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Determination of Compatibility of Fosaprepitant Dimeglumine and Magnesium Sulfate Injections by High-Performance Liquid Chromatography

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Abstract Fosaprepitant dimeglumine relieves nausea and vomiting caused by highly emetogenic chemotherapy agents such as high-dose cisplatin. Magnesium has renoprotective effects against cisplatin-induced damage. Thus, both drugs are sometimes used concomitantly, but administering them together intravenously may cause occlusion of the in-line filter. We aimed to clarify the extent to which the delivery of intravenous fosaprepitant dimeglumine is reduced by magnesium sulfate. Fosaprepitant dimeglumine was combined with magnesium sulfate and then filtered. Two ratios and concentrations of magnesium sulfate were tested (1:1 and 7:3 corresponding to 1.5 mg/mL fosaprepitant dimeglumine solution to 3.85% and 0.99% magnesium sulfate solution (v/v), respectively). The concentration of fosaprepitant dimeglumine in the filtrates was measured via high-performance liquid chromatography to determine the rate of decline in fosaprepitant dimeglumine. These experiments were performed in triplicate. When the ratio of fosaprepitant dimeglumine to magnesium sulfate was 1:1, the maximum rate of decline for fosaprepitant dimeglumine was 38.67%. At a ratio of 7:3, the maximum rate of decline was 7.62%. Fosaprepitant dimeglumine likely reacted with magnesium sulfate, which might inhibit the efficacy of fosaprepitant. To prevent this, we recommend flushing the in-line filter with 50 mL of normal saline before and after the administration of fosaprepitant dimeglumine.

Key words: fosaprepitant dimeglumine, magnesium sulfate, drug compounding, high-performance liquid chromatography, infrared spectroscopy

Introduction

There are many approved drugs, and medication treatment options are increasing. As a result, patients are receiving better medical care. However, the efficacy of some drugs has not been demonstrated, and studies on databases have revealed reports of drug incompatibilities.[1,2] It is important to consider drug compatibility when using injectable medications. This is an area where pharmacists can fully demonstrate their ability.[3]

In order to improve the quality of drug treatment at Yamaguchi University Hospital, pharmacists confirm drug compatibilities at patient's bedside. Fosaprepitant dimeglumine is a drug that relieves nausea and vomiting caused by highly emetogenic cancer chemotherapy such as high-dose cisplatin. Magnesium is useful for protection against cisplatin-induced renal damage.[4,5] Thus, both drugs are often administered concomitantly

via the same route to shorten the drip time, which can result in the phosphate group of fosaprepitant dimeglumine to chemically react with magnesium.

In the present study, we examined to what extent the amount of fosaprepitant dimeglumine delivered decreases when mixed with magnesium sulfate. High-performance liquid chromatography (HPLC) was used for verification. Further, infrared (IR) spectroscopy was used to identify the cloudy solution.

Materials and Methods

Patient Selection

We utilized the electronic medical records of Yamaguchi University Hospital to determine the number and setting of patients who received anticancer drug treatments that contained fosaprepitant dimeglumine as an antiemetic and magnesium as a renoprotective agent from January 2016 to December 2016. Also, our hospital has a report system to our pharmacy regarding route trouble including occlusion of the intravenous in-line filters so that we utilized the records to confirm the number of in-line filter occlusion. Approval was obtained from the Yamaguchi University Hospital Institutional Review Board (approval number: H29-209). This study was conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labour and Welfare, Japan.

Reagents and Materials

We purchased 85 wt% HPLC-grade phosphoric acid solution, HPLC-grade water, and HPLC-grade acetonitrile from Kanto Chemical Co., Inc. Fosaprepitant dimeglumine (Proemend®) was purchased from Ono Pharmaceutical Co., Ltd. (Note that the trade name Proemend® in Japan corresponds to Emend® in the United States). Magnesium sulfate was purchased as magnesium sulfate corrective injection 1 mEq/mL from Otsuka Pharmaceutical Factory, Inc. The infusion pump adopted at our hospital was manufactured by the Terumo Corporation, and the catheter was supplied by the Covidien Corporation.

Furthermore, because a standard reagent of fosaprepitant dimeglumine was not commercially available when this study was conducted, a calibration curve was established using Proemend® according to validation of analytical procedures of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Apparatus

This study was conducted using the apparatus of Yamaguchi Prefecture Industrial Technology Institute. The precision of apparatus was properly controlled and validated according to the Japanese Pharmacopoeia.

A Shimadzu Prominence series was used for HPLC. The SPD-20A UV-Vis detector was set at 215 nm. The CTO-20AC column oven was set at 20 ℃, and the sample injection amount for the SIL-20AC autosampler was set at 10 μL. An LC-20AT was used as the gradient pump. Shimadzu LabSolutions was used for data analysis.

JASCO Corporation FT/IR-6300 was used for IR spectroscopy.

Chromatographic Conditions

A Phenomenex Luna 5u C18(2) 100A HPLC column (250 mm × 4.6 mm i.d., 5 μm particles) was used for the separation of fosaprepitant dimeglumine. A 0.1% v/v aqueous phosphoric acid solution (Solvent A) and HPLC-grade acetonitrile (Solvent B) were used for the mobile phase. Gradient elution was performed according to the method described by Peter.[6] However, the pressure limitations of our instrument forced us to maintain the flow rate at 1.0 mL/min for all experiments. The ratio of Solvent A to Solvent B (v/v) was initially 75:25. That ratio decreased to 55:45 at 10.5 min and 10:90 at 25.5 min, after which the ratio was maintained at 10:90 for 4.5 min and then raised to 75:25 for 10 min to re-equilibrate (Fig. 1). The reproducibility of the assay was confirmed.

Sample Preparation

Proemend® was diluted with normal saline to make five solutions of fosaprepitant dimeglumine: 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL, 1.2 mg/mL, and 1.5 mg/mL. Next, 50 μL of methyl *p*-hydroxybenzoate (20 μg/mL; diluted with acetonitrile for HPLC as

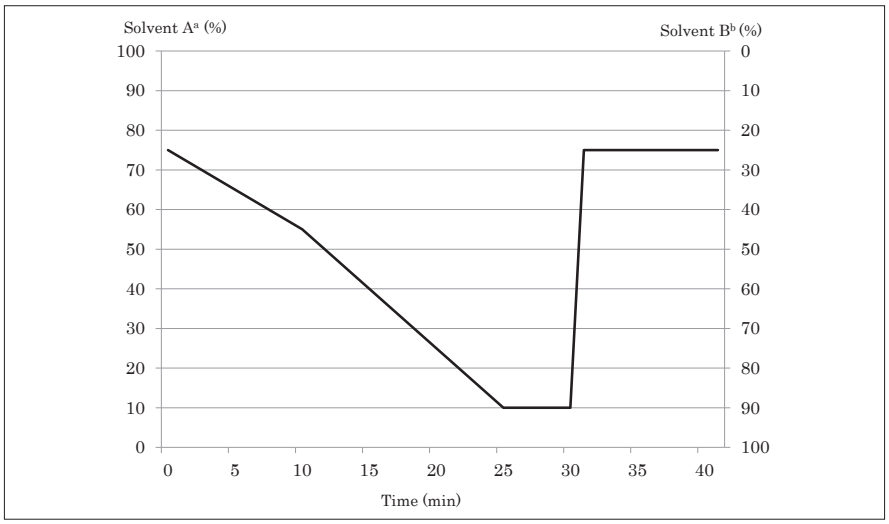

Fig. 1 Gradient elution.
[a] 0.1% v/v aqueous phosphoric acid
[b] HPLC-grade acetonitrile

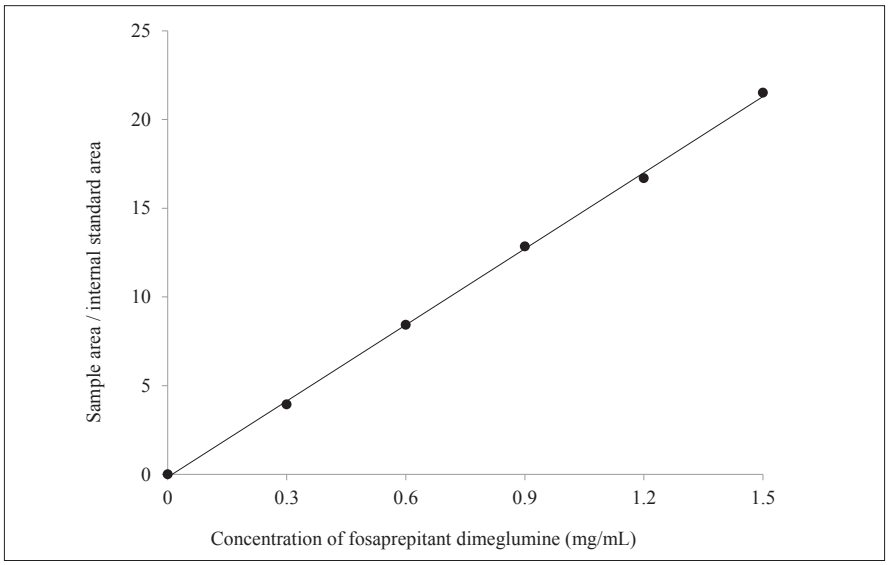

Fig. 2 Calibration curve of five fosaprepitant dimeglumine solutions: blank, 0.3, 0.6, 0.9, 1.2, and 1.5 mg/mL.[a]
[a] All values were calculated by dividing the fosaprepitant dimeglumine area by the substance area of the internal standard.

an internal standard) was added to 200 μL of each solution. The amount of fosaprepitant dimeglumine in each of the five solutions was measured and a calibration curve was established (Fig. 2).

Magnesium sulfate solutions were prepared and allowed to react with 1.5 mg/mL fosaprepitant dimeglumine, which was the most commonly used concentration in wards. For renoprotection, 3.85% (v/v) and 0.99% (v/v) magnesium sulfate solutions were used, which are the two most commonly used concentrations at Yamaguchi University Hospital. To prepare the 3.85% and 0.99% (v/v) magnesium sulfate solution, 20 mL of a 1 mEq/mL magnesium sulfate corrective injection solution was diluted in 500 mL and 2000 mL of normal saline, respectively. Regarding flow rates in

medical records, patients were administered 1.5 mg/mL fosaprepitant dimeglumine for 30 min (200 mL/h). In addition, a 3.85% (v/v) magnesium sulfate solution was administered to patients for 3 h (173.3 mL/h), and a 0.99% (v/v) magnesium sulfate solution was administered to patients for 24 h (84.2 mL/h). Both drugs were administered simultaneously using primary and secondary intravenous lines.

We also ensured that the concentration and the mixing ratio well reflected those used in clinical settings. Moreover, fosaprepitant dimeglumine was added to the magnesium sulfate solutions. In the first mixture, the ratio of 1.5 mg/mL fosaprepitant dimeglumine to 3.85% (v/v) magnesium sulfate was 1:1. In the second mixture, the ratio of 1.5 mg/mL fosaprepitant dimeglumine to 0.99% (v/v) magnesium sulfate was 7:3. For the control experiments, normal saline was substituted for magnesium sulfate to make 1:1 and 7:3 ratios of fosaprepitant dimeglumine to normal saline. Each fosaprepitant dimeglumine/magnesium sulfate solution was passed through a membrane filter (0.22 μm) that had nearly the same diameter as the Safe Access Infusion Set (Covidien Corporation) 0.2 μm in-line filter used at our hospital. After filtration, 200 μL of each solution was prepared as samples for HPLC analysis. We added 20 μg/mL of methyl *p*-hydroxybenzoate dissolved in acetonitrile (the internal standard) to 50 μL of each sample. Each experiment was performed in triplicate, with the exception of the control experiments, which were performed one time each.

A linear approximation curve ($y = 14.306x - 0.1613$) and correlation coefficient ($r = 0.9997$) were calculated from the blank and the calibration curve derived from the five concentrations of fosaprepitant dimeglumine. Theoretical values were obtained from the linear approximation curve. Control experiments were used to verify the accuracy of those theoretical values. Then, the changes in the measured area ratios were compared to theoretical values. For data processing purposes, the area ratios obtained by dividing the peak area of fosaprepitant dimeglumine by the peak area of methyl *p*-hydroxybenzoate were treated as measured values. The concentrations were obtained by substituting the area ratios into the calibration curve.

Further, 3.85% (v/v) magnesium sulfate solution was reacted with 1.5 mg/mL fosaprepitant dimeglumine, and the solution was passed through a membrane filter (0.22 μm). After filtration, the filter was disassembled and allowed to dry in order to recover the substance clogged in the pores, which were used as samples for IR spectroscopy.

Results

IR spectroscopy

The material clogged in the filter pores showed an IR spectral pattern different from that of fosaprepitant dimeglumine used in Japan (patent number 6305464) and showed an IR spectral pattern very similar to aprepitant used in the United States (patent number US9,227,958B2), which has a structure devoid of the phosphate group (Fig. 3).

Clinical Situation

The departments of dental oral surgery, otolaryngology, pediatrics, digestive surgery, and radiology at Yamaguchi University Hospital were the most likely to treat patients with cancer. We confirmed the anti-cancer regimens of each department, and found that from January 2016 to December 2016, 97 patients received anticancer drug treatments that utilized fosaprepitant dimeglumine and magnesium. Next, we examined cases in which fosaprepitant dimeglumine and diluted magnesium sulfate solution were administered simultaneously using primary and secondary intravenous lines. In two cases, confirmed by medical records, an infusion pump alarm went off because of occlusion of the intravenous in-line filters, leading to replacement of the administration lines. In both cases, 3.85% (v/v) magnesium sulfate solution diluted with normal saline was administered via the primary line, and 1.5 mg/mL fosaprepitant dimeglumine was administered via the secondary line. No other divalent cations such as calcium ion were used in both cases. Aprepitant, which is devoid of the phosphate group, clogged the in-line filters. Moreover, as a phosphate group was released, the buoyant crystal may be magnesium phosphate.

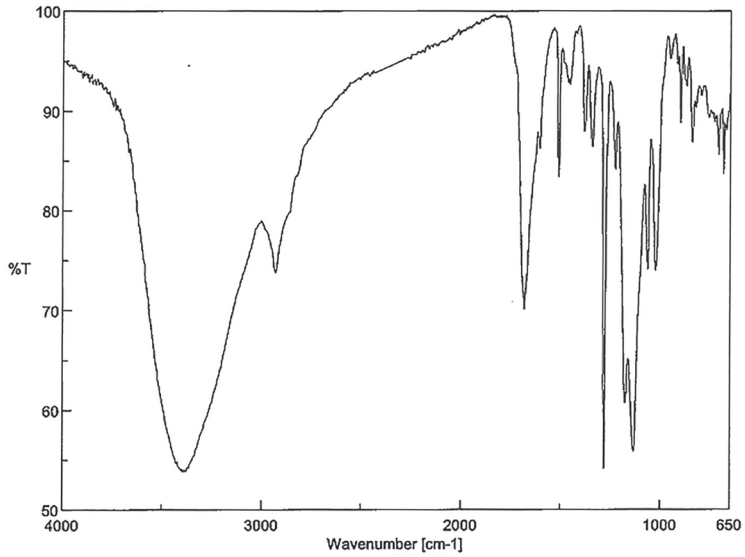

Fig. 3 Infrared spectral pattern of the mixture of fosaprepitant dimeglumine and magnesium sulfate.[a]
[a] 4000～2500 cm^{-1}: absorption band of bond with hydrogen atom, 2500～1300 cm^{-1}: multiple bond absorption band, 1300～650 cm^{-1}: fingerprint region.

Results of Decline Rate of Fosaprepitant Dimeglumine

The concentration of fosaprepitant dimeglumine after mixing with magnesium sulfate (3.85%, v/v) at 1:1 ratio was 0.75 mg/mL. By substituting 0.75 mg/mL for the x value in the linear approximation curve equation, we were able to calculate that the theoretical area ratio of the 1.5 mg/mL fosaprepitant dimeglumine / 3.85% (v/v) magnesium sulfate solution was 10.568. In comparison, the measured area ratios for the experimental and control samples were 6.458, 7.506, 7.572, and 10.371; the calculated concentrations substituted into the calibration curve were 0.46 mg/mL, 0.54 mg/mL, 0.55 mg/mL, and 0.74 mg/mL, respectively. The control sample had 98.7% concentration. The decline rates of experimental samples were 38.67%, 28.00%, and 26.67%, respectively (Table 1).

Similarly, the concentration of fosaprepitant dimeglumine after it was mixed with magnesium sulfate (0.99%, v/v) at 7:3 ratio was 1.05 mg/mL. By substituting 1.05 mg/mL for the x value in the above equation, we calculated the theoretical area ratio of the 1.5 mg/mL fosaprepitant dimeglumine/0.99% (v/v) magnesium sulfate solution to be 14.860.

Table 1 Rate of decline of fosaprepitant dimeglumine in 1:1 mixture

No.	Fosaprepitant dimeglumine conc. (mg/mL)	Sample area / i.s. area	Calculated conc. (mg/mL)	Rate of decline (%)
1	0.75	6.4581	0.46	38.67
2	0.75	7.5060	0.54	28.00
3	0.75	7.5721	0.55	26.67
Control	0.75	10.3706	0.74	1.33
Calibration curve	0.75	10.5682	0.75	

Rate of decline with respect to the theoretical value when 1.5 mg/mL fosaprepitant dimeglumine solution was mixed with 3.85% (v/v) magnesium sulfate solution at a ratio of 1:1.
Abbreviations: conc., concentrations; i.s., internal standard.

Table 2 Rate of decline of fosaprepitant dimeglumine in 7:3 mixture

No.	Fosaprepitant dimeglumine conc. (mg/mL)	Sample area / i.s. area	Calculated conc. (mg/mL)	Rate of decline (%)
1	1.05	13.6933	0.97	7.62
2	1.05	14.0916	1.00	4.76
3	1.05	14.6525	1.04	0.95
Control	1.05	14.9169	1.05	0.00
Calibration curve	1.05	14.8600	1.05	

Rate of decline with respect to the theoretical value when 1.5 mg/mL fosaprepitant dimeglumine solution was mixed with 0.99% (v/v) magnesium sulfate solution at a ratio of 7:3.
Abbreviations: conc., concentrations; i.s., internal standard.

In comparison, the measured area ratios of the experimental and control samples were 13.693, 14.092, 14.653, and 14.917; and 0.97 mg/mL, 1.00 mg/mL, 1.04 mg/mL, and 1.05 mg/mL, respectively. The control sample concentration was set as 100%. The concentration decline rates of experimental samples were 7.62%, 4.76%, and 0.95%, respectively (Table 2). Both the 1:1 and 7:3 mixtures of fosaprepitant dimeglumine/magnesium sulfate were cloudy and released buoyant substances as soon as the two drugs were mixed.

Discussion

Fosaprepitant dimeglumine is incompatible with many medications. In this study, when magnesium sulfate and fosaprepitant dimeglumine were mixed, a cloudy buoyant substance and magnesium phosphate crystals were released, which clogged in-line filters during drug delivery, probably leading to reduced drug titer and efficacy.

Although there were only two cases of confirmed in-line filter occlusion in the medical records at our hospital in 2016, it is possible that the filter was clogged in the other 95 cases, because all samples produced buoyant substances instantaneously when the two drugs were mixed. Clogging of the filter could cause the drip rate to drop. There may have been problems with membrane permeability; however, in our current study, the fosaprepitant dimeglumine concentration did not decrease in the absence of magnesium sulfate; that is, there was no problem with filter permeability. A point of note is that aprepitant did not pass through the filter and was the cause for filter clogging.

Moreover, magnesium phosphate was not identified by IR spectroscopy at this time point because FT/IR has good reactivity to organic substances. In order to identify inorganic substances such as magnesium phosphate, a scanning electron microscope energy dispersive X-ray spectrometer (SEM-EDX) or an electron probe X-ray micro analyzer (EPMA) is required. However, as our laboratory is not equipped with SEM-EDX or EPMA, we could not carry out further analytical studies; this is a limitation to our study; however, we considered that the released phosphate group reacted with magnesium and generated magnesium phosphate.

When 1.5 mg/mL fosaprepitant dimeglumine and 3.85% (v/v) magnesium sulfate solution were mixed at 1:1 ratio, the maximum rate of decline for fosaprepitant dimeglumine was 38.56%. The amount of fosaprepitant dimeglumine that passed through the filter decreased even when the magnesium sulfate solution was diluted to a low concentration of 0.99% (v/v). Therefore, although described only during preparation in the package insert of Proemend® (Ono Pharmaceutical Co., Ltd., Revised: March/2016), fosaprepitant dimeglumine should not come in contact with medicines containing divalent cations even primary and secondary intravenous lines.

In addition to reduced efficacy, a reduction in drug concentration leads to major economic losses. Thus, we recommend flushing the intravenous line and the inside of the filter with 50 mL of normal saline before and after the administration of fosaprepitant dimeglumine. A volume of 50 mL normal

saline is sufficient to clean the lumen of the primary intravenous line and the filter.[7] It is a safe and practical solution that is unlikely to cause side effects[8] and imposes little medical economic burden.

Conflict of Interest

The authors declare no conflict of interest.

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