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Stability of Ondansetron and Fluconazole in 5% Dextrose Injection and Normal Saline during Y-Site Administration

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The stability of ondansetron and fluconazole in 5% dextrose injection and normal saline during simulated Y-site injection at room temperature was studied. Ondansetron 0.03, 0.1 and 0.3 mg/ml were admixed 1:1 with fluconazole 2 mg/ml. The solutions were stored at room temperature and samples were retrieved at time 0, 1, 2, 4 and 12 hr for immediate assay. At the time of the assay and before any dilution, each sample was visually inspected for clarity, color, precipitation, and the pH was determined. Drug concentrations were measured by a stability-indicating high performance liquid chromatograph. Ondansetron 0.03, 0.1 and 0.3 mg/ml were stable when mixed with concentration of fluconazole 2 mg/ml. There were no change in clarity and color and no precipitates in any admixture for 12 hr of inspection. The pH measurements did not have a particular trend in any direction over time.

Key Words : Stability, Ondansetron, Fluconazole, Y-Site Administration

INTRODUCTION

Ondansetron is a selective serotonin type 3 (5-hydroxytryptamine) receptor antagonist. It is currently indicated for use in the prevention of nausea and vomiting associated with chemotherapy (Chaffee *et al.*, 1991). With its low incidence of adverse effects, ondansetron is a welcomed alternative to conventional antiemetic therapies used in chemotherapy protocols. With the move of chemotherapy and auxiliary treatments towards the home setting, there is a need for stability studies of ondansetron in Y-site administration. A few studies have been reported to date. Bosso *et al.* (1992) and Graham *et al.* (1992) found that ondansetron in 0.9% sodium chloride injection or 5% dextrose injection was stable under refrigeration for up to 14 days. Stiles et al. (1992) reported stability in portable infusion pump reservoirs and also we reported stability of ondansetron with paclitaxel or ranitidine during simulated Y-site administration (Burm *et al.*, 1994).

Fluconazole has already achieved broad use in a number of indications because of its high clinical response rates and relatively low incidence of side effects and drug interactions (Pfizer, 1990). In a recent position statement by the Society of Infectious Diseases Pharmacists, fluconazole was recommended as first line therapy in suppression of *Cryptococcal meningitis* and as a back up to amphotericin B in the treatment of local and systemic candidal infections (Garrelts *et al.*, 1990). Lor *et al.* (1991) reported the visual compatibilty of fluconazole with commonly used injectable drugs during Y-site administration and we reported stability of fluconazole with paclitaxel during simulated Y-site administration (Burm *et al.*, 1994).

Severely ill patients often require extensive multiple intravenous drug therapy during their treatment regimens. Critically ill patients such as those in intensive care may receive as many as 20 medications (Gundlach *et al.*, 1991) making management of IV administration and access a challenge. Patients treated with fluconazole may receive serotonin receptor antagonist for prevention of nausea and vomiting. Since ondansetron may be given as a continuous infusion, consideration of compatibility becomes necessary upon concomitant administration. In a review of the literature, we found no studies on the stability and compatibility of ondansetron and fluconazole. Thus, the purpose of this study is to evaluate the stability of ondansetron and fluconazole during simulated Y-site administration at clinically relevant concentrations.

MATERIALS AND METHODS

Materials

Ondansetron (lot Z270052BW) was kindly provided by Glaxo Inc. and fluconazole (lot PSO17434) was

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kindly provided by Roerig-Pfizer. Polyvinyl chloride (PVC) bags containing 50 ml of 5% dextrose or 0.9% sodium chloride injection were purchased from Baxter Healthcare Corporation. All other chemicals were reagent grade.

Preparation of solutions

Stock solutions were prepared from manufacturer's formulations of ondansetron and fluconazole at concentrations of 2 mg/ml respectively. Three stock solutions of ondansetron 0.03, 0.1 and 0.3 mg/ml were prepared by adding 0.75, 2.5 and 7.5 ml of ondansetron 2 mg/ml (as the hydrochloride salt) to polyvinyl chloride (PVC) bags containing 50 ml of 5% dextrose or 0.9% sodium chloride injection. Fluconazole injection was used as received from the manufacturer as 400 mg in 200 ml Viaflex bags. All solutions were prepared in triplicate and each drug was assayed in duplicate. Allen et al. (1992) and Allen and Stiles (1981) demonstrated that secondary admixtures injected through a Y-injection port, were mixed with the primary i.v. fluid at a 1:1 ratio. To simulate this condition for high and low concentrations of each drug, 2 ml of ondansetron stock solution was mixed with 2 ml of fluconazole solution. Separate admixtures were prepared for the assay of each drug. Samples were removed at room temperature under fluorescent room light at time 0, 1, 2, 4 and 12 hr for immediate assay. At the time of sampling and before any dilution, each sample was visually inspected for clarity, color, precipitation and the pH was determined at time 0, 4 and 12 hr by digital pH meter (Model 3500, Beckman instruments).

HPLC assay

The ondansetron HPLC assay was modified from the method of Jhee et al. (1993) and fluconazole assay procedure was a modification of the methods of Inagaki *et al.* (1993) deleting the extraction steps. The mobile phases were filtered through a Sartorius 0.45 μm nylon filter and degassed under vacuum in an ultrasonic bath. A Hitachi Intelligent Pump (Model L-6200) delivered the mobile phase at the flow rate appropriate for each drug analysis as listed in Table I. The column used for ondansetron was a Accubond CN (5 μm particle size, 250×4.6 mm I.D., J&W Scientific), while the column for fluconazole was a Adsorbosphere C_{18} (5 μm particle size, 250×4.6 mm I.D., Alltech Assoc. Inc.). A Hitachi UV-VIS detector (Model L-4200) was set at wavelengths listed in Table I. Injections were made using a Hitachi autosampler (Model AS2000). Ondansetron 0.3 mg/ml and fluconazole 2 mg/ml samples were diluted 1:2, and 50 μl were injectioned. Chromatographic data were recorded on a Hitachi Chromato-Integrator (Model D-2500) and the peak area was used for quantitation. The various concentrations were determined by comparing the peak area with the standard curve. A standard curve was determined daily using five standard concentrations. In addition, a quality control samples were run daily. The standard curves had ranges of 10-100 μg/ml for ondansetron and 200-1000 μg/ml for fluconazole. Standard curves in the linear analytical concentration range for each drug were constructed for calibration. The correlation coefficient of each curve was more than 0.999. The intraday and interday coefficients of variation were < 5% for each of the standard solutions.

Validation of assay

In our previously published paper, we reported the stability indicating nature of the ondansetron (Jhee *et al.*, 1993). The chromatographic measurement of ondansetron was established by chromatographic separation of ondansetron from its related compound (mannich compound), its preservatives (methyl paraben and N-propyl paraben) and fluconazole. The chromatographic measurement of fluconazole was established by chromatographic separation of fluconazole from ondansetron, its related compound and its preservatives. Samples were exposed to 1 N HCl or 1 N NaOH for 12 hours at 58°C, 3% hydrogen peroxide for 17 hours at room temperature and ultraviolet light for 24 hours. All degradation products did not interfere with the intact drug in the assay.

Table I. High-performance liquid chromatographic conditions used

Drug	Column	Mobile phase	Detector setting (nm)	Retention time (min)	CV (%)[a]	
					Interday	Intraday
Ondansetron	Nitrile column	Acetonitrile: 0.02 M monobasic potassium phosphate and 5 mM octanesulfonic acid (50:50 v/v), pH adjusted to 6.0 with 1 N NaOH solution	216	10.6	5	3
Fluconazole	C_{18} column	Acetonitrile:water (26:74 v/v)	260	6.5	4	2

[a]CV: Coefficient of variation (%).

Analysis of data

The initial concentration was defined as 100% and subsequent sample concentrations were expressed as percentage of initial concentration. Stability was defined as greater than 90% remaining of the post-admixturel drug concentration.

RESULTS AND DISCUSSION

Ondansetron in concentrations of 0.03, 0.1 and 0.3 mg/ml was stable when mixed with concentrations of fluconazole 2 mg/ml. Specifically, ondansetron 0.3 mg/ml maintained a mean relative concentration of at least 95.5% in 5% dextrose injection (see Table II) with fluconazole 2 mg/ml which retained at least 96. 4% for 12 hr. At the lower concentration of 0.03 mg/ml, ondansetron retained at least 97.7% in normal saline (see Table III) while fluconazole 2 mg/ml retained at least 97.5% of the original for 12 hr. In terms of visual changes, no precipitates, color changes, or haziness appeared in any admixture for 12 hr of inspection. The pH changes were minor with the greatest magnitude being an increase of 0.43 pH units for the combination of ondansetron 0.3 mg/ml and fluconazole 2 mg/ml in 5% dextrose injection. The pH measurements did not have a particular trend in any direction over time (see Table IV).

In this study, I would present general guidelines for avoiding common flaws in stability and compatibility studies of injectable drugs (Connors *et al.*, 1986; Trissel, 1986). First, completely describe the materials, test conditions and methods. The drugs and other materials used in the testing should be completely described including sources and quantities or concentrations. Similar products from different suppliers may have differing formulations that can affect results. Varying the concentrations tested may also alter results. All conditions of test should be included and thoroughly described. Some variables that are frequently unmentioned include the actual temperature, presence or absence of light and container materials. In addition, the analytical methods used should be described in detail and basic items such as pH, color and clarity determined should be described. The materials, test conditions and methods should be described sufficiently well to permit replication of the study. Second, use a stability-indicating assay. The most common flaw is the failure to use an analytical method that has been demonstrated to be stability-indicating (Trissel *et al.*, 1988). It is incumbent on researchers to demonstrate that the methods they are using will detect and separate the intact drug in the presence of its decomposition products and other drugs and components. Third, perform an analytical determination at the outset. A time-zero determination of drug concentration is essential.

Table II. Stability of ondansetron with fluconazole in 5% dextrose injection

Drug combination	Initial concentration (mg/ml)[a,b]	% of Initial concentration remaining[b]			
		1 hr	2 hr	4 hr	12 hr
Ondansetron 0.03 mg/ml	0.014±0.002	101.8±1.2	102.9±1.1	101.5±1.5	98.8±1.6
with fluconazole 2 mg/ml	1.016±0.016	100.7±1.7	99.7±2.7	98.5±1.7	97.8±1.1
Ondansetron 0.1 mg/ml	0.047±0.001	99.1±1.1	99.7±0.9	98.9±0.7	96.8±1.9
with fluconazole 2 mg/ml	1.026±0.014	101.6±2.4	98.8±3.6	100.4±1.8	98.5±1.6
Ondansetron 0.3 mg/ml	0.143±0.002	99.5±0.9	99.8±0.7	99.1±0.8	95.5±1.9
with fluconazole 2 mg/ml	0.974±0.022	100.4±1.4	99.9±0.8	100.0±1.5	96.4±1.6

[a]After 1:1 dilution with two drugs.
[b]Mean±S.D., n=6

Table III. Stability of ondansetron with fluconazole in normal saline

Drug combination	Initial concentration (mg/ml)[a,b]	% of Initial concentration remaining[b]			
		1 hr	2 hr	4 hr	12 hr
Ondansetron 0.03 mg/ml	0.0146±0.009	99.8±1.4	98.8±1.4	100.2±1.5	97.7±1.5
with fluconazole 2 mg/ml	1.062±0.014	98.2±0.8	98.7±1.0	97.9±1.8	97.5±1.8
Ondansetron 0.1 mg/ml	0.047±0.008	99.7±2.0	98.7±1.2	101.4±1.0	98.2±0.9
with fluconazole 2 mg/ml	1.051±0.011	100.4±1.4	99.8±2.1	98.7±1.58	100.2±1.6
Ondansetron 0.3 mg/ml	0.146±0.007	102.4±1.2	99.8±0.7	98.4±0.8	97.8±0.8
with fluconazole 2 mg/ml	0.977±0.016	101.8±2.1	98.5±1.0	98.5±1.2	98.9±1.1

[a]After 1:1 dilution with two drugs.
[b]Mean±S.D., n=6

Table IV. pH of 5% dextrose injection and normal saline containing both of ondansetron and fluconazole

Drug combination	pH in 5% dextrose injection[a]			pH in normal saline[a]		
	Initial	4 hr	12 hr	Initial	4 hr	12 hr
Ondansetron 0.03 mg/ml with fluconazole 2 mg/ml	6.54±0.02	6.57±0.03	6.97±0.01	6.68±0.02	6.67±0.01	6.54±0.02
Ondansetron 0.1 mg/ml with fluconazole 2 mg/ml	6.42±0.03	6.40±0.05	6.55±0.02	6.66±0.02	6.45±0.03	6.55±0.04
Ondansetron 0.3 mg/ml with fluconazole 2 mg/ml	6.01±0.02	6.02±0.03	6.11±0.05	6.33±0.02	6.45±0.05	6.24±0.02

[a]Mean±S.D., n=6

Without such a determination of initial concentration, there is no definitely known starting point. Fourth, use replicate assays at adequate and appropriate intervals. Initially and at all test intervals, multiple assays of mutiple test solutions should be performed. Performing several determinations on replicate test solutions at each interval will help to increase confidence in the accuracy of the results obtained by minimizing the effects of assay variability and human error. As a general rule, duplicate assay of three replicate test solutions are considered a minimum. Finally, make the conclusions fit the results. Conclusions should be only as definite as all relevant facts permit. And also conclusion should take into account all of the data. If these problems are avoided at the outset in the design of the study and through project completion and writing of the paper, much wasted effort will be eliminated and higher quality papers on drug stability and compatibility will result.

In summary, ondansetron at concentrations of 0.03, 0.1 and 0.3 mg/ml may be administered through a Y-injection port along with fluconazole of 2 mg/ml in 5% dextrose injection and normal saline for periods of at least 12 hr at room temperature.

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