Predicting Incompatibility of Ceftriaxone Sodium with Calcium Ions Using the Ionic Product

Yuka Nakai, Emi Tokuyama, Miyako Yoshida, and Takahiro Uchida

School of Pharmaceutical Science, Mukogawa Women’s University, 11-68 Koshien 9-Bancho, Nishinomiya 663-8179, Japan, and Department of Pharmacy, Bell Land General Hospital, 500-3 Higashiyama Naka-ku, Sakai 599-8247, Japan

(Received May 16, 2009; Accepted September 11, 2009)

The purpose of this study was to evaluate the incompatibility of ceftriaxone sodium with calcium-containing products using the ionic product of precipitation, and the measurement of insoluble microparticles using a light obscuration particle counter. Appropriate volumes of 2% (w/v) calcium chloride solution were added to 0.4-3 mg/ml ceftriaxone isotonic sodium chloride solution, to make solutions with a final calcium ion concentration of 1.25 mmol/l. The solutions were gently agitated and stored at 37°C for 24 h. The number of insoluble microparticles with a diameter less than 10 μm in the mixed sample solution, determined using a light obscuration particle counter, was increased when the ceftriaxone concentration was ≥0.8 mg/ml. The Saturation Index (defined as the ratio of the ionic product to the solubility product constant) of the prepared mixed solution was 1.1. A white precipitate could be observed visually when the ceftriaxone concentration of the sample solution was 7 mg/ml. The Saturation Index of the solution was 9.7. The effect of the calcium source on incompatibility with ceftriaxone sodium was also evaluated. The numbers of insoluble microparticles in sample solutions made by adding calcium chloride to the sample were significantly higher than those made by adding calcium gluconate. These results suggest that ceftriaxone should not be co-administered with calcium-containing products even if no precipitation is observed visually. There will still be insoluble microparticles caused by incompatibility in the sample solution when the Saturation Index of the solution is over 1.0.

Key words—ceftriaxone; calcium; incompatibility; ionic product; insoluble microparticle; light obscuration particle counter

INTRODUCTION

A varied amount (33-67%) of a ceftriaxone dose is excreted in the urine as unchanged drug, while the remainder is secreted in the bile and ultimately found in the feces as microbiologically inactive compounds. After a 1 g intravenous dose of ceftriaxone, the average tissue concentrations determined 1-3 h after dosing were 581 μg/ml in the gallbladder bile, 788 μg/ml in the common bile duct, 898 μg/ml in the cystic bile duct, 78.2 μg/ml in the gallbladder wall, and 62.1 μg/ml in the plasma, as described in a previous article.1

In 2007, the US FDA issued a safety alert2 on the interaction of ceftriaxone with calcium-containing products, due to a number of neonatal deaths caused by ceftriaxone-calcium precipitates in lungs and kidneys. Cases of biliary concretions or sludge have been reported as adverse events associated with the interaction of ceftriaxone with calcium-containing products; these events are mentioned in the package insert. It was recommended that ceftriaxone should not be mixed with calcium-containing products and not administered in the same or different infusion lines or sites in any patient within 48 h (given the long half-life of ceftriaxone). Symptomatic biliary sludge made of ceftriaxone has frequently been observed in children,3-5 and abnormal gallbladder sonograms were demonstrated in 17.3% of children receiving high doses of ceftriaxone to treat infection.6 There is also a report in an adult without gall bladder inflammation.7

According to a study of the interaction from the standpoint of solubility,8 although the theoretical solubility product constant K’sp (defined as the maximum solubility) for ceftriaxone-calcium salt was 1.62 × 10^-6 mol²/l², precipitates were observed at an ionic product, [Ca^{2+}] × [C_{18}H_{15}N_{8}O_{7}S_{3}]^-, of 1.69 × 10^-3 mol²/l², more than 10-fold greater than K’sp, that is, the Saturation Index (defined as the ratio of the ionic product to K’sp) was 10. The area between K’sp and the observed ionic product at which precipitate...
forms, defines the metastable zone for ceftriaxone-
calcium salt solubility.

In this study, the incompatibility of ceftriaxone so-
dium for injection and calcium-containing products 
was evaluated from the viewpoint of solubility by 
measuring the number of insoluble microparticles 
using a light obscuration particle counter.

**EXPERIMENTAL**

**Materials** Rocephin® for injection containing 1 g 
ceftriaxone (Chugai Pharmaceutical Co., Ltd., 
Tokyo, Japan), and 100 ml isotonic sodium chloride 
solution (Terumo Co., Ltd., Tokyo) were purchased 
for use in this study. As calcium-containing injec-
tions, 20 ml calcium chloride injection 2% (Otsuka 
Pharmaceutical Co., Ltd., Tokyo) and Calciol® 
(Dainippon Sumitomo Pharma Co., Ltd., Tokyo) were 
also purchased. Further, as calcium-contain-
ting solutions, 500 ml Solacet®F, 500 ml Solulact®, 
700 ml Hicaliq®-2 (Terumo Co., Ltd.), 1000 ml Ne-
oparen No.1, 1000 ml Neoparen No.2, 500 ml 
Bluida® (Otsuka Pharmaceutical Co., Ltd.), 500 ml 
Solitax®-H, and 500 ml Bicarbon® (Ajinomoto Phar-
ma Co., Ltd., Tokyo) were also purchased.

**Measurement of Insoluble Microparticles Using a 
Light Obscuration Particle Counter** The em-
ployed method was essentially the same as the ‘In-
soluble Particulate Matter Test for Injection Method 
1. Light Obscuration Particle Count Test’ described 
in the 15th edition of the Japanese Pharmacopoeia 
(2006). 9

All procedures were carried out at a clean bench. 
The number and size of microparticles were deter-
mined using a light obscuration particle counter KL-
04 (RION Co., Ltd.). The thresholds of microparti-
cle size were 1.3, 2.0, 5.0, 10.0, 20.0, 25.0, 40.0, 50.0, 
and 100.0 μm. The volume of each sample was 5 ml, 
and the mean value of three sample measurements 
was calculated. All instruments were washed with 
water after sample injection to eliminate insoluble 
microparticles derived from the devices.

The results of the incompatibility of ceftriaxone so-
dium for injection with calcium-containing solutions 
were evaluated according to the criteria for the maxi-
mum allowable number of insoluble microparticles in 
the 15th edition of the Japanese Pharmacopoeia. For 
injection preparations administered at a volume over 
100 ml, the tolerated number of insoluble microparti-
cles with a diameter 10 μm or greater is 25 or less, 
while that of microparticles with a diameter 25 μm or 
greater is 3 or less, per ml.

**Calculation of Concentration of Ceftriaxone Ion** 
The concentration of ceftriaxone ion [C18H17N8O7S-
]− was calculated by,

\[ \text{Ka}_1 \times \text{Ka}_3 = \frac{[\text{C18H17N8O7S}^-]}{[\text{C18H17N8O7} \text{S}_2]} \]

where \([\text{C18H17N8O7S}^-]\) is the total concentration of 
ceftriaxone and,

\[ \text{Ka}_1 = [\text{H}^+] \times \frac{[\text{C18H17N8O7} \text{S}_2]}{[\text{C18H17N8O7S}^-]} \]

(2)

\[ \text{Ka}_2 = [\text{H}^+] \times \frac{[\text{C18H17N8O7S}_3]}{[\text{C18H17N8O7S}_2]} \]

(3)

\[ \text{Ka}_3 = [\text{H}^+] \times \frac{[\text{C18H17N8O7S}_3]}{[\text{C18H17N8O7S}_2]} \]

(4)

The pKa of ceftriaxone are pKa1=1.72, pKa2=3.15, 
pKa3=4.34.

**Prediction of Incompatibility Using the Ionic 
Product and K'sp**

**Measurement of Insoluble Microparticles** The 
plasma concentration of ionized calcium was postu-
lated to be 1.25 mmol/l. When the calcium ion 
concentration was fixed at 1.25 mmol/l, the ceftriaxone 
concentration was assumed to be 0.8 mg/ml or 
higher, \([\text{C18H17N8O7S}_2]^- \times \text{Ca}^{2+} \times \text{C18H17N8O7} \text{S}_2]^- \) exceeded K'sp 
for ceftriaxone-calcium salt. Appropriate volumes of 
2% (w/v) calcium chloride solution were added to 0, 
0.4, 0.8, 1.2, 1.6, or 2 mg/ml ceftriaxone isotonic so-
dium chloride solution, to make solutions with a final 
calcium ion concentration of 1.25 mmol/l. The solu-
tions were gently agitated and stored at 37°C 
for 24 h, at which point the reaction of ceftriaxone and calcium 
had reached a state of equilibrium. The numbers of 
insoluble microparticles were measured 24 h after 
sample preparation, according to the method 
described in the previous section.

**Judgment of Precipitation by Visual Observation** 
Appropriate volumes of 2% (w/v) calcium chlo-
ride solution were added to 1, 3, 5, 7, 8 and 10 mg/ml 
ceftriaxone isotonic sodium chloride solution, to 
make solutions with a final calcium ion concentration 
of 1.25 mmol/l. The solutions were gently agitated 
and stored at 37°C for 24 h. The mixtures were ob-
served visually 24 h after sample preparation.

**Identification of Precipitate Caused by Incom-
patibility** Appropriate volumes of 2% (w/v) cal-
cium chloride solution were added to 10 mg/ml
Ceftriaxone isonic sodium chloride solution, to make solutions with a final calcium ion concentration of 2.5 mmol/l. The solutions were gently agitated and stored at 25°C for 6 h. The elementary analysis of samples was done after filtration and drying under reduced pressure by an Instrument for Organic Elemental Micro Analysis (Chncorder MT-3, Yanagimoto Mfg Co., Ltd.).

Incompatibility of Ceftriaxone with Calcium Chloride and Calcium Gluconate Solutions

Measurement of Insoluble Microparticles Appropriate volumes of 2% (w/v) calcium chloride solution or 8.5% (w/v) calcium gluconate solution were added to 10 mg/ml ceftriaxone isonic sodium chloride solution, to make solutions with a final calcium ion concentration of 0.5, 1, 1.5, 2 and 2.5 mmol/l. The solutions were gently agitated and stored at 20°C, 25°C or 30°C. The numbers of insoluble microparticles were measured according to the method described previously, both immediately after mixing and 3 and 6 h later.

Judgment of Precipitation by Visual Observation

Appropriate volumes of 2% (w/v) calcium chloride solution or 8.5% (w/v) calcium gluconate solution were added to 10 mg/ml ceftriaxone isonic sodium chloride solution, to make solutions with a final calcium ion concentration of 2.5 mmol/l. The solutions were gently agitated and stored at 20°C, 25°C or 30°C for 6 h. The mixtures were observed visually and by stereomicroscope (SZX10, Olympus Co., Ltd.).

Measurement of Precipitate Weight Appropriate volumes of 2% (w/v) calcium chloride solution or 8.5% (w/v) calcium gluconate solution were added to 10 ml of 10 mg/ml ceftriaxone isonic sodium chloride solution, and the final calcium ion concentrations adjusted to 1.5, 2, or 2.5 mmol/l. The solutions were gently agitated and stored at 25°C for 6 h. Samples were weighed after filtration and drying under reduced pressure.

Incompatibility of Ceftriaxone with Commercial Calcium-containing Products Allen et al.10 reported that the mixing of an intravenous fluid in an administration set with a secondary additive through a Y-injection site occurs in a 1:1 ratio. To simulate this inline mixing, 100 ml of calcium-containing solutions (Bfluid®, Bicarbon®, Hicaliq®-2, Neoparen® No.1, Neoparen® No.2, Solacet®F, Solita®-H, and Solulact®) were added to 100 ml of 10 mg/ml ceftriaxone isonic sodium chloride solution. The solutions were gently agitated and stored at 25°C for 6 h. The pH of each solution and the numbers of insoluble microparticles were measured according to the method described previously. The mixtures were also observed visually.

Statistical Analysis The numbers of insoluble microparticles represent the mean of three values, plus or minus the standard deviation. The data on ionic products and K'sp were analyzed by one-way ANOVA with the Dunnet test. The data on incompatibility of ceftriaxone with calcium chloride or calcium gluconate were analyzed by two-way repeated ANOVA followed by Tukey's HSD test; statistical significance was accepted at the p<0.05 or p<0.01 level.

RESULTS AND DISCUSSION Prediction of Incompatibility Using Saturation Index The number of insoluble microparticles increased with increasing ceftriaxone concentration. In particular, the insoluble microparticles with a diameter less than 10 μm increased significantly in number when the ceftriaxone concentration of the sample solution was 0.8 mg/ml or higher (Fig. 1), [Ca2⁺] × [C18H15N8O7S3] was 1.79×10⁻⁶ mol²/l², which was 1.1-fold greater than K'sp, that is, the Saturation Index was 1.1. This suggests that microparticles caused by incompatibility of ceftriaxone with calcium seemed to form immediately, when [Ca2⁺] × [C18H15

![Fig. 1. Number of Insoluble Microparticles with a Diameter Less than 10 μm in Ceftriaxone Solution with Added Calcium Chloride Solution Using a Light Obscuration Particle Counter](image)

The number of insoluble microparticles with a diameter less than 10 μm (n=3±S.D.) formed when 2% (w/v) calcium chloride solution was added to ceftriaxone injection (0.4–2 mg/ml) made with isonic sodium chloride solution, and stored at 37°C for 24 h. Dunnet test; *p<0.05; **p<0.01.
N\textsubscript{3}O\textsubscript{7}S\textsubscript{3}\textsuperscript{3-} exceeded K'sp for ceftriaxone-calcium salt. Some insoluble microparticles were observed even in 0 and/or 0.4 mg/ml ceftriaxone isotonic sodium chloride solution. This would confirm the previously reported findings of such microparticles in the isotonic sodium chloride solution.\(^{11}\)

Figure 2 shows the results of visual observation. Precipitation was observed visually when the ceftriaxone concentration of the sample solution was 7 mg/ml or higher, and \([\text{Ca}^{2+}] \times [\text{C}_{18}\text{H}_{16}\text{N}_{8}\text{O}_{7}\text{S}_{3}\text{Ca}^{2-}]\) was 1.56×10\(^{-3}\) mol\(^2\)/F, which was 9.7-fold greater than K'sp, that is, the Saturation Index was 9.7. Precipitation under conditions in which the Saturation Index between 1 and 10 was not evaluated in the previous article.\(^8\)

The average concentration of ceftriaxone determined 1–3 h after dosing, was 898 \(\mu\)g/ml in the cystic bile duct after intravenous administration of 1 g of ceftriaxone,\(^9\) and \([\text{Ca}^{2+}] \times [\text{C}_{18}\text{H}_{16}\text{N}_{8}\text{O}_{7}\text{S}_{3}\text{Ca}^{2-}]\) in the cystic bile duct was 2.01×10\(^{-6}\) moles/F, which was 1.2-fold greater than K'sp for ceftriaxone-calcium salt when the calcium ion concentration in the plasma was assumed to be 1.25 mmol/l. In our study, an increase of microparticles caused by incompatibility of ceftriaxone with calcium was confirmed at 1.79×10\(^{-6}\) moles/F, which was 1.1-fold greater than K'sp for ceftriaxone-calcium salt \textit{in vitro}. This suggests that biliary concretions or sludge are associated with the interaction of ceftriaxone with calcium-containing products.

Around 9 g of ionized calcium in the plasma is filtered from the glomerulus\(^{25}\) and 33–67% of a ceftriaxone dose is excreted in the urine as unchanged drug.\(^3\) We could not ignore the possibility of the precipitation of ceftriaxone with plasma calcium ion in the kidney, even if ceftriaxone was not administered simultaneously with calcium-containing products. This would correspond to the reason for the FDA Alert about the death of newborn and premature infants of precipitation in the kidney.

**Identification of Precipitate Caused by Incompatibility** According to the elementary analysis, it was concluded that the precipitate consisted of ceftriaxone and calcium molecules at a ratio of 1:1, as described in previous reports.\(^{8,13}\) The chemical formula of precipitate predicted from its composition was C\(_{18}\)H\(_{16}\)N\(_{8}\)O\(_{7}\)S\(_{3}\)Ca. 

**Incompatibility of Ceftriaxone with Calcium Chloride or Calcium Gluconate** Figure 3 shows the number of insoluble microparticles in the sample solution made from 2% (w/v) calcium chloride solution after 6 h storage. Figure 4 shows the number of insoluble microparticles in the sample solution made with 8.5% (w/v) calcium gluconate solution after 6 h storage.

In the case of 2% (w/v) calcium chloride solution, the number of insoluble microparticles immediately after sample preparation was under the permissible limit in all samples. Their number increased on storage, and by 3 h after sample preparation exceeded the permissible range at all temperatures when the sample solution contained ≥1 mmol/l calcium ion. At 6 h after sample preparation the number of insoluble microparticles exceeded the permissible range in a few samples when the sample solutions contained ≥0.5 mmol/l calcium ion. The microparticles were fewer at higher temperatures, 6 h after sample preparation.

In the case of 8.5% (w/v) calcium gluconate solution, the number of insoluble microparticles exceeded the permissible range at all temperatures when the sample solution contained ≥1 mmol/l calcium ion by 3 h after sample preparation, similar to the sample with added calcium chloride. At 6 h after sample preparation, the number of insoluble microparticles exceeded the permissible range in samples stored at 30°C only when the sample solutions contained ≥0.5 mmol/l calcium ion. In samples stored at 20°C or 25°C the number of insoluble microparticles increased on storage and exceeded the permissible range when the sample solution contained ≥1 mmol/l calcium ion.
The number of insoluble microparticles with a diameter of \( \geq 10 \) \( \mu \text{m} \) (A) and \( \geq 25 \) \( \mu \text{m} \) (B) \( (n=3 \pm \text{S.D.}) \) formed when 2% (w/v) calcium chloride solution was added to ceftriaxone injection (10 mg/ml) made with isotonic sodium chloride solution, and stored at 20°C (◇), 25°C (□) and 30°C (△) for 6 h. Tukey’s HSD test; \(^* p<0.05; \quad ^{**} p<0.01\).

The number of insoluble microparticles in ceftriaxone solution with added calcium gluconate solution using a light obscuration particle counter

The number of insoluble microparticles with a diameter of \( \geq 10 \) \( \mu \text{m} \) (A) and \( \geq 25 \) \( \mu \text{m} \) (B) \( (n=3 \pm \text{S.D.}) \) formed when 8.5% (w/v) calcium gluconate solution was added to ceftriaxone injection (10 mg/ml) made with isotonic sodium chloride solution, and stored at 20°C (◇), 25°C (□) and 30°C (△) for 6 h. Tukey’s HSD test; \(^* p<0.05; \quad ^{**} p<0.01\).

In the sample solutions containing calcium chloride, the numbers of insoluble microparticles were significantly higher than those in the solutions containing calcium gluconate at all temperatures. Insoluble particles with a diameter of \( \geq 10 \) \( \mu \text{m} \) and \( \geq 25 \) \( \mu \text{m} \) numbered \( p<0.01 \) in all solutions except those stored at 25°C for 3 h, which numbered \( p<0.05 \). The results of the measurement of sample solutions stored at 25°C are shown in Fig. 5.

On visual observation, the surface of the precipitate formed when 2% (w/v) calcium chloride solution was added to 10 mg/ml ceftriaxone isotonic sodium chloride solution was rough; in contrast, in the solution to which 8.5% (w/v) calcium gluconate solution was added, the surface was smooth. Under the stereomicroscope, the precipitate in the latter solution was greater than that in the former solution (Fig. 6).

The weight of the precipitate in the solution when 2% (w/v) calcium chloride solution was added to ceftriaxone isotonic sodium chloride solution, was significantly larger than that when 8.5% (w/v) calcium gluconate solution was added, as shown in Fig. 7.

In an examination of the incompatibility of calcium with phosphate, Henry et al.\(^{14}\) reported that calcium chloride and calcium gluconate have different dissociation characteristics. A greater concentration of calci-
Fig. 5. Number of Insoluble Microparticles in Ceftriaxone Solution with Added Calcium Chloride Solution or Calcium Gluconate Solution Using a Light Obscuration Particle Counter

The number of insoluble microparticles with a diameter of $\leq 10 \mu m$ (A, B) and of $\leq 25 \mu m$ (C, D) formed when 2% (w/v) calcium chloride solution (■) or 8.5% (w/v) calcium gluconate solution (□) was added to ceftriaxone injection (10 mg/ml) made with isotonic sodium chloride solution, and stored at 25°C for 3 h (A, C) or 6 h (B, D). Tukey's HSD test; *$p<0.05$; **$p<0.01$.

Fig. 6. Stereomicroscope Photographs of Insoluble Microparticles

Insoluble microparticles in the solution of ceftriaxone isotonic sodium chloride solution (10 mg/ml) mixed with 2% (w/v) calcium chloride solution (A), or 8.5% (w/v) calcium gluconate solution (B), stored at 25°C for 6 h.

Incompatibility of Ceftriaxone with Commercial Calcium-containing Product Solutions

Table 1 shows the calcium source and concentration of eight kinds of calcium-containing solutions used in the experiment. Table 2 shows the number of insoluble microparticles in the solutions that mixed 10 mg/ml ceftriaxone isotonic sodium chloride solution with calcium-containing solutions. The number of insoluble microparticles in all samples was within the per-

um gluconate can be mixed with sodium phosphate than is possible for calcium chloride, because the degree of dissociation of calcium gluconate decreases as concentration increases. In other words, when the calcium concentrations were the same, precipitates were formed more easily by ceftriaxone with calcium chloride than with calcium gluconate. It is suggested that the difference is due to the number of insoluble microparticles formed and weight of the precipitate.
The number of insoluble microparticles in the solution of 10 mg/ml ceftriaxone isotonic sodium chloride solution mixed with Solacet®F, Solulact® and Bicarbon®, which had lower calcium concentrations. The different sources of calcium in the products are thought to be the reason. An organic source of calcium, from calcium gluconate, is contained in Hicaliq®-2, while the source of the calcium in Solacet®F, Solulact® and Bicarbon®, is inorganic calcium chloride. The number of insoluble microparticles of solutions containing different calcium sources is shown in Table 1. The number of insoluble microparticles per ml (mean ± S.D.) is given in Table 2. The number of insoluble microparticles with a diameter of 10 μm or greater was added to ceftriaxone injection (10 mg/ml) made with isotonic sodium chloride solution, and stored at 25°C for 3 or 6 h.

Table 1. pH, Concentration of Calcium Ion and Calcium Source in Eight Different Calcium-containing Solutions Used in the Present Study

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>pH</th>
<th>Calcium concentration (mmol/l)</th>
<th>Calcium source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bfluida</td>
<td>About 6.7</td>
<td>2.5</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Bicarbon*</td>
<td>6.8~7.8</td>
<td>1.5</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Hicaliq®-2</td>
<td>3.5~4.5</td>
<td>6.05</td>
<td>Calcium gluconate</td>
</tr>
<tr>
<td>Neoparen® No. 1</td>
<td>About 5.6</td>
<td>2</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Neoparen® No. 2</td>
<td>About 5.4</td>
<td>2.5</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Solacet® F</td>
<td>6.0~7.5</td>
<td>1.5</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Solulact®-H</td>
<td>5.7~6.5</td>
<td>2.5</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>Solulact*</td>
<td>6.0~7.5</td>
<td>1.5</td>
<td>Calcium chloride</td>
</tr>
</tbody>
</table>

Table 2. Number of Insoluble Microparticles in Ceftriaxone Solution with Added Calcium-containing Solutions Using a Light Obscuration Particle Counter

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Particle size</th>
<th>Number of insoluble microparticles per ml (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>After preparation</td>
</tr>
<tr>
<td>Bfluida</td>
<td>10 μm or greater</td>
<td>7.00 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>25 μm or greater</td>
<td>0.67 ± 0.58</td>
</tr>
<tr>
<td>Bicarbon*</td>
<td>10 μm or greater</td>
<td>12.33 ± 4.04</td>
</tr>
<tr>
<td></td>
<td>25 μm or greater</td>
<td>2.00 ± 2.00</td>
</tr>
<tr>
<td>Hicaliq®-2</td>
<td>10 μm or greater</td>
<td>10.33 ± 4.73</td>
</tr>
<tr>
<td></td>
<td>25 μm or greater</td>
<td>2.00 ± 2.00</td>
</tr>
<tr>
<td>Neoparen® No. 1</td>
<td>10 μm or greater</td>
<td>7.33 ± 3.06</td>
</tr>
<tr>
<td></td>
<td>25 μm or greater</td>
<td>1.33 ± 1.15</td>
</tr>
<tr>
<td>Neoparen® No. 2</td>
<td>10 μm or greater</td>
<td>10.67 ± 2.31</td>
</tr>
<tr>
<td></td>
<td>25 μm or greater</td>
<td>1.33 ± 1.15</td>
</tr>
<tr>
<td>Solacet® F</td>
<td>10 μm or greater</td>
<td>11.33 ± 7.02</td>
</tr>
<tr>
<td></td>
<td>25 μm or greater</td>
<td>1.33 ± 1.15</td>
</tr>
<tr>
<td>Solulact®-H</td>
<td>10 μm or greater</td>
<td>8.67 ± 2.52</td>
</tr>
<tr>
<td></td>
<td>25 μm or greater</td>
<td>1.00 ± 0.00</td>
</tr>
<tr>
<td>Solulact*</td>
<td>10 μm or greater</td>
<td>7.00 ± 2.00</td>
</tr>
<tr>
<td></td>
<td>25 μm or greater</td>
<td>0.67 ± 0.58</td>
</tr>
</tbody>
</table>

Fig. 7. Weight of the Precipitate
The weight of the precipitate (n=3 ± S.D.) for each sample to which 2% (w/v) calcium gluconate solution or 5% (w/v) calcium gluconate solution was added to ceftriaxone injection (10 mg/ml) made with isotonic sodium chloride solution, and stored at 25°C for 6 h after sample preparation. Tukey's HSD test; *p<0.05; **p<0.01.
microparticles is believed to be less than that predicted using the Saturation Index, because the dissociation characteristics of the calcium from gluconate and from chloride are different.

Although the calcium ion concentrations in Solitax*-H, Neoparen No.2 and Błuide were the same, the number of insoluble microparticles was highest in Neoparen No.2. The Saturation Index, calculated from the pH of the mixed solutions, was Hiclid®-2 (9.07) > Błuide (6.93) > Solitax*-H (6.78) > Neoparen No.2 (6.35) > Neoparen No.1 (5.27) > Bicarbon® (4.16) > Solacel® (4.15) > Solulact® (4.12). The number of insoluble microparticles in the mixed solutions did not follow this order. High concentrations of glucose in the calcium-containing solutions may also affect the calcium dissociation; further examination is therefore necessary.

In this study, the number of insoluble microparticles in all samples was within the permissible range, and no precipitation was observed visually. When the Saturation Index of the solution was ≥1.0, however, the number of insoluble microparticles increased due to the incompatibility of ceftriaxone with calcium, as shown by examination of the ionic product and K’sp. Therefore, when selecting ceftriaxone for the treatment of an infectious disease, co-administration with infusion solutions including calcium should be avoided. The possibility of causing a serious adverse event due to ceftriaxone-calcium complex formation in vivo, for example, by co-administration of multivitamins containing vitamin D or total parenteral nutrition containing high concentrations of calcium, or in conditions where the ionic calcium concentration in the plasma rises, even if ceftriaxone is administered by another route.

CONCLUSION

These results suggested that ceftriaxone should not be co-administered with calcium-containing products, even if no precipitation is visible, because there may still be insoluble microparticles caused by incompatibility in solutions of Saturation Index >1. We cannot exclude the possibility of a serious adverse event arising, based on ceftriaxone-calcium complex formation in vivo, when ceftriaxone is co-administered with multivitamins including vitamin D, with total parenteral nutrition including high concentrations of calcium, and in conditions where the ionic calcium concentration in the plasma rises, even if ceftriaxone is administered by another route.

REFERENCES

1) Roccephin® Prescribing Information, Roche Pharmaceuticals in the U.S., 2008.