Temozolomide Stability in Extemporaneously Compounded Oral Suspensions

Abstract

Temozolomide, commercially available in capsules, is an oral alkylating agent used to treat brain tumors. The purpose of this study was to determine the pharmaceutical acceptability and chemical stability of temozolomide in two extemporaneously compounded suspension formulations prepared from the capsules. The temozolomide oral suspensions were prepared from 100-mg commercial capsules yielding a nominal temozolomide concentration of 10 mg/mL. The suspension vehicles selected for testing were an equal parts mixture of Ora-Plus and Ora-Sweet and an equal parts mixture of Ora-Plus and Ora-Sweet SF. The suspensions were packaged in amber plastic screw-cap prescription bottles, which were stored at 23°C for 21 days or 4°C for 60 days.

Stability-indicating high-performance liquid chromatographic analysis revealed that the temozolomide concentration in both suspension vehicle combinations exhibited little or no loss for 60 days at 4°C. At 23°C, temozolomide losses were somewhat greater. In the Ora-Sweet formulation, the loss was 6% at 7 days; in the Ora-Sweet SF formulation, losses were about 8% at 14 days and 10% to 11% at 21 days.

Temozolomide extemporaneously prepared as oral suspensions from capsules in equal parts mixtures of Ora-Plus suspension vehicle with Ora-Sweet and with Ora-Sweet SF syrups with added povidone k-30 and acidified with citric acid were pharmaceutically acceptable and chemically stable for at least 60 days at 4°C. Refrigerated storage is recommended. The suspensions should not be stored at room temperature longer than 1 week if Ora-Sweet is used or longer than 2 weeks if Ora-Sweet SF is used.

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Introduction

Temozolomide, an analog of dacarbazine, received US Food and Drug Administration (FDA) approval in 1999 for the treatment of refractory anaplastic astrocytoma in adult patients. This drug is a major advance in the treatment of malignant gliomas, being only the third drug approved for the treatment of brain tumors since the 1960s. Temozolomide is an oral prodrug that is converted rapidly to its active form in an alkaline environment and acts as an alkylating agent. It is completely absorbed after oral administration, and crosses the blood-brain barrier. The drug is supplied in capsules of four different strengths (5 mg, 20 mg, 100 mg, and 250 mg),[1] and the most common side effects reported during clinical investigations were nausea, vomiting, headache, and fatigue; the dose-limiting toxic effect is myelosuppression.[1,2]

The activity of temozolomide in the treatment of anaplastic astrocytoma refractory to nitrosoureas and procarbazine and of newly diagnosed glioblastoma multiforme with concomitant radiotherapy has been established in adult patients.[1,3-5] Temozolomide has produced favorable results in other tumor types, such as untreated metastatic melanoma,[6,7] although further studies are warranted to establish its exact role in the treatment of these cancers. The safety and tolerability of temozolomide have been determined for children with solid tumors,[8,9] but studies on its efficacy specifically for the treatment of pediatric brain tumors have produced conflicting results.[1,10,11] Further studies on temozolomide's use in pediatric malignancies are warranted, and such studies are now being conducted by the Children's Oncology Group.

A variety of temozolomide dosing regimens have been investigated and are employed in clinical practice today. The FDA-approved regimen for refractory anaplastic astrocytoma is 150 mg/m^2/day orally, given once a day for 5 consecutive days per 28-day treatment cycle. It is recommended that capsules be swallowed whole and intact. It is further recommended that the capsule contents not be inhaled or come in direct contact with skin or mucous membranes.[1]

Although the drug is supplied in several dosage strengths for added flexibility, many patients are required to swallow several capsules (range, 1 to 8) to meet their daily dose.[1] This may be challenging for certain patient populations, such as children or adults with swallowing impairments. We investigated the feasibility of compounding temozolomide in oral suspension formulations to provide an additional method of drug delivery for such patients. The use of an oral suspension may allow more patients to receive temozolomide and could reduce the potential for drug exposure to healthcare workers and/or family members in situations where capsules are opened and mixed with food or liquid in an effort to ease the drug's administration.

However, no information currently exists on the pharmaceutical acceptability, including chemical stability, of such suspensions.

The purpose of this study was to determine the pharmaceutical acceptability and chemical stability of temozolomide in two extemporaneously compounded oral suspension formulations prepared from the capsules.

Materials and Methods

Materials

Temozolomide 100-mg capsules (Lot 4-DCW-3; Schering, Kenilworth, New Jersey) were obtained commercially. Ora-Plus suspension vehicle (Lot 2497086; Paddock Laboratories, Inc., Minneapolis, Minnesota), Ora-Sweet sucrose-based syrup (Lot 4191096; Paddock Laboratories, Inc.), Ora-Sweet SF sucrose-free syrup (Lot 4211218; Paddock Laboratories, Inc.), povidone K-30 (Lot SD0437; Spectrum Chemical Manufacturing Corporation, Gardena, California), and citric acid anhydrous (Lot 915067; Fisher Chemical, Fairlawn, New Jersey) were also obtained commercially. Mobile phase components were all suitable for use in high-performance liquid chromatographic analysis (HPLC), as was the water (Milli-Q Plus; Millipore Corporation, Bedford, Massachusetts), which was prepared immediately before use.

Preparation and Storage of Suspensions

Temozolomide is an oral prodrug that is hydrolyzed *in vivo* to the alkylating antineoplastic agent 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide.[1] Hydrolysis proceeds rapidly at neutral and alkaline pH, but the drug is more stable at acidic pH values of less than 5.[1] Thus the oral suspension formulations investigated for this study incorporated a small amount of citric acid. Moreover, povidone K-30 was incorporated to delay or prevent the formation of crystals that had been observed in preliminary attempts to prepare acceptable oral suspensions of this drug.

Two temozolomide 10-mg/mL suspensions were evaluated. The suspensions were prepared from temozolomide capsule contents, povidone K-30, and Anhydrous Citric Acid USP, using two different vehicles: an equal parts mixture of Ora-Plus and Ora-Sweet, and an equal parts mixture of Ora-Plus and Ora-Sweet SF. The compounding procedure is provided in the accompanying box. The finished suspensions were found to have a pH near 4. A total of 180 mL of each suspension was prepared and divided into 30-mL portions packaged in 60-mL amber polyethylene terephthalate screw cap bottles (Owens-Brockway Prescription Products, Berlin, Ohio). Three bottles of each formulation were stored at 23°C for 21 days and another three bottles were stored at 4°C for 60 days. The suspensions were evaluated for pharmaceutical acceptability initially and after storage periods of 1, 7, 14, and 21 days at both temperatures, and 30, 45, and 60 days for the refrigerated samples.

Inspection of Suspensions

At each of the evaluation time points, each of the undisturbed sample suspensions were visually inspected for layering and signs of caking. The sample bottles were shaken for about 10 seconds, and the suspensions were reexamined for ease of resuspension, evidence of caking, pourability, and lack of uniformity, including crystal formation. Samples were removed from the amber bottles and examined for color changes.

Temozolomide 10-mg/mL Oral Suspensions

Rx

For 100 mL		
Temozolomide		
(from 10 Temodar 100-mg capsules)		1,000 mg
Povidone K-30		500 mg
Anhydrous citric acid		25 mg
Purified water		1.5 mL
Ora-Plus		50 mL
Ora-Sweet or Ora-Sweet SF	qs	100 mL

METHOD OF PREPARATION

Note: It is necessary to wear suitable protective garb and to perform this procedure in a fume hood.

1. Empty the contents of 10 temozolomide 100-mg capsules in a glass mortar of sufficient size.
2. Weigh 500 mg of povidone K-30 powder and add to the mortar.
3. Triturate to assure thorough mixing and that the mixture is reduced to a fine powder.
4. Dissolve 25 mg of anhydrous citric acid in 1.5 mL of purified water.
5. Add the mixture of anhydrous citric acid and purified water to the mortar to wet the powder.
6. Mix thoroughly to form a uniform paste.
7. Add a small amount of Ora-Plus suspension vehicle to the triturated paste with thorough mixing to ensure a uniform mixture.
8. Add the balance of the Ora-Plus suspension vehicle with thorough mixing to ensure a uniform mixture.
9. Transfer the resulting mixture to a glass graduated cylinder.
10. Rinse the mortar and pestle with small aliquots of the appropriate syrup (Ora-Sweet or Ora-Sweet SF); repeat the rinsing three additional times.
11. Add an additional quantity of the appropriate syrup vehicle to the bottle to bring the final volume to 100 mL and shake the resulting suspension well.
12. Package in amber plastic prescription bottles and label the containers with "Shake Well" and "Refrigerate" and the beyond-use date.

Sample Preparation for Chemical Analysis

The sample bottles were shaken for approximately 10 seconds. One-milliliter aliquots were taken from each sample after resuspension at each time point. The samples were prepared for analysis by transferring 0.5 mL of each suspension into a 15-mL glass tube with a polypropylene screw cap. These samples were diluted with 9.5 mL of mobile phase to yield a final volume of 10 mL. The samples were then subjected to thorough vortex mixing for 30 seconds. The resulting samples were subjected to centrifugation for 10 minutes at 1,500 × g and filtered through appropriate 0.22-µm filters (Millex-GV, Millipore). At least 0.5 mL was allowed to pass out of the filter

unit before the sample was collected in a vial. This solution was then diluted fivefold with mobile phase for chromatographic analysis. The nominal temozolomide concentration of the filtered sample was 100 µg/mL; 15 µL of this sample was injected for chromatography.

Reference Preparation

Temozolomide reference standard was unavailable from the manufacturer. A reference material was prepared from the capsule contents (method of preparation included with this article) and was stored at –70°C for comparison with the samples.

Stability Analysis

A stability-indicating HPLC method developed in our laboratory was used in this study. Temozolomide concentrations in the sample suspensions were determined by using this stability-indicating HPLC assay method. The analysis employed an Alliance 2690 Separation Module chromatograph (Waters Chromatography, Milford, Massachusetts) equipped with a multiple-solvent delivery pump and autosampler and a Waters 2487 dual wavelength detector, which was controlled by a personal computer running Millennium 2010 software (Waters Chromatography). Chromatographic separation was achieved by using a Kromasil C_{18}, 5 µm, 250 × 4.6 mm analytical column (Phenomenex, Torrance, California). The mobile phase consisted of 88% 10 mM ammonium phosphate (pH 3.25) and 12% methanol and was delivered isocratically at 1 mL/min. Ultraviolet detection was performed at a wavelength of 245 nm. Utilizing this analytical method, the retention time for temozolomide was about 7.9 min.

The analytical method was confirmed to be stability indicating by accelerated decomposition of intact temozolomide using heat, 0.1 N hydrochloric acid, 0.1 N sodium hydroxide, and 0.3% hydrogen peroxide. Substantial loss of peak area for intact temozolomide occurred, and new decomposition product peaks formed, including two principal peaks that eluted at about 2.7 and 4.7 minutes. The decomposition product peaks did not interfere with the intact drug peak. For a nominal 100-µg/mL temozolomide solution, the mean ± standard deviation precision of the assay determined from 10 replicate injections was 100.0 ± 0.2 µg/mL. Precision expressed as a percentage of the relative standard deviation was 0.2%. Calibration curves were constructed for the concentration range of 50 to 150 µg/mL from a linear plot of peak area versus concentration of freshly prepared temozolomide reference material. The correlation coefficient was greater than 0.9996. The intraday and interday coefficients of variation were 1.0% and 0.5%, respectively, from the assays of the reference material.

The initial temozolomide concentration in the suspension was defined as 100%, and subsequent sample concentrations were expressed as a percentage of the initial concentration. Chemical stability was defined as not less than 90% of the initial temozolomide concentration remaining in the suspension.

Temozolomide 0.5-mg/mL Reference Material

METHOD OF PREPARATION

1. Accurately weigh the contents of five temozolomide 100-mg capsules placed in a tared weigh boat or weighing paper and determine the amount of capsule powder equivalent to 12.5 mg of temozolomide based on the nominal labeled amount.
2. Transfer the powder to a glass mortar and triturate to a fine powder.
3. Weigh the appropriate amount of capsule powder equivalent to 12.5 mg of temozolomide.
4. Transfer the powder to a 25-mL volumetric flask.
5. Add mobile phase to dissolve the drug and bring to volume with additional mobile phase.
6. Transfer the mixture to centrifuge tubes and subject to centrifugation at 1,500 × g for 10 minutes.
7. Filter the supernatant liquid through an appropriate 0.45-µm filter into glass vials.
8. Store frozen at –70°C.

Results and Discussion

Both the equal parts mixtures of Ora-Plus/Ora-Sweet and Ora-Plus/Ora Sweet SF were found to be pharmaceutically acceptable vehicles for the preparation of temozolomide oral suspension when povidone K-30 and citric acid also were incorporated. The compounded suspensions had a pinkish color, which was retained throughout the study in the refrigerated suspensions. Samples stored at room

Table 1. Stability of Temozolomide 10-mg/mL[a] Oral Suspensions.

	% Initial Concentration Remaining[b]						
Sample	*Day 1*	*Day 7*	*Day 14*	*Day 21*	*Day 30*	*Day 45*	*Day 60*
Ora-Plus:Ora-Sweet (1:1)							
4°C	—	100.0 ± 1.2	99.5 ± 1.1	—	98.7 ± 0.6	100.8 ± 1.2	99.2 ± 1.4
23°C	98.3 ± 1.4	94.4 ± 1.0	86.3 ± 2.3	79.0 ± 2.1[c]	—	—	—
Ora-Plus:Ora-Sweet SF (1:1)							
4°C	—	99.2 ± 0.7	100.9 ± 0.1	—	101.5 ± 1.5	101.0 ± 0.9	100.3 ± 1.6
23°C	97.0 ± 0.6	95.4 ± 0.9	92.6 ± 0.3	89.9 ± 0.7	—	—	—

[a]Nominal concentration: Actual initial concentration after 100-fold dilution for analysis was 101.1 ± 2.7 µg/mL.
[b]Triplicate determinations of triplicate samples except where noted. Mean ± SD (n = 9) shown.
[c]Only two samples tested. Mean ± SD (n = 6) shown.
— = Not tested at this time point.

temperature darkened in color over 14 days as decomposition increased, eventually developing a brownish color by 21 days. The suspensions settled slowly, and the earliest visible changes appeared in 1 week for both suspension formulations. No caking of the solids present in the suspensions or lack of uniformity, including large crystal growth, was observed throughout the study. The suspensions were easily resuspended with inversion and gentle shaking of about 5 to 10 seconds duration even after 60 days of refrigerated storage. The suspensions poured very easily and remained homogeneous for dosing throughout the study.

The temozolomide concentration in both of these suspension vehicle combinations exhibited little or no loss for 60 days under refrigeration. At 23°C, loss of temozolomide was 6% at 7 days in the Ora-Sweet formulation. Losses were about 8% at 14 days and 10% to 11% at 21 days in the Ora-Sweet SF formulation. Therefore, refrigerated storage of the temozolomide suspensions is recommended. The temozolomide concentrations at each of the time points tested are presented in Table 1.

Inclusion of povidone K-30 to inhibit crystal growth within the study period was found to be necessary to yield acceptable suspensions of temozolomide. Preliminary attempts to prepare the suspensions without povidone k-30 resulted in formation of crystals in the suspensions within a few days at both storage temperatures, which made the suspensions pharmaceutically unacceptable and could result in inaccurate dosing.

Conclusion

Temozolomide extemporaneously prepared as oral suspensions from capsules and formulated with povidone K-30 and acidified with Anhydrous Citric Acid USP, in equal parts mixtures of Ora-Plus suspension vehicle with Ora-Sweet and with Ora-Sweet SF syrups, were pharmaceutically acceptable and chemically stable for at least 60 days at 4°C. Refrigerated storage is recommended. The suspension should not be stored at room temperature longer than 1 week if Ora-Sweet is used or longer than 2 weeks if Ora-Sweet SF is used. Having the option of using temozolomide oral suspensions may allow patients who are unable to swallow capsules to receive temozolomide treatment and, if compounded in a suitable protected environment, could reduce the potential for drug exposure to healthcare workers and/or family members from opening capsules.

References

1. Temodar [package insert]. Kenilworth, New Jersey: Schering Corporation, November 2004.
2. Danson SJ, Middleton MR. Temozolomide: A novel oral alkylating agent. *Expert Rev Anticancer Ther* 2001; 1(1): 13–19.
3. Yung WK, Prados MD, Yaya-Tur R et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. *J Clin Oncol* 1999; 17(9): 2762–2771.
4. Newlands ES, O'Reilly SM, Glaser MG et al. The Charing Cross Hospital experience with temozolomide in patients with gliomas. *Eur J Cancer* 1996; 32A(13): 2236–2241.
5. Bower M, Newlands ES, Bleehen NM et al. Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. *Cancer Chemother Pharmacol* 1997; 40(6): 484–488.
6. Bleehen NM, Newlands ES, Lee SM et al. Cancer Research Campaign phase II trial of temozolomide in metastatic melanoma. *J Clin Oncol* 1995; 13(4): 910–913.
7. Middleton MR, Grob JJ, Aaronson GN et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000; 18(1): 158–166.
8. Nicholson HS, Krailo M, Ames MM et al. Phase I study of temozolomide in children and adolescents with recurrent solid tumors: A report from the Children's Cancer Group. *J Clin Oncol* 1998; 16(9): 3037–3043.
9. Estlin EJ, Lashford L, Ablett S et al. Phase I study of temozolomide in paediatric patients with advanced cancer. United Kingdom Children's Cancer Study Group. *Br J Cancer* 1998; 78(5): 652–661.
10. Lashford LS, Thiesse P, Jouvet A et al. Temozolomide in malignant gliomas of childhood: A United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. *J Clin Oncol* 2002; 20(24): 4684–4691.
11. Kuo DJ, Weiner HL, Wisoff J et al. Temozolomide is active in childhood progressive, unresectable, low-grade gliomas. *J Pediatr Hematol Oncol* 2003; 25(5): 372–378.

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