TOPAMAX® (topiramate)
Dosing - Crushing Tablets and Special Administration: Suspension, NG tube, and Rectal

SUMMARY

- Evaluations have not been performed to assure drug stability, safety or efficacy when using broken, crushed or otherwise altered TOPAMAX tablets.
- TOPAMAX tablets are film coated.[1] Crushing tablets will compromise the film coating unmasking the bitter taste of the compound.
- Variation in dose due to incomplete administration of crushed tablets could lead to adverse clinical outcomes.
- TOPAMAX is not approved for administration via suspension or nasogastric (NG) tube.
- There is no marketed topiramate suspension available in the U.S.
- If a suspension is necessary, TOPAMAX may be crushed and suspended in water and Several publications have reported the use of topiramate via nasogastric administration.[2-6]
- A pharmacokinetic study found that topiramate is absorbed rectally. The bioavailability of rectally administered topiramate was similar to that of orally administered topiramate falling within a range of 80–120% of oral topiramate.[7]

CLINICAL DATA

CRUSHING TABLETS

TOPAMAX tablets are not scored and are film coated to mask the bitter taste and to provide stability.[1] If the tablets are broken or crushed, their stability cannot be guaranteed for any period of time. Furthermore, once the integrity of the film coat is compromised, the bitter taste may no longer be masked.

ADMINISTRATION USING A SUSPENSION

There is no marketed topiramate suspension available. If a suspension is necessary, TOPAMAX tablets may be crushed and suspended in water. The solubility of topiramate in water is 9.8 mg/mL. No data is available regarding the stability of this mixture; therefore, it should be used immediately. Since the excipients may be insoluble they may not dissolve. Tablets should not be broken to administer fractional doses. If the tablets are broken their stability cannot be guaranteed for any period of time and should be discarded. It should not be stored for future use.

No information has been identified pertaining to the suspension of topiramate with other diluents or flavorings.

ADMINISTRATION VIA NASOGASTRIC (NG) TUBE

TOPAMAX tablets have been crushed, suspended in water, and administered via NG tube.[2-5] The **sprinkle capsule** formulation of TOPAMAX should not be used in NG tubes due to aggregation and clogging that have been observed.

Several publications have reported the use of topiramate via nasogastric administration.[2-6, 8] One study reported using topiramate tablets that were crushed into a powder and then mixed with water. After the mixture was allowed to sit for several minutes to avoid clumping, it was administered into a nasogastric tube via syringe.[4]

RECTAL ADMINISTRATION

Randomized, crossover, bioavailability study

Conway et al (2003)[7] investigated the rectal absorption of topiramate in 12 healthy individuals.

Study Design/Methods

- Randomized, crossover, bioavailability study, (N=12)
- Volunteers received oral topiramate 100 or 200 mg/day, or 200 mg rectally, crushed and dissolved in 10 ml of water and administered via 35 ml syringe attached to a catheter and inserted approximately 2.5 inches into the rectum.
- Crossover occurred after a 2-week washout
- Plasma samples were collected at the time of topiramate administration and monitored for 96 hours
- Relative bioavailability (Frel) was calculated using the ratio of the dose-normalized area under the concentration time curves ($AUC_{0-\infty}/D$) for the rectal and oral doses using the following equation: $F_{rel} = (AUC_{0-\infty,\ rectal}/\ D_{rectal})/(AUC_{0-\infty,oral}/\ D_{oral})$.

Results

- Solubility of the rectal topiramate formulation (prepared using the 200 mg tablet) was determined to be 2.78 mg/ml, which differs from previously reported values.[1]
- Relative bioavailability (n=10) of rectal administration of topiramate was 0.95 ± 0.17 with a range of 0.68-1.2. The rectal topiramate bioavailability (extent of absorption) fell within a range of 80-120% for 9 of the 10 patients. No statistical difference was observed between the pharmacokinetic values for the oral and rectal doses.
- Average $AUC_{0-\infty}/D$ for the rectal dose was 0.72 ± 0.18 h/l and for the oral dose was 0.76 ± 0.20 h/l. (Table: Pharmacokinetics of Orally and Rectally Administered Topiramate).
- Two of the first seven patients dropped out because of side effects following the 200 mg oral dose. The remaining patients received a topiramate dose of 100 mg/day.

Pharmacokinetics of Orally and Rectally Administered Topiramate*

	Rectal (mean)	***Oral (mean)***	***P value***
$AUC_{0-\infty/D\ (h/l)}$	0.72	0.76	0.61
Tmax (h)	2.5	1.8	0.19
$C_{Pmax\ (}$mg/l per dose)	1.89	2.34	1.14
Elimination half-life (h)	26.7	28.36	0.33
Apparent volume of distribution (l)	57.03	56.3	0.91
Elimination rate constant (h^{-1})	0.0264	0.0248	0.34
Apparent clearance (ml/min)	24.7	22.9	0.53
**adapted from Conway et al.*[7]			

- Solubility was less than expected, however, adequate amounts of drug were absorbed rectally.
- Rectally administered 10 mg/mL suspension of a crushed topiramate tablet may be a useful alternative administration method when oral administration cannot be used.

Case Reports - Rectal Administration

Vuong et al (2021)[9] described three cases at a single children's hospital where topiramate was administered as a rectal suspension for a 2-4 day period after patients (<1 year-old) were placed on nil per os (NPO) status. According to physician notes, seizure frequency either decreased or ended during that period; no adverse effects were reported.

Bonwetsch et al (2001)[10] found that topiramate administered rectally in a critically ill patient was systemically absorbed. However, blood levels following rectal administration were lower than those following oral administration two days prior and up to four months after the rectal dose. Topiramate blood levels were as follows: 4.5 µg/ml with 200 mg/day oral dosing prior to hospitalization, 1.7 µg/ml after three rectal doses (200 mg, 100 mg, and 200 mg, respectively) over 36 hours, and 4.3-4.8 µg/ml with 300 mg/day oral dosing during a four month follow up.

LITERATURE SEARCH

A literature search of MEDLINE® pertaining to this topic was conducted on 2022 November 22.

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