Original Article

Stability of temozolomide in solutions aimed for oral treatment prepared from a commercially available powder for infusion

Abstract

Background: Temozolomide (TMZ) is an alkylating agent with a broad spectrum of antitumor activity, including brain tumors in children. The oral use of TMZ is hampered by the lack of a suitable galenic formulation, since the capsules of TMZ (Temodal™) are large and difficult to swallow. A powder for preparation of a TMZ solution for intravenous administration (2.5 mg/mL) has recently been approved. A possibility to use this formulation for oral administration would facilitate TMZ administration. **Aim:** The aim of the present study was to investigate the stability of TMZ in solutions prepared from the commercially available powder for intravenous infusion. **Materials and Methods:** Solutions were prepared from the intravenous formulation by dissolving the powder in water. The degradation of TMZ was studied photometrically at 330 nm in two solutions, 2.5 mg/mL at room temperature (RT; 22°C) and 1.25 mg/mL at 5°C, prepared from the intravenous formulation. **Results:** More than 90% of TMZ remained intact after storage for 9 days at RT (2.5 mg/mL) and 13 weeks at 5°C (1.25 mg/mL). **Conclusions:** The high stability of a TMZ solution prepared from the powder for infusion formulation makes it suitable for oral administration. Oral use of a TMZ solution facilitates administration of the drug to patients with difficulties to swallow capsules, and enables a more flexible and precise dosing.

Key words: Cancer patients, oral administration, stability, solution, temozolomide

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INTRODUCTION

Temozolomide (TMZ) is a pro-drug of 3-methyl-(triazen-1-yl)imidazol-4-carboxamide. It is an alkylating agent with a broad spectrum of antitumor activity, including brain tumors in children.[1-3] TMZ is supplied as capsules of 5 different strengths (Temodal™; 20 mg, 100 mg 140 mg, 180 mg, and 250 mg). Unfortunately the capsules are large [Figure 1] and therefore difficult for many patients to swallow. It is possible to prepare a TMZ suspension by opening the capsules and transferring the powder into a vial containing a liquid.[4] However, such a procedure of preparing an extemporaneous formulation of TMZ should be avoided due to risks of exposing personnel to this carcinogenic and teratogenic compound. Recently, a powder for preparation of a TMZ solution for intravenous administration (2.5 mg/mL) was approved by the United States Food and Drug Administration (FDA) and the EU Commission. A possibility to use this formulation for oral administration would facilitate drug administration, but unfortunately information concerning the stability of TMZ in this solution is lacking. The aim of the present study was to evaluate the stability of TMZ in aqueous solutions prepared from the commercially available lyophilized powder for intravenous administration.

MATERIALS AND METHODS

Temodal™ powder for infusion solution was obtained from Schering-Plough AB (Stockholm, Sweden). Each vial contains 100 mg of sterile and pyrogen-

free TMZ lyophilized powder for intravenous injection, mannitol (600 mg), L-threonine (160 mg), polysorbate 80 (120 mg), sodium citrate dihydrate (235 mg), hydrochloric acid (160 mg). The infusion solution (2.5 mg/mL) was prepared according to the manufactures instructions and kept dark at room temperature (22°C). The stock solution was further diluted to 1.25 mg/mL with distilled water and stored in a refrigerator (5°C). To study the degradation time course, aliquots of the 2.5 and 1.25 mg/mL solutions of TMZ were diluted with 15 and 7.5 parts of the McIlvaine's citric acid phosphate buffer (pH 3.0), respectively, at different time points. The absorbance of the diluted aliquots was measured at 330 nm using a Shimadzu UV 2401PC UC-VIS Recording Spectrophotometer (Shimadzu Corporation, Kyoto, Japan). The degradation time course was evaluated using the one-phase decay fitting option in the GraphPAD Prism for Windows (version 5.04; GraphPad Software, Inc. La Jolla, CA, USA), using the weighing option 1/Y. Water was obtained from a Milli-Q Water Purification System (Millipore Corporation, Billerica, MA, USA). All other chemicals were purchased from Merck KGaA (Darmstadt, Germany) and were of analytical grade.

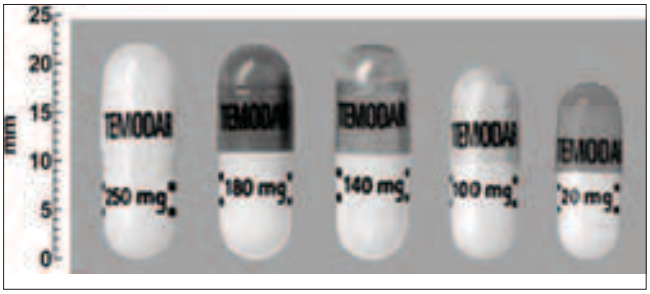

Figure 1: Commercially available temozolomide capsules (Temodal™).

RESULTS AND DISCUSSION

A 10% degradation of the 2.5 mg/mL TMZ solution occurred after storage in the dark for 9 days at room temperature (22°C) [Figure 2a]. The degradation half life was 65 days (95% CI: 64-66 days), as determined from photometric data during a study period of 224 days (n=27). A precipitation occurred in the 2.5 mg/mL TMZ solution within 24 hours during storage in a refrigerator (5°C).

A 10% degradation of the 1.25 mg/mL TZM solution occurred after storage for 13 weeks in a refrigerator (5°C) [Figure 2b]. The degradation half life was 87 weeks (95% CI: 85-90 weeks), as estimated from photometric data during a study period of 32 weeks (n=26). No precipitation could be observed in the 1.25 mg/mL TMZ solution during the study period.

Capsules are the only available formulation of TMZ for oral treatment today. These large capsules are difficult to swallow and hence there is a need for an alternative oral formulation, preferably a solution. Evaluation of the stability of TMZ in solutions prepared from the content of opened capsules shows that the stability of TMZ under acidic conditions might be sufficiently high to prepare solutions for oral use.[4] This finding has subsequently been confirmed by Trissel *et al*.[5] who prepared an extemporaneously compounded oral suspension of TMZ from 100-mg capsules. However, preparation of extemporaneous formulations of TMZ from capsules might be hazardous to the personnel due to risks of being exposed to this carcinogenic and teratogenic compound and should therefore be avoided.

In the present study, TMZ solutions were prepared

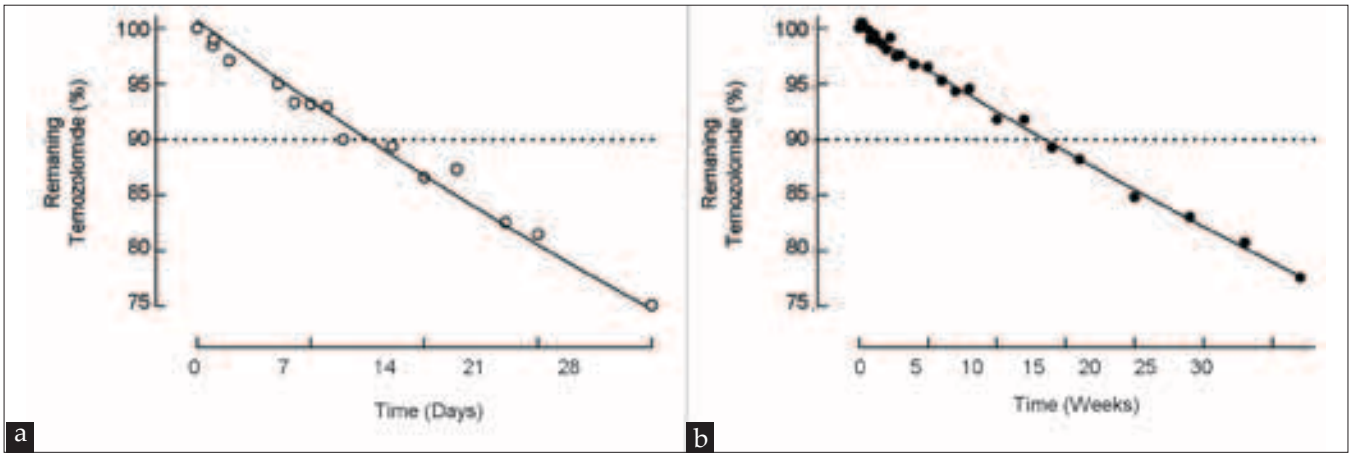

Figure 2: Stability of temozolomide in solutions aimed for oral use prepared from Temodal ™ powder for infusion solution. (a) Initial concentration: 2.5 mg/mL; Temperature: 22°C. The solid line is given by nonlinear regression analysis (one-phase decay; weighted 1/y; r^2=0.9990; total n=27). (b) Initial concentration: 1.25 mg/mL; Temperature 5°C. The solid line is given by nonlinear regression analysis (one-phase decay; weighted 1/y; r^2=0.9955; total n=26)

from the commercially available intravenous formulation within the original bottle. The stability of TMZ was studied by a previously described photometric procedure.[6] Unfortunately, the higher concentration, 2.5 mg/mL, precipitated during storage over night in the refrigerator. In room temperature the 2.5 mg/mL TMZ solution was clear and remained stable (> 90% intact TMZ) for 9 days. In many clinical situations this stability is sufficient, but an even higher stability would be of an advantageous e.g., for patients with glioblastoma who are treated daily with TMZ for up to 49 days.[7] In such cases the high stability of the 1.25 mg/mL TMZ solution kept in a refrigerator enables preparation of oral TMZ solutions in the hospital pharmacy for the entire treatment period.

The use of liquid formulations for oral administration is of special importance for treatment of pediatric patients.[8,9] It facilitates drug administration and also enables a flexible and precise dosing which is of particular importance for treatment with drugs with low therapeutic index, e.g., antineoplastics.[10,11] It should be noticed that changes of drug formulations for oral use might have an impact on the pharmacokinetics. A change from capsules to oral solution might result in increased bioavailability and maximum plasma concentration as well as a decreased time for maximum plasma concentration (T_{max}). However, a change from TMZ capsules to oral TMZ solutions will most likely not result in changes of the pharmacokinetics of clinical importance since the bioavailability of TMZ after administration as capsules is close to 100% with T_{max} of about 1 hour.[12,13]

We have found that the taste of the prepared TMZ solutions was well tolerated by the patients, cf.[9] However, the addition of a small amount of apple juice (pH~4) or Coca Cola™ (pH~2.5) facilitated the drug administration to some pediatric patients.

CONCLUSIONS

The high stability of a TMZ solution prepared from the powder for infusion formulation makes it suitable for oral administration. Oral use of a TMZ solution facilitates administration of the drug to patients with difficulties to swallow capsules and also enables a more flexible and precise dosing.

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