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Stability of temazepam in parenteral formulations

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Summary

An HPLC method was developed to examine the stability of temazepam in a variety of propylene glycol/water mixtures at different temperatures with the view of developing a parenteral formulation. Arrhenius data indicated that the activation energy for the degradation process was relatively high and, as a result of this, predicted stability at ambient temperatures was excellent. Actual storage data, accrued over a 190-day period, indicated that although discoloration occurred in some of the samples, no degradation could be detected in any samples stored at 4 or 25°C. Samples stored for the same period at 37°C lost approximately 3% temazepam. It was observed that increasing the water content of the formulations did not appear to adversely affect temazepam stability. The results of this study suggest that temazepam could be formulated as a stable parenteral solution using propylene glycol/water mixtures.

Introduction

Although temazepam has been widely used as an oral premedicant for minor surgical and investigative procedures it has been suggested that there is a need for an intravenous preparation. Currently, for example, intravenous diazepam is used extensively for patients (often elderly) presenting for gastroscopy and these patients are often under the influence of the injection for some 24–48 h post-procedure. This occurs since relatively large doses are required for adequate preparation of these patients. In contrast, the short-acting midazolam has a very brief duration of action and the repeated administration of this drug, necessary to maintain effect, can lead to prolonged somnolence. Temazepam is perceived as possessing the appropriate pharmacokinetic properties having both a rapid onset of action and a fairly short half-life which is terminated by the combined effects of tissue redistribution and glucuronidation (Pickup et al., 1984). Furthermore, the initial results from an in vivo assessment of a propylene glycol based temazepam parenteral formulation were encouraging (McCafferty et al., 1985). However, temazepam has both poor aqueous solubility and stability (Launchbury, 1984). Therefore, since a parenteral temazepam formulation would require an adequate shelf-life, the stability of the drug in a variety of propylene glycol/water blends was examined in the present study.

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Materials and Methods

Chemicals

Temazepam and 2-methylamino-5-chlorobenzophenone were supplied by Farmitalia Carlo Erba, St. Albans. All other chemicals used were of B.P. or Analar quality.

Analytical procedure

Determination of temazepam in the presence of its degradation products was undertaken using a high-performance liquid chromatographic (HPLC) method. Temazepam solutions, suitably diluted, were introduced onto a Waters 15 cm × 3.9 mm (i.d.) reversed-phase column (packed with μBondapack ODS 5 μm) via a Rheodyne 7125 injection valve fitted with a 20 μl loop. The mobile phase (Milli-Q type I reagent grade water, 35%; HPLC grade methanol, 35%; HPLC grade acetonitrile, 30%) was delivered at 1 $ml \cdot min^{-1}$ (Gilson Model 302 pump) in conjunction with a variable wavelength detector (Model 2151 LKB) operated at 230 nm. The signals were processed by a Hewlett Packard 3390A integrator. Diazepam was employed as the internal standard and under the above conditions satisfactory component separation was achieved (Fig. 1). The approximate retention times were temazepam, 1.5 min; diazepam, 2 min; 2-methylamino-5-chlorobenzophenone, 6 min. Calibration graphs for temazepam were rectilinear in the concentration range 1–50 $\mu g \cdot ml^{-1}$ with typical correlation coefficients of 0.999. The precision of the method was determined by assaying five replicate samples containing 5 $\mu g \cdot ml^{-1}$ of temazepam and the relative standard deviation was found to be 0.24%. The limit of detection for 2-methylamino-5-chlorobenzophenone was 40 $ng \cdot ml^{-1}$.

Preparation and storage of solutions

Temazepam (5 $mg \cdot ml^{-1}$) was dissolved in a range of propylene glycol/water mixtures and stored in sealed borosilicate glass ampoules at 4, 25, 37 and 55°C for a period of 190 days. Triplicate samples were analyzed by HPLC at suitable time periods. Temazepam formulations were also subjected to autoclaving at 121°C for a 40-min period followed by visual examination and HPLC analysis.

Accelerated storage testing

A selected temazepam formulation was stored at 80, 73 and 64°C and assayed for temazepam content over a 730-h period. Samples were cooled rapidly (using ice) and stored at 4°C, if necessary, before analysis. The mean of three replicate determinations was taken.

Results and Discussion

Prior to assessment of temazepam stability it was considered necessary to develop a suitable analytical method. Although a wide variety of analytical methods are available (Belvedere et al., 1972; Divoll and Greenblatt, 1981; Vree et al., 1979; Chan and Fogg, 1981) many of these have been designed for analysis of biological samples and are more complex than necessary for the present study. Others make the detection of the major degradation product of temazepam (2-methylamino-5-chlorobenzophenone) inconvenient due to the excessively long retention time of this compound. Therefore, the HPLC method used in this study was developed to allow both rapid analysis of temazepam and detection of its major degradation product (Fig. 1).

Formulations of temazepam based on PG rather than PEG 400 were used in this study since initial testing indicated that temazepam was more stable in the former solvent. This observation has also been noted by other workers (Launchbury, 1984). It is possible that this difference in temazepam stability in the two glycols might be due to the reaction of temazepam with reactive peroxide intermediates formed by air oxidation of PEG 400 (Johnston and Taylor, 1984). It has been observed that diazepam also appears to be more stable in PG based systems (Mayer et al., 1974).

From a formulation design viewpoint it is desirable to have as low a concentration of PG as possible in a parenteral preparation since otherwise there is an increased risk of venous intolerance (Graham et al., 1977). Furthermore, formulations containing high concentrations of PG are difficult to inject due to increased viscosity. However, decreasing the proportion of PG reduces the concentration of temazepam which can be dissolved.

In the present study it was considered that a solubility of temazepam less than 5 mg · ml^{-1} was unacceptable. It was found that at least 80% w/w PG was required to maintain this concentration of temazepam in solution at 4°C. This temperature was chosen since it might well be necessary to store the temazepam formulation under these conditions for stability reasons.

Since it has been suggested (Launchbury, 1984) that temazepam stability is adversely affected when more than about 10% water is present in the formulation an accelerated storage test was undertaken on the 80% PG-temazepam formulation (containing the highest percentage of water). Temazepam degradation was treated as apparent first-order and the apparent first-order rate constants were determined (by linear regression) at three different temperatures (Table 1). From the data it was possible to develop an Arrhenius equation, using linear regression, as shown in Eqn. 1.

$$\ln k_1 = -11146\ (\pm 1430)/T + 24(\pm 4.14)$$

$$(r = 0.992) \qquad (1)$$

where k_1 is the apparent first-order rate constant at temperature T.

The energy of activation (E_a) for the hydrolysis of temazepam was obtained from this equation (92.7 ± 16.8 kJ · mol^{-1}). It was also observed that all test solutions gradually discoloured during the heating process. This was due to the formation of 2-methylamino-5-chlorobenzophenone which is the major degradation product of temazepam (Schuetz, 1978). Predicted t_{90} (time required for 10% drug degradation) values for this formulation at a variety of storage temperatures are shown in Table 2. It is clear from these results that this temazepam formulation has excellent predicted stability at ambient temperatures. This is not perhaps surprising since the activation energy for the degradation process is relatively high. A possible explanation for this is that the 3-hydroxy-1,4-benzodiazepin-2-ones (which includes temazepam) belong to the rare heterocycles with the relatively stable carbinolamine (or amino hemiacetal) function (Sunjic et al., 1979). It is interesting to note that the energy of activation for the degradation of diazepam in a PG based system was calculated to be 22.7 kcal · mol^{-1}, i.e. 94.98 kJ · mol^{-1} which is very similar to that for temazepam in PG. It has been suggested that the presence of the 2-methyl moiety stabilizes the 1,4-benzodiazepines and that the use of solvent systems results in enhanced diazepam stability relative to aqueous systems (Dobrinska and Lee, 1979).

Although no detectable loss of temazepam was

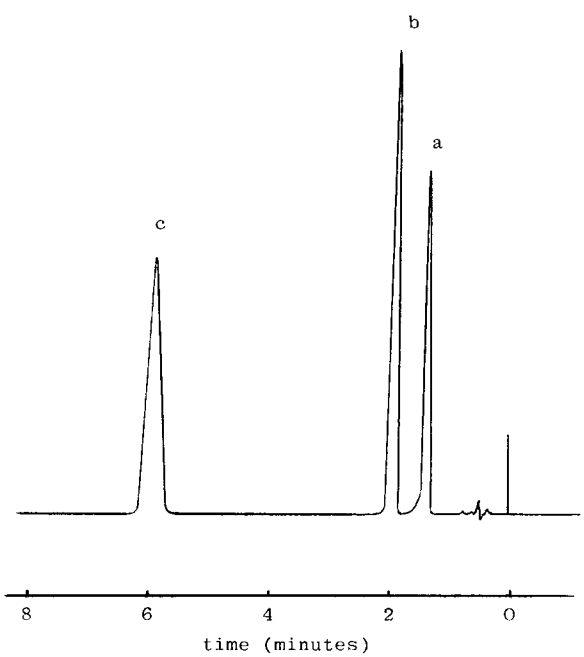

Fig. 1. Chromatogram of (a) temazepam, (b) diazepam (internal standard) and (c) 2-methylamino-5-chlorobenzophenone in acetonitrile–methanol–water (30:35:35 v/v). The concentration of each component was 5 μg·ml^{-1} and the attenuation used was 0.16 a.u.f.s.

TABLE 1

APPARENT FIRST-ORDER RATE CONSTANTS (k_1) FOR HYDROLYSIS OF TEMAZEPAM IN 80% PG/WATER BLEND

Temperature (°K)	k_1 (10^{-4}) h^{-1}	s (10^{-4})	r
337	1.209	±0.202	0.92
346	2.435	±0.241	0.95
353	5.474	±0.581	0.95

apparent in any of the stored formulations (with the exception of those held at 37 and 55°C) it was observed that all temazepam preparations gradually became discolored (yellow). The discoloration was temperature dependent, i.e. the time required for colour to become visually apparent was approximately 7 days at 55°C, 14 days at 37°C and 30 days at 25°C. The effect of 190 days storage on the temazepam formulations is shown graphically in Fig. 2. It is clear from the graph that marked loss of temazepam (approximately 20% degradation in all of the formulations examined) occurred at 55°C over the total storage period. The approximate t_{90} value for the 80% PG temazepam formulation stored at 55°C was 130 days (Fig. 2) which was considerably longer than the predicted value (Table 2). This could perhaps indicate that the shelf-life of the temazepam formulation at ambient temperatures would be superior to the predicted values shown in Table 2. At 37°C all formulations examined lost about 3% temazepam over the 190-day period (Fig. 2). Although the solutions stored below 37°C became discoloured during storage this did not correlate with detectable loss of temazepam. Furthermore, there was no detectable HPLC peak due to the presence of 2-methylamino-5-chlorobenzophenone. It is not unusual for drug solutions to become discoloured due to minute amounts of degradation. For example, it is interesting to note that as far as Valium injection (contains 40% PG) is concerned, it is acceptable that the solution may range from colourless to greenish-yellow in colour (ABPI, 1985). Diazepam degrades in solution to form the same major degradation product (2-methylamino-5-chlorobenzophenone) as temazepam (Violon and Vercruysse, 1980). Although all temazepam formulations exhibited slight discolouration after autoclaving there was no detectable loss of the compound in any of the formulations.

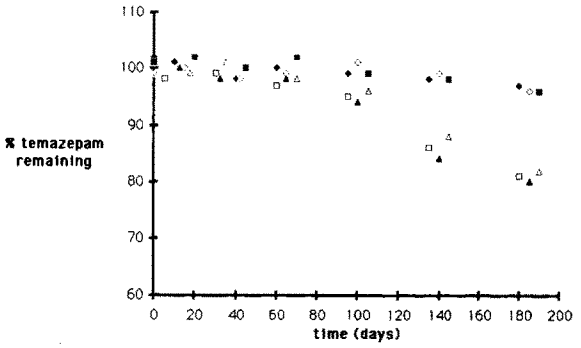

Fig. 2. Stability of various PG based liquid temazepam (5 $mg \cdot ml^{-1}$) formulations stored over a period of 190 days at 37 and 55°C. ◆, 100% PG; ○, 90% PG; ■, 80% PG stored at 37°C. □, 100% PG; ▲, 90% PG; △, 80% PG stored at 55°C.

The results of this study indicate that increasing the water content of temazepam formulations beyond 10% does not appear to have an adverse effect on the stability of the drug. Consequently, it should be possible to formulate temazepam as a stable parenteral solution (sterilized by autoclaving) using PG/water mixtures.

TABLE 2

PREDICTED APPARENT FIRST-ORDER RATE CONSTANTS (k_1) AND TIME PERIODS FOR 10% DEGRADATION OF TEMAZEPAM (t_{90}) IN 80% PG/WATER BLEND FOR VARIOUS STORAGE TEMPERATURES

Temperature (°C)	k_1 (10^{-6}) h^{-1}	t_{90} (years)
25	1.511	7.93
37	6.428	1.86
55	46.24	0.26

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