Relative bioavailability of topiramate administered rectally

Jeannine M. Conway a,∗, Angela K. Birnbaum b, Robert L. Kriel a, b, James C. Cloyd a

a Experimental and Clinical Pharmacology, Epilepsy Research and Education Program, College of Pharmacy, University of Minnesota, 7-170 WDH, 308 Harvard St. SE, Minneapolis, MN 55455, USA
b Departments of Pediatrics and Neurology, Hennepin County Medical Center, Minneapolis, MN, USA

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Abstract

Objective: To determine the relative bioavailability and tolerability of a topiramate (TPM) suspension after rectal administration.

Design/method: Seven healthy men and five healthy non-pregnant women were enrolled. A 100 or 200 mg tablet of TPM was given orally and a 200 mg dose was given rectally in a randomized, open-label, crossover study with at least a 2-week washout period between doses. Plasma samples were collected prior to dosing and the following times after each dose: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 h. Relative bioavailability was determined by calculating the ratio of the dose-normalized area under the curve (AUC/D) for the rectal and oral doses.

Results: Ten subjects completed the study. Two of the first seven subjects who received a 200 mg initial oral dose, withdrew because of side effects. The remaining subjects received a 100 mg oral dose. Three subjects received a 200 mg dose orally and rectally, and seven subjects received 100 mg orally and 200 mg rectally. The average AUC/D was 0.72 ± 0.18 h/l for the rectal dose and 0.76 ± 0.20 h/l for the oral dose. The relative bioavailability (n = 10) for TPM administered rectally was 0.95 ± 0.17 with a range of 0.68–1.2. There were no statistically significant differences between the oral or rectal pharmacokinetic parameters.

Conclusions: In healthy adults, rectally administered TPM is absorbed to a similar extent as the oral dosage form. Rectal administration is an acceptable route of administration for TPM, when the oral route is temporarily unavailable.

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1. Introduction

A common cause of seizure breakthrough is interruption in antiepileptic drug (AED) therapy (Krumholz et al., 1989). Missing doses may have catastrophic effects on a patient’s seizure control, including increased frequency, intensity, or duration of seizures (Stanaway et al., 1985). Although noncompliance is the most common reason for interruptions of oral therapy, there are a variety of other reasons such as vomiting, gastrointestinal illness, fasting prior to and after surgery, and impairment of consciousness that may result in a precipitous decrease in AED blood concentrations.

Alternatives to oral AED therapy are limited. Among all the AEDs only three are available as parenteral formulations: phenobarbital, phenytoin, and sodium valproate. This leaves many patients...
and clinicians with the dilemma of using a different AED based on availability of a parenteral solution. Such circumstances expose the patient to both unpredictable side effects and the potential loss of seizure control. Even when a parenteral formulation is available, administration requires the presence of skilled medical personnel in a healthcare facility with all the attendant costs and inconveniences. The preferred approach would be to maintain the patient on her or his current medication by using an alternate route of administration.

Rectal administration may be used as a bridge when oral AED therapy is not possible and a parenteral formulation does not exist or is impractical. An acceptable alternative to the oral route may be rectal administration if the drug is adequately and consistently absorbed, and the formulation is well tolerated. Many AEDs possess physical-chemical characteristics that make them candidates for rectal administration. Carbamazepine (Graves et al., 1985), valproic acid (Cloyd and Kriel, 1981), diazepam (Dhillon et al., 1982; Minagawa et al., 1986; Remy et al., 1992; Cloyd et al., 1998), phenobarbital (Matsukura et al., 1981; Graves et al., 1989) and lamotrigine (Birnbaum et al., 2000, 2001) can be given via the rectal route. These studies demonstrate that it is possible to take commercially available oral formulations and, with a few simple steps that can be done in the pharmacy or home, prepare a rectal formulation.

Topiramate (TPM) is an AED approved for use as adjunctive therapy for partial onset seizures or primary generalized tonic clonic seizures in children (ages 2–16) years and adults. It is also indicated as adjunctive therapy for children 2 years of age or older with seizures due to Lennox-Gastaut syndrome. TPM is available only as oral formulations: 25, 100, and 200 mg tablets or 15 and 25 mg sprinkle capsules. It has multiple mechanisms of action that work for many seizure types (Shank et al., 1994). Recent literature suggests, it is useful for childhood epilepsies including partial and generalized seizures (Biton et al., 1999), Lennox-Gastaut (Sachdeo et al., 1999), juvenile myoclonic epilepsy (Wheless, 2000), infantile spasms (Glasser et al., 1998), and absence seizures (Wheless, 2000). TPM would appear to be a viable candidate for rectal administration. Its chemical-physical properties indicate that it is sufficiently soluble in water (9.8 mg/ml) to deliver a clinically relevant dose as a suspension in a volume ≤20 ml. TPM is also lipophilic enough (log P = 0.573) to facilitate relatively rapid absorption after rectal administration (Johnson & Johnson Pharmaceutical Research Institute).

The objective of this study was to determine the relative bioavailability and tolerability of TPM suspension after rectal administration using a formulation that is easily prepared from commercially available tablets. Information on the absorption and safety of rectal administration of TPM can guide the practitioner when oral administration is not possible.

2. Methods

2.1. Study design

The subject population was healthy volunteers from 18 to 65 years of age. Subjects were excluded from the study if they had a previous history of nephrolithiasis, were not in good health, were taking other medications, were unwilling or unable to receive medications rectally, were unwilling or unable to tolerate multiple venipunctures, or had a hemoglobin <12 g/dl. The study was approved by the IRB’s at both the University of Minnesota (Minneapolis, MN) and Hennepin County Medical Center (Minneapolis, MN). Subjects were informed of the study and gave written consent. For each phase of the study, subjects were admitted to the DaVita Clinical Research Unit (CRU) located at Hennepin County Medical Center, where they remained for approximately 24 h. A 100 or 200 mg tablet of TPM was given orally or a 200 mg dose was given rectally in a randomized, open-label, crossover study with at least a 2-week washout period between doses. The original study design was for each subject to receive a 200 mg oral dose; however, two of the subjects that received a 200 mg oral dose withdrew from the study due to adverse events. Hence, the remaining subjects received a 100 mg oral dose. For the oral dose, the subject swallowed either the commercially available 100 or 200 mg tablet with 120 ml of water. The 200 mg dose was selected based on the predicted concentrations that would be seen in humans following a single dose and the sensitivity of the assay (Doose et al., 1996).

The rectal dose was prepared by crushing a 200 mg tablet with a mortar and pestle, and adding 10 ml of
tap water to suspend the material. The contents of the mixture were then drawn into a 35 ml syringe and the mortar was rinsed with 5 ml of water twice and then drawn into the syringe after each rinse. The syringe was inverted 10 times to mix the contents. The subjects were placed in the right lateral decubitus position and the 35 ml syringe with an attached catheter was inserted approximately 2.5 in. into the rectum. The subjects rested in a supine position for at least 60 min and were monitored to ensure that rectal expulsion did not occur over that period.

Plasma samples were collected just prior to and at the following times after each dose: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 h. Blood samples were centrifuged and plasma was transferred to separate containers for storage at −80 °C. Adverse event data were collected, as a self-report, at each blood sample collection. The scale was designed to measure the level of comfort of the side effects that were thought to be the most likely to occur: speech impairment, dizziness, nausea, headache, difficulties in concentrating, sleepiness, unusual sensations, discomfort due to administration of the rectal dose, and abnormal vision. Severity of adverse events was rated on a scale from 0 to 5, with 0 indicating no noticeable adverse event and 5, a severe adverse event. Side effects and discomfort associated with oral and rectal administration were assessed. Subjects were also asked to report adverse events not specifically listed.

3. Sample analysis

TPM concentrations were determined by a GC-MS method that was modified from one described by Gidal and Lensmeyer (1999) and validated in our laboratory. TPM reference standard was provided by Johnson & Johnson Pharmaceutical Research and Development (Raritan, NJ). For extraction, 50 μl of the internal standard, cyheptamide (Sigma, St. Louis, MO) and 500 μl of saturated ammonium acetate were added to 500 μl of sample or standard. Samples were vortexed and transferred to an Empore® cartridge (3M, St. Paul, MN) C18 solid-phase extraction disk cartridge. The disk was primed and the sample was forced through the disk by centrifugation. The eluate was evaporated to dryness under nitrogen and the final samples were reconstituted with 100 μl of toluene. A 2 μl sample was injected on to the column and quantified by GC-MS in the SIM mode. The GC-MS system consisted of a HP5890 Series II Gas Chromatograph; HP5971 Mass Selective Detector; HP7673 Autoinjector; using a DB-5MS 30 m × 0.25 mm i.d. capillary of 0.5 μm film thickness column (J&W Scientific, Folsom, CA). The program for sample analysis was an injection volume of 2 μl, transfer line temperature of 280 °C, initial temperature of 230 °C, initial time of 0.5 min, program rate was 10 °C/min, final temperature of 290 °C, final time of 1.0 min, and detector temperature of 300 °C. Ions monitored were 193.1 and 324.1 mz. The peak times were 4.5 min (TPM) and 5.4 min (I.S.). Each subject’s oral and rectal blood samples were extracted and analyzed on the same day and compared on the same standard curve. Triplicate quality control samples were run with plasma samples and were deemed acceptable if the values were within two standard deviations of the mean quality control values for all previous runs. The solubility of the suspension was determined by preparing the rectal dose, as described above, and filtering the suspension. Unextracted triplicate samples and standard curves were analyzed by GC-MS.

4. Pharmacokinetic analyses

All pharmacokinetic analyses were completed with WinNonlin version 3.1 (Pharsight, Mountain View, CA) using a noncompartmental approach. The area under the TPM plasma concentration time curve was determined using the trapezoidal rule from time 0 to 96h (AUC0–96). The total AUC was calculated by adding the AUC0–∞ (C0/ke) to AUC0–96. The elimination rate constant (ke) was determined by the log-linear regression analysis of the terminal plasma TPM concentration time points. Relative bioavailability (Frel) was determined by calculating the ratio of the dose-normalized area under the concentration time curves (AUC0–∞,rel/Doral) for the rectal and oral doses using the following equation: Frel = (AUC0–∞,oral/Doral)/(AUC0–∞,rel/Drel). We assumed linear pharmacokinetics for both the 100 and 200 mg oral doses (Doose et al., 1996).
5. Statistical analysis

The mean and standard deviation were determined for all pharmacokinetic parameters. ANOVA was used to compare the oral to the rectal treatments (Microsoft Excel 2000). A $P \leq 0.05$ was considered statistically different. Bioequivalence was determined using WinNonlin version 3.1 and the Westlake method.

6. Results

Ten of 12 subjects, who gave consent, completed the study (Table 1). Two of the first seven subjects withdrew because of side effects following the initial 200 mg oral dose. Because of the unacceptable adverse effects, the oral dose was reduced to 100 mg for the remaining subjects. Three subjects received 200 mg orally and rectally and seven subjects received 100 mg orally and 200 mg rectally. Our laboratory determined the solubility of the rectal TPM formulation made from the 200 mg tablet to be 2.78 mg/ml.

The average $\text{AUC}_{0-\infty}/D$ for the rectal and oral doses was $0.72 \pm 0.18 \text{h/l}$ and $0.76 \pm 0.20 \text{h/l}$, respectively (Table 2). There were no statistical differences between the pharmacokinetic parameters for the oral and rectal doses. The relative bioavailability ($n = 10$)

Table 1

| Subject characteristics for pharmacokinetic analysis ($n = 10$) |
|-------------------------|-------|
| Age (year)              | 29.8 ± 7.4 |
| Weight (kg)             | 72.7 ± 13.0 |
| Gender                  |         |
| Male                    | 6      |
| Female                  | 4      |

Table 2

<table>
<thead>
<tr>
<th>Pharmacokinetic values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}/D$ (h/l)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/l per dose)</td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
</tr>
<tr>
<td>Apparent volume of distribution (l)</td>
</tr>
<tr>
<td>Elimination rate constant (h$^{-1}$)</td>
</tr>
<tr>
<td>Apparent clearance (ml/min)</td>
</tr>
</tbody>
</table>

* Values divided by dose for statistical comparison.
Table 3
Side effects vs. route: a comparison of the highest score reported by a subject at any time point the time it occurred

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Rectal (n = 10)</th>
<th>Oral (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level of maximum discomfort (median/mode)</td>
<td>Time (h) of maximum discomfort (median/mode)</td>
</tr>
<tr>
<td>Speech impairment</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1/1</td>
<td>1.25/1.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Headache</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Difficulties in concentrating</td>
<td>0.5/0</td>
<td>0.25/0</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>1/1</td>
<td>0.5/0</td>
</tr>
<tr>
<td>Unusual sensations</td>
<td>1.5/0</td>
<td>1.5/0</td>
</tr>
<tr>
<td>Discomfort due to administration</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

Side effects were rated from 0 (no discomfort) to 5 (severe discomfort).

7. Discussion

In healthy adults, rectally administered TPM suspension is bioequivalent to the orally administered tablet. This study demonstrated a relative bioavailability of 0.95 ± 0.17 for rectally administered TPM with a 90% confidence interval of 81.9–118. The plasma TPM concentrations attained by rectal administration tended to be lower and peak plasma concentration tended to occur later compared to the oral dose, but neither difference was statistically different. There were no statistical differences between the routes of administration or other pharmacokinetic parameters including clearance, half-life, elimination rate constant, or volume of distribution.

The variability in rectal TPM bioavailability could be due to several factors. We found that the amount of a crushed 200 mg tablet that dissolves in water is 2.78 mg/ml. This is much lower than the predicted solubility of 9.8 mg/ml. Despite the solubility being less than expected, it appears that an adequate amount was absorbed rectally. Drug dissolution can be affected by the fineness of the particles, the presence of other excipient particulates, and water temperature (Sharf and Yu, 1999). It is likely that one or more of these factors varied when preparing each subject’s rectal dose. Rectal doses with a high percentage of TPM in suspension, as opposed to solution, may have resulted in lower bioavailability. The assumption of linear pharmacokinetics between the 100 and 200 mg doses was made for the bioavailability calculation. If the pharmacokinetics of TPM is not linear between 100 and 200 mg doses, the calculations may underestimate or overestimate bioavailability. Nonetheless, rectal TPM displays high and relatively consistent absorption relative to other rectally administered AEDs (Brimbaum et al., 2000, 2001; Kriel et al., 1997; Burstein et al., 2000).

Our data suggest that a rectally administered 10 mg/ml suspension of a crushed TPM tablet may be used when oral administration is not possible. Volume considerations may limit the usefulness of this
formulation if patients require dosages greater than 200 mg per dose. Alternatively, given the low solubility of the rectal formulation used in this study, it may be possible to achieve the same results with a more concentrated suspension. The plasma concentrations attained following rectal administration should be sufficient when replacing a dose if a person cannot take their regular dose orally. The $T_{\text{max}}$ and elimination half-life indicate that rectal TPM can be given at the same interval as oral TPM (once or twice daily). This information will help guide the clinician and caregivers about an alternate route of administration when oral delivery is not possible.

This study was conducted in healthy adult volunteers. Further research is needed to determine if rectal TPM administration can be used for more extended periods of time in adult and pediatric patients with epilepsy. Rectal administration may also be useful in situations where patients on TPM go into status epilepticus due to an abrupt decrease in plasma concentrations (e.g. noncompliance, malabsorption, drug interactions, etc.). Until further information is available, dose substitution should be done carefully with close supervision by a healthcare provider.

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References


Johnson & Johnson Pharmaceutical Research Institute Topamax (topiramate) Data on File. Raritan, NJ.


