

Incompatibility of Piritramide with Cephalosporins

TO THE EDITOR: Piritramide (1-(3-cyano-3,3-diphenyl-propyl)-4-(1-piperidyl)piperidine-4-carboxamide) is a commonly used opioid for postoperative pain treatment in Germany.¹ Cephalosporins such as cefuroxime or cefazolin are commonly administered as prophylactic antibiotic therapy for surgical procedures.² Thus, simultaneous use of piritramide and antibiotics might occur often in a perioperative setting. We report the case of a woman who was administered cefuroxime and piritramide concomitantly. The precipitate that formed indicated the incompatibility of the 2 drugs.

Case Report. A 37-year-old woman who was scheduled for diagnostic laparoscopy received a single dose of cefuroxime intravenously as routine prophylactic antibiotic therapy after induction of general anesthesia. At this time the patient additionally received, through the same intravenous line, piritramide 7.5 mg/mL for postoperative pain management since the surgical procedure was almost completed. Piritramide immediately precipitated as white "snow." Fortunately, the precipitate could be completely aspirated so that there was no risk of serious complications for the patient.

Discussion. The phenomenon of precipitation is well known for thiopental in combination with neuromuscular blocking agents.³ Serious complications such as pulmonary embolism have been demonstrated in experiments *in vivo*.⁴ Significant differences in pH are proposed as the mechanism for the formation of the precipitate by these 2 drugs (eg, thiopental pH 11.0-12.0; rocuronium pH 4.0).³ A similar explanation is given for the precipitation of protamine by the antibiotic cefazolin.⁵

To elucidate the observed precipitation of piritramide, we tested the compatibility of a series of opioids (piritramide, alfentanil, fentanyl, sufentanil) in combination with the cephalosporins cefuroxime or cefazolin *in vitro*. In a 2-mL syringe, 1 mL of the opioid was mixed with 1 mL of cefuroxime 30 mg/mL or cefazolin 20 mg/mL. These concentrations are commonly used in clinical practice. Each combination was test-

ed 3 times. Only piritramide 7.5 mg/mL precipitated with both antibiotics (Table 1). However, a 15 times lower concentration of piritramide did not precipitate with cefuroxime, pointing to a concentration-dependent effect.

The pH of the drug solutions was measured by a 3-point calibrated pH meter (CyberScan 10, Firma Eutech Cybernetics) at room temperature (23.3 °C). Each substance was tested 3 times. The mean (SD) pH values of the tested drugs were 3.89 (0.01) for piritramide, 5.35 (0.01) for alfentanil, 6.63 (0.12) for fentanyl, 6.35 (0.08) for sufentanil, 7.37 (0.01) for cefuroxime, and 4.81 (0.02) for cefazolin. Interestingly, the pH difference between alfentanil and cefuroxime was 2.02, yet both drugs were compatible. On the other hand, the pH difference of piritramide and cefazolin was 0.92, and precipitation occurred (Table 1). Therefore, a pH incompatibility did not seem a likely reason for the observed precipitation.

One explanation for the substance-specific precipitation is formation of an amide bond between piritramide's amino group and the carboxyl residue of the cephalosporins. A comparable amide bond formation also might be the cause for the reported precipitation of protamine with cefazolin.⁵ Protamine contains an amino group similar to that of piritramide and might react with the carboxyl group of cefazolin.

In conclusion, our study clearly shows that piritramide 7.5 mg/mL is not compatible with cephalosporins. We speculate that the precipitation is caused by a reaction between the amino group of piritramide and the carboxyl residue of cephalosporins.

Because a pulmonary embolism can be caused by precipitation,⁴ precautionary measures should be established for patients treated with both piritramide and cephalosporins. Particularly, pure piritramide (7.5 mg/mL) should not be administered. However, a diluted piritramide preparation (0.5 mg/mL) seemed to be compatible with the tested cephalosporin. Patients receiving piritramide by a patient-controlled analgesia (PCA) pump system are especially at risk.¹ It is not advised to use the same intravenous line for PCA and single-dose antibiotic therapy.

Table 1. Results of Precipitation Between Opioids and Cephalosporins

Cephalosporin	Precipitation				
	Sufentanil Citrate 5 µg/mL	Piritramide 7.5 mg/mL	Piritramide 0.5 mg/mL ^a	Alfentanil Hydrochloride 0.5 mg/mL	Fentanyl Citrate 0.05 mg/mL
Cefuroxime 30 mg/mL	No	Yes	No	No	No
Cefazolin 20 mg/mL	No	Yes	Not tested	No	No

^aA 15 times lower concentration of piritramide was made by diluting pure piritramide 7.5 mg/mL in distilled water.

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Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1R777

Conflict of interest: Authors reported none

Published Online, 27 Feb 2013, *theannals.com*
doi: 10.1345/aph.1R777

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