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Compatibility and Stability of Nab-Paclitaxel in Combination with Other Drugs

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Albumin-bound paclitaxel (Abraxane®, nab-paclitaxel) is not recommended to be administered concurrently or sequentially with other drugs due to concern for instability. The need to administer drugs separately increases infusion time. We evaluated the compatibility and stability of solutions containing nab-paclitaxel and other drugs, including gemcitabine hydrochloride, carboplatin, dexamethasone sodium phosphate, granisetron hydrochloride, and palonosetron hydrochloride. We visually examined changes in appearance, pH, and concentration of the mixed solutions of nab-paclitaxel and other drugs for up to 24 h. Concentration was measured using high-performance liquid chromatography (HPLC). The appearance and pH of the mixed solutions did not change for up to 24 h. The change in concentration up to 24 h was within 2%. The chromatogram did not change until 8 h. The results showed that the physical compatibility and chemical stability of nab-paclitaxel were not influenced when it was combined with other drugs until 8 h. This study suggests that nab-paclitaxel could be administered in a mixture or sequentially with other drugs to reduce administration time.

INTRODUCTION

The formulation of albumin-bound paclitaxel (Abraxane®, nab-paclitaxel) combines albumin and paclitaxel to produce nanoparticles [2,7]. Nab-paclitaxel was originally developed to avoid the toxicities (i.e. hypersensitivity reactions) typically associated with Cremophor ®EL and ethanol in solvent-based paclitaxel [6]. Nab-paclitaxel, like paclitaxel, has been shown to be effective in treating various cancers [5].

Since 1997, gemcitabine has been the standard first-line treatment for unresectable locally advanced or metastatic pancreatic cancer [1]. The combination of nab-paclitaxel and gemcitabine has been reported to be more effective than gemcitabine alone in patients with metastatic pancreatic cancer [18,19]. Solvent-based paclitaxel and carboplatin are most commonly used for non-small cell lung cancer (NSCLC) in the US [8,13]. Nab-paclitaxel administered weekly and carboplatin administered every 3 weeks have been reported to show better safety and efficacy than solvent-based paclitaxel and carboplatin administered every 3 weeks in advanced NSCLC [12]. Nab-paclitaxel has also been reported to show safety and efficacy as second-line chemotherapy for unresectable or recurrent gastric cancer [16]. In addition, nab-paclitaxel was safe and increased the overall response rate and time to progression in metastatic breast cancer compared to solvent-based paclitaxel [4,6,18]. Regimens combining nab-paclitaxel with other anticancer drugs, such as gemcitabine hydrochloride and carboplatin, are therefore currently widely used for treating various tumors.

Nausea and vomiting are the most common adverse effects of cancer chemotherapy. The Perugia Antiemetic Consensus Guideline Meeting established standards for classifying chemotherapy agents into four groups according to emetic risk: high, moderate, low, and minimal emetic risk [15]. According to the Japan Society of Clinical Oncology antiemetic guideline, nab-paclitaxel is classified as a low emetogenic chemotherapeutic agent (LEC), while the combination of nab-paclitaxel plus gemcitabine and nab-paclitaxel plus carboplatin are each classified as a moderate emetogenic chemotherapeutic agent (MEC). The combination of 5-hydroxytryptamine 3 (5-HT3) receptor antagonist and dexamethasone is used as an antiemetic therapy for drugs classified as MEC;

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dexamethasone alone is used as an antiemetic agent for drugs classified as LEC [3,10,14]. In patients with diabetes, however, a 5-HT3 receptor antagonist may be administered alone to avoid dexamethasone-induced elevation in blood glucose levels [11]. When nab-paclitaxel is administered, an antiemetic agent is also administered.

Mixing two or more drugs together in an infusion solution can lead to drug incompatibility or loss of stability. Chemical incompatibility and instability of the drug mixtures will result in an inadequate therapeutic outcome, and the degradation products may cause undesirable side effects [9]. Some drugs must therefore be administered separately, increasing administration time. Nab-paclitaxel is not recommended to be administered concurrently or sequentially with other drugs due to concern for instability. This leads to inconvenience in oncology practice. We evaluated the compatibility and stability of solutions containing nab-paclitaxel and other drugs that may be used in combination, including gemcitabine hydrochloride, carboplatin, dexamethasone sodium phosphate, granisetron hydrochloride, and palonosetron hydrochloride, at room temperature for up to 24 h.

MATERIALS AND METHODS

1. Materials and reagents

Nab-paclitaxel 100 mg (Abraxane®) and palonosetron hydrochloride 0.75 mg (Aloxi®) for injection were obtained from Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). Gemcitabine hydrochloride for injection 200 mg (Gemzar®), carboplatin for injection 50 mg (Carboplatin [Nichi-Iko]®), dexamethasone sodium phosphate for injection 6.6 mg (Dexart®), granisetron hydrochloride for injection 1 mg (Granisetron intravenous solution [MEIJI]®) were from Eli Lilly Japan K.K. (Kobe, Japan), Nichi-Iko Pharmaceutical Co., Ltd. (Toyama, Japan), Fuji Pharma Co., Ltd. (Toyama, Japan), and Meiji Seika Pharma Co., Ltd. (Tokyo, Japan), respectively. The 0.9 mg/mL sodium chloride injection (Otsuka normal saline®) and 5% glucose injection (Otsuka glucose injection 5%®) were from Otsuka Pharmaceutical Factory, Inc. (Tokushima, Japan). All other materials, paclitaxel, and gemcitabine hydrochloride were from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). High-performance liquid chromatography (HPLC) grade reagents were used for the mobile-phase components, such as acetonitrile, for the HPLC analysis. Water was purified using a Milli-Q system (Merck Millipore, Darmstadt, Germany).

2. Analytical method

The concentrations of nab-paclitaxel and other drugs used in this study were determined using a validated HPLC method. The HPLC analyses were performed using the Prominence HPLC system (Shimadzu, Kyoto, Japan) equipped with a system controller (SCL-10Avp), a liquid chromatograph (LC-20AT), a column oven (CTO-20A), an autosampler (SL-20AC), and ultraviolet detector (UV detector, SPD-10A). Chromatography was performed using the Symmetry C18 column (5-μm, 4.6 mm i.d. × 150 mm; Waters, Milford, MA, USA). The mobile phase A (0.1% phosphoric acid in water) and B (0.1% phosphoric acid in water: acetonitrile, 20:80, v/v) were prepared. The initial ratio (A:B) was 98:2 (v/v); paclitaxel and gemcitabine hydrochloride or carboplatin were separated by running a linear gradient of B from 2% to 100%, from 5 to 10 min at a flow rate of 1.0 mL/min. The drugs were monitored at 220 nm. Paclitaxel and antiemetic drugs were separated at an initial ratio (A:B) of 98:2 (V/V), a linear gradient of B, from 2% to 100%, from 0 to 15 min at a flow rate of 1.0 mL/min. The drugs were monitored at 240 nm (Table I-1, I-2).

Table I-1.
Gradient condition of HPLC mobile phase used for the analysis of paclitaxel and anticancer drugs.

	Concentration (%)	
time (min)	**0.1% Phosphoric acid in water**	**0.1% Phosphoric acid in water /acetonitrile** (20/80, v/v)
0.01	98	2
5.00	98	2
5.01	98	2
10.00	0	100
15.00	0	100

Table I-2.
Gradient condition of HPLC mobile phase used for the analysis of nab-paclitaxel and antiemetic drugs.

	Concentration (%)	
time (min)	**0.1% Phosphoric acid in water**	**0.1% Phosphoric acid in water /acetonitrile** (20/80,v/v)
0.01	98	2
15.00	0	100
20.00	0	100

3. The compatibility and stability of nab-paclitaxel in combination with other drugs

Nab-paclitaxel and gemcitabine hydrochloride were dissolved in 0.9% sodium chloride to concentrations of 5 and 16 mg/mL, respectively. Carboplatin was dissolved with 5% glucose solution to a concentration of 2.5 mg/mL. The antiemetic drugs were used at commercially available concentrations. Equal amounts of nab-paclitaxel and each drug were mixed and left to stand at room temperature. To determine the compatibility and stability of nab-paclitaxel in combination with the other drugs, the following two assay methods were used. The physical compatibility of the mixed drugs was determined by investigating the physical appearance and changes in pH of the solution. The samples were collected for chemical stability analysis 8 and 24 h later.

3-1. Physical compatibility of injection combinations

In the physical compatibility study, appearance analyses were performed at predetermined times (0, 1, 2, 4, 8, and 24 h). At the indicated times, the color change, cloudiness, and precipitation were evaluated against light and dark backgrounds. The pH value of each sample was also determined at each time point using a LAQUAact portable pH meter (HORIBA Ltd., Kyoto, Japan).

3-2. Chemical stability of injection combinations

To investigate the chemical stability of nab-paclitaxel in combination with other drugs, drug concentrations were measured at 0, 8, and 24 h. The prepared nab-paclitaxel (5 mg/mL) was diluted with a 5% human serum albumin solution to various concentrations (paclitaxel concentrations of 5 to 125 μg/mL), and the particle size of nab-paclitaxel at each concentration was measured over time. The results confirmed that the particle size of nab-paclitaxel rapidly disintegrated at a paclitaxel concentration of approximately 50 to 60 μg/mL irrespective of the measurement time, and the disruption threshold of nab-paclitaxel was less than 50 μg/mL of paclitaxel concentration [17]. Based on this report, nab-paclitaxel was diluted 100 times or more and measured by HPLC. The mixed solutions of nab-paclitaxel with gemcitabine and carboplatin were diluted 100 times with 0.9% sodium chloride and 5% glucose, respectively. The mixture of nab-paclitaxel and an antiemetic drug was diluted 75 times with water, and the mixture of nab-paclitaxel and two antiemetic drugs was diluted 50 times with water. Nab-paclitaxel was diluted to less than 50 μg/mL, albumin release occurred, and paclitaxel concentration was measured. The samples were injected into the HPLC system, and five-fold measurements were performed. The concentration of each sample was determined as a percentage of that of the initial sample (0 h).

RESULTS

Physical compatibility

The results of the physical compatibility study are summarized in Table II. In all drug combinations, a cloudy state was maintained for up to 24 h later with no precipitation. The pH of the mixed solutions with nab-paclitaxel at room temperature did not change significantly for 24 h (Table II).

Table II.
Physical compatibility of drugs in a mixture.

(A) Nab-paclitaxel and gemcitabine hydrochloride

Storage period (h)	0	1	2	4	8	24
pH values *	3.95 ± 0.01	3.96 ± 0.01	3.94 ± 0.01	3.94 ± 0.01	3.93 ± 0.01	3.95 ± 0.01
Color and appearance	white turbidity	NC	NC	NC	NC	NC
Precipitation	ND	ND	ND	ND	ND	ND

(B) Nab-paclitaxel and carboplatin

Storage period (h)	0	1	2	4	8	24
pH values *	6.75 ± 0.01	6.75 ± 0.01	6.74 ± 0.01	6.72 ± 0.01	6.72 ± 0.01	6.73 ± 0.01
Color and appearance	white turbidity	NC	NC	NC	NC	NC
Precipitation	ND	ND	ND	ND	ND	ND

(C) Nab-paclitaxel and dexamethasone sodium phosphate

Storage period (h)	0	1	2	4	8	24
pH values *	7.43 ± 0.01	7.43 ± 0.01	7.44 ± 0.01	7.45 ± 0.01	7.47± 0.01	7.49 ± 0.01
Color and appearance	white turbidity	NC	NC	NC	NC	NC
Precipitation	ND	ND	ND	ND	ND	ND

(D) Nab-paclitaxel and granisetron hydrochloride

Storage period (h)	0	1	2	4	8	24
pH values *	5.90 ± 0.01	5.91 ± 0.01	5.92 ± 0.01	5.93 ± 0.01	5.96 ± 0.01	6.00 ± 0.01
Color and appearance	white turbidity	NC	NC	NC	NC	NC
Precipitation	ND	ND	ND	ND	ND	ND

(E) Nab-paclitaxel and palonosetron hydrochloride

Storage period (h)	0	1	2	4	8	24
pH values *	5.38 ± 0.01	5.38 ± 0.01	5.39 ± 0.01	5.40 ± 0.01	5.44 ± 0.01	5.46 ± 0.01
Color and appearance	white turbidity	NC	NC	NC	NC	NC
Precipitation	ND	ND	ND	ND	ND	ND

(F) Nab-paclitaxel, dexamethasone sodium phosphate and granisetron hydrochloride

Storage period (h)	0	1	2	4	8	24
pH values *	6.90 ± 0.01	6.91 ± 0.01	6.92 ± 0.01	6.93 ± 0.01	6.94 ± 0.01	6.96 ± 0.01
Color and appearance	white turbidity	NC	NC	NC	NC	NC
Precipitation	ND	ND	ND	ND	ND	ND

(G) Nab-paclitaxel, dexamethasone sodium phosphate and palonosetron hydrochloride

Storage period (h)	0	1	2	4	8	24
pH values *	6.22 ± 0.01	6.23 ± 0.01	6.24 ± 0.01	6.23 ± 0.01	6.26 ± 0.01	6.31 ± 0.01
Color and appearance	white turbidity	NC	NC	NC	NC	NC
Precipitation	ND	ND	ND	ND	ND	ND

*mean ± SD; n = 5, NC : no change, ND : not detected

Chemical stability

The retention time of nab-paclitaxel under each condition was 14.48 ± 0.01 and 16.54 ± 0.02 min. The retention times of the anticancer drugs and antiemetic drugs under the respective conditions were 3.00 ± 0.05 min for gemcitabine hydrochloride, 3.04 ± 0.02 min for carboplatin, 15.42 ± 0.03 min for dexamethasone sodium phosphate, 9.01 ± 0.02 min for granisetron hydrochloride, and 9.78 ± 0.01 min for palonosetron hydrochloride (Tables III-1, III-2). The drugs showed good linearity in the concentration range of 0.5-2.5 μg/mL for paclitaxel, 1.0-5.0 μg/mL for gemcitabine hydrochloride, 0.25-1.0 μg/mL for carboplatin, 0.33-1.65 μg/mL for dexamethasone sodium phosphate, 0.125-0.5 μg/mL for granisetron hydrochloride, and 0.02-0.1 μg/mL for palonosetron hydrochloride (Tables III-1, III-2).

Table III-1.

HPLC conditions used for the analysis of paclitaxel and anticancer drugs.

	Paclitaxel	Gemcitabine hydrochloride	Carboplatin
Retention time (min)*	14.48 ± 0.01	2.84 ± 0.02	3.04 ± 0.02
Linear range (μg/mL)	0.5-2.5	1.0-5.0	0.25-1.0
Linear equation	y = 1334746x + 78683	y = 554644x + 6999.6	y = 309139x + 20313
Linearity (r^2)	0.9992	0.9996	0.9998

*mean ± SD, n = 5

Table III-2.

HPLC conditions used for the analysis of paclitaxel and antiemetic drugs.

	Paclitaxel	Dexamethasone sodium phosphate	Granisetron hydrochloride	Palonosetron hydrochloride
Retention time (min)*	16.54 ± 0.02	15.42 ± 0.03	9.01 ± 0.02	9.78 ± 0.01
Linear range (μg/mL)	0.5-2.5	0.33-1.65	0.125-0.5	0.02-0.1
Linear equation	y = 1482733x + 5714.1	y = 554644x + 6999.6	y = 1689598x - 8272.6	y = 1647486x - 472.09
Linearity (r^2)	0.9996	0.9996	0.9992	0.9999

*mean ± SD, n = 5

There was no significant difference in the concentrations of paclitaxel and other drugs for up to 24 h after mixing (Table IV). These results showed that each drug was stable when mixed with the drugs tested.

Table IV.

Drug concentrations (mean ± SD [μg/mL]; n = 5) of paclitaxel and other drugs.

Storage period (h)	0	8	24
Gemcitabine hydrochloride	4.19 ± 0.13 (100)	4.18 ± 0.10 (99.8 ± 4.2)	4.22 ± 0.19 (100.7 ± 4.9)
Paclitaxel	1.20 ± 0.02 (100)	1.21 ± 0.04 (100.8 ± 1.9)	1.20 ± 0.03 (100.0 ± 4.6)
Carboplatin	0.57 ± 0.01 (100)	0.57 ± 0.01 (99.8 ± 1.9)	0.56 ± 0.03 (98.6 ± 2.8)
Paclitaxel	1.15 ± 0.04 (100)	1.16 ± 0.02 (100.3 ± 4.7)	1.14 ± 0.04 (98.4 ± 3.7)
Dexamethasone sodium phosphate	1.13 ± 0.02 (100)	1.14 ± 0.02 (100.6 ± 2.0)	1.13 ± 0.01 (100.4 ± 1.3)
Paclitaxel	1.27 ± 0.04 (100)	1.30 ± 0.02 (102.0 ± 2.9)	1.29 ± 0.02 (101.8 ± 2.3)
Granisetron hydrochloride	0.34 ± 0.01 (100)	0.34 ± 0.01 (99.6 ± 3.3)	0.34 ± 0.01 (100.0 ± 3.0)
Paclitaxel	1.37 ± 0.01 (100)	1.38 ± 0.01 (100.4 ± 1.9)	1.37 ± 0.01 (100.0 ± 1.4)
Palonosetron hydrochloride	0.05 ± 0.01 (100)	0.05 ± 0.01 (100.7 ± 1.4)	0.05 ± 0.01 (100.8 ± 1.5)
Paclitaxel	1.37 ± 0.01 (100)	1.37 ± 0.03 (100.0 ± 2.0)	1.38 ± 0.02 (100.8 ± 1.2)
Dexamethasone sodium phosphate	1.12 ± 0.02 (100)	1.12 ± 0.01 (100.6 ± 1.8)	1.12 ± 0.01 (100.4 ± 2.3)
Granisetron hydrochloride	0.33 ± 0.01 (100)	0.34 ± 0.01 (100.4 ± 3.0)	0.34 ± 0.01 (101.0 ± 2.0)
Paclitaxel	1.28 ± 0.01 (100)	1.29 ± 0.03 (101.0 ± 2.4)	1.29 ± 0.02 (101.2 ± 1.4)
Dexamethasone sodium phosphate	1.13 ± 0.01 (100)	1.14 ± 0.02 (100.4 ± 2.2)	1.14 ± 0.02 (100.8 ± 1.8)
Palonosetron hydrochloride	0.05 ± 0.01 (100)	0.05 ± 0.01 (100.9 ± 0.9)	0.05 ± 0.01 (101.7 ± 1.4)
Paclitaxel	1.32 ± 0.02 (100)	1.33 ± 0.02 (100.5 ± 1.1)	1.34 ± 0.04 (101.5 ± 1.3)

The numbers in parentheses are indicated as a percentage (0 h) of the concentration of the initial sample (mean ± SD [%]; n = 5).

The chromatograms of the mixed solution of paclitaxel and other drugs at room temperature are shown in Figures 1-1 to 1-7. There were no additional peaks in the chromatograms at 8 and 24 h, compared to that at 0 h, except for the mixture containing dexamethasone sodium phosphate. These results showed that undesirable compounds such as degradation products were not present in the mixture and indicated that the concentrations of these drugs were not changed for up to 24 h after mixing. In contrast, the solution containing dexamethasone sodium phosphate showed a new peak in the chromatogram at 24 h (Figure 1-3, -6, and -7).

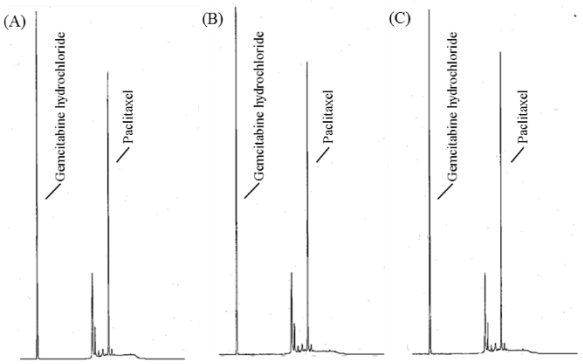

Figure.1-1 Chromatogram of paclitaxel and gemcitabine hydrochloride
(A) 0 h (B) 8 h (C) 24 h

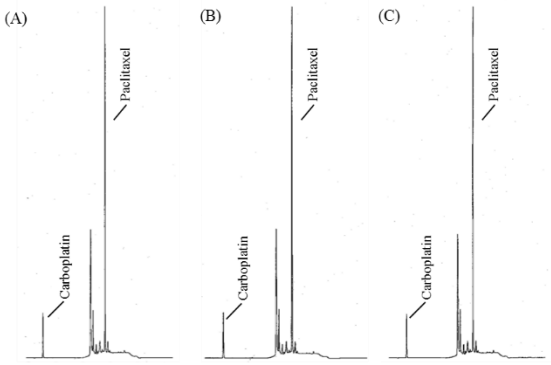

Figure.1-2 Chromatogram of paclitaxel and carboplatin
(A) 0 h (B) 8 h (C) 24 h

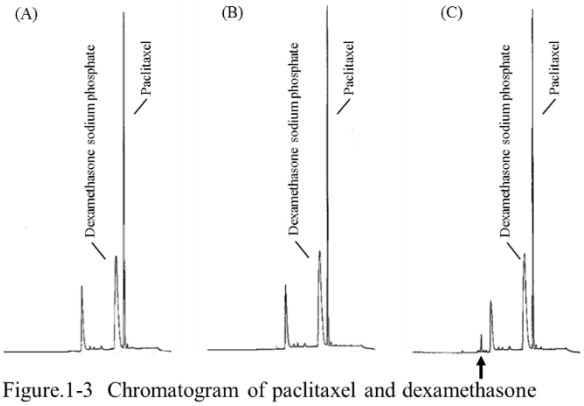

Figure.1-3 Chromatogram of paclitaxel and dexamethasone sodium phosphate
(A) 0 h (B) 8 h (C) 24 h
The arrow shows a newly appearing peak.

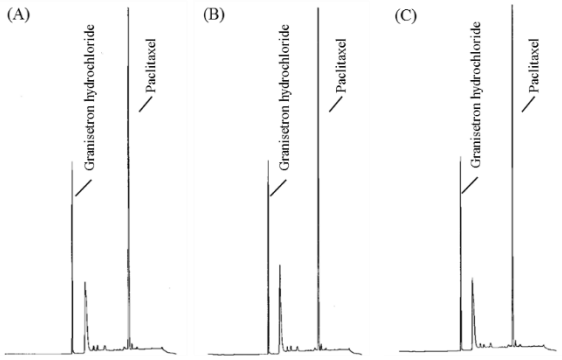

Figure.1-4 Chromatogram of paclitaxel and granisetron hydrochloride
(A) 0 h (B) 8 h (C) 24 h

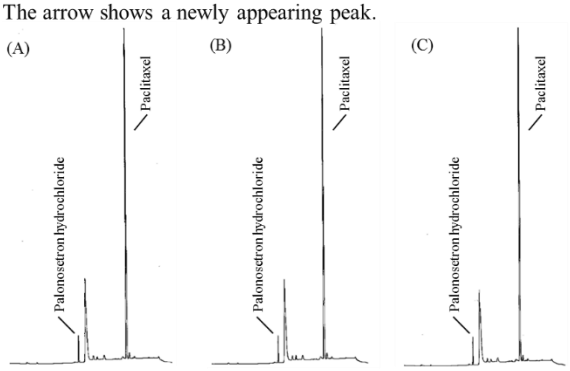

Figure.1-5 Chromatogram of paclitaxel and palonosetron hydrochloride
(A) 0 h (B) 8 h (C) 24 h

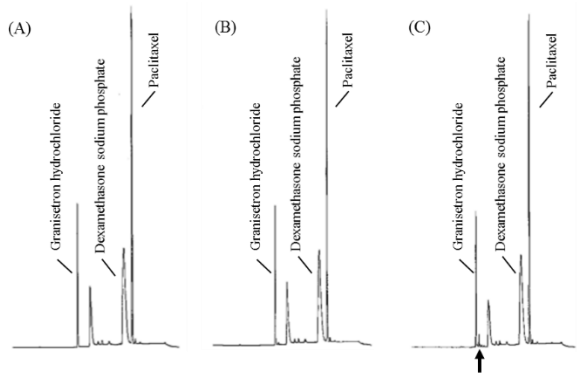

Figure.1-6 Chromatogram of paclitaxel, dexamethasone sodium phosphate and granisetron hydrochloride
(A) 0 h (B) 8 h (C) 24 h
The arrow shows a newly appearing peak.

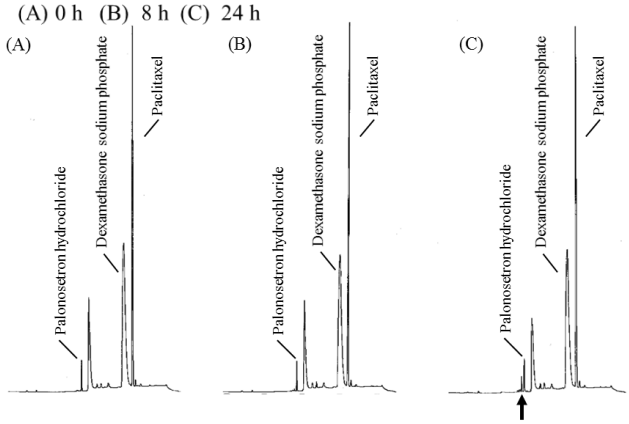

Figure.1-7 Chromatogram of paclitaxel, dexamethasone sodium phosphate and palonosetron hydrochloride
(A) 0 h (B) 8 h (C) 24 h
The arrow shows a newly appearing peak.

DISCUSSION

Due to concerns of instability when administered with other drugs, either concurrently or sequentially, nab-paclitaxel is administered separately by flushing the infusion tube with 0.9% sodium chloride before and after administering the other drugs [17]. This leads to prolongation of administration time and burden on medical staff. We evaluated the compatibility and stability of solutions containing nab-paclitaxel and other drugs that may be used in combination.

In this study, the appearance, pH, and concentrations of all the mixed solution did not change for up to 24 h after mixing, which suggests that nab-paclitaxel was compatible with each drug tested and stable in the mixture. (Table II, IV, Figure 1) The results of this study suggest that the combinations of nab-paclitaxel with anticancer and antiemetic drugs at room temperature were compatible.

An additional peak was, however, detected in the mixture containing dexamethasone sodium phosphate at 24 h (Figures 1-3, 6, and 7) with no decrease in dexamethasone sodium phosphate concentration. No new peak appeared for Dexart® alone. The results suggest that the newly detected peak might have been caused from the additive in the Dexart®. No additional peak was observed up to 8 h. A large-scale study is necessary to investigate whether the newly generated compound is safe for patients. Moreover, further studies are needed to investigate whether the same peak would be detected when original or generic medicines other than Dexart® are used. In addition, it is necessary to study whether the same peak would be detected in cases in which the mixtures are stored under cold conditions. Chemical stability, biological stability, and bioavailability can be affected by a combination of two or more drugs. The pharmacological action of individual drugs can also be influenced by polypharmacy. Measuring drug concentrations in model organisms to test whether the combination affects the anticancer effect of paclitaxel is a viable and useful method. Further study is needed to characterize the effect of combined drug use on biological stability, bioavailability, and pharmacological action.

The results of this study suggest that the combinations of nab-paclitaxel with anticancer and antiemetic drugs at room temperature were compatible for up to 8 h. Clinicians can therefore use these drugs as mixtures stored at room temperature or via sequential administration without flushing the infusion system between each drug administration. It is necessary, however, to observe patients for toxicities when nab-paclitaxel and other drugs are administered concurrently or sequentially. Treatment with nab-paclitaxel is mainly performed on an outpatient basis; simplification of the administration method would shorten the administration time as well as the patient's restraint time. The ability to co-administer drugs without interim flushing simplifies the work of medical staff, reduces the burden, and eliminates the administration of unnecessary 0.9% sodium chloride.

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