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Short Communication

Compatibility of Intravenous Fat Emulsion and Antibiotics in Secondary Piggyback Transfusion

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NC and SX collected the samples. NC and SX analysed the data. JL and MLN conducted the experiments and analysed the results. All authors discussed the results and wrote the manuscript.

Key words
Fat emulsion, Injection, Compatibility, Antibiotics, Piggyback infusion

ABSTRACT

According to the change of fat particle size distribution, this study aimed explore the compatibility of fat emulsion and antibiotics in piggyback infusion. In this study 5% glucose solution, fat emulsion and mixture containing 25 kinds of antibiotics were prepared by the proportion suitable for piggyback infusion (33:10:40). The number of fine particles was analyzed by automatic particle counter. According to results, even 24 h after preparation, 12 β-lactam antibiotics, clindamycin phosphate, teicoplanin, trimethoprim/ sulfamethoxazole and micafungin sodium did not change significantly. The particle size of the mixture containing vancomycin hydrochloride, levofloxacin hydrate, metronidazole and fluconazole increased gradually. The particle size of fosfomycin sodium in the mixture containing gentamicin sulfate, abacain sulfate, minocycline hydrochloride, ciprofloxacin and/ or ciprofloxacin also changed significantly after preparation. We concluded the particle size changes of some drugs indicate that these drugs may cause changes in fat particle size during administration. Therefore, these antibiotic preparations should not be administered in conjunction with fat emulsion.

In total parenteral nutrition (TPN), the administration of fat emulsion can not only serve as an energy source, but also play a key role in preventing essential fatty acid deficiency, liver dysfunction and fatty liver (Danko *et al*., 2019; Mehta *et al*., 2017). Fat emulsion is made from soybean oil by emulsifying lecithin with egg yolk, while the influence of divalent cation, amino acid or pH will lead to unstable emulsification and particle coarsening (López *et al*., 2018; Magriet *et al*., 2018). Therefore, solutions of TPN preparations containing carbohydrates, electrolytes and amino acids as well as fat emulsions cannot be mixed into a single bag (Broadhurst *et al*., 2017). On the other hand, the Japanese guidelines for parenteral and enteral nutrition (Mehta *et al*., 2017) indicate that fat emulsion can be used as a piggyback infusion of central venous catheters to patients receiving TPN solution. In addition, it was found that fat emulsions were usually administered at a rate of 0.1g/kg/h or less (Mehta *et al*., 2017). Therefore, when using 250mL of 20% fat emulsion, more than 10h of fat emulsion should be administered in patients weighing 50kg. For patients whose venous routes are difficult to determine, an antimicrobial agent may be administered via a pack-back infusion, with multiple times a day. Therefore, it is speculated that the fat emulsion and antibacterial agent can be mixed when administration. In this study, fat emulsion and antimicrobial agents were used together as piggyback infusion for TPN administration. The mixture of preparations was used as samples, and the particle size of each sample was measured successively by the automatic particle measurement device of shading.

Materials and methods

For fat emulsions, 20% fat emulsion was used (20% 100mL for Intralipos®, Otsuka Pharmaceutical Factory, Inc.). For infusion preparations, a 5% glucose solution (Otsuka Glucose injection 5% 500mL, Otsuka Pharmaceutical Factory, Inc.) was used. In this study, a 5% glucose solution that did not affect the size of the

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fat emulsion was used as an infusion preparation because the purpose of the study was to elucidate the composition changes of the fat emulsion and the antibiotic agent. A 5% glucose solution was used (Otsuka Glucose injection 5% 100mL, Otsuka Pharmaceutical Factory, Inc.) to dissolve the antibiotic. Supplementary Table I shows the correspondence between the active ingredients and abbreviations of all the drugs described in this article.

As the dose from the primary line, 25mL/h of fat emulsion and 100mL/h of antibiotic were administered from the backpack mode. For fat emulsion, patients weighing 50kg were administered at a dose rate of 0.1g/kg/h at 20% fat emulsion. The antibiotic agents other than CPFX, MNZ and FLCZ were dissolved in a 5% glucose solution. 33mL of 5% glucose solution, 10mL of fat emulsion, and 40mL of antibiotic in a 100mL glass bottle (Mighty Vials, Maruemu Corporation) and sampled in a 100-grade clean workbench. Mix 5% glucose solution, fat emulsion and antibiotic at a ratio of 33:10:40.

The measurement of insoluble particulate matter was carried out according to the method of "Insoluble particle test for injection, Method 1, Shading particle count Test" in the 16th edition of The Japanese Pharmacopoeia. The optical shield automatic fine particle counter (KL-04A: RION Co., Ltd) was used to count fine particles. Measurements of particle size over a range of 1.3-2,2-5,5-10,10-25,25-50, 50μm or greater were carried out, with quantities recorded. Particle size less than 1.3μm was not detectable. The measurement quantity of a sample was set to 5mL and the measurement was made for 4 times. The three measured values after the second measurement were averaged, and the mean value was taken as the finally measured value. Dilute the sample with ultrapure water. After each sample was prepared, 0.5mL was diluted with 80mL of ultra-pure water. The ultrapure water filtered by 0.22 filter was placed for 2 days for degassing, and the insoluble particles were counted by an automatic fine particle counter with light shielding. All instruments used for measuring fine particles were cleaned with ultra-pure water to remove impurities. The solution was measured immediately after preparation and measured at 1, 3, 6, 9, and 24h after preparation. The samples were stored at 25±1°C under dark conditions. In this study, the number of fine particles was measured for over 24h, and the compatibility also changed when we considered that the number of fine particles changed.

Results and discussion

The measurements of the observed incompatibility samples are shown in Fig. 1. In 12 β-lactam antibacterial agents, no particle size change of 1.3 m or greater was observed in CLDM, TEIC, ST and MCFG; in VCM, LVFX, MNZ and FLCZ, fine particles with diameters of 1.3-2,2-5 and 5-10 m increased after preparation and continued to increase with time; in GM, ABK, MINO, CPFX and FOM, particle size coarsing was observed immediately after sample preparation (Fig. 1).

Contraindications between fat emulsions and antibiotic drugs do not show any change in the incompatability with reference to toxicant, PIPC, ABPC/SBT, CEZ, CTM, SBT/CPZ, CTRX, CAZ, CFPM, CMZ, FMOX, IPM/CS, MEPM, GM, CLDM, TEIC, ST and MCFG. There is change in the incompatibility of ABK, MINO, VCM, LVFX, CPFX, FOM, MNZ and FLCZ.

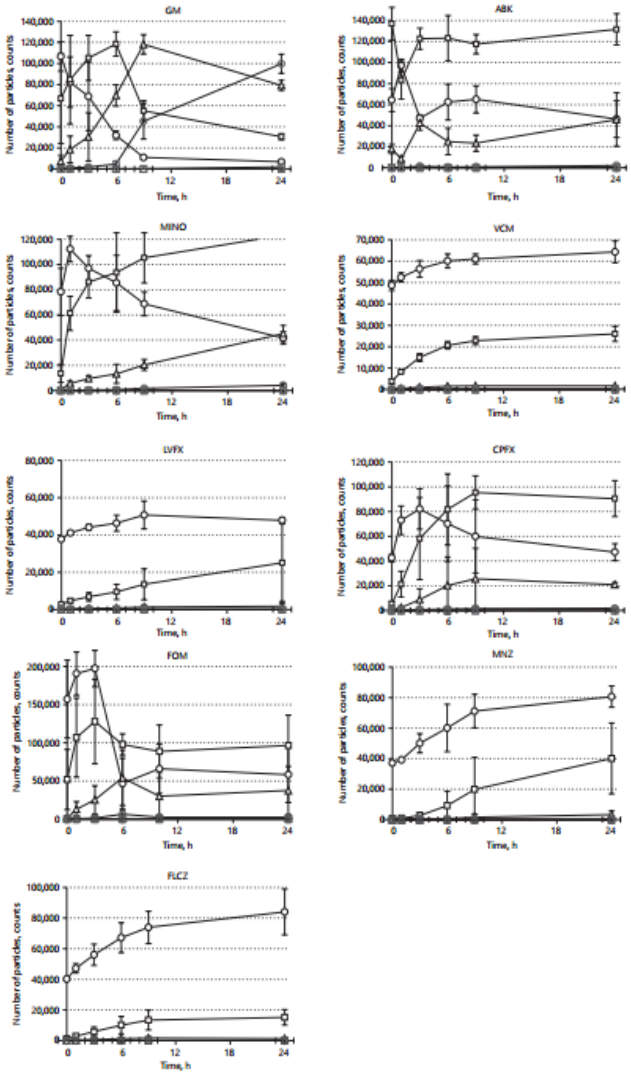

Fig. 1. The number of insoluble fine particles whose particle size varies over time●, 1.3-2μm, ■, 2-5μm, ▲, 5-10μm, ○, 10-25μm, □, 25-50μm, ρ, 50μm or greater, mean±SD, n = 3.

Fat emulsion is a white turbidity preparation. Broadhurst *et al*. (2017) and Yanagisawa (2016) reported that most of the experimental drugs were physically compatible with nine representatives 3 in 1 parenteral nutrient mixture. Drug incompatibility may occur even if it cannot be visually confirmed. The drugs interact with each other. However, it is difficult to be detected with the naked eye due to the coarsening of crude fat particles after mixing with other preparations. However, if the fat particles are large, serious complications may occur, such as pulmonary embolism (Boullata *et al*., 2013). Therefore, in order to measure the coarsening of fat particles, we adopted the shielded automatic fine particle counter for measurement. During the administration of TPN, 10% to 20% fat emulsion is recommended to meet the total energy requirements (Mehta *et al*., 2017). Stock *et al*. (2018) and Ramanjaneya *et al*. (2019) reported that fat emulsion should be used at dose of 0.1g/kg/h or lower. During the administration of TPN, the administration of fat emulsion by piggyback infusion mode takes longer time, so antibiotic preparations can also be administered simultaneously.

We investigated compatibility changes between 25 antibiotics and fat emulsions. We found no incompatibility when mixing a 100mL 20% fat emulsion with a 500mL 5% glucose solution (Boullata *et al*., 2013). As the purpose of the study was to study the composition changes of fat emulsions and antibiotic agents, 5% glucose solution was used as an infusion preparation in the study. Among the 12 -lactam antimicrobials, no changes in the size of fat emulsions were observed in CLDM, TEIC, ST and MCFG, as was the case with 5% glucose solution alone. Coarsening of particle size can be observed in other antibiotic agents. Factors affecting the accumulation of fat particles include temperature (Watrobska *et al*., 2019), pH, sugar, electrolytes, amino acids, and plasma increments such as glucan or gelatin preparations (Magriet *et al*., 2018). The pH of the neutral region does not significantly affect the stability of the fat particles, but in the acidic region, the fat particles become unstable to a certain extent. The pH values of MINO, VCM, LVFX and CPFX are all in the acidic region. In particular, since the pH value of MINO is 2.0-3.5 and the pH value of VCM is 2.5-4.5, both of them are under strong acidic conditions, which will lead to particle coarsening due to their influence on the stability of fat particles. Since lecithin is an amphoteric surfactant, it acts as an emulsifier for fat emulsifiers, and the surface of fat particles is weakly charged. Therefore, especially when there is cation with two or more valence, the electrical repulsion between fat particles will be significantly weakened, and the aggregation of fat particles will be converted into emulsification and oil droplets separation, and emulsion collapse will occur (López *et al*., 2018; Magriet *et al*., 2018). Our study found that when saline was mixed with 20% fat emulsion in a ratio of 5:1, the fat particles became coarse (Broadhurst *et al*., 2017). Although not shown in this data, no change in the number of fine particles was observed in sodium chloride solutions with a sodium concentration of 77.0mEq/L or lower. It can be seen from the above results that coarsening occurs not only in divalent or more valence cations, but also in univalent cations containing sodium ions. NaCl, as a component of normal saline, has strong polarity. Therefore, in the solution mixed with fat emulsion, it is believed that fat emulsion will destroy the charge balance, resulting in instability and roughness. Sodium ions are present in many antibiotic agents (Supplementary Table I). FOM contains 28.98mEq sodium ions. When it is dissolved in 100mL 5% glucose solution, the sodium concentration is 289.8mEq/L, which is almost twice the concentration of normal saline sodium. As normal saline is used as diluents for CPFX, MNZ and FLCZ, it can be seen that the sodium concentration is very high, as shown in Supplementary Table I. Therefore, the high concentration of sodium in the sample may be the factor leading to the coarsening of fat emulsion particle size. Sodium ions are also included in other antimicrobials. However, the sodium concentration in these antibiotics is within the range of 0.2-50.2mEq/L, and if the sodium concentration is low, there is no effect on the fat emulsion. GM and ABK are both basic substances with high polarity. Due to the charge deviation caused by the influence of multiple amino groups and reducing sugars, it is believed that the size coarsening of fat emulsions occurred in the samples.

In this study, to investigate the effect of antibiotic agents on fat emulsions, 5% glucose solution that did not affect the size of fat emulsions was used as an infusion preparation from the primary line, and the TPN solution containing glucose, electrolyte and amino acid was used as the infusion preparation from the primary production line. Since the electrolyte composition of the TPN solution was the maintenance solution, its sodium concentration was about 50mEq/L. In this study, of the 12 β-lactam antibiotics dissolved in 5% glucose solution, the content of sodium ABPC/SBT was the highest, which was 50.2mEq/L. The concentration of sodium in the solution prepared by mixing TPN solution with ABPC/SBT at a ratio of 33:40 was about 50mEq/L. By mixing, the amount of divalent cations and amino acids contained in the TPN solution was approximately half that which caused the coarsening of fat emulsion. In the study of the piggyback administration of fat emulsion using TPN solution, the average particle size and the proportion of coarse particles with diameter of 5 m or greater as defined in USP32/NF27 general test

method 729 were significantly less than the reference value (Gallegos *et al*., 2012), which is consistent with the results of (Jonckers *et al*., 2014). In a mixture of 5% glucose and TPN solutions containing β-lactam antibiotic preparation, the sodium concentration was approximately the same as that of the TPN solution, and the amount of divalent cations and amino acids was approximately half. The effect of fat emulsion on particle size in mixed solution was estimated to be smaller than that of single dose of TPN solution.

In this study, we investigated the effect of antibiotic preparations on the particle size of fat emulsion. Moreover, we must also consider incompatibility of fat emulsion with other drugs. As the TPN solution contains calcium ions, ceftriaxone sodium becomes ceftriaxone calcium salt and causes crystal precipitation when the CTRX of the antibiotic agent is administered in conjunction with the infusion preparation containing calcium. Death case has been reported due to the formation of ceftriaxone calcium salt crystals in the lungs and kidneys (Lacroix *et al*., 2019; Gessese *et al*., 2017; Yao *et al*., 2012). When the infusion agent from the mainline and the infusion agent from the saddle line come into contact with each other, a change in composition of precipitation will be resulted. In this case, drugs that may cause changes in compatibility with TPN infusion need to be avoided in the piggyback administration. If necessary, another drug must be considered (Duan *et al*., 2020). Antibiotics are not only dissolved in 5% glucose solution, but also in normal saline solution. Based on these results, we conclude that the sodium content of the drug is an important factor leading to the coarsing of fat emulsions, and that saline solution should therefore be avoided in the application of antibiotics from backpack lines (Jia *et al*., 2020).

Of the 12 β-lactam antibiotics, for CLDM, TEIC, ST, and MCFG, no coarsening of fat emulsion particle was observed in the mixgture of fat emulsions and antibiotic compositions even after 24h. The fat emulsion became coarser in the mixture of aminoglycosides, quinolones, MINO, VCM, FOM, MNZ and FLCZ antibiotics. In view of these results, these drugs should be administered by other routes instead of being applied with TPN solution. If it is difficult to ensure alternative routes, the lines must be flushed with saline before and after the administration of these drugs.

Supplementary material

There is supplementary material associated with this article. Access the material online at: https://dx.doi.org/10.17582/journal.pjz/20201113161154

Statement of conflict of interest

The authors have declared no conflict of interest.

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