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Stability of Paclitaxel with Cephalosporines in 0.9% Sodium Chloride Injection and 5% Dextrose Injection During Simulated Y-Site Administration

Y-Site 동시투여 동안 0.9% 생리식염수와 5% 포도당 용액에서의 Paclitaxel과 Cephalosporines의 안전성 연구

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Paclitaxel과 cephalosporines(제1세대인 ceftezole sodium과 cephradine, 제2세대인 cefamandole sodium과 cefmetazole sodium, 제3세대인 cefoperazone sodium과 cefotaxime sodium 그리고 제4세대인 cefepime hydrochloride)을 5% 포도당주사액 그리고 0.9% 염화나트륨주사액과 함께 Y-Site 장치를 써서 환자에게 주입할 때 paclitaxel의 안정성에 관하여 연구하였다. Paclitaxel 0.3 mg/ml 및 1.2 mg/ml과 cephalosporines 20 mg/ml을 각각 1 : 1로 혼합한 후 0, 1, 2, 4, 12시간 시점에서 paclitaxel의 농도를 HPLC로 분석하였다. 방해물질에 의한 분석오차를 줄이기 위해 분석법을 여러 상태에서 확인하였으며, 각 농도에서 3차례씩 실험하였고 각 샘플은 2차례 반복하여 HPLC로 분석하였다. 분석전에 각 시료의 투명도, 색의 변화, 침전상태 및 pH를 검사하였다. Paclitaxel 0.3 mg/ml 및 1.2 mg/ml와 cephalosporines 20 mg/ml를 각각 혼합하였을 때 12시간 동안 안정하였으며, 주사액의 혼탁이나 색의 변화 및 침전은 나타나지 않았으며 pH도 변하지 않았다.

☐ Key words – Stability, Paclitaxel, Cephalosporines, Y-Site Administration

Severely ill patients often require extensive multiple intravenous drug therapy during their treatment; those in intensive care may receive as many as 20 medications[1], making management of i.v. administration and access a challenge.

Paclitaxel is one of the most active new agents introduced into cancer therapy recently[2,3]. The drug is most commonly administered as a continuous infusion over 24 hours every three weeks. In clinical trials, the drug should be 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[4-7]. With the recent FDA approval of paclitaxel for the treatment of ovarian cancer[8], many questions concerning the compatibility and stability of paclitaxel in a variety of containers and with various drugs need to be addressed.

The cephalosporins are frequently prescribed beta-lactam antibiotics. Cephalosporins are divided into first-, second-, third- and fourth-generation drug. Cephalosporins have been increasingly used as an antimicrobial agent in patients with cancer[9].

Patients treated with paclitaxel may receive cephalosporins against the infection associated with antineoplastic therapy. Since cephalosporins may be given as a continuous infusion, consideration of compatibility becomes necessary upon concomitant administration. Waugh *et al.*[7] reported on the stability, compatibility and plasticizer extraction of paclitaxel when paclitaxel was diluted by various solutions and stored in various containers. Trissel *et al.*[10,11] reported turbidimetric assessment of the stability of paclitaxel when the drug was mixed with other drugs. The stability of paclitaxel in the presence of fluconazole[12], ondansetron[13] and vancomycin[14] during simulated Y-site administration was also investigated. The stability of cephalosporins was reported compatibility of cefazolin sodium in two

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intravenous solutions[15], compatibility and stability of cefmetazole sodium[16] and ceftazidime[17] with ranitidine hydrochloride during simulated Y-site administration and in peritoneal dialysis solutions[18,19], and turbidimetric assessment of the paclitaxel with ceforanide, cefotetan disodium, ceftazidime and ceftriaxone sodium during simulated Y-site injection[10]. In a review of the literature, we found no studies analyzing the compatibility and stability of paclitaxel with cephalosporins.

Thus, the purpose of this study is to evaluate the compatibility and stability of paclitaxel with cephalosporins (ceftezole sodium, cephradine, cefamandole sodium, cefmetazole sodium, cefoperazone sodium, cefotaxime sodium and cefepime hydrochloride) in 5% dextrose injection and 0.9% sodium chloride injection during simulated Y-site administration at clinically relevant concentrations.

Materials and Methods

Materials

Paclitaxel (lot L2F35A) was kindly provided by Bristol-Myers Squibb Co.. Ceftezole sodium and cephradine (first-generation cephalosporins) were kindly provided by Shinpoong Co., cefamandole sodium and cefmetazole sodium, (second-generation cephalosporins) were kindly provided by Daewoo and Daewoong Co., cefoperazone sodium and cefotaxime sodium (third-generation cephalosporins) were kindly provided by Daehwa and Kukje Co., and cefepime hydrochloride (fourth-generation cephalosporin) was kindly provided by Boryung Co.. 5% dextrose injection and 0.9% sodium chloride injection were purchased from Choongwae Co.. All other chemicals were reagent grade.

Preparation of solutions

Two stock solutions of paclitaxel 0.3 mg/ml and 1.2 mg/ml were prepared by diluting 2.5 and 10 of 6 mg/ml paclitaxel by using pipett respectively with 50 ml of 5% dextrose injection and 0.9% sodium chloride injection in glass bottles.

One stock solutions of cephalosporins 20 mg/ml were prepared by diluting 1 g vial of cephalosporins respectively with 50 ml of 5% dextrose injection and 0.9% sodium chloride injection in glass bottles.

Allen *et al.*[20] and Allen and Stiles[21] 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 low and high concentrations of paclitaxel, 2 ml of paclitaxel stock solution was mixed with 2 ml of cephalosporins stock solution. Separate admixtures were prepared for the assay of paclitaxel.

Samples were removed at room temperature at time zero, one, two, four and twelve hours for immediate assay. All solutions were prepared in triplicate, and each drug was assayed in duplicate. 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 paclitaxel HPLC assay was modified from the method reported before by of Burm[22]. The mobile phase consisted of Acetonitrile: 12.5 mM ammonium phosphate (60 : 40 v/v), The pH was adjusted to 4.5 with 1 N hydrochloric acid. 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 (1 ml/min) appropriate for paclitaxel analysis. The column used for paclitaxel was a 4.6 mm × 25 cm adsorbosphere packed with C_{18} 5 μm particle size. A Hitachi UV-VIS detector was set at wavelength of 227 nm. Injections were made using a Hitachi autosampler. Paclitaxel 1.2 mg/ml samples were diluted 1 : 4 and 20 μl of the resulting solution injected. Chromatographic data 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 injection and 0.9% sodium chloride injection were run daily. The standard curves had ranges of 40-200 μg/ml (200, 150, 100, 60 and 40 μg/ml) for paclitaxel. Paclitaxel standard solutions were made by dissolving paclitaxel 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. 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. Detection limit was

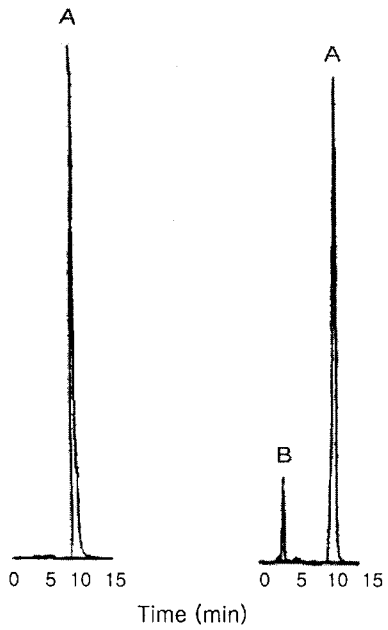

Fig. 1. Chromatogram of paclitaxel (peak A, left) and ceftezole (peak B) and paclitaxel (peak A, right) in 0.9% sodium chloride injection.

defined below 100 ng/ml and the intraday and interday coefficients of variation were <4% for each of the standard solutions.

Validation of assay

The chromatographic measurement of paclitaxel was established by chromatographic separation of paclitaxel from its preservatives (Cremophor and dehydrated alcohol) from cephalosporins (Fig. 1). The stability indicating nature of the assays was established by forcible degradation of the paclitaxel 200 μg/ml and cephalosporins 400 μg/ml solutions. Samples were exposed to 1 N hydrochloric acid or 1 N sodium hydroxide for 5 hours at 60°C, 3% hydrogen peroxide for 17 hours at room temperature, and ultraviolet light and 1 N hydrochloric acid for 22 hours. All degradation products of paclitaxel and cephalosporins 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

Paclitaxel in concentrations of 0.3 and 1.2 mg/ml was stable when mixed with concentrations of cephalospor-

Table 1. Stability of paclitaxel with cephalosporins in 5% dextrose injection during Y-site administration

Drug combination	Initial concentration (mg/ml)[a,b]	% of Initial concentration remaining[b]			
		1 hr	2 hr	4 hr	12 hr
Paclitaxel 0.3 mg/ml					
with ceftezole sodium 20 mg/ml	0.146±0.005	99.6±1.7	98.6±1.9	96.6±2.2	95.2±1.5
cephradine 20 mg/ml	0.151±0.010	98.6±2.2	98.8±2.2	97.4±2.7	96.7±1.2
cefamandole sodium 20 mg/ml	0.155±0.006	98.2±1.6	97.5±1.7	98.0±1.9	97.4±0.9
cefmetazole sodium 20 mg/ml	0.149±0.003	102.3±1.9	99.7±1.9	96.4±1.3	95.2±1.9
cefoperazone sodium 20 mg/ml	0.145±0.008	97.8±3.4	98.7±3.4	96.6±1.1	97.7±2.4
cefotaxime sodium 20 mg/ml	0.158±0.004	98.9±1.0	99.0±1.9	97.5±2.7	94.2±2.0
cefepime hydrochloride 20 mg/ml	0.145±0.007	99.7±1.7	97.2±2.0	95.5±2.1	95.7±1.7
Paclitaxel 1.2 mg/ml					
with ceftezole sodium 20 mg/ml	0.588±0.019	97.6±1.1	98.0±1.8	97.5±2.4	96.7±0.8
cephradine 20 mg/ml	0.592±0.025	98.2±1.9	99.2±2.9	98.2±2.9	97.5±2.0
cefamandole sodium 20 mg/ml	0.579±0.027	99.7±2.2	98.2±3.8	95.7±1.9	95.7±2.4
cefmetazole sodium 20 mg/ml	0.621±0.032	102.4±3.0	98.6±2.0	98.7±3.7	97.8±1.9
cefoperazone sodium 20 mg/ml	0.611±0.011	108.1±2.8	99.9±2.7	98.7±2.6	97.8±1.7
cefotaxime sodium 20 mg/ml	0.578±0.030	98.7±2.4	97.6±1.3	97.2±2.8	95.9±1.1
cefepime hydrochloride 20 mg/ml	0.627±0.021	99.1±1.8	98.7±2.7	99.0±1.7	96.5±2.5

[a]After 1 : 1 dilution with two drugs. [b]Mean ± S.D., n = 3

Table 2. Stability of paclitaxel with cephalosporins 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
Paclitaxel 0.3 mg/ml					
with ceftezole sodium 20 mg/ml	0.141±0.008	99.5±2.3	98.6±1.7	96.6±2.7	95.7±2.7
cephradine 20 mg/ml	0.148±0.005	102.5±1.4	97.9±3.0	96.7±4.1	94.4±2.4
cefamandole sodium 20 mg/ml	0.152±0.006	98.6±1.7	101.0±1.8	96.7±1.2	96.4±2.6
cefmetazole sodium 20 mg/ml	0.159±0.012	99.2±1.0	97.8±2.0	96.7±0.9	94.9±1.9
cefoperazone sodium 20 mg/ml	0.155±0.006	100.9±2.9	98.7±1.7	98.7±1.3	97.7±2.2
cefotaxime sodium 20 mg/ml	0.146±0.005	97.9±2.7	99.5±2.1	96.7±1.5	96.4±1.4
cefepime hydrochloride 20 mg/ml	0.156±0.003	98.1±1.3	99.7±2.4	97.7±2.9	95.5±3.0
Paclitaxel 1.2 mg/ml					
with ceftezole sodium 20 mg/ml	0.604±0.015	99.6±1.1	96.7±2.7	98.8±1.9	97.8±2.5
cephradine 20 mg/ml	0.624±0.025	98.1±2.7	98.9±2.2	95.6±1.8	94.6±1.1
cefamandole sodium 20 mg/ml	0.599±0.037	99.6±1.7	100.2±2.7	96.3±1.5	98.6±0.9
cefmetazole sodium 20 mg/ml	0.608±0.022	104.8±1.8	99.7±2.1	98.5±1.9	97.8±1.8
cefoperazone sodium 20 mg/ml	0.624±0.019	100.0±0.8	99.3±2.7	97.5±2.0	95.0±2.2
cefotaxime sodium 20 mg/ml	0.468±0.016	97.5±2.3	98.5±1.7	96.7±1.7	96.7±3.0
cefepime hydrochloride 20 mg/ml	0.488±0.023	99.8±2.3	98.7±3.8	97.8±2.7	96.5±1.5

[a]After 1 : 1 dilution with two drugs. [b]Mean ± S.D., n = 3

ins 20 mg/ml (ceftezole sodium, cephradine, cefamandole sodium, cefmetazole sodium, cefoperazone sodium, cefotaxime sodium and cefepime hydrochloride) for twelve hours in 5% dextrose injection and 0.9% sodium chloride injection during simulated Y-site administration. Specifically, paclitaxel 0.3 mg/ml in 5 dextrose injection maintained a mean relative concentration of at least 94.2% with cephalosporins (cefotaxime sodium 20 mg/ml) and also paclitaxel 1.2 mg/ml maintained a mean relative concentration of at least 95.9% (see Table 1) with cephalosporins (cefotaxime sodium 20 mg/ml). At the 0.9% sodium chloride injection, paclitaxel 0.3 mg/ml maintained a mean relative concentration of at least 94.9% with cephalosporins (cefmetazole sodium 20 mg/ml) and also paclitaxel 1.2 mg/ml maintained a mean relative concentration of at least 94.6% (see Table 2) with cephalosporins cephradine 20 mg/ml).

In terms of visual changes, no precipitates, color changes, or haziness appeared in any admixture for the twelve hours of inspection. The pH changes were minor with the greatest magnitude being a decrease of pH 0.34 units for the combination of paclitaxel 1.2 mg/ml and cefoperazone sodium 20 mg/ml in 5 dextrose injection. The pH measurements did not have a particular trend in any direction over time.

In this study, It is important to avoid common flaws in stability and compatibility studies of injectable drugs[23,24]. 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[25]. 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

Table 3. pH of 5% dextrose injection and 0.9% sodium chloride injection containing both of paclitaxel and cephalosporins

Drug combination	pH in 5% dextrose injection[a]			pH in 0.9% sodium chloride injection[a]		
	Initial	4 hr	12 hr	Initial	4 hr	12 hr
Paclitaxel 1.2 mg/ml						
with ceftezole sodium 20 mg/ml	6.32±0.10	6.21±0.11	6.30±0.09	6.14±0.08	6.12±0.18	6.09±0.09
cephradine 20 mg/ml	6.68±0.08	6.54±0.09	6.59±0.11	6.32±0.19	6.22±0.16	6.18±0.05
cefamandole sodium 20 mg/ml	6.51±0.09	6.64±0.11	6.49±0.05	6.19±0.15	6.29±0.11	6.03±0.14
cefmetazole sodium 20 mg/ml	6.46±0.12	6.49±0.15	6.57±0.13	6.24±0.18	6.29±0.12	6.27±0.09
cefoperazone sodium 20 mg/ml	6.62±0.11	6.77±0.18	6.28±0.15	6.07±0.11	6.08±0.09	6.18±0.16
cefotaxime sodium 20 mg/ml	6.59±0.08	6.48±0.19	6.37±0.14	6.18±0.09	6.11±0.13	6.27±0.20
cefepime hydrochloride 20 mg/ml	6.17±0.18	6.14±0.08	6.28±0.04	6.05±0.19	6.09±0.21	6.19±0.13

[a]Mean ± S.D., n = 3

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, paclitaxel at concentrations of 0.3 and 1.2 mg/ml may be administered through a Y-injection port along with cephalosporins (ceftezole sodium, cephradine, cefamandole sodium, cefmetazole sodium, cefoperazone sodium, cefotaxime sodium and cefepime hydrochloride) of 20 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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