Stability of sulfadiazine oral liquids prepared from tablets and powder.

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Abstract  Purpose: To assess the stability of sulfadiazine (SDZ) oral liquids prepared from tablets and powder at two temperatures. Methods: Solutions of SDZ 200 mg/mL were prepared from commercially available 500 mg tablets and powder in sterile water for irrigation. They were stored in amber glass bottles at 4°C and 23°C. The concentrations of SDZ were determined in duplicate by high-performance liquid chromatography at 0, 1, 3, 7 and 14 days. The initial and final pH of solutions was compared. The recovery of SDZ from tablets was determined. A loss exceeding 10% of the initial concentration of SDZ was considered excessive degradation. Results: The recovery of SDZ from tablets was 100 ± 3%. The initial pH values were significantly different between solutions prepared from tablets and powder, 6.9 and 9.8 respectively. No significant difference was found between initial and final pH values for the two all formulations. Detectable change in odor was observed for the solutions stored at 23°C. The solution prepared from powder was stable 3 days stored at 4°C. Other formulations lost over 10% of the initial SDZ concentration within 2 days. Conclusions: SDZ 200 mg/mL oral solution prepared from powder could be used to facilitate drug administration to very young children by nurses but by taking account of its fast degradation.

INTRODUCTION
Toxoplasmosis is caused by the protozoan parasite Toxoplasma gondii. Congenital infection with this germ may result in spontaneous abortion, fetal death or severe disease (1, 2). The sequelae in live-born infants with signs of infection are generally severe and include a potentially fatal syndrome in which hydrocephalus, mental retardation and chorioretinitis may occur (3-7). The recommended dose of sulfadiazine in children is 25 to 50 mg/kg four times daily (8). Sulfadiazine, a 2-sulfanilamidopyrimidine (SDZ), is a sulfa-

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Storage of solutions

Six bottles from each formulation were stored at room temperature (22 ± 3°C) with direct exposition at the sunlight and at 4 ± 2°C. Five bottles of SDZ suspension prepared independently were stored at +40 ± 3°C for forced degradation. The room temperature was measured each day by a pH meter (Model pH 302) with a temperature probe.

Sampling

From each bottle, 1 ml sample was taken, diluted in 2 ml of NaOH 1N and shacked. After 5 minutes, 50 µL of this solution were diluted in 50 mL of sodium bicarbonate 4.2%. The diluted sample was assayed in duplicate by high-performance liquid chromatography (HPLC), immediately after preparation, 1, 3, 7 and 14 days. The appearance and color were assessed by observing the samples against black and white backgrounds under normal light. The pH was measured with a pH meter (Model pH302, Hanna Instruments, Tanneries, France) in triplicate initially and at 14 days after preparation.

HPLC Analysis

SDZ was quantified by using a modified HPLC method (10). The HPLC system consisted of a pump7, a 20 µL manual injector8, and a C18 column9. The mobile phase, consisting of sterile water for irrigation, methanol and diethylamine (60:39:1 v/v/v). A flow rate of 1 mL/min was used throughout the run. The ultraviolet variable-wavelength detector10 was set at 270 nm. Stock standard solutions of SDZ (2 g/L) and of ranitidine (5 g/L) were prepared in sterile water for irrigation and stored at 4°C. Six calibration standards were prepared by diluting SDZ stock standard solution with sterile water for irrigation to concentrations of 5, 10, 25, 30, 40 and 50 mg/L with 200 mg/mL, each containing of internal standard 200 mg/mL. The standard curve was constructed by plotting the peak-height ratio of SDZ to ranitidine against the SDZ concentration and was used for calculating the drug concentrations of the samples. The straight line of linear regression of SDZ HPLC assay was y = 0.047x + 0.226 ± 0.021. The standard curve was linear with a coefficient of correlation of 0.999 ± 0.002. The limits of detection and quantification of SDZ were 1.3 and 3.9 mg/L, respectively. The intraday coefficients of variation were 3.5% (n=10) and 1.4% (n=10) for respectively concentrations of 5 and 40 mg/L. The interday coefficients of variation were 4.5% (n=10) and 1.0% (n=10) for respectively concentrations of 5 and 40 mg/L. The retention times for the SDZ and internal standard were 0.8 and 2.4 minutes, respectively (Figure 1). In order to establish the stability-indicating nature of the assay, SDZ solutions obtained from powder and tablets were stored at 40°C until the chromatographic peak was not detected. Any degradation peak appeared during the study period.

Figure 1: Chromatograms of sulfadiazine solutions partially degraded (A) and not degraded (B). Peak 1: Sulfadiazine (retention time = 0.8 min), peak 2: internal standard (retention time = 2.4 min).

Data analysis

The initial concentration of SDZ was defined as 100%, and sample concentrations were expressed as a percentage of the initial concentration remaining as the Anaizi et al. Method (11). A loss exceeding 10% of the initial concentration of SDZ was considered excessive degradation. The pH values were expressed as mean ± standard deviation (S.D.). Difference of initial and final pH values was evaluated by a student’s t test (α=0.05).

RESULTS AND DISCUSSION

The recovery of SDZ solution from compressed tablets was of 100 ± 3% (n=5). The initial pH values were significantly different between liquids prepared from tablets and those prepared from the powder, 6.9 ± 0.1 and 9.8 ± 0.07 respectively. No significant difference was found between initial and final pH values for all formulations. Detectable change in odour was observed at the end of the study for the solutions stored at room temperature. The solution prepared from powder was
stable 3 days stored at 4°C. The formulation prepared using the tablet lost over 10% of the initial SDZ concentration within 2 days (Table 1). SDZ can be prepared extemporaneously in liquid formulations from tablets or powder. However, the SDZ oral liquids are not stable for long time and cannot be prepared by pharmacists. Excipients and pH of suspensions prepared from tablets could explain the difference in stability with solutions prepared from powder. SDZ is not available in a liquid dosage form for the management of paediatric patients. SDZ 200 mg/mL oral solution prepared from powder was stable 3 days at 4°C and could be used to facilitate drug administration to very young hospitalized children by taking account of her fast degradation. However, the formulations are not suitable for preparation in large batches.

Table 1: Stability of SDZ 200 mg/mL oral liquids prepared from tablets and powder at two temperatures.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Tablets</th>
<th>Powder</th>
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<tbody>
<tr>
<td>4°C</td>
<td>210.1 ± 6.3 µg/mL</td>
<td>213.2 ± 8.5 µg/mL</td>
</tr>
<tr>
<td>25°C</td>
<td>196.4 ± 6.9 µg/mL</td>
<td>201.3 ± 9.0 µg/mL</td>
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</table>

a Reported as mean ± S.D. of duplicate determinations for six samples.

b The actual mean ± S.D. initial concentration was 210.1 ± 6.3 µg/mL.
c The actual mean ± S.D. initial concentration was 213.2 ± 8.5 µg/mL.
d The actual mean ± S.D. initial concentration was 196.4 ± 6.9 µg/mL.
e The actual mean ± S.D. initial concentration was 201.3 ± 9.0 µg/mL.

REFERENCES

APPENDICES
1 Sulfadiazine powder, Sigma, St Quentin, France, lot 91K1044
2 Adiazine®, Bouchara, Levallois-Perret, France, lot 8647
3 Raniplex® for injection, Fournier, Dijon, France
4 Sterile water for irrigation, Fresenius, Sévres, France, lot 0146/36
5 Methanol, Chromanorm®, Prolabo, Paris, France
6 Diethylamine, Chromanorm®, Prolabo, Paris, France
7 LC-6A, Shimadzu Corporation, Duisbourg, Germany
8 Rheodyne®, Bensheim, Germany
9 Lichrospher® 25 cm, 100 RP-C18, 5 µm, Merck, Darmstadt, Germany
12 SPD-6A, Shimadzu Corporation, Duisbourg, Germany