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Stability of Ketoconazole in Ethanolic Solutions

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ABSTRACT

The stability of the antifungal drug Ketoconazole (Kz) in an ethanolic solution was examined. The ethanolic solutions of Kz were placed in either clear or amber glass bottles and stored either at room temperature or at 8 C for 29 days. Kz was assayed using, a sensitive simple high pressure liquid chromatography procedure. Results demonstrated no statistically significant difference between or among the test solutions over time, regardless of the storage conditions or the concentrations ($P>0.05$).

INTRODUCTION

Ketoconazole, cis-1-acetyl-4(4-(2-(2,4-dichlorophenyll)-2-(1H-imidazol-1-ylimethlyl)-1-,3-dioxolan-4-yl) methoxy)phenly) piperazine is a new antifugal agent (1). It was developed as a solid oral dosage form to circumvent the problems associated with prolonged intravenous therapy (eg. phlebitis, infection, post-phlebitic syndrome). Ketoconazole displays a broad spectrum of in-vivo antifugal activity and it has been shown to be particularly effective against fungal infections resistant to other conventional therapies (1). Kz is available as 200mg tablets and it has been shown that dosing for children may vary from 20 mg three times daily to 200 mg once daily (1). Thus, the problem of administering a solid oral dosage form to pediatric population may include lack of uniformity of dose due to splitting of the tablet. To alleviate the problems associated with administering ketoconazole to selected patient populations not capable of tolerating a solid oral dosage form, a stable solution of the drug is desirable.

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Therefore, the purpose of this investigation was to study the stability of Kz solution stored in a different light and temperature conditions over a twenty-nine day period.

MATERIALS AND METHODS

An isocratic HPLC procedure was developed for the assay of ketoconazole. A reciprocating piston solvent delivery system set at a flow rate of 2ml/min, was used to deliver the mobile phase onto a stainless steel reverse phase column (uBondapak/CN; 30 cm by 3.9mm, Waters Assoc.). Samples were delivered onto the system via a septumless universal liquid chromatograph injector (Waters Assoc. Model u6K). Absorbance was measured using a variable wavelength detector (Waters Assoc., Model 450) set at 234 nm.

Ketoconazole (Lot No. B0502, Janssen Pharmaceutica, New Brunswick, NJ) in the powder form was used to prepare standard and test solutions. Ethyl alcohol and HPLC grade water, served as vehicles for ketoconazole. A 0.005M solution of potassium phosphate (monobasic) was prepared and its pH was adjusted to 6.0 using 2N NaOH. Potassium phosphate was combined with HPLC grade acetonitrile, 60:40 (v/v) respectively. Two concentrations of each test solution to study the effect of light, temperature and time on the stability of ketoconazole, solutions were subjected to four different experimental conditions, namely ambient temperature, refrigeration, light exposed and light protected.

The test solutions of Kz were made by preparing stock and from this stock, 50 ng/20 ul and 100 ng/20 ul test solutions were prepared. From these test solutions the following experimental conditions were maintained for a total of 29 days: 50 ng/20 ul ambient temperature exposed to light, 50 ng/20 ul ambient temperature protected from light, 100 ng/20 ul ambient temperature exposed to light, 50 ng/20 ul refrigerated exposed to light, and 100 ng/20 ul refrigerated protected from light. All groups of the test solutions were placed under these conditions for 29 days. Each group was made up of two test solutions run in duplicates. Samples were assayed on days 1, 2,3,5,8, 15, 22, and 29. All data were subjected to a two way analysis of variance with repeated measures.

RESULTS

Using this HPLC procedure it was found that assay procedure produced a standard curve with linearity varied from .997 to 0.999. The mean slope for all regression lines was 0.055 with a relative standard deviation of 0.008. The y-interecept

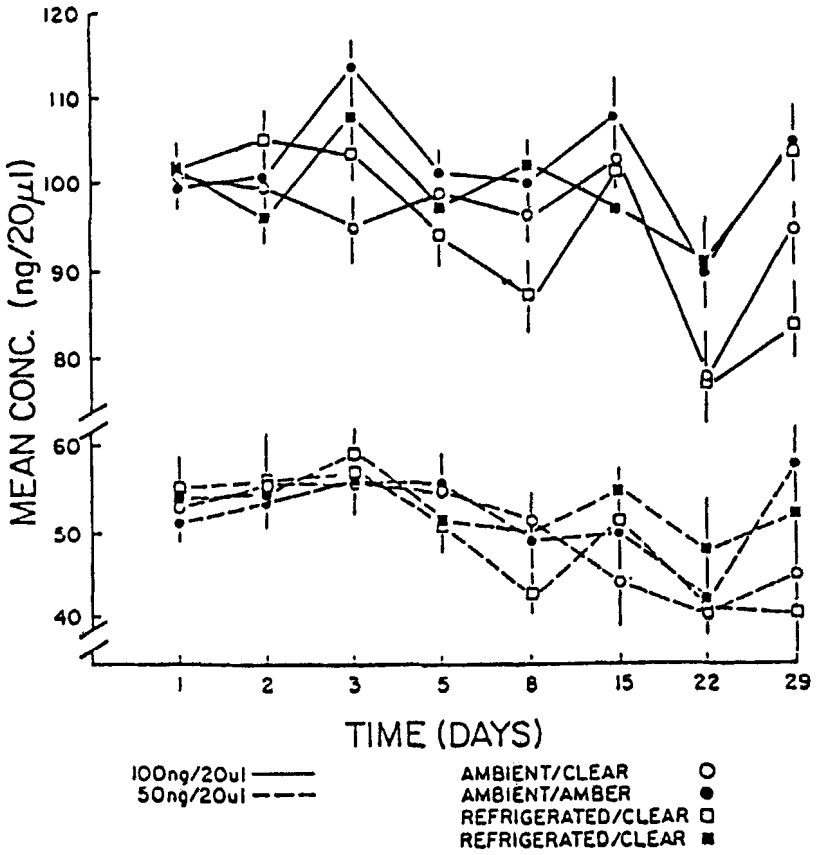

Figure 1: Effect of type of container, temperature and time on the stability of ketoconzole in ethanolic solution.

averaged 0.467 with a relative standard deviation of 0.092. The results of the study relating to the effect of light, temperature and time on the stability of ketoconazole is presented in figure 1. The results indicate that the storage temperature, light or the duration of ketoconazole storage in ethanolic solution have no significant effect ($p>0.05$) on the concentration of this drug.

DISCUSSION

Kz determinations have been demonstrated by gas chromatography (2-4) and bioassay (5-7) procedures. The HPLC procedure developed in our laboratory is rapid, specific and sensitive. In HPLC analysis peak migration due to the use of H_2O in ethanol solution is very unlikely. The possiblity of degradation of ketoconzole was

verified by conducting a standard curve with all the tested ketoconzaole samples. Everytime the analysis was ran there was no observable difference in the U.V. spectrum of our standard ketoconazole material when compared to the tested ketoconazole material, thus indicating relative stability.

The present study describes the stability of ketoconazole in an ethanolic solution. To our knowledge, this is the first report that demonstrates the feasibility of storing ketoconazole, that remains unchanged, in solution. This ethanolic ketoconazole solution may prove suitable for human consumption. The data presented here suggests that such a solution could be produced in order to alleviate the problems of administering a tablet to patients who may be unable to swallow a solid oral dosage form, which is typical of the pediatric populations. The oral solution would be relatively easy to administer, thereby decreasing patient anxiety and decreasing frustration to the personnel administering the drug. Preparing a stock solution of ketoconazole would also eliminate the daily laborious task of crushing tablets. Finally, it would offer an alternative mode of administration, thus providing a convenient time-saving formulation.

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