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Pharmacokinetics and Pharmacodynamics of Famotidine and Ranitidine in Critically Ill Children

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Abstract

To characterize and compare acid suppression (pharmacodynamics) and pharmacokinetics of IV famotidine and ranitidine in critically ill children at risk for stress gastritis. Single-blind, randomized study in PICU patients 6 months to 18 years requiring mechanical ventilation with continuous gastric pH monitoring, randomized to IV famotidine 12 mg/m^2 or ranitidine 60 mg/m^2 when gastric pH $< 4.0 > 1$ hour with serial blood sampling following first dose. Twenty-four children randomized to either famotidine (n = 12) or ranitidine (n = 12). Sixteen out of twenty-four completed both PK and PD study arms (7/12 famotidine; 4.7 ± 3.4 years; 9/12 ranitidine; 6.6 ± 4.7 years; $p = 0.38$). Time to gastric pH 4.0 and total time pH above 4.0 similar with no difference in pH at 6 and 12 hours ($p > 0.2$). No difference between drugs in clearance, volume of distribution and half-life ($p > 0.05$). Ratio of AUC pH to AUC drug concentration 0–12 hours after first dose was significantly greater for famotidine (0.06849 ± 0.01460 SD) than ranitidine (0.02453 ± 0.01448; $p < 0.001$) demonstrating greater potency of famotidine. pH lowering efficacy of both drugs is similar. Greater potency of famotidine may offer clinical advantage due to lower drug exposure and less frequent dosing to achieve same pH lowering effect.

Keywords

famotidine, ranitidine, pediatric intensive care unit, pharmacokinetics, pharmacodynamics, gastric acid suppression

Gastric acid secretion is essential for development of stress induced gastroduodenal lesions in critically ill children.[1] Under conditions of stress, ischemia leads to mucosal acidification and results in ulceration.[1,2] Patients receiving mechanical ventilation for longer than 2 days are at high risk for stress induced bleeding.[2,3] Stress ulcers leading to gastrointestinal bleeding occur in 5–20% of critically ill patients.[3] Despite availability of proton pump inhibitors and limited evidence to guide agent selection and dosing, H2 receptor blocker prophylaxis is administered routinely in the pediatric intensive care unit (PICU).[4–8]

Histamine receptor blockers inhibit histamine-stimulated acid secretion by reversible, competitive inhibition of H_2 receptors of the parietal cells.[3] Ranitidine was the second histamine receptor blocker to be released after cimetidine and has claimed the majority of hospital use replacing cimetidine secondary to less microsomal enzyme based drug interactions and dosing ease.[4–6] Famotidine has been used less frequently primarily secondary to expense, yet may present advantages in terms of potency and decreased dosing frequency.

Famotidine has been shown to be 7.5 times more potent than ranitidine in suppressing acid with a longer duration of action in adults.[4,5] Data on IV famotidine use in the PICU setting is limited, particularly in comparison to other H2 receptor blocker therapy.[8–12] Altered biodisposition of H2 receptor blockers in children compared to adults has been demonstrated secondary to immature hepatic and renal function.[9–15] In addition to effects of immaturity, children in PICU often have organ function compromised by disease, further affecting pharmacokinetics and pharmacodynamics of drug therapy.[11–18] A paucity of

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data persists regarding the comparative efficacy and pharmacokinetics of these agents in a PICU population. In this study the gastric acid suppression and pharmacokinetics of IV doses of ranitidine and famotidine were compared in a sample of children admitted to PICU.

Methods

Patients and Dosing

A prospective, single blind randomized parallel study was conducted in the PICU at Children's Hospital of Michigan. Patients 3 months to 18 years with head injury, respiratory failure, shock, sepsis, status post major surgery or other serious illnesses requiring mechanical ventilation and an intravenous H_2 receptor blocker were eligible. Informed consent was obtained from the parent(s) or legal guardian by the Principal Investigator (SM) upon arrival to PICU. Infants 3–12 months, weighing $\leq$10 kg with hemoglobin of $\leq$8.0 g/dL and hematocrit $\leq$24.5% were excluded from the pharmacokinetic portion of the study to avoid blood loss from PK sampling. However, they were included in the pharmacodynamic portion of the study. The study, including serial blood sampling for the pharmacokinetics (PK) phase, was approved by the Wayne State University (WSU) IRB.

Patients 12 months to 18 years weighing 10 kg or more with hemoglobin and hematocrit of $\geq$8.0 g/dL and $\geq$24.5%, respectively, were enrolled for both pharmacodynamic and pharmacokinetic phases. Exclusions to participation were creatinine clearance less than 80% for age, abdominal trauma with hollow viscus perforation, established diagnosis of infectious, traumatic, metabolic, or neoplastic liver disease, and use of H_2 blockers 2 weeks prior to study. Patients were randomized from a computerized random assignment list to receive IV doses of famotidine 12 mg/m^2 or ranitidine 60 mg/m^2 by the Children's Hospital of Michigan Investigational Drug Service pharmacist who prepared and dispensed all study drug doses.

Intragastric pH Monitoring

Gastric pH was monitored using a digital intragastric pH probe (Digitrapper III). A 2.3 mm pH microelectrode pH probe (Zinectics single-use pH catheters) was inserted through the nostril to lie in midbody of the stomach. Subjects were fasting at time of study as they were newly admitted to PICU. Location of the probe tip was indicated by a prompt and persistent drop in pH to less than 4.0 and confirmed. Continuous nasogastric pH probe monitoring was performed for 18–24 hours. The pH data were recorded on a battery-operated portable Digitrapper III (Synectics Medical Corp., Enfield, EN) providing digital intragastric pH reading every 4 seconds. Documentation of an intragastric pH remaining less than 4.0 for 1 hour was a requirement for initiating the study. Then, the first dose of famotidine or ranitidine was administered IV over 15 minutes via a syringe device. Patients with persistent gastric pH above 4.0 after probe placement were disqualified from the study.

Intragastric pH was documented at times corresponding to pharmacokinetic blood samples to monitor response to study drug and determine requirement for a second dose. A second dose of study drug was administered if intragastric pH did not increase above 4.0 within 3 hours of first study drug dose or if pH decreased and remained below 4.0 for 1 hour after initially increasing to above 4.0. Blood sampling was discontinued following the second dose. However, nasogastric pH monitoring continued, to assess response and determine need for subsequent doses.

Gastric pH data were analyzed using EsopHogram software (Medtronic, Inc., Shoreview, MN). Study variables post infusion of the first dose of study drug were: pH value at time 0, area under curve (AUC) of gastric pH (pH units multiplied by hours) at 6 and 12 hours, time (minutes) to achieve pH of 4.0, total time pH remained above 4.0. Ratio of AUC pH to drug AUC for 12 hours after first dose was used as a measure of relative potency of the study drugs.

Safety Monitoring

Subjects were monitored for adverse effects commonly related to famotidine or ranitidine, including thrombocytopenia, elevation of liver enzymes, and/or BUN/serum creatinine elevations, rash, arrhythmias and documented according to routine PICU nursing protocol. Safety labs, including CBC with platelets, renal and hepatic function panels, and INR and or PTT, were obtained at enrollment and at 24 and 48 hours after administration of study drug. Safety labs were coordinated with routine PICU blood draws to minimize blood loss. Patients were discontinued from study in event of intragastric pH failing to increase above 4.0 after second dose of study drug, overt significant bleeding, significant adverse reaction associated with study drug, or parent or physician withdrew participation.

Pharmacokinetic/Pharmacodynamic Analysis. Patients participating in both the pharmacodynamic and pharmacokinetic phase had 2.5 mL blood drawn at 0, 15, 30, 45, 60 minutes and 2, 3, 4, 6, 10 and 16 hours post-infusion of the first study drug dose. Samples were collected in oxalate tubes, held on ice until serum was centrifuged and stored at -70°C for final analysis. Famotidine and ranitidine were extracted from serum samples using solid phase extraction techniques and analyzed by HPLC with UV detection using a modification of the methods of Wincek[19] and Karnes et al.[20]

Plasma pharmacokinetic parameters for each patient were estimated from a non-linear least squares fit of ranitidine or famotidine plasma concentrations versus time to a bi-exponential model with a 15 minutes zero-order infusion function using PKAnalyst software (MicroMath

Scientific, Salt Lake City, Utah). Best statistical fit was determined from Akaike information criterion. Serum concentrations sampled between 0 and 10 hours were used for analysis as the majority of subjects had no detectable drug beyond 10 hours or had received a second dose between the 10 and 16 hours sample. Terminal elimination rate constant and terminal half-life were determined from the model fitted. Pharmacokinetic variables including beta half-life, volume of distribution (Vd), maximum concentration (C_{max}), and clearance (Cl) were analyzed using RSTRIP. Area under the drug concentration curve from time 0–10 hours (AUC_{0-10}) was obtained using the trapezoid method. Total area ($AUC_{0-\infty}$) was calculated by summation of $AUC_{0-10} + Cp_{10}/\lambda_n$ where Cp_{10} is the plasma drug concentration at 10 hours and λ is the terminal elimination rate constant. Clearance was calculated as dose/$AUC_{0-\infty}$ and apparent volume of distribution (Vd) was calculated from dose/AUC $\times \lambda_n$. Relative potencies of famotidine and ranitidine were expressed as the respective ratios of pH AUC_{0-12}/concentration AUC_{0-10}.

Statistical Analysis

Descriptive statistics were used for patient characteristics and pharmacokinetic data. Central tendency of normally distributed data was expressed as mean ± SD and as median (range) for non-normal data sets. When assumptions of normality could be met Student's *t* tests or one-way analyses of variances were used to compare differences between groups, subgroups or parameters as appropriate. Mann–Whitney test was used for analysis of non-parametric data. Statistical significance was set a priori at $p < 0.05$. Analyses were conducted using SPSS version 20.0 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Results

Thirty-two children were enrolled with 24 children randomized to receive either famotidine (n = 12) or ranitidine (n = 12). Eight of 32 children did not complete the study after randomization for the following reasons: persistent hypochlorhydria prior to drug administration (3 children), inability to place probe (1 child), complications unrelated to study prior to drug administration (3 children), and treatment failure after the second drug dose (1 child). The remaining 24 subjects ranged in age from 6 months to 16 years. Eight of the twenty-four children did not participate in the PK portion of the study because of age and size; two subjects were 6 months of age and 6 were 12 months old. Diagnoses and characteristics of the 16 study participants who completed both the PK and PD portions of the study are summarized in Table 1. No patient experienced any adverse effects attributable to the study, including significant decrease in hemoglobin and or hematocrit. No blood transfusions were required by any patient during the study period including those in the PK phase. Of the 16 patients completing both the PK and PD portions of the study, nine were randomized to receive ranitidine and seven received famotidine (Table 2).

The two treatment groups did not significantly differ with respect to baseline pH values, time for median pH to increase to pH 4.0, total time pH remained above 4.0 after first dose of study drug, and area under the pH versus time curve. However, the lower famotidine dose resulted in a mean serum concentration AUC of famotidine that was significantly lower than ranitidine (59,830.43 ± 9,009.48 and 192,855.4 ± 84,397.6 ($p = 0.008$), respectively). This resulted in a significant difference in the ratio of AUC pH to AUC drug concentration from 0 to 12 hours after the first dose (mean ratios of 0.06849 ± 0.01460 and 0.02453 ± 0.01448 ($p < 0.001$) for famotidine and ranitidine, respectively), reflecting the greater mg for mg potency of famotidine.

Mean PK values for famotidine and ranitidine are summarized in Table 3. As with drug serum AUC, the mean serum concentration maximum (C_{max}) values for famotidine were significantly lower than for ranitidine (963.3 ± 230.9 and 3,291.2 ± 917.1 ng/mL respectively; $p = 0.02$), consistent with the lower mg/kg famotidine dose. Calculated clearance (L/kg/h), Volume of distribution (L/kg), and half-life did not differ between the two treatment groups (all *p* values >0.05).

Discussion

Provision of optimal stress ulcer prophylaxis continues to challenge clinicians and remains an important component of supportive management for PICU patients. There is a general consensus that maintaining gastric pH above 4.0 is associated with less risk of mucosal ulceration and bleeding in critically ill pediatric patients.[3–5] However this goal may not always be attained given the effect of acute illness and development on pharmacodynamics and pharmacokinetics of various agents, such as the H2 receptor blockers[6–9] that are administered to decrease gastric acid production.

Harrison and coworkers demonstrated that administering usual therapeutic doses of ranitidine to critically ill children may not provide adequate gastric pH control.[17] In addition to the effects of immaturity, children in the PICU often have organ function further compromised by disease, affecting drug metabolism and response to therapy.[9,11–15,21] Gastric pH monitoring, individualization of H2 receptor blocker therapy, use of continuous infusion regimens, and selection of the most effective H2 blocker may improve clinical outcomes in stress ulcer prophylaxis.[2,16,17]

The present study confirmed the greater potency of famotidine compared to ranitidine in critically ill children, similar to what has been demonstrated in previous studies.[2–5] However, greater potency does not necessarily

Table 1. Characteristics of Subjects Completing Both PK and PD Portions of Study (n = 16)

Characteristic	Famotidine (n = 7/16)	Ranitidine (n = 9/16)
Diagnosis		
Cardiovascular surgery	5/7	5/9
Posterior spinal fusion	1/7	3/9
Neurosurgery (brain)	0/7	1/9
Status epilepticus	1/7	0/9
Age (mean ± SD, years)	4.7 ± 3.9	6.6 ± 4.7 ($p = 0.39$)
Weight (mean ± SD, kg)	20.4 ± 8.1	26.6 ± 15.9 ($p = 0.33$)
Ethnicity	3 white, 3 black, 1 middle Eastern	2 white, 7 black
Gender (male/female)	2/5	4/5

Table 2. Pharmacodynamic Data (n = 16)

Group	pH[a]: 0, 6, 12 (hours)	Time (minutes) pH 4.0, pH < 4.0	AUC pH	AUC pH/AUC drug[b,c]
Famotidine	2.7, 7.1, 7.0	25.5, 563	3,836.45 ± 741.46	0.0685 ± 0.01460 (n = 7)
Ranitidine	2.3, 6.7, 5.0	26.5, 543	3,966.4 ± 664.92	0.0245 ± 0.01448 (n = 9)

[a]Median values unless indicated; pH similar between groups ($p = 0.2$).
[b]Mean ± SD values.
[c]$p \leq 0.001$, Mann–Whitney test.

Table 3. Pharmacokinetic Parameters of Famotidine and Ranitidine[a] (n = 16)

Group	C_{max} (ng/mL)	$t_{1/2}$ (hours)	Cl (L/h/kg)	Vd (L/kg)	AUC drug (μg/mL)
Famotidine	963.3 ± 230.9[b]	2.25 ± 1.1	0.53 ± 0.17	0.38 ± 0.23	59,830.53 ± 9,009.5 (n = 7)
Ranitidine	3,291.2 ± 917.1	1.67 ± 1.2	0.77 ± 0.41	0.45 ± 0.20	192,855.44 ± 84,397.6[c] (n = 9)

[a]Mean ± SD values.
[b]C_{max} $p = 0.02$.
[c]AUC drug $p = 0.008$.
$t_{1/2}$, $p = 0.5$; Cl, $p = 0.16$; Vd, $p = 0.3$.

mean superior efficacy or clinical superiority. In this study, both agents were shown to be effective in gastric acid suppression in PICU patients. Nevertheless, greater potency does allow for less systemic exposure to the drug to achieve the same pharmacodynamic effect and may translate to clinical advantage if this decreases adverse effects or allows less frequent dosing. The lower dose and less frequent dosing of famotidine relative to ranitidine may offer potential advantages for the PICU population in terms of medication cost savings, less line access, nursing and pharmacy time and adverse effects. Famotidine therapy also avoids risk of ranitidine induced thrombocytopenia.[4]

Several pharmacokinetic parameters in our PICU sample (including mean Cl value for famotidine 0.53 ± 0.17 L/h/kg; half-life 2.25 ± 1.1 hours) were similar to those reported in the general pediatric population (mean Cl 54 ± 0.34 L/h/kg, half-life 2.3 ± 1.3).[7,8] Conversely, the calculated mean volume of distribution (Vd) for both agents was lower than reported in previous investigations. Several factors may have contributed to this difference. Our patients received a maximum of two H2 receptor doses equivalent to 0.5 mg/kg famotidine and 2 mg/kg ranitidine during the study and were not at steady state concentrations at the time of sampling. The low Vd value may reflect use of diuretics and strict fluid monitoring in our PICU sample which included a disproportionate number (63%) of cardiac surgery patients. In addition to fluid restriction, these infants and children often have decreased renal and hepatic blood flow.[21] However the inclusion criteria for the present study stipulated normal renal function upon entry therefore our patients did not have documented renal compromise. The half-life of famotidine has been shown to be longer compared to ranitidine in previous studies of both children and adults.[4,5,7,8] In contrast, we did not observe a significant difference in half-life or Cl between the two drugs in our sample of critically ill children. Furthermore, we did not see a significant difference in duration of acid suppression between the two drugs.

There are several limitations to our study including lack of monitoring until steady state serum concentrations were

achieved. However performing a longer-term study in PICU over several days in critically ill, unstable patients was not practical. We did not compare the acuity of illness or concomitant medications between study groups. In addition, concomitant medications were not examined and analyzed for potential drug interactions with the study agents. A child in PICU may be exposed to 20 or more medications per day.[11] Without these data we were unable to account for the effect of acuity of illness and other medications on the acid suppression efficacy in addition to the PK parameters of the study agents. Maximal effect at steady state of these H2 receptor blockers was not compared although peak effect occurs within 3 hours after IV doses of these agents.[4,7–9] Intragastric pH probe monitoring is limited when the probe is misplaced or meals interfere with pH reading. These technical limitations were mitigated as our subjects were fasting, receiving mechanical ventilation and had probe placement radiographically confirmed.

Conclusion

It is important to characterize the pharmacokinetics and pharmacodynamics of medications that are used in these complex, high risk patients. At present there are no pediatric dosing regimens based on PK or PD for stress ulcer prophylaxis therapies other than increasing dosage of H2 receptor blockers to maintain an elevated gastric pH. The American Society of Health-System Pharmacists (ASHP) published the only available guidelines in 1999 addressing use of stress ulcer prophylaxis in pediatric ICU patients.[4] These guidelines are under revision and will be published during 2013. This study provides pharmacokinetic/pharmacodynamic data on ranitidine and famotidine to assist in selection and dosing of these two H2 blockers in PICU patients.[1–4]

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