Compatibility of dexamethasone sodium phosphate with 5-HT_3 receptor antagonists in infusion solutions: a comprehensive study

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ABSTRACT

Objectives Patients can benefit from the coadministration of several medications because of the shorter infusion time and more rapid administration. The use of extemporaneously prepared admixtures of dexamethasone sodium phosphate (DSP) and 5-HT_3 receptor antagonists (5-HT3RAs) must be supported by sufficient documentation of their compatibility. The objective of this study was to comprehensively investigate the compatibility of DSP with 5-HT3RAs in infusion solutions.

Methods Admixtures of DSP with six different 5-HT3RAs (ondansetron hydrochloride, tropisetron hydrochloride, dolasetron mesylate, azasetron hydrochloride, palonosetron hydrochloride and ramosetron hydrochloride) were prepared in non-polyvinyl chloride (non-PVC) infusion bags filled with 5% glucose or 0.9% NaCl. Bags were stored at ambient temperature (25±2°C) without protection from light. Samples were taken immediately after preparation (0 hour) and at predetermined intervals (12, 24 and 48 hours after preparation). Particulate matter of admixtures was inspected visually and particles were counted with a particle counter. The pH of each sample was also determined. Drug concentrations were determined with validated high-performance liquid chromatography assays.

Results No visible haze or particulate formation, colour change or gas evolution and no notable changes in pH were observed, and particulate matter was acceptable up to 48 hours. All preparations maintained more than 90.0% of the initial concentration over the study period.

Conclusions All the admixtures of DSP and the 5-HT3RAs studied were compatible and stable for at least 48 hours in a 5% glucose injection or a 0.9% NaCl injection stored in non-PVC infusion bags under ambient conditions.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is one of the greatest problems for patients with cancer receiving treatment.[1] Adequately controlled CINV can improve their functional activity and quality of life, decrease their use of healthcare resources, and enhance their adherence to treatment.[1] 5-HT_3 receptor antagonists (5-HT3RAs) offer potent antiemetic effects by binding and inhibiting the 5-HT_3 receptor.[1–3] 5-HT3RAs approved in America, Europe, Japan and China among other countries include granisetron hydrochloride, ondansetron hydrochloride, tropisetron hydrochloride, dolasetron mesylate, azasetron hydrochloride, palonosetron hydrochloride and ramosetron hydrochloride.[1–4] Corticosteroids, another kind of effective antiemetic agent, are always used in combination with 5-HT3RAs.[1–3]

A number of large clinical trials have established that coadministration of dexamethasone sodium phosphate (DSP) and 5-HT3RAs improves the management of CINV.[1–5] For instance, DSP with ondansetron hydrochloride is more efficacious than ondansetron hydrochloride monotherapy in protecting patients from cisplatin-induced nausea and vomiting.[5] DSP combined with granisetron hydrochloride has been found to be effective for the prevention of vomiting induced by moderately emetogenic chemotherapy.[6] Furthermore, the regimen of 5-HT3RAs plus DSP is recommended for CINV by the European Society of Medical Oncology (ESMO), the Multinational Association of Supportive Care in Cancer (MASCC) and the National Comprehensive Cancer Network (NCCN).[2 7]

Patients can benefit from the coadministration of several medications because of the shorter infusion time and more rapid administration. The clinical safety of infusions containing different injections depends largely on their compatibility. Although there have been several reports on the compatibility of DSP with 5-HT3RAs in infusion solutions,[8] the available evidence is not yet conclusive. Up to now, the compatibility of DSP with tropisetron hydrochloride, dolasetron mesylate, azasetron hydrochloride and ramosetron hydrochloride has not been reported. The purpose of this study was to assess the compatibility of DSP with common 5-HT3RAs in infusion bags under ambient conditions.

METHODS

Materials

All formulations were obtained commercially in China (table 1). The infusion bags filled with 5% glucose or 0.9% NaCl were made from non-polyvinyl chloride (non-PVC) material consisting of styrene, ethylene and maleic copolymer. Reference standards (chemical purity >99.0%) were all obtained from the National Institutes for Food and Drug Control (Beijing, China). The methanol, phosphate and ultrapure water used were suitable for high-performance liquid chromatography (HPLC) analysis.

The 5-HT3RAs infusions, ondansetron hydrochloride, dolasetron mesylate, palonosetron

Table 1 Drugs studied for compatibility of dexamethasone sodium phosphate with 5-HT_3 receptor antagonists

Drug	Formulation	Specification	Excipient	Manufacturer	Lot number
Dexamethasone sodium phosphate	Powder for injection	5 mg	Mannitol, water for injection	BBCA Pharmaceutical Co (Anhui, China)	150130-1
Ondansetron hydrochloride	Injection	8 mg/4 mL	Citric acid, sodium citrate, NaCl	Ningbo Team Pharmaceutical Co (Zhejiang, China)	140294A02
Tropisetron hydrochloride	Infusion	5 mg/100 mL	NaCl, HCl	Qilu Pharmaceutical Co (Shangdong, China)	3C14111803
Dolasetron mesylate	Injection	12.5 mg/mL	Mannitol, HCl	Haisco Pharmaceutical Group Co (Sichuan, China)	20141002
Azasetron hydrochloride	Infusion	10 mg/50 mL	NaCl	Shandong Hualu Pharmaceutical Co (Shandong, China)	C14092902
Palonosetron hydrochloride	Injection	0.25 mg/5 mL	NaCl, citric acid, sodium citrate, sodium calcium edetate	Hangzhou Jiuyuan Gene Engineering Co (Zhejiang, China)	20150102
Ramosetron hydrochloride	Powder for injection	0.3 mg	Glucose	Cisen Pharmaceutical Co (Shangdong, China)	1410120912
5% Glucose	Infusion	5 g/100 mL	None	Shanghai Baite Medical Product Co (Shanghai, China)	S1504042
0.9% NaCl	Infusion	0.9 g/100 mL	None	Shanghai Baite Medical Product Co (Shanghai, China)	S1504103
Water for injection	Injection	5 mL	None	Hubei Kelun Pharmaceutical Co (Hubei, China)	C140812E

Table 2 Admixture of dexamethasone sodium phosphate (DSP) with selected 5-HT_3 receptor antagonists (5-HT3RAs)

			Nominal concentration (μg/mL)	
Code of admixtures	5-HT3RA	Solvent	DSP	5-HT3RAs
A	Ondansetron hydrochloride	5% glucose	100.0	80.0
B	Ondansetron hydrochloride	5% glucose	200.0	80.0
C	Ondansetron hydrochloride	0.9% NaCl	100.0	80.0
D	Ondansetron hydrochloride	0.9% NaCl	200.0	80.0
E	Tropisetron hydrochloride and 0.9% NaCl	None	100.0	50.0
F	Tropisetron hydrochloride and 0.9% NaCl	None	200.0	50.0
G	Dolasetron mesylate	5% glucose	100.0	1000.0
H	Dolasetron mesylate	5% glucose	200.0	1000.0
I	Dolasetron mesylate	0.9% NaCl	100.0	1000.0
J	Dolasetron mesylate	0.9% NaCl	200.0	1000.0
K	Azasetron hydrochloride and 0.9% NaCl	None	100.0	200.0
L	Azasetron hydrochloride and 0.9% NaCl	None	200.0	200.0
M	Palonosetron hydrochloride	5% glucose	100.0	2.5
N	Palonosetron hydrochloride	5% glucose	200.0	2.5
O	Palonosetron hydrochloride	0.9% NaCl	100.0	2.5
P	Palonosetron hydrochloride	0.9% NaCl	200.0	2.5
Q	Ramosetron hydrochloride	5% glucose	100.0	3.0
R	Ramosetron hydrochloride	5% glucose	200.0	3.0
S	Ramosetron hydrochloride	0.9% NaCl	100.0	3.0
T	Ramosetron hydrochloride	0.9% NaCl	200.0	3.0

hydrochloride, ramosetron hydrochloride, were prepared by transferring the injections to 100 mL 5% glucose or 0.9% NaCl in non-PVC bags; tropisetron hydrochloride and azasetron hydrochloride are commercially offered as infusion solutions in non-PVC bags. The appropriate amount of DSP, prepared for injection by dissolving powder in water, was then added to each 5-HT3RA infusion. Finally, admixtures of DSP and each 5-HT3RA were prepared. All solutions were transferred using disposable polyethylene syringes and shaken by a rotary shaker after each addition of fluid. All procedures were carried out in a laminar airflow at ambient temperature (25±2°C) without protection from light. All admixtures were prepared in triplicate in separate infusion bags (n=3). In each case, the final nominal concentrations of DSP and 5-HT3RAs corresponded to those used in daily medical practice (table 2). Admixtures were stored at ambient temperature (25±2°C) without protection from light. Samples were collected immediately after preparation (0 hour) and at predetermined intervals (12, 24 and 48 hours after preparation).

Physical and chemical analysis

The physical properties of the above samples were visually inspected for particles, discoloration and bubbles against ambient light and dark backgrounds at each test time point. Particulate matter was counted with a particle counter (GWF-8JA particle detector; Tianjin Tianhe Analytical Instrument Co, Tianjin,

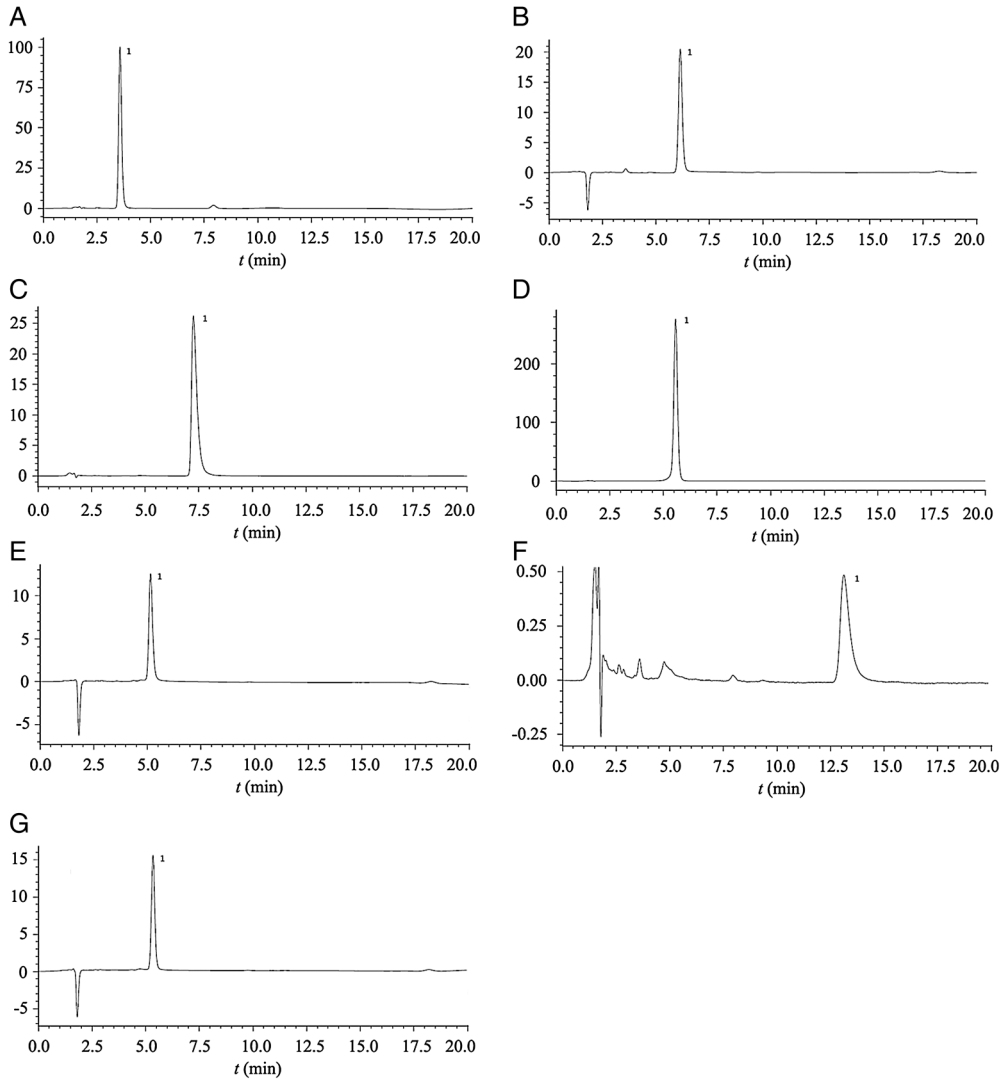

Figure 1 Chromatograms. (A) Dexamethasone sodium phosphate; (B) ondansetron hydrochloride; (C) tropisetron hydrochloride; (D) dolasetron mesylate; (E) azasetron hydrochloride; (F) palonosetron hydrochloride; (G) ramosetron hydrochloride. Peak 1 represents the correspondent component. The retention time was 3.6, 6.1, 7.3, 5.6, 5.2, 13.1 and 5.3 min, respectively.

China). In addition, the pH of each sample was determined with a pH meter (Seveneasy S20 pH Meter; Mettler Toledo (Shanghai) Co, Shanghai, China). The concentrations of DSP and 5-HT3RAs were determined using seven validated HPLC assays described below, which were based on previous studies with slight modification.[9 10] The initial concentration of DSP and 5-HT3RAs was defined as 100%, and subsequent sample concentrations were expressed as a percentage of the initial concentration. Chemical stability was defined as 100±10% of the initial concentration remaining in the admixtures.

HPLC analysis was carried out using a Shimadzu HPLC system (Kyoto, Japan) composed of a DGU-20A5R degasser, an LC-16 quaternary gradient pump, an SIL-16 autosampler, a CTO-10A column temperature oven, and an SPD-16UV detector. The column was an Intersil ODS-3 C_{18} column (4.6 mm×150 mm, 5 µm) (Shimadzu, Japan) fitted with a guard column. Samples were injected into an autosampler and isocratically eluted with a solvent system containing solvent A (10 mM phosphate aqueous solution, pH 7.4) and solvent B (methanol) at a ratio of 40/60 (v/v) at a flow rate of 1.0 mL/min. The detection wavelength was 240 nm. The data were processed using LC solution V.1.21 software from Shimadzu.

The HPLC methods all provided good baseline separation of DSP and each 5-HT3RA (figure 1), revealing them to be highly specific for the drugs studied. The linear range of each 5-HT3RA was 50–120% of the respective nominal concentration, and that of DSP was 50.0–250.0 ng/mL. The methods were highly linear, with the correlation coefficient (R^2) always exceeding 0.999 over the linear range. Quality control (QC) samples were set at low QC (150% lower limit of linear ranges), median QC (nominal concentration of each drug in admixtures) and high QC (80% higher limit of linear ranges) (n=6). The accuracy was expressed as QC recovery. The accuracies of DSP and 5-HT3RA determinations were all within 100.0±3.0% of the nominal concentration. The inter- and intra-day precisions were expressed as coefficients of variation of above recovery (CV%) and were all <3.0%. The QC samples were stored at ambient temperature for 48 hours, and the final recoveries were all within 100.0±3.0%. The validation studies confirmed the accuracy, precision and stability of the methods to be high, making them suitable for study of the chemical stability of admixtures of DSP with 5-HT3RAs.

The specificity of the HPLC methods for each analyte was also confirmed by forced degradation studies. QC samples of

Table 3 pH values of admixtures

Admixture code*	Storage time (hours) 0	48
A	4.7±0.0	4.6±0.0
B	5.8±0.0	5.7±0.0
C	5.3±0.0	5.2±0.0
D	5.9±0.1	5.8±0.0
E	6.8±0.1	6.6±0.1
F	6.9±0.0	6.8±0.0
G	4.8±0.0	4.7±0.0
H	5.1±0.0	5.1±0.0
I	5.0±0.0	5.0±0.0
J	5.4±0.0	5.4±0.0
K	3.9±0.0	3.7±0.0
L	5.0±0.0	4.6±0.0
M	5.5±0.1	5.5±0.0
N	6.3±0.0	6.3±0.0
O	6.1±0.0	6.1±0.0
P	6.4±0.0	6.4±0.0
Q	6.2±0.0	6.1±0.0
R	6.7±0.0	6.6±0.0
S	6.9±0.0	6.8±0.0
T	7.1±0.0	7.0±0.0

Results are expressed as mean±SD (n=3).
*Codes of admixtures are noted in table 2.

Table 4 Chemical stability of dexamethasone sodium phosphate (DSP) with different 5-HT_3 receptor antagonists (5-HT3RAs) in infusion solutions

Admixture code*	Initial concentration (μg/mL) DSP	5-HT3RA	% of initial concentration remaining after 48 hours DSP	5-HT3RA
A	91.8±1.0	74.5±0.9	101.2±0.1	101.5±0.2
B	181.3±2.1	72.2±0.8	101.2±0.1	101.4±0.2
C	92.7±1.1	74.5±0.9	101.6±0.2	99.9±0.1
D	179.6±1.8	72.4±0.5	99.1±0.1	99.9±0.1
E	99.1±0.4	50.5±0.5	99.2±0.1	99.3±0.2
F	198.3±2.2	50.1±0.4	100.5±0	99.0±0.4
G	91.4±1.2	924.6±8.5	99.6±0.8	99.7±1.0
H	185.1±1.1	918.1±7.9	100.0±0.6	98.8±0.3
I	91.2±0.9	916.6±10.1	99.1±0.7	99.0±0.5
J	188.2±1.5	934.6±10.6	98.8±0.5	99.1±0.7
K	98.9±0.5	198.7±2.6	97.5±0.5	99.3±0.4
L	197.7±2.4	197.9±2.3	97.4±0.4	99.7±0.4
M	90.2±2.1	2.3±0.1	98.9±0.9	100.1±0.3
N	181.4±2.9	2.2±0.1	99.5±1.2	99.8±0.3
O	90.8±1.3	2.3±0.0	98.7±1.2	99.2±1.0
P	182.1±2.6	2.3±0.1	99.1±1.6	99.4±1.1
Q	88.5±0.9	2.7±0.1	99.3±1.0	100.2±0
R	183.1±1.5	2.7±0.1	98.3±0.9	99.5±0
S	91.3±0.8	2.8±0.0	98.6±0.3	100.2±0.5
T	180.2±2.4	2.7±0.1	101.6±0.3	100.7±0

Results are expressed as mean±SD (n=3).
*Codes of admixtures are noted in table 2.

each analyte were degraded at 60°C for 5 hours with 0.1 M HCl, 0.1 M NaOH and 3% H_2O_2, respectively. Degradation samples were analysed using the above HPLC methods. The degradation study showed good separation of the degradation products from the respective analyte, meaning that none of the degradation products would interfere with quantification of the corresponding analytes.

RESULTS

Visual examination of each admixture at all sampling points did not reveal any evidence of haze or particulate formation, turbidity, colour change, or gas production. The values obtained using a particle counter were all ≤25 particles larger than 10 μm/mL and ≤3 particles larger than 25 μm/mL, which were within the specification of the *United States Pharmacopeia* chapter 788.[11] The pH values of admixtures prepared with 0.9% NaCl were 0–0.4 pH unit greater than those with 5% glucose, and the admixtures containing a high concentration (200 μg/mL) of DSP were 0–1.2 pH unit greater than those containing a low concentration (100.0 μg/mL) of DSP. pH changes in all admixtures were <0.2 pH unit (table 3).

The chemical stability of DSP with 5-HT3RAs in infusion solutions is shown in table 4 and online supplementary material after storage at ambient temperature. Throughout the 48 hour storage period, the initial concentrations of the analytes all remained at 100.0%±10.0%. No abnormal peaks were observed on chromatography of each admixture during the study period.

DISCUSSION

In this comprehensive study on the compatibility of DSP with six different 5-HT3RAs in infusion solutions, no evidence of incompatibility was observed. Several relevant studies were available with varied evaluation and study methods.[8–10 12–18] As the compatibility of DSP with granisetron hydrochloride has already been reported and verified by several studies,[9 12 13] we did not include it in our study. PVC or unknown bags were used in studies of compatibility of DSP with other 5-HT3RAs in infusion solutions.[10 12–18] Our study demonstrated the compatibility of DSP with palonosetron hydrochloride, which is consistent with the report of Trissel and Zhang.[14] The compatibility of DSP with ondansetron hydrochloride was also investigated by Evrard *et al*,[10 15 16] but pH values and drug concentrations were not determined in some of these studies.[15 16] The compatibility of fosaprepitant with intravenous 5-HT3RAs (ondansetron, granisetron, palonosetron and tropisetron) and corticosteroids (DSP or methylprednisolone sodium succinate) was studied by Sun *et al*,[17] but the chemical stability of 5-HT3RAs and corticosteroids was not investigated except for fosaprepitant. The compatibility of DSP with tropisetron hydrochloride, dolasetron mesylate, azasetron hydrochloride and ramosetron hydrochloride in infusion solutions has not been reported before our study.

Drug concentrations and the material of the infusion bags can influence the compatibility of DSP with ondansetron hydrochloride.[10 18] Admixture of DSP (67 μg/mL) with ondansetron hydrochloride (1.07 mg/mL) was incompatible after 3 days in a syringe.[10] In our study, the concentrations of admixtures (ondansetron hydrochloride 80.0 μg/mL, DSP 100.0 μg/mL or 200.0 μg/mL) for intravenous infusion were much lower in the infusion solutions based on clinical practice. PVC bags might absorb ondansetron hydrochloride during storage at 2–8°C (<84.7% remaining) or 15–25°C (<88.2% remaining) filled with 5% glucose.[18] Our results show that non-PVC bags do not

absorb ondansetron hydrochloride (98.6–103.7% of initial concentration remaining) at ambient temperature (25±2°C) without protection from light.

Although our study supports the compatibility and stability of DSP with 5-HT3RAs in infusion solutions, there are several limitations to the study. First, the sterility of these admixtures was not tested. According to the *United States Pharmacopeia* chapter 797 guidelines, low-risk compounded sterile products are permissible within a maximum-use period of 48 hours for non-refrigerated samples.[19] Second, the investigated duration in other reports was much longer than the 48 hours used in our study.[12 17] However, infusions are always used immediately after preparation, so our research may provide valuable evidence on compatibility of DSP with 5-HT3RAs in infusion solutions.

CONCLUSION

All the admixtures of DSP with 5-HT3RAs were compatible and stable for at least 48 hours in non-PVC infusion bags using 5% glucose or 0.9% NaCl as diluent under ambient conditions.

Key messages

What is already known on this subject?

- There have been several reports on the compatibility of dexamethasone sodium phosphate (DSP) with 5-HT_3 receptor antagonists (5-HT3RAs) in infusion solutions, but the available evidence is not yet conclusive.
- The use of extemporaneously prepared admixtures of DSP with 5-HT3RAs must be supported by sufficient documentation of their compatibility.

What this study adds?

- This study provides valuable evidence on the compatibility of dexamethasone sodium phosphate with 5-HT_3 receptor antagonists in infusion solutions.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data from our study are included.

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