0.5 mg/kg versus 1 mg/kg of Intravenous Omeprazole for the Prophylaxis of Gastrointestinal Bleeding in Critically Ill Children: A Randomized Study

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Objective To compare the effect of 2 doses of intravenous omeprazole on gastric pH, gastrointestinal bleeding, and adverse effects in critically ill children.

Study design We undertook a prospective randomized clinical trial in critically ill children at risk of gastrointestinal bleeding. The effect of 2 intravenous omeprazole regimens (0.5 or 1 mg/kg every 12 hours) on the gastric pH and incidence of gastrointestinal hemorrhage was compared. The efficacy criteria were a gastric pH >4 and the absence of clinically significant gastrointestinal bleeding.

Results Forty patients, 20 in each treatment group, were studied. Overall, the gastric pH was greater than 4 for 57.8% of the time, with no difference between the doses ($P = .66$). The percentage of time with a gastric pH > 4 increased during the study (47.8% between 0 and 24 hours vs 76% between 24 and 48 hours, $P = .001$); the greater dose showed a greater increase in the percentage of time with a pH > 4: between hours 24 and 48 of the study, the gastric pH was greater than 4 for 84.5% of the time with the 1 mg/kg dose and for 65.5% of the time with the 0.5 mg/kg dose ($P = .036$). Plasma omeprazole levels were greater with 1 mg/kg dose, but no correlation was found between omeprazole plasma levels and gastric pH. No toxic adverse effects were detected, and there was no clinically significant bleeding.

Conclusion Neither of the 2 omeprazole regimens achieved adequate alkalinization of the gastric pH during the first 24 hours. Between 24 and 48 hours, the 1 mg/kg dose maintained the gastric pH greater than 4 for a greater percentage of the time. *(J Pediatr 2013;162:776-82)*.

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Critically ill patients have a greater risk of gastrointestinal hemorrhage, usually as the result of acute gastroduodenal mucosal lesion (AGML).[1-3] The incidence of gastrointestinal bleeding in the critically ill patient is low,[4,5] but its presence significantly increases morbidity and mortality.[6] Although an acid gastric pH is not the only factor responsible for AGML, alkalinization of the gastric pH to a level greater than 4 does help to prevent gastrointestinal bleeding.[7,8] A number of studies in adults and children have shown that the use of antacids, sucralfate, H_2-receptor antagonists, and proton pump inhibitors (PPIs) reduces the incidence of gastrointestinal bleeding.[9-12]

Omeprazole, one of the most widely used PPIs for the prevention of gastrointestinal bleeding in critically ill patients.[13,14] has been shown to be superior to ranitidine in increasing the gastric pH and maintaining gastric alkalinization after the first 24 hours.[15,16] However, the most effective dose of intravenous omeprazole in critically ill children has not been defined.[17]

The objective of this study was to compare the effect of 2 doses of intravenous omeprazole on gastric pH and gastrointestinal bleeding and to study their adverse effects in critically ill children. In addition, we correlated the effect with the plasma levels of the drug.

Methods

This was a prospective, single-blind, randomized clinical trial. The study population comprised patients between 1 month and 14 years of age admitted to the pediatric intensive care unit (PICU) during a period of 18 months; the inclusion criteria were a need for mechanical ventilation and at least 2 risk factors for gastrointestinal bleeding according to the Zinner index modified for children (Table I; available at www.jpeds.com).[18] Those patients who had received H_2-receptor antagonists or PPIs before admission to the PICU were excluded,

AGML	Acute gastroduodenal mucosal lesion
PELOD	Pediatric Logistic Organ Dysfunction
PICU	Pediatric intensive care unit
PIM2	Pediatric Risk of Mortality, revised
PPIs	Proton pump inhibitors
PRISM	Pediatric Risk Score of Mortality

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as were patients in whom insertion of a nasogastric tube was contraindicated or who presented with active gastrointestinal bleeding at the time of admission.

The clinical trial was registered in the European Clinical Trials Database (EudraCT: OM1/2007-006102-19). The protocol was approved by the institutional review board of the hospital, and patients were included in the study after we obtained written informed consent from their parents or legal guardians.

Patients were included in the study at the admission in the PICU. A multichannel nasogastric tube was inserted and connected to a monitor (Sandhill Scientific, Highlands Ranch, Colorado). This device has 2 channels for measuring the pH, one esophageal and one gastric, and uses antimony electrodes to provide continuous pH monitoring.[19] Immediately before insertion, the pH electrodes were calibrated by the use of solutions at pH 4 and pH 7. The position of the tube in the stomach was confirmed radiologically.

After insertion of the nasogastric tube, patients were distributed into the 2 treatment groups with the use of a randomization sheet with the program GRANMO 7.12 (Institut Municipal d'Investigació Mèdica, Barcelona, Spain). Twenty patients were included in each group: group A, intravenous omeprazole, 0.5 mg/kg every 12 hours; and group B, intravenous omeprazole, 1 mg/kg every 12 hours. The patients continued on the same dose of omeprazole until they were discharged from the PICU. Patients did not receive enteral nutrition during gastric pH monitorization (the first 48 hours of the study). The omeprazole infusion was prepared by diluting the vial of 40 mg of omeprazole in 100 mL of normal saline. The dose was administered by infusion over the course of 20 minutes via the use of a continuous infusion pump.

The following data were recorded for each patient: age; sex; weight; height; diagnosis; clinical severity indices—Pediatric Risk Score of Mortality (PRISM),[20] Pediatric Risk of Mortality, revised (PIM2),[21] Pediatric Logistic Organ Dysfunction (PELOD),[22] modified Zinner index of risk of upper gastrointestinal hemorrhage (Table I); heart rate; blood pressure and central venous pressure; gastric pH; the presence of blood in the gastric aspirate or in the feces; adverse effects attributable to the administration of the drug (diarrhea, nausea, vomiting, dry mouth, candidiasis, increased transaminases, dizziness, drowsiness, agitation, tremor, tachycardia, bradycardia, hypertension, rash, anaphylactic reaction, leukopenia, thrombocytopenia, anemia, excessive sweating, bronchospasm); nosocomial infection; and mortality.

The gastric pH was recorded continuously for 24 to 48 hours, as this was the maximum capacity of the memory of the monitor, and was interrupted according to protocol after this period. We defined a gastric pH > 4 as the target of drug treatment according to previously published studies.[7,8] Analysis of the gastric pH and of the percentage of time with a pH > 4 was performed with BioVIEW software, version 5.0.9 (Sandhill Scientific) and was reviewed manually by an expert.

Gastrointestinal bleeding was determined according to the presence of blood in the gastric aspirate and was classified qualitatively as negative (no macroscopic hemorrhage), mild (coffee grounds in the gastric aspirate), moderate (small volume of red blood in the gastric aspirate with no hemodynamic or hematological repercussions), significant (continuous active bleeding and/or melena with a decrease in the hemoglobin >2 g/dL or in the systolic blood pressure >20 mmHg), and massive (continuous bleeding with major hemodynamic or hematological repercussions that required frequent transfusions, more than 2 within the space of 24 hours). Monitoring for gastrointestinal bleeding and for adverse effects of the drug was continued until discharge of the patient from the PICU.

Measurement of the Plasma Levels of Omeprazole

The plasma levels of omeprazole were determined at 30 minutes, 2 hours, and 6 hours after the first dose of the drug and before the doses at 12 and 24 hours. Samples were introduced into lithium-heparin-coated tubes and were centrifuged at 3100 rpm for 10 minutes at 4°C. Two aliquots of 0.75 mL of the plasma were extracted and stored in round-bottom plastic tubes at −80°C until analysis. Measurement of the omeprazole levels was performed by the use of high-performance liquid chromatography coupled to tandem mass spectrometry. The lower limit of quantification using this technique was 1 ng/mL.

Data Analyses

The statistical analysis was performed using the SPSS statistical package, version 18.0 (IBM, Armonk, New York). Comparison between the 2 treatment groups was performed using the *t* test and the Mann-Whitney U test. Comparison of the qualitative variables was performed using the χ^2 test or Fisher exact test. Correlation between omeprazole levels and gastric pH as well as with other measures was analyzed using the Spearman rank correlation.

Results

Forty patients (25 boys) between 1 month and 7 years of age (median, 7 months; IQR, 4-30 months) were included in the study. Thirty-nine of the patients were included after cardiac surgery and 1 with fetal alcohol syndrome who underwent mandibular distraction surgery. The risk of death according to the clinical severity scores at the start of the study were as follows: PRISM, 14.3 ± 5.9%; PIM2, 5.9 ± 6.0%; and PELOD, 11.6 ± 6.4%. The mean value of the Zinner index was 2.2 + 0.4. Data of patients are summarized in Table II.

Twenty patients received omeprazole at a dose of 0.5 mg/kg every 12 hours and 20 received a dose of 1 mg/kg every 12 hours. None of the patients received drugs that induced or inhibited the cytochrome P450 enzymes during the 48-hour study period of pH recording.

A total of 180 measurements were made of the plasma concentration of omeprazole in the 40 patients, although the gastric pH recording was only completed in 35 patients