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Stability of Taxol and Ondansetron Hydrochloride in 5% Dextrose Injection and 0.9% Sodium Chloride Injection during Simulated Y-Site Administration

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Y-Site 투여시 5% 포도당액과 생리식염수에서 탁솔과 온단세트론의 안정성

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Y-Site 투여시 5% 포도당액과 생리식염수에서 탁솔과 온단세트론의 안정성에 관해 실온과 형광등 아래서 연구하였다. 온단세트론 0.03 mg/ml, 0.1 mg/ml, 0.3 mg/ml와 탁솔 0.3 mg/ml, 1.2 mg/ml를 각각 1:1로 혼합한 후 0, 1, 2, 4, 12시간에서 즉시 약물농도를 HPLC로 분석하였다. 방해물질에 의한 분석오차를 줄이기 위해 분석법을 여러상태에서 확인하였으며, 각 농도에서 3차례씩 실험하였고 각 샘플은 2차례 연속 HPLC 분석하였다. 분석전에 각 시료의 투명도, 색의 변화, 침전상태 및 pH를 검사하였다. 온단세트론 0.03, 0.1 및 0.3 mg/ml와 탁솔 0.3 및 1.2 mg/ml를 각각 혼합하였을 때 12시간 동안 안정성이 있었다. 혼탁이나 색의 변화 및 침전은 나타나지 않았으며 12시간 동안 pH의 변화는 특별한 경향이 없었다.

☐ Keywords: Stability, Ondansetron, Taxol, Y-Site administration

Severely ill patients often require extensive multiple intravenous drug therapy during their treatment regimens. Critically ill patients such as those in intensive making managementcare may receive as many as 20 medications[1] of IV administration and access a challenge.

Ondansetron hydrochloride 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.[2] With its low incidence of adverse effects, ondansetron hydrochloride 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 hydrochloride in Y-site administration. A few studies have been reported to date. Boss et al.[3] and Graham et al.[4] found that ondansetron hydrochloride in 0.9% sodium chloride injection or 5% dextrose injection was stable under refrigeration for up to 14 days. Stiles et al.[5] reported stability in portable infusion pump reserviors and we reported stability of ondansetron and fluconazole in 5% dextrose injection and 0.9% sodium chloride injection during Y-site administration.[6]

Taxol is one of the most active new agents introduced into cancer therapy in recent years.[7,8] The drug is most commonly administered as a continuous infusion over 24 hours every three weeks. In clinical trials, the drug was prepared in glass bottles and administered through tubing of material other than polyvinylchloride (PVC) because of the evidence that the plasticizer, diethylhexyl phthalate, was extracted from the PVC tubing and containers.[9-12] With the recent FDA approval of taxol for the treatment of ovarian cancer,[13] many questions concerning the compatibility and stability of taxol in a variety of containers and with various drugs need to be addressed.

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Patients treated with taxol may receive serotonin receptor antagonist for prevention of nausea and vomiting associated with antineoplastic therapy. Since ondansetron hydrochloride may be given as a continuous infusion, consideration of compatibility becomes necessary upon concomitant administration. Waugh et al.[12] reported on the stability, compatibility and plasticizer extraction of taxol diluted in various solutions and stored in various containers, and Trissel et al.[14,15] reported on the turbidimetric assessment of taxol with other drugs and also we reported stability of paclitaxel and fluconazole during simulated Y-site administration.[16] In a review of the literature, we found no studies analyzing the compatibility and stability of ondansetron hydrochloride with taxol.

Thus, the purpose of this study is to evaluate the compatibility and stability of ondansetron hydrochloride with taxol in 5% dextrose and 0.9% sodium chloride injection during simulated Y-site injection at clinically relevant concentrations.

Materials and Methods

Materials

Ondansetron hydrochloride (lot Z270052BW) was kindly provided by Glaxo Inc. and taxol (lot L2F35A) was kindly provided by Bristol-Myers Squibb Co. 50 ml glass bottles containing 5% dextrose and 0.9% sodium chloride injection respectively were purchased from Baxter Healthcare Cor-poration. All other chemicals were reagent grade.

Preparation of Solutions

Stock solutions were prepared from manufacturer's formulations of ondansetron hydrochloride and taxol at concentrations of 2 mg/ml, 6 mg/ml respectively. Three stock solutions of ondansetron hydrochloride 0.03, 0.1 and 0.3 mg/ml were prepared by diluting 0.75, 2.5 and 7.5 ml of ondansetron hydrochloride respectively with 50 ml of 5% dextrose in water and 0.9% sodium chloride injection for injections in glass bottles. Two stock solutions of taxol 0.3 mg/ml and 1.2 mg/ml were prepared by diluting 2.5 and 10 ml of taxol respectively with 50 ml of 5% dextrose in water and 0.9% sodium chloride injection for injections in glass bottles. All solutions were prepared in triplicate, and each drug was assayed in diplicate. Allen et al.[17] and Allen and Stiles[18] demonstrated that secondary admixtures injected through a Y-injection port, mix with the primary i.v. fluid in a 1 : 1 ratio. To simulate this condition for high and low concentrations of each drug, 2 ml of ondansetron hydrochloride stock solution was mixed with 2 ml of taxol stock solution. Separate admixtures were prepared for the assay of each drug.

Samples were removed at room temperature under fluorescent room light at time zero, one, two, four and twelve hours for immediate assay. At the time of sampling assay and before any dilution, each sample was visually inspected for clarity, color and precipitation. The pH was also determined.

High-performance liquid chromatographic assays

The ondansetron hydrochloride HPLC assay was modified from the method of Jhee et al.[19] The taxol HPLC assay was modified from the method of Longnecker et al.[20] The mobile phases were filtered through a Sartorius 0.45 micrometer nylon filter and degassed under vacuum in an ultrasonic bath. A Hitachi Intelligent Pump delivered the mobile phase at the flow rate appropriate for each drug analysis as listed in Table 1. The column used for taxol was a 4.6 mm×25 cm Adsorbosphere packed with C_{18} 5 μm particle size while the column for ondansetron hydrochloride was a 4.6 mm×25 cm Accubond packed with CN 5 μm particle size. A Hitachi UV-VIS Detector was set at wavelengths listed in Table 1. Injections were made using a Hitachi autosampler. Taxol 1.2 mg/ml samples were diluted 1 : 4 and 20 l of the resulting solution injected. Ondansetron hydrochloride 0.3 mg/ml samples were diluted 1 : 2 and 50 l injected. Chromatographic data

Table 1. High-performance liquid chromatographic conditions used

Drug	Column	Mobile phase	Detector setting (nm)	Retention time (min)	CV(%)[a]	
					Interday	Intraday
Ondansetron	CN column	Acetonitrile : 0.02M 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
Taxol	C_{18} column	Acetonitrile: 12.5 mM ammonium phosphate (60 : 40 v/v), pH adjusted to 4.5 with 1 N hydrochloric acid	227	10.0	2	2

[a]CV : Coefficient of variation (%)

were recorded on a Hitachi Chromato-Integrator 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 sample and blank 5% dextrose in water and 0.9% sodium chloride injection were run daily. The standard curves had ranges of 10-100 μg/ml for ondansetron hydrochloride, 40-200 μg/ml for taxol. Taxol standard solutions were made by dissolving taxol in methanol and diluting them with 60% acetonitrile. All solutions were kept refrigerated at −4°C when not in use to avoid evaporation of the organic solvent. Ondansetron hydrochloride standard solutions were prepared in 5% dextrose in water and 0.9% sodium chloride injection. Standard curves in the linear analytical concentration range for each drug were constructed for calibration. The correlation coefficient of each curve was higher than 0.999. The intraday and interday coefficients of variation were < 5% for each of the standard solutions.

Validation of assay

The measurement of ondansetron hydrochloride was established by chromatographic separation of ondansetron hydrochloride from its related compound and preservatives, taxol and its preservatives. In our previously published papers, we reported on the stability indicating nature of the ondansetron hydrochloride.[19] The chromatographic measurement of taxol was established by chromatographic separation of taxol from its preservatives (cremophor and dehydrated alcohol) from ondansetron hydrochloride, and its related

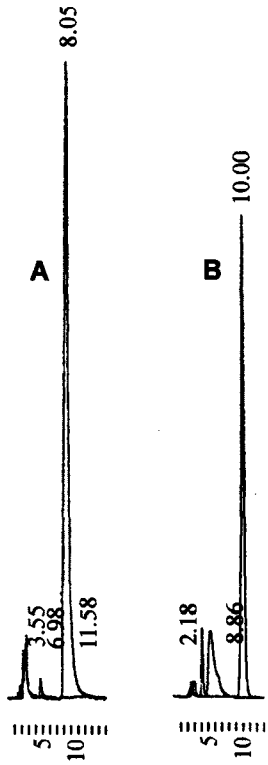

Fig. 1. Chromatograms of taxol 1.2 mg/ml and ondansetron hydrochloride 0.3 mg/ml. A; Taxol assay with taxol eluting at 8.05 minutes. B; ondansetron hydrochloride assay with ondansetron hydrochloride elutins at 10.0 minutes.

Table 2. Stability of ondansetron hydrochloride and taxol in 5% dextrose injection during simulated Y-site administration

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	99.8±1.3	100.2±1.8	99.8±1.6	97.8±1.5
and taxol 0.3 mg/ml	0.148±0.012	100.2±1.2	99.9±2.1	98.5±1.7	96.8±1.2
Ondansetron 0.03 mg/ml	0.013±0.001	99.9±1.8	99.2±0.9	98.9±0.7	96.8±1.4
and taxol 1.2 mg/ml	0.589±0.065	99.1±2.1	98.5±2.6	98.1±1.8	98.5±1.6
Ondansetron 0.1 mg/ml	0.052±0.004	99.5±0.9	99.7±1.2	99.0±0.9	95.3±1.7
and taxol 0.3 mg/ml	0.144±0.021	100.8±1.7	99.1±0.6	100.1±1.7	94.1±1.8
Ondansetron 0.1 mg/ml	0.054±0.006	100.4±1.8	101.0±1.4	99.2±1.4	96.9±2.0
and taxol 1.2 mg/ml	0.577±0.069	98.4±0.9	99.1±1.5	98.2±2.1	96.4±1.8
Ondansetron 0.3 mg/ml	0.155±0.014	99.5±1.8	99.1±1.2	97.9±1.7	97.8±2.0
and taxol 0.3 mg/ml	0.146±0.019	101.4±1.9	97.9±2.9	96.8±1.8	98.2±0.8
Ondansetron 0.3 mg/ml	0.146±0.020	99.8±0.8	99.7±0.9	99.0±1.8	98.5±1.8
and taxol 1.2 mg/ml	0.614±0.075	101.2±1.8	98.0±0.9	99.1±1.9	97.4±2.6

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

Table 3. Stability of ondansetron hydrochloride and taxol in 0.9% sodium chloride injection during simulated Y-site administration

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	0.016±0.003	98.9±1.8	99.7±2.1	97.5±2.1	96.2±1.9
and taxol 0.3 mg/ml	0.145±0.021	99.2±2.0	98.2±1.7	97.5±3.1	97.1±1.8
Ondansetron 0.03 mg/ml	0.014±0.002	98.9±1.1	98.4±1.2	97.2±0.9	97.1±2.4
and taxol 1.2 mg/ml	0.597±0.050	98.9±2.2	96.1±1.9	97.9±2.9	95.6±3.4
Ondansetron 0.1 mg/ml	0.059±0.007	99.2±1.5	101.1±1.8	98.2±1.0	96.4±1.7
and taxol 0.3 mg/ml	0.162±0.032	101.7±2.9	98.9±2.9	98.8±1.8	97.1±2.4
Ondansetron 0.1 mg/ml	0.058±0.004	101.8±1.7	98.2±2.9	98.0±2.1	95.9±2.2
and taxol 1.2 mg/ml	0.623±0.081	97.6±1.3	98.4±2.5	96.7±2.9	96.2±1.4
Ondansetron 0.3 mg/ml	0.151±0.020	97.5±1.8	98.4±1.7	96.9±3.8	96.7±2.8
and taxol 0.3 mg/ml	0.141±0.028	98.9±1.4	97.1±1.2	97.6±118	97.0±1.5
Ondansetron 0.3 mg/ml	0.144±0.027	100.8±1.2	99.8±1.0	97.5±1.1	97.0±3.1
and taxol 1.2 mg/ml	0.578±0.088	99.9±2.4	98.8±2.1	98.8±1.1	96.6±3.3

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

Table 4. pH of 5% dextrose injection and 0.9% sodium chloride injection containing both of ondansetron hydrochloride and taxol

Drug combination initial	pH in 5% dextrose injection[a]			pH in normal saline[a]		
	4 hr	12 hr	Initial	4 hr	12 hr	
Ondansetron 0.03 mg/ml and taxol 1.2 mg/ml	6.89±0.11	6.77±0.09	6.28±0.05	6.45±0.02	6.59±0.05	6.67±0.03
Ondansetron 0.1 mg/ml and taxol 1.2 mg/ml	6.67±0.04	6.54±0.04	6.59±0.10	6.76±0.03	6.64±0.11	6.49±0.05
Ondansetron 0.3 mg/ml and taxol 1.2 mg/ml	6.34±0.04	6.24±0.07	6.28±0.04	6.49±0.18	6.57±0.08	6.33±0.03

[a]Mean±S.D., n=6

compound (Mannich compound) and preservatives (methyl paraben and propyl paraben). Sample chromatograms are shown in Fig. 1. The stability indicating nature of the assays was established by forcible degradation of the taxol 240 μg/ml solutions. Samples were exposed to 1 N HCl or 1 N NaOH for 5 hours at 58°C, 3% hydrogen peroxide for 17 hours at room temperature, and ultraviolet light and 1 N HCl for 22 hours. All degradation products of taxol did not interfere with the intact drug in the assay.

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-admixture drug concentration.

Results and Discussion

Ondansetron hydrochloride in concentrations of 0.03, 0.1 and 0.3 mg/ml was stable when mixed with concentrations of taxol, 0.3 and 1.2 mg/ml. Specifically, ondansetron hydrochloride 0.1 mg/ml in 5% dextrose injection maintained a mean relative concentration of at least 95.34% (Table 2) with taxol 0.3 mg/v which retained at least 94.1%. At the 0.9% sodium chloride injection, ondansetron hydrochloride 0.1 mg/ml retained at least 95.9% (Table 3) while taxol 1.2 mg/ml retained at least 96.2% of the original. In terms of visual changes, no precipitates, color changes, or haziness appeared in any admixture for the four hours of inspection. The pH changes

were minor with the greatest magnitude being a decrease of 0.61 pH units for the combination of ondansetron hydrochloride 0.03 mg/ml and taxol 1.2 mg/ml in 5% dextrose injection. The pH measurements did not have a particular trend in any direction over time.

In this study, I would present general guidelines for avoiding common flaws in stability and compatibility studies of injectable drugs.[21,22] 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 different formulations that can affect results. Varying the concentrations tested may also alter results. All conditions of a 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.[23] 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. 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 hydrochloride at concentrations of 0.03, 0.1 and 0.3 mg/ml may be administered through a Y-injection port along with taxol of 0.3 and 1.2 mg/ml in 5% dextrose injection and 0.9% sodium chloride injection for periods of at least twelve hours at room temperature.

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