kg t.i.d.)
5. Tolerability of a meglumine-based solution of TPM after SE in rats	No obvious adverse effects and no mortality following i.v. doses of 15–120 mg/kg TPM, injected 15 min after diazepam

Abbreviations: ATV, atorvastatin; FPI, fluid percussion injury; LEV, levetiracetam; SE, status epilepticus; t.i.d., three times daily; TPM, topiramate.



**FIGURE 2** Solubility of topiramate (TPM) in aqueous solutions of meglumine (A) vs sulfobutylether- $\beta$ -cyclodextrin (SBE- $\beta$ -CD; Captisol [B]). Data on SBE- $\beta$ -CD were taken from the patent of James Cloyd.<sup>11</sup> Correlation analysis was performed by the method of Pearson.

being 8.5 for 0.5% and 1% meglumine, 9.0 for 2.5%, and 9.66 for 3.5% meglumine, respectively, but could be easily adjusted to <9.0 by dilute HCl. The solutions were stable for at least 20 h; longer periods were not tested. No precipitation occurred, if stored at 2–8°C or room temperature.

### 3.2 | Solutions of TPM combinations in meglumine

Next we tested whether TPM can be dissolved together with LEV in a meglumine solution. In contrast to TPM, LEV is highly water soluble (~1 g/mL). Based on typical antiseizure and neuroprotective doses of TPM and LEV in rodents, that is, 30 mg/kg TPM and 200 mg/kg LEV,<sup>6,28,29</sup> and an intended injection volume of 3 mL/kg, we attempted to dissolve 10 mg/mL TPM and 67 mg/mL LEV

in one solution. This was possible in water without any excipient but required ~30 min of stirring and moderate heating. When using aqueous meglumine (0.5%, 1%, or 2.5%) solutions, both ASMs were dissolved immediately without any heating. The same was true when the TPM concentration was further increased, for example, to 20 mg/mL. The solutions were stable for at least 20 h at room temperature without signs of precipitation.

We then tested whether a triple-drug combination of TPM, LEV, and ATV sodium can be dissolved in aqueous meglumine solutions, intending an ATV dose of ~10 mg/kg in an injection volume of 3 mL/kg (i.e., ~3.5 mg/mL). The dose of ATV was based on preclinical data substantiating its neuroprotective potential.<sup>18</sup> All three drugs could be dissolved easily in a 0.3% meglumine solution (TPM, 10 mg/mL; LEV, ~67 mg/mL; ATV, ~3.5 mg/mL) under stirring for about 20 min at room

temperature. The pH of the solution was 8.9. Increasing the meglumine concentration to 0.5%, 1%, or 2.5% did not reduce the time required to dissolve the three compounds together. The solution was initially clear but some precipitate was observed after 20 h at room temperature. This was avoided by the addition of 0.3% Tween 80 to the solution to inhibit recrystallization.

In an additional experiment, we used a 10% solution of HP- $\beta$ -CD (Kleptose) to dissolve the three drugs. This was possible by stirring for 30 min. The clear solution became cloudy after 21 h storage at room temperature, indicating partial precipitation. When compared to the experiments with meglumine, the concentration of HP- $\beta$ -CD needed to dissolve the three drugs was 33 times higher, and the stability was limited.

### 3.3 | Pharmacokinetics of meglumine-based solutions of TPM and TPM combinations in rats

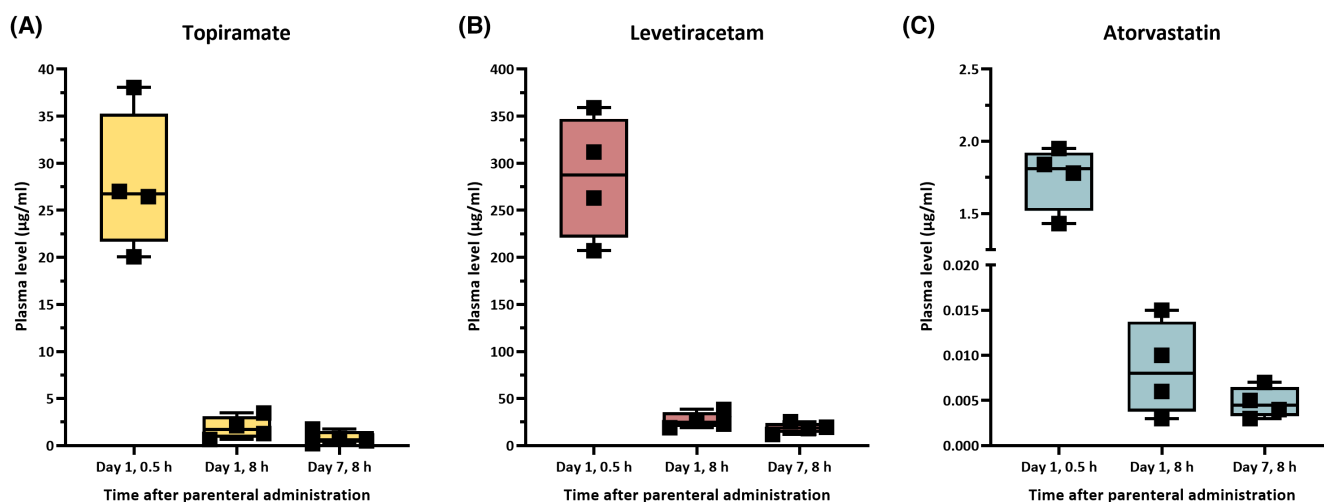
As shown in Figure 3A, 30 min after i.p. injection of 30 mg/kg TPM, the median plasma level in a group of four rats was 27  $\mu$ g/mL. Plasma levels declined to 1.7  $\mu$ g/mL within 8 h, indicating an elimination half-life of  $\sim$ 2 h, which corresponds to published values in rats.<sup>1</sup> When TPM (30 mg/kg) was i.p. administered t.i.d. over 1 week and plasma levels were determined 8 h after the last dose on day 7, the median plasma level was 0.64  $\mu$ g/mL, which was not significantly different from the 8-h value determined after the first administration ( $p = .0818$ ).

As shown in Figure 3B, 30 min after i.p. injection of 200 mg/kg LEV, the median plasma level in a group of four rats was 288  $\mu$ g/mL. Plasma levels declined to 24.9  $\mu$ g/mL within 8 h, indicating an elimination half-life of  $\sim$ 2 h, which corresponds to published values in the rat.<sup>1</sup> When LEV (200 mg/kg) was i.p. administered t.i.d. over 1 week and plasma levels were determined 8 h after the last dose on day 7, the median plasma level was 18.8  $\mu$ g/mL, which was not significantly different from the 8-h value determined after the first administration ( $p = .2431$ ).

As shown in Figure 3C, 30 min after i.p. injection of 10 mg/kg ATV, the median plasma level in a group of four rats was 1.81  $\mu$ g/mL. Plasma levels declined to 0.008  $\mu$ g/mL within 8 h, indicating an elimination half-life of  $\sim$ 1.7 h, which is lower than the published half-life of 4.4 h determined after oral administration in male rats.<sup>30</sup> When ATV (10 mg/kg) was i.p. administered t.i.d. over 1 week and plasma levels were determined 8 h after the last dose on day 7, the median plasma level was 0.0045  $\mu$ g/mL, which was not significantly different from the 8-h value determined after the first administration ( $p = .2939$ ).

### 3.4 | Tolerability of meglumine-based solutions of TPM and TPM combinations in rats following fluid percussion injury

For tolerability testing, the triple-drug cocktail of TPM (30 mg/kg), LEV (200 mg/kg), and ATV (10 mg/kg) in 0.3% meglumine was administered three times daily at 8-h intervals over 7 days after FPI in a group of 14 rats. Two



**FIGURE 3** Pharmacokinetics of topiramate (A), levetiracetam (B), and atorvastatin (C) following i.p. administration of a triple-drug solution in meglumine in a group of four rats. The three drugs were dissolved in an aqueous solution of 0.3% meglumine and administered at the following doses t.i.d.: TPM, 30 mg/kg; LEV, 200 mg/kg; ATV, 10 mg/kg, respectively. Blood was withdrawn at 0.5 h and 8 h following the first administration on day 1 and 8 h after the last administration on day 7. Data are shown as boxplots with whiskers from minimum to maximal values; the horizontal line in the boxes represents the median value. In addition, individual data are shown. Plasma levels determined 8 h after the first and last drug administrations were not significantly different (see text).

rats (14%) died within 1 h after FPI (i.e., before the onset of drug treatment) compared to 1 of 15 (6.7%) vehicle-treated control rats. During drug treatment, no rats died. All treated animals had normal grooming behavior, activity level, and body weight growth, indicating an absence of distress. Therefore, there was no evidence that 1 week of treatment with the meglumine-based drug cocktail increases mortality or distress of the animals.

### 3.5 | Tolerability of a meglumine-based solution of TPM injected i.v. after diazepam in rats with status epilepticus

This experiment aimed to examine whether the meglumine-based TPM solution is tolerable when i.v. administered after diazepam in rats with a pilocarpine-induced SE, thus simulating the situation in established SE. In five rats in which diazepam (5 or 10 mg/kg) was injected i.p. either 10 or 30 min after pilocarpine, no rat died within 24 h following an injection of the convulsant. In the first experiment with TPM in two rats, 5 mg/kg of diazepam was injected i.v. 15 min after SE onset, followed 5 min later by rapid i.v. injection of 15 mg/kg TPM. One rat died 24 h after pilocarpine and the other rat had to be sacrificed because of poor health conditions. We, therefore, modified the experimental protocol by (1) reducing the i.v. dose of diazepam from 5 to 1 mg/kg, (2) increasing the interval between diazepam and TPM from 5 to 15 min, and (3) slowing the injection speed. In this respect, it is important to note that 5 mg/kg diazepam, which is typically used with i.p. administration in this model,<sup>27,31</sup> is a huge dose when injected i.v., because most of the i.p. administered diazepam is subject to rapid first-pass metabolism, which does not occur with i.v. administration.<sup>32</sup> Thus, at least in part, the toxicity that occurred in our initial protocol with diazepam and TPM may have been due to a too high dose of diazepam and too rapid injection of both diazepam and TPM. For clinical treatment of SE, diazepam is i.v. injected at a dose of 0.15 mg/kg with 5 mg/min.<sup>33</sup> Using a factor of 6 for dose conversion between humans and rats,<sup>34</sup> a dose of 0.15 mg/kg in humans would correspond to a dose of 0.9 mg/kg in rats, which was rounded to 1 mg/kg for the present study. Therefore, in the subsequent experiments with the modified experimental protocol, rats received an i.v. dose of 1 mg/kg diazepam 15 min after SE onset. Fifteen minutes later, TPM was slowly injected i.v. at doses of 15, 30, or 120 mg/kg in two rats per dose. These doses of TPM were based on previous experiments with i.p. administration of TPM in the pilocarpine model in rats.<sup>35,36</sup> With this modified protocol, no obvious adverse effects and no mortality were observed, even

when the i.v. dose of diazepam was increased to 3 mg/kg. Because of the low sample size per dose, antiseizure efficacy was not determined in these experiments.

## 4 | DISCUSSION

In the present study, we demonstrate that TPM can be dissolved easily in water using relatively low concentrations of meglumine. Furthermore, low concentrations of meglumine can be used to dissolve TPM in combinations with other drugs such as LEV and ATV.

### 4.1 | The highly tolerable amino sugar meglumine as a drug solvent

Most drugs have very limited solubility in water and some can be extremely difficult to formulate as parenteral solutions. For parenteral solutions, the dose of the drug should preferably be dissolved in a small volume of aqueous media without the use of organic solvents or surface-active agents, because that can result in drug precipitation upon injection, pain, inflammation, and hemolysis.<sup>37</sup> Meglumine, an amino sugar derived from sorbitol, is used as a highly tolerable solubilizing agent in several FDA-approved parenteral pharmaceutical formulations and is regarded as an inert and nontoxic vehicle at the levels usually employed as an excipient.<sup>13</sup> Typical FDA-approved meglumine concentrations in drug solutions, for example, in intravascular contrast media with iodine-containing compounds or gadolinium-containing contrast media, range from 2.5% to 15% for meglumine iotroxate (Biliscopin) and meglumine iotalamate (Conray), respectively. The total meglumine dose administered amounts to 2.5 g in the case of meglumine iotroxate, if dosed as prescribed at a volume of 100 mL. Meglumine-based drug solutions are also approved for prolonged (or repeated) i.v. administration in humans; for instance, in the treatment of diabetic peripheral neuropathy with a meglumine-based solution of the antioxidant alpha-lipoic acid (ALA).<sup>38</sup> The ALA solution contains 600 mg ALA and 567 mg meglumine in 50 mL, which corresponds to a meglumine concentration of 1.23%. For the treatment of patients with diabetic peripheral neuropathy, 50 mL of the solution is infused per day over 2–4 weeks, corresponding to a daily dose of meglumine of 567 mg. In contrast to SBE- $\beta$ -CD (Captisol; see below), there is no FDA-stipulated limit for daily exposure to meglumine. The i.p. median lethal dose (LD<sub>50</sub>) of meglumine in mice is 1.7 g/kg, and full life-span studies with high-dose meglumine in rodents reported no detrimental effects.<sup>39</sup>

## 4.2 | Solubility of topiramate in meglumine vs cyclodextrins

When TPM solubility in meglumine was compared with its published solubility in SBE- $\beta$ -CD (Captisol), the advantage of meglumine became rapidly apparent (Figure 2). For dissolving TPM over the chosen concentration range of 10–50 mg/mL, meglumine concentrations of 0.5%–3.5% were sufficient, whereas >10-fold higher concentrations of SBE- $\beta$ -CD were needed. When this comparison was based on the molecular weight of the solvents (meglumine, 195.21 g/mol; SBE- $\beta$ -CD, 1451.287 g/mol), the capacity of meglumine to dissolve TPM in water was ~80 times higher than that of SBE- $\beta$ -CD.

Cyclodextrins (CDs) have been used extensively to increase the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs.<sup>37,40</sup> The ability of CDs to modify these characteristics has been attributed to the formation of an inclusion complex between cyclodextrins and “guest” drug molecules. Whereas unsubstituted crystalline CDs had limitations such as renal toxicity, more recently developed modified  $\beta$ -CDs such as HP- $\beta$ -CD (Kleptose) and SBE- $\beta$ -CD (Captisol) have more acceptable tolerability, but still renal toxicity potential at high doses.<sup>37</sup> For humans, permitted daily i.v. exposures (PDEs) are 320 mg/kg/day for HP- $\beta$ -CD and 280 mg/kg/day for SBE- $\beta$ -CD (European Medicines Agency [EMA], 2014). However, PDEs may be much lower in children and patients with renal impairment.

As described in the introduction, for TPM, an i.v. solution in SBE- $\beta$ -CD has been developed and patented.<sup>11</sup> The formulation has not been evaluated for efficacy in epilepsy patients or in SE or RSE models. In epileptic dogs, i.v. TPM doses of 10 or 20 mg/kg were well tolerated and EEG recordings indicated a rapid onset of action,<sup>41</sup> which is in line with the rapid brain penetration of TPM in rodents after i.p. or i.v. administration.<sup>6,42</sup> In healthy volunteers or patients with epilepsy or migraine, single i.v. doses of 25–200 mg TPM dissolved by SBE- $\beta$ -CD were well tolerated.<sup>43–46</sup> Following i.v. TPM in volunteers, maximal plasma levels were higher and occurred earlier than with oral TPM.<sup>44</sup> In the studies in humans, the TPM solution contained 10 mg/mL TPM, solubilized with 100 mg/mL SBE- $\beta$ -CD, that is, a 10% solution of SBE- $\beta$ -CD, but such a solution has not yet been approved for clinical use.

In theory, a 1% TPM solution in 10% SBE- $\beta$ -CD could also be suitable for the treatment of SE or RSE. However, this may result in safety issues. Based on clinical studies with oral or nasogastric administration of TPM<sup>8,47</sup> and our own clinical experience (P.K., unpublished observations), the initial i.v. loading dose of TPM should be ~400–1200 mg; if 1200 mg, then followed by 600 mg, 6 and 12 h later. This would result in a daily dose of 24 g SBE- $\beta$ -CD

(or ~370 mg/kg/day), which is above its PDE of 280 mg/kg/day. The injection volume for such a dose would be 240 mL.

Similar problems exist for SBE- $\beta$ -CD solutions of carbamazepine, which is the only ASM for which a parenteral solution with a substituted  $\beta$ -cyclodextrin has been approved.<sup>48</sup> According to the prescription information, this solution (Carnexiv) should generally not be used in patients with moderate or severe renal impairment. Currently, Carnexiv is not on the market, apparently because of FDA issues with precipitation of the product, which is another issue with drug solutions in SBE- $\beta$ -CD.

Given the much higher solubility of TPM in meglumine, for instance, a 4% TPM solution (i.e., 40 mg/mL) can be achieved with only 3% meglumine. The injection volume for a daily dose of 2400 mg would be only 60 mL, and the meglumine dose (1.8 g or ~28 mg/kg) would not be associated with any safety issues, including for patients with renal impairment. Based on the high safety of meglumine, the injection volume of the TPM solution could be further decreased by increasing the concentration of meglumine and thus the solubility of TPM.

## 4.3 | Mechanism of TPM dissolution by meglumine

Meglumine does not form a salt with TPM. Because of the strong electron withdrawing -S=O of the sulfamate moiety (see Figure 1), the -NH<sub>2</sub> group of topiramate will not be ionized at physiological pH—which is also why TPM has very poor water solubility—and not be able to participate in salt formation. However, the polyol (numerous hydroxyl groups) structure of meglumine and that of topiramate strongly favors hydrogen bond interactions. Thus the various oxygen atoms of the fructopyranose ring of TPM as well as the oxygens in the SO<sub>2</sub> group could interact with the hydrogens from the numerous hydroxy groups in meglumine in hydrogen bonding, thus forming a meglumine:TPM complex that is highly water soluble. Such complex or supramolecular adduct formation with meglumine has been shown previously for several water insoluble drugs, such as for instance some nonsteroidal anti-inflammatory drugs.<sup>49</sup>

## 4.4 | Potential clinical use of meglumine-based solutions

Based on studies with oral or nasogastric tube administration of TPM or administration by percutaneous endoscopic gastrostomy, the clinical perspective of an i.v. TPM solution for the treatment of SE or RSE is promising.<sup>7–9,47,50</sup>



In clinical practice, TPM has been used when first- or second-line ASMs failed to terminate SE.<sup>7</sup> For the treatment of RSE, in one retrospective study, TPM successfully terminated RSE in over 70% of patients when it was given as the fourth to seventh ASM,<sup>50</sup> although another study did not observe such high efficacy.<sup>10</sup> Nasogastric administration of TPM as used in the above studies leads to variable absorption with unpredictable plasma levels and time to peak concentration, for example, in patients in whom RSE may be accompanied by paralytic ileus, as well as first-pass metabolism by the liver—similar to oral administration. An intravenous TPM formulation can be expected to result in a more rapid onset of action and improved efficacy.

#### 4.5 | Experiments with topiramate in the pilocarpine rat model

In preclinical studies using the pilocarpine model of SE and RSE, parenteral (i.p.) administration of TPM was reported to suppress pilocarpine-induced SE at doses of 10 mg/kg<sup>36</sup> or 40–80 mg/kg<sup>51</sup>; however, similar to oral administration, first-pass liver metabolism after i.p. administration will reduce the antiseizure potency of TPM.<sup>52</sup> To our knowledge, i.v. administration of TPM has not been tested previously in rodent models of SE or RSE.

In the present study, we examined whether a meglumine-based solution of TPM is safe when administered i.v. after diazepam in the pilocarpine model of established SE in rats. No obvious adverse effects or mortality were observed. Likewise, the solution was well tolerated following FPI in rats.

#### 4.6 | Combinations of topiramate with levetiracetam and atorvastatin

In contrast to TPM, the commonly used ASM LEV is available as an FDA-approved aqueous solution for i.v. administration as adjunct therapy in patients with epilepsy when oral administration of LEV is temporarily not feasible. The LEV i.v. solution is increasingly being used in the treatment of SE and RSE.<sup>53–55</sup>

LEV acts predominantly by modulation of the presynaptic synaptic vesicle glycoprotein 2A (SV2A), which is involved in the release of neurotransmitters.<sup>56</sup> In contrast to LEV, TPM acts primarily via postsynaptic targets, including  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptor and different subtypes of glutamate receptors.<sup>5</sup> Thus a combination of TPM and LEV may provide synergistic efficacy, which was reported for seizure models but not yet for SE models.<sup>57</sup> As shown here, meglumine allows dissolving of

TPM and LEV in the same solution, which would facilitate their combined use in the treatment of SE.

In addition to the treatment of SE, TPM combinations are promising candidates for interfering with epileptogenesis after brain injury. TPM alone exerts neuroprotective effects when administered after SE.<sup>28</sup> We recently reported that a combination of TPM and LEV exerted an antiepileptogenic effect when administered after SE induced by intrahippocampal kainate injection in mice.<sup>14</sup> Based on preclinical and clinical evidence that ATV may have an antiepileptogenic potential, due possibly to its neuroprotective and anti-inflammatory effects,<sup>58</sup> we hypothesized that adding ATV to the combination of TPM and LEV should increase their antiepileptogenic efficacy, which needs to be proven. Here, we show that such a triple-drug combination can be dissolved in low concentrations of meglumine. Furthermore, we characterized the pharmacokinetics and tolerability of this meglumine-based triple-drug solution in rats (Table 1). It is important to note that as yet no parenteral solution of ATV is commercially available.

#### 4.7 | Further development of the meglumine-based solution of topiramate

The novel meglumine-based TPM solution presented here is well-suited for clinical development. In addition to the treatment of SE, this solution should also be suited as short-term parenteral replacement therapy for oral TPM in patients with epilepsy or migraine when oral administration is temporarily not feasible. As expected from other meglumine-based drug formulations, the tolerability of the novel TPM solution was high in experimental animals and can be expected to be also high in patients. This expectation is substantiated by a recent case report in which the meglumine-based TPM solution was well tolerated following i.v. administration in a patient with epilepsy.<sup>59</sup> The planned development path of the novel meglumine-based TPM solution will include (1) the evaluation of the efficacy of different i.v. doses of TPM to terminate established SE in the pilocarpine rat model, using LEV as a reference drug; (2) the determination of plasma and brain pharmacokinetics of effective doses of i.v. TPM in rats; (3) the pharmaceutical optimization of the i.v. formulation, including the determination of chemical and physical stability and establishment of a GMP (Good Manufacturing Practice) manufacturing process to enable clinical trial supply; (4) a GLP (Good Laboratory Practice)-compliant multiple dose PreEp004 toxicity study in rats to establish local tolerance at the injection site, blood compatibility, and systemic toxicity of the formulation; (5) conduct of a single and multiple-dose phase I clinical study in healthy

volunteers, in which the safety and pharmacokinetics of i.v. TPM will be compared with oral TPM. The outcome of these studies will then determine the further clinical development path.

## 4.8 | Conclusions

The results of this study provide support for the further development of meglumine-based solutions of TPM for i.v. treatment of SE and short-term replacement therapy for oral TPM.

## AUTHOR CONTRIBUTIONS

Conceptualization and methodology: C.R., W.L., D.B., R.D., and H.P.G.; validation, formal analysis, investigation, and data curation: W.L.; D.B., R.D., C.E., B.P., M.M., and H.P.G.; resources: W.L., D.B., R.D., and H.P.G.; writing—original draft preparation: W.L.; writing—review and editing: C.R., P.K., D.B., A.R., M.M., and H.P.G.; preparation of figures: W.L.; project administration: W.L., P.K., D.B., and H.P.G.; funding acquisition: P.K., W.L., and A.R. All authors reviewed the manuscript.

## ACKNOWLEDGMENTS


We thank Dr. Raman Sankar (David Geffen School of Medicine at UCLA, Los Angeles, CA) for discussion on the formation of a meglumine:TPM complex. Open Access funding was enabled and organized by Projekt DEAL and provided by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation; Bonn, Germany) within the program LE 824/10-1 “Open Access Publication Costs” and University of Veterinary Medicine Hannover, Foundation. Open Access funding enabled and organized by Projekt DEAL.

## CONFLICT OF INTEREST STATEMENT

P.K., C.R., D.B., A.R., and W.L. are cofounders of PrevEp Inc. (Bethesda, MD, USA). R.D., C.E., B.P., M.M., and H.P.G. declare that they have no conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## ORCID

Pavel Klein  <https://orcid.org/0000-0001-7244-3722>

Wolfgang Löscher  <https://orcid.org/0000-0002-9648-8973>

## REFERENCES

1. Löscher W, Klein P. The pharmacology and clinical efficacy of antiseizure medications: from bromide salts to cenobamate and beyond. *CNS Drugs*. 2021;35:935–63.
2. Lyseng-Williamson KA, Yang LP. Topiramate: a review of its use in the treatment of epilepsy. *Drugs*. 2007;67:2231–56.
3. Silberstein SD. Topiramate in migraine prevention: a 2016 perspective. *Headache*. 2017;57:165–78.
4. Idrees Z, Cancarevic I, Huang L. FDA-approved pharmacotherapy for weight loss over the last decade. *Cureus*. 2022;14:e29262.
5. Rogawski MA, Löscher W, Rho JM. Mechanisms of action of antiseizure drugs and the ketogenic diet. *Cold Spring Harb Perspect Med*. 2016;6:pii: a022780.
6. Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. *Epilepsia*. 2000;41(Suppl 1):S3–9.
7. Brigo F, Bragazzi NL, Igwe SC, Nardone R, Trinka E. Topiramate in the treatment of generalized convulsive status epilepticus in adults: a systematic review with individual patient data analysis. *Drugs*. 2017;77:67–74.
8. Fechner A, Hubert K, Jahnke K, Knake S, Konczalla J, Menzler K, et al. Treatment of refractory and superrefractory status epilepticus with topiramate: a cohort study of 106 patients and a review of the literature. *Epilepsia*. 2019;60:2448–58.
9. Löscher W, Trinka E. The potential of intravenous topiramate for the treatment of status epilepticus. *Epilepsy Behav*. 2023;138:109032.
10. Madzar D, Kuramatsu JB, Gerner ST, Huttner HB. Assessing the value of topiramate in refractory status epilepticus. *Seizure*. 2016;38:7–10.
11. Cloyd JC. Topiramate compositions and methods for their use. *United States Patent US 2008/0194519 A1* 2008.
12. Sheskey PJ, Hancock BC, Moss GP, Goldfarb DJ. *Handbook of pharmaceutical excipients*. 9th ed. London, U.K.: Pharmaceutical Press; 2020.
13. Rowe RC, Sheskey PJ, Owen SC. *Handbook of pharmaceutical excipients*. Fifth ed. London: Pharmaceutical Press; 2006.
14. Schidlitzki A, Bascunana P, Srivastava PK, Welzel L, Twele F, Töllner K, et al. Proof-of-concept that network pharmacology is effective to modify development of acquired temporal lobe epilepsy. *Neurobiol Dis*. 2020;134:104664.
15. Gorski LA, Hagle ME, Bierman S. Intermittently delivered IV medication and pH: reevaluating the evidence. *J Infus Nurs*. 2015;38:27–46.
16. Manrique-Rodríguez S, Heras-Hidalgo I, Pernia-López MS, Herranz-Alonso A, Río Pisabarro MC, Suárez-Mier MB, et al. Standardization and chemical characterization of intravenous therapy in adult patients: a step further in medication safety. *Drugs R D*. 2021;21:39–64.
17. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: selection of polymer-surfactant combinations using solubility parameters and testing the processability. *Int J Pharm*. 2007;328:119–29.
18. Scicchitano F, Constanti A, Citraro R, De Sarro G, Russo E. Statins and epilepsy: preclinical studies, clinical trials and statin-anticonvulsant drug interactions. *Curr Drug Targets*. 2015;16:747–56.
19. Blonk MI, van der Nagel BC, Smit LS, Mathot RA. Quantification of levetiracetam in plasma of neonates by ultra performance liquid chromatography-tandem mass spectrometry. *J Chromatogr B Anal Technol Biomed Life Sci*. 2010;878:675–81.

20. El Zailik A, Cheung LK, Wang Y, Sherman V, Chow DS. Simultaneous LC-MS/MS analysis of simvastatin, atorvastatin, rosuvastatin and their active metabolites for plasma samples of obese patients underwent gastric bypass surgery. *J Pharm Biomed Anal.* 2019;164:258–67.
21. Wang L, Wang J, Zhang J, Jiang Q, Zhao L, Zhang T. Simultaneous determination of topiramate, carbamazepine, oxcarbazepine and its major metabolite in human plasma by SFC-ESI-MS/MS with polarity switching: application to therapeutic drug monitoring. *Arab J Chem.* 2019;12:4775–83.
22. Löscher W. Fit for purpose application of currently existing animal models in the discovery of novel epilepsy therapies. *Epilepsy Res.* 2016;126:157–84.
23. D'Ambrosio R, Eastman CL, Darvas F, Fender JS, Verley DR, Farin FM, et al. Mild passive focal cooling prevents epileptic seizures after head injury in rats. *Ann Neurol.* 2013;73:199–209.
24. Eastman CL, Fender JS, Klein P, D'Ambrosio R. Therapeutic effects of time-limited treatment with brivaracetam on post-traumatic epilepsy after fluid percussion injury in the rat. *J Pharmacol Exp Ther.* 2021;379:310–23.
25. Löscher W. Single versus combinatorial therapies in status epilepticus: novel data from preclinical models. *Epilepsy Behav.* 2015;49:20–5.
26. Reddy DS, Kuruba R. Experimental models of status epilepticus and neuronal injury for evaluation of therapeutic interventions. *Int J Mol Sci.* 2013;14:18284–318.
27. Reddy DS, Zaayman M, Kuruba R, Wu X. Comparative profile of refractory status epilepticus models following exposure of cholinergic agents pilocarpine, DFP, and soman. *Neuropharmacology.* 2021;191:108571.
28. Niebauer M, Gruenthal M. Topiramate reduces neuronal injury after experimental status epilepticus. *Brain Res.* 1999;837:263–9.
29. Shetty AK. Prospects of levetiracetam as a neuroprotective drug against status epilepticus, traumatic brain injury, and stroke. *Front Neurol.* 2013;4:172.
30. Reddy GD, Reddy AG, Rao GS, Kumar MV. Pharmacokinetic interaction of garlic and atorvastatin in dyslipidemic rats. *Indian J Pharmacol.* 2012;44:246–52.
31. Curia G, Longo D, Biagini G, Jones RS, Avoli M. The pilocarpine model of temporal lobe epilepsy. *J Neurosci Methods.* 2008;172:143–57.
32. Frey H-H, Löscher W. Anticonvulsant potency of unmetabolized diazepam. *Pharmacology.* 1982;25:154–9.
33. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline Committee of the American Epilepsy Society. *Epilepsy Curr.* 2016;16:48–61.
34. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. *J Basic Clin Pharm.* 2016;7:27–31.
35. Francois J, Koning E, Ferrandon A, Nehlig A. The combination of topiramate and diazepam is partially neuroprotective in the hippocampus but not antiepileptogenic in the lithium-pilocarpine model of temporal lobe epilepsy. *Epilepsy Res.* 2006;72:147–63.
36. Suchomelova L, Baldwin RA, Kubova H, Thompson KW, Sankar R, Wasterlain CG. Treatment of experimental status epilepticus in immature rats: dissociation between anticonvulsant and antiepileptogenic effects. *Pediatr Res.* 2006;59:237–43.
37. Loftsson T. Cyclodextrins in parenteral formulations. *J Pharm Sci.* 2021;110:654–64.
38. Bartkoski S, Day M. Alpha-lipoic acid for treatment of diabetic peripheral neuropathy. *Am Fam Physician.* 2016;93:786.
39. Manley K, Bravo-Nuevo A, Minton AR, Sedano S, Marcy A, Reichman M, et al. Preclinical study of the long-range safety and anti-inflammatory effects of high-dose oral meglumine. *J Cell Biochem.* 2019;120:12051–62.
40. Stella VJ, Rajewski RA. Sulfobutylether- $\beta$ -cyclodextrin. *Int J Pharm.* 2020;583:119396.
41. Vuu I, Coles LD, Maglalang P, Leppik IE, Worrell G, Crepeau D, et al. Intravenous topiramate: pharmacokinetics in dogs with naturally occurring epilepsy. *Front Vet Sci.* 2016;3:107.
42. Masucci JA, Ortegón ME, Jones WJ, Shank RP, Caldwell GW. In vivo microdialysis and liquid chromatography/thermospray mass spectrometry of the novel anticonvulsant 2,3,4,5-bis-O-(1-methylethylidene)- $\beta$ -D-fructopyranose sulfamate (topiramate) in rat brain fluid. *J Mass Spectrom.* 1998;33:85–8.
43. Ahmed GF, Marino SE, Brundage RC, Pakhomov SV, Leppik IE, Cloyd JC, et al. Pharmacokinetic-pharmacodynamic modelling of intravenous and oral topiramate and its effect on phonemic fluency in adult healthy volunteers. *Br J Clin Pharmacol.* 2015;79:820–30.
44. Clark AM, Kriel RL, Leppik IE, White JR, Henry TR, Brundage RC, et al. Intravenous topiramate: safety and pharmacokinetics following a single dose in patients with epilepsy or migraines taking oral topiramate. *Epilepsia.* 2013a;54:1106–11.
45. Clark AM, Kriel RL, Leppik IE, Marino SE, Mishra U, Brundage RC, et al. Intravenous topiramate: comparison of pharmacokinetics and safety with the oral formulation in healthy volunteers. *Epilepsia.* 2013b;54:1099–105.
46. Lim CN, Birnbaum AK, Brundage RC, Leppik IE, Cloyd JC, Clark A, et al. Pharmacokinetic-pharmacodynamic modeling of intravenous and Oral topiramate and its effect on the symbol-digit modalities test in adult healthy volunteers. *J Clin Pharmacol.* 2016;56:714–22.
47. Towne AR, Garnett LK, Waterhouse EJ, Morton LD, DeLorenzo RJ. The use of topiramate in refractory status epilepticus. *Neurology.* 2003;60:332–4.
48. Klein P, Tolbert D. Intravenous carbamazepine: a new formulation of a familiar drug. *Expert Rev Neurother.* 2017;17:851–60.
49. Cassimiro DL, Ferreira LM, Capela JM, Crespi MS, Ribeiro CA. Kinetic parameters for thermal decomposition of supramolecular polymers derived from diclofenac-meglumine supramolecular adducts. *J Pharm Biomed Anal.* 2013;73:24–8.
50. Hottinger A, Sutter R, Marsch S, Rüegg S. Topiramate as an adjunctive treatment in patients with refractory status epilepticus: an observational cohort study. *CNS Drugs.* 2012;26:761–72.
51. Shishmanova-Doseva M, Peychev L, Yoanidu L, Uzunova Y, Atanasova M, Georgieva K, et al. Anticonvulsant effects of topiramate and Lacosamide on pilocarpine-induced status epilepticus in rats: a role of reactive oxygen species and inflammation. *Int J Mol Sci.* 2021;22:22.
52. Matar KM, Tayem YI. Effect of experimentally induced hepatic and renal failure on the pharmacokinetics of topiramate in rats. *Biomed Res Int.* 2014;2014:570910.
53. Beuchat I, Novy J, Rossetti AO. Newer antiepileptic drugs for status epilepticus in adults: What's the evidence? *CNS Drugs.* 2018;32:259–67.

54. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019;381:2103–13.
55. Xue T, Wei L, Shen X, Wang Z, Chen Z, Wang Z. Levetiracetam versus phenytoin for the pharmacotherapy of benzodiazepine-refractory status epilepticus: a systematic review and meta-analysis of randomized controlled trials. *CNS Drugs*. 2020;34:1205–15.
56. Löscher W, Gillard M, Sands ZA, Kaminski RM, Klitgaard H. Synaptic vesicle glycoprotein 2A ligands in the treatment of epilepsy and beyond. *CNS Drugs*. 2016;30:1055–77.
57. Kaminski RM, Matagne A, Patsalos PN, Klitgaard H. Benefit of combination therapy in epilepsy: a review of the preclinical evidence with levetiracetam. *Epilepsia*. 2009;50:387–97.
58. Klein P, Friedman A, Hameed M, Kaminski R, Bar-Klein G, Klitgaard H, et al. Repurposed molecules for antiepileptogenesis: missing an opportunity to prevent epilepsy? *Epilepsia*. 2020;61:359–86.
59. Apostolakopoulou L, Bosque-Varela P, O'Sullivan C, Rossini F, Löscher W, Kuchukhidze G, et al. Intravenous topiramate for seizure emergencies – first in human case report. *Epilepsy Behav*. 2023; in press.

**How to cite this article:** Rundfeldt C, Klein P, Boison D, Rotenberg A, D'Ambrosio R, Eastman C, et al. Preclinical pharmacokinetics and tolerability of a novel meglumine-based parenteral solution of topiramate and topiramate combinations for treatment of status epilepticus. *Epilepsia*. 2023;64:888–899. <https://doi.org/10.1111/epi.17520>