Pharmacokinetics of the H₂ Blocker Roxatidine Acetate Hydrochloride in Pediatric Patients, in Comparison with Healthy Adult Volunteers

Hidefumi NAKAMURA¹, Hisashi KAWASHIMA², Rieko AZUMA³,*, Ikuya SATO³, Koji NAGAO³ and Katsuhiko MIYAZAWA³

¹National Center for Child Health and Development, Tokyo, Japan
²Tokyo Medical University, Tokyo, Japan
³Clinical Development Center, ASKA Pharmaceutical Co., Ltd., Tokyo, Japan

Summary: Clinical studies were conducted to investigate the pharmacokinetics of roxatidine acetate hydrochloride capsules (ALTAT® CAPSULES) in children. In a single-dose pharmacokinetic (PK) study in pediatric patients aged between 6 and 14 years with acid-related diseases, 37.5 mg or 75 mg roxatidine capsules were given orally, and blood samples were collected to determine the plasma roxatidine concentrations. Meanwhile, a single-dose PK study in healthy adult volunteers was newly conducted; subjects were given 37.5 mg, 75 mg or 150 mg roxatidine capsules. Differences were present between the PK parameters in pediatric patients and those in healthy adult volunteers. However, the CL/F and Vd/F adjusted by body surface area (BSA) or body weight (BW) were comparable. A close correlation of the Cmax and AUC0→∞ to the dose per unit BSA (mg/m²) or BW (mg/kg) was also shown. In the multiple-dose study in pediatric patients, no roxatidine accumulation in plasma was observed, as was the case with a previous study in adults. These data show that the PK profile of roxatidine in pediatric patients is similar to the profile in healthy adult volunteers when adjusted by BSA or BW.

Keywords: roxatidine; pediatric patients; single-dose; multiple-dose; pharmacokinetics

Introduction

A sustained release capsule formulation of the histamine H₂ receptor antagonist roxatidine acetate hydrochloride (ALTAT® CAPSULES, ASKA Pharmaceutical, Tokyo, Japan: hereinafter called roxatidine capsules) potently and continuously suppresses gastric acid secretion by competitively inhibiting the histamine H₂ receptors located in gastric parietal cells,¹² like other H₂ receptor antagonists. Large-scale trials have shown that roxatidine acetate is as effective as standard doses of cimetidine and ranitidine in the treatment of patients with duodenal or gastric ulcer, and the prevention of peptic ulcer recurrence.¹³ Previous studies in adults showed at least 95% of the roxatidine acetate hydrochloride is absorbed into the blood after oral administration,¹⁴ and the serum protein binding ratio is 9%.¹⁵ The roxatidine does not inhibit the human cytochrome P450 in vitro.¹⁶ The drug is mainly excreted into the urine and at least 70% of the amount administered is excreted within 24 h.¹⁷ The elimination from the plasma is dependent on renal function (creatinine clearance).¹⁸

Oral administration of 75 mg of roxatidine twice daily has been approved in adults for the treatment of acid-related diseases, such as gastric ulcers, duodenal ulcers, and reflux esophagitis. The drug has been used to treat acid-related diseases with excellent efficacy and safety since being introduced over 20 years ago.

There has been extensive experience of roxatidine use in adults, and information regarding safety, efficacy and pharmacokinetics has been accumulated. On the other hand, there has been minimal accumulation of data for dosage, safety or efficacy although H₂ receptor antagonists in children have been commonly prescribed off-label in Japan. To the best of our knowledge, there has been no publication specifically addressing the pharmacokinetics of roxatidine in pediatric patients.

In this article, the pharmacokinetics of roxatidine in pediatric patients of age 6 to 14 years with acid-related...
diseases is described and compared with that of healthy adult volunteers.

**Methods**

**Clinical study:** Three pharmacokinetic (PK) studies, one single-dose study in pediatric patients, one in healthy adult volunteers, and a multiple-dose study in pediatric patients, were conducted. All studies were reviewed and approved by the Institutional Review Board of each clinical trial site.

**Single-dose PK study in pediatric patients**

This study was a multi-center, open-label, dose-escalating trial. Admitted pediatric patients aged between 5 and 14 years, diagnosed with or suspected of having a gastric ulcer, duodenal ulcer, anastomotic ulcer, Zollinger-Ellison syndrome, reflux esophagitis, acute gastritis, or a gastric mucosal lesion of chronic gastritis with an acute exacerbation (erosion, bleeding, redness, and edema), were included; patients with serum creatinine exceeding the upper limit of normal range for age at each clinical study site were excluded. Some of the study sites used the published reference ranges of laboratory data in children.\(^9\)

A total of 25 pediatric patients were enrolled in this study after obtaining informed consent from the patients when applicable and informed consent from their parents or legally acceptable representatives. The pediatric patients were divided into four groups based on their age (5–9 or 10–14 years) and the dosage (37.5 or 75 mg). Roxatidine capsules were given as follows: 37.5 mg for age 5–9 years (6 patients), 37.5 mg for age 10–14 years (6 patients), 75 mg for age 5–9 years (6 patients), and 75 mg for age 10–14 years (7 patients). The patients were given the roxatidine capsule orally with water in the morning after breakfast. Blood samples of 1 mL each were collected at 0, 1, 2, 3, 4, 6, 10, and 24 h after administration to determine the plasma roxatidine concentrations.

This study was conducted at National Center for Child Health and Development (Tokyo), Tokyo Metropolitan Kiyose Children’s Hospital (Tokyo Metropolitan Children’s Medical Center, presently Tokyo), Kanagawa Children’s Medical Center (Kanagawa), Osaka Medical Center and Research Institute for Maternal and Child Health (Osaka), Tokyo Medical University Hospital (Tokyo), and Sapporo-Kosei General Hospital (Hokkaido) in Japan.

**Single-dose PK study in healthy adult volunteers**

This study was randomized, open-label, parallel-group trial. The subjects were in good health based on medical history, physical examination, and clinical laboratory examinations. Twenty-four healthy male subjects were enrolled in this study after their informed consent was obtained.

The subjects were divided into three groups and given a roxatidine capsule of 37.5 mg (8 subjects), 75 mg (8 subjects), or 150 mg (8 subjects) orally with water in the morning after a fast of more than 10 h. Blood samples of 2 mL each were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after administration to determine the plasma roxatidine concentrations. This study was conducted at Maruyama Hospital (Shizuoka, Japan).

**Multiple-dose PK evaluation in pediatric patients**

This multiple-dose PK evaluation was conducted as a part of a phase 3, multi-center, open-label trial. Pediatric patients diagnosed with or suspected of having gastric ulcer, duodenal ulcer, or reflux esophagitis and requiring treatment were included; patients with serum creatinine exceeding the upper limit of normal range for age at each clinical study site were excluded.

A total of 21 patients 6–14 years of age were enrolled in this study after obtaining informed consent from the patients and informed consent from their parents or legally acceptable representatives. The patients were divided into two groups on the basis of their body weight (BW): a 37.5 mg roxatidine capsule was given orally to pediatric patients weighing less than 30 kg (6 patients), and 75 mg was given to pediatric patients weighing 30 kg or more (15 patients) with water twice a day for 8 weeks.

Blood samples of 1 mL each were collected in the 4th week and 8th week of administration to determine the trough plasma roxatidine concentrations (C\(_{\text{trough}}\)). This study was conducted at Sapporo-Kosei General Hospital (Hokkaido), Tokyo Medical University Hospital (Tokyo), National Center for Child Health and Development (Tokyo), Tokyo Metropolitan Children’s Medical Center (Tokyo), Saiseikai Yokohamashi Tobu Hospital (Kanagawa), Kanagawa Children’s Medical Center (Kanagawa), Osaka General Medical Center (Osaka) and Osaka Medical Center and the Research Institute for Maternal and Child Health (Osaka) in Japan.

**Roxatidine assays:** The roxatidine acetate hydrochloride is rapidly converted to its active metabolite, roxatidine, by esterase in the plasma, liver, and small intestine.\(^{10}\) Therefore, the roxatidine concentration in plasma samples was determined using a LC/MS/MS method. The LC/MS/MS method was validated for selectivity, accuracy, precision, recovery and stability in accordance with FDA guidance\(^{11}\) for bioanalytical method validation.

To a plasma sample aliquot (50 µL), 1,000 µL of distilled water, 100 µL of methanol, and 100 µL of internal standard (roxatidine-\(\text{d}_{10}\)) working solution were added. The solution was mixed and loaded on to the C8 solid-phase extraction column, which was conditioned with 3 mL of acetonitrile and 3 mL of methanol, followed by 3 mL of distilled water. The column was washed with 3 mL of distilled water and 2 mL of acetonitrile. The extracted roxatidine and internal standard were eluted with 2 mL of methanol/triethylamine (200:1, v/v). The eluate was evaporated to dryness under a stream of nitrogen gas on an aluminum block heater at 40°C. The residue was dissolved in 1 mL of 0.05 mol/L ammonium acetate/methanol (9:1, v/v) and injected into the LC/MS/MS.

The processed sample was analyzed using a Waters
ACQUITY UPLC® system (Waters Corp., Milford, MA) coupled to an AB/MDS Sciex API5000 triple quadrupole mass spectrometer (AB Sciex, Foster City, CA). Chromatography was performed using a Shiseido CAPCELLPAK C18 MGII, 2.0 mm I.D. × 35 mm, 5-µm column (Shiseido, Tokyo, Japan). Mobile phase A was 0.05 mol/L ammonium acetate/acetic acid (1,000:1, v/v), and mobile phase B was methanol/acetic acid (1,000:1, v/v). Roxatidine and the internal standard were separated from endogenous matrix components using a gradient elution. The initial mobile phase condition (70/30, A/B) was held for 0.5 min, followed by a linear gradient from 70/30 (A/B) to 5/95 (A/B) over 2.5 min. The mobile phase composition was then returned to the initial condition for an additional 1 min. The flow rate was 0.2 mL/min, and the column temperature was 40°C.

The sample was ionized using a Turboionspray probe in the positive-ion mode. The mass spectrometer was tuned for unit mass resolution, and data were collected using the multiple positive-ion mode. The mass spectrometer was tuned for unit mass resolution, and data were collected using the multiple positive-ion mode. The mass spectrometer was tuned for unit mass resolution, and data were collected using the multiple positive-ion mode. The mass spectrometer was tuned for unit mass resolution, and data were collected using the multiple positive-ion mode. The mass spectrometer was tuned for unit mass resolution, and data were collected using the multiple positive-ion mode. The mass spectrometer was tuned for unit mass resolution, and data were collected using the multiple positive-ion mode. The calibration range was 1.00 ng/mL to 1,000 ng/mL, with the lower limit of quantitation being 1.00 ng/mL. The calibration curve was linear over a concentration range of 1.00–1,000 ng/mL and the correlation coefficient (r) was >0.999. Precision and accuracy for this method were evaluated by calculating the intra- and inter-batch variations of QC samples in five replicates at four concentrations (1.00, 2.00, 40.0 and 800 ng/mL) for roxatidine. The intra- and inter-day precision (CV%) were less than 6.8% for roxatidine. The intra- and inter-day accuracy was within 95.5% to 104.5% for roxatidine. The recovery of the sample preparation by solid-phase extraction on a C8 column from plasma was estimated at three concentration levels of roxatidine. The extraction recoveries were 92.9, 88.4 and 92.5% at levels of 2.00, 40.0 and 800 ng/mL, respectively. In freeze and thaw stability (−20°C to room temperature), short-term stability at room temperature and post-preparative stability (in an autosampler set at 10°C), roxatidine was stable for three cycles, 24 h and 76 h, respectively. Roxatidine in human plasma was stable for 185 days storage at −20°C or −80°C. These validation results satisfied the criteria.

**Pharmacokinetic analysis:** The PK parameters were estimated by non-compartment methods with WinNonlin Professional Ver. 5.2.1 Software (Pharsight Corp., Mountain View, CA).

Maximum plasma concentration (C\text{max}), time of maximum plasma concentration (T\text{max}), and trough plasma concentration (C\text{trough}) were obtained from the observed data. Elimination half-life (T\text{1/2}) was obtained as ln 2/λ, where λ was calculated by least squares linear regression of the terminal portion of the log-transformed plasma concentration–time curve. The area under the plasma concentration vs. time curve from 0 to the last quantifiable concentration (AUC\text{0–∞}) was estimated using the linear trapezoidal rule. The AUC from 0 to infinity (AUC\text{0–∞}) was obtained as the sum of the (AUC\text{0–1}) and C\text{trough}/λ, where C\text{trough} is the last measurable drug concentration. Apparent Total Body Clearance (CL/F) was calculated by DOSE/AUC\text{0–∞}, and Volume of Distribution (Vd/F) was calculated by (CL/F)/λ\text{1/2}. Correlation coefficients were calculated using SAS 9.1.3 (SAS Institute Inc., Cary, NC). The PK parameters adjusted by body surface area (BSA) were obtained from (PK parameters)/BSA, where BSA was calculated from the DuBois formulas.\textsuperscript{12} The PK parameters adjusted by BW were obtained from (PK parameters)/BW. The differences between groups were tested by Student’s t test or analysis of covariance using SAS 9.1.3.

**Simulation of multiple-dose:** The multiple-dose data in pediatric patients were simulated with the superposition method using the mean plasma concentrations of roxatidine from a single-dose PK study in pediatric patients weighing less than 30 kg who took a 37.5 mg roxatidine capsule (n = 4) or weighing 30 kg or more who took 75 mg (n = 6).

**Results**

**Analytical validation:** The analysis of roxatidine and I.S. was highly selective with no interfering compounds. The calibration curve was linear over a concentration range of 1.00–1,000 ng/mL and the correlation coefficient (r) was >0.999. Precision and accuracy for this method were evaluated by calculating the intra- and inter-batch variations of QC samples in five replicates at four concentrations (1.00, 2.00, 40.0 and 800 ng/mL) for roxatidine. The intra- and inter-day precision (CV%) were less than 6.8% for roxatidine. The intra- and inter-day accuracy was within 95.5% to 104.5% for roxatidine. The recovery of the sample preparation by solid-phase extraction on a C8 column from plasma was estimated at three concentration levels of roxatidine. The extraction recoveries were 92.9, 88.4 and 92.5% at levels of 2.00, 40.0 and 800 ng/mL, respectively. In freeze and thaw stability (−20°C to room temperature), short-term stability at room temperature and post-preparative stability (in an autosampler set at 10°C), roxatidine was stable for three cycles, 24 h and 76 h, respectively. Roxatidine in human plasma was stable for 185 days storage at −20°C or −80°C. These validation results satisfied the criteria.

**Demographics:** A list of the demographics of the subjects in the single-dose PK study in pediatric patients, the single-dose PK study in healthy adult volunteers, and the multiple-dose PK evaluation in pediatric patients was provided in Table 1. None of the demographic characteristics was abnormal. Serum creatinine of pediatric patients and healthy adult volunteers were within normal range for age at each clinical study site.

Differences in age, BW, and BSA were present between the dosage groups in the multiple-dose PK evaluation in pediatric patients as the dosage was determined according to BW. The patients in the 37.5-mg group of the multiple-dose PK evaluation in pediatric patients were younger and had a lower BW and BSA than those in other pediatric dosage groups.

**Single-dose PK study in pediatric patients and healthy adult volunteers:** The plasma concentration-time curves for pediatric patients aged 6 to 14 years and healthy adult volunteers are shown in Figure 1. The profiles of the plasma roxatidine concentrations in the pediatric patients were similar to those in the healthy adult volunteers. Pharmacokinetic parameters of roxatidine in the pediatric patients and healthy adult volunteers are shown in Table 2. In the pediatric patients, C\text{max}, AUC\text{0–t}, and AUC\text{0–∞} increased proportionally for dose. T\text{max} and T\text{1/2} were generally constant, CL/F and Vd/F were similar across the dosing groups. C\text{max}, AUC\text{0–t}, and AUC\text{0–∞} in the healthy adult volunteers increased linearly with the dose.
When the PK parameters of roxatidine in the pediatric patients and healthy adult volunteers were compared, the mean C_{max} and AUC_{0-∞} in the pediatric patients following 37.5 and 75 mg was significantly higher than those in healthy adult volunteers [C_{max}: approx. 2.2-fold (p < 0.001) and 1.6-fold (p < 0.01), respectively, AUC_{0-∞}: approx. 1.5-fold (p < 0.01) at each dose].

Meanwhile, CL/F and Vd/F in the pediatric patients following 37.5 and 75 mg was significantly lower than those in healthy adult volunteers [CL/F: approx. 0.69-fold (p < 0.01) and 0.70-fold (p < 0.01), respectively, Vd/F: approx. 0.59-fold (p < 0.001) and 0.59-fold (p < 0.01), respectively].

An investigation of the relationships of CL/F and Vd/F to BSA or BW revealed a close correlation (Fig. 2). When adjusted by BSA or BW, the CL/F and Vd/F in the pediatric patients and healthy adult volunteers were comparable (Table 3). Both C_{max} and AUC_{0-∞} in the pediatric patients and healthy adult volunteers were closely correlated with the dose per unit BSA (mg/m\(^2\)) (C_{max}: r = 0.8406, AUC_{0-∞}: r = 0.9329) and also closely correlated with the dose per unit BW (mg/kg) (C_{max}: r = 0.8257, AUC_{0-∞}: r = 0.8455, Fig. 3).

Multiple-dose PK evaluation in pediatric patients: Steady state plasma trough roxatidine concentrations (C_{trough}) at the 2nd, 4th, and 8th week of repeated

**Table 1. Demographics of each study**

<table>
<thead>
<tr>
<th></th>
<th>37.5 mg</th>
<th>75 mg</th>
<th>150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose PK study in pediatric patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Sex male</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.8 ± 2.1</td>
<td>10.3 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>34.68 ± 9.34</td>
<td>33.70 ± 11.51</td>
<td></td>
</tr>
<tr>
<td>BSA (m(^2))</td>
<td>1.128 ± 0.157</td>
<td>1.135 ± 0.248</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.410 ± 0.118</td>
<td>0.417 ± 0.121</td>
<td></td>
</tr>
<tr>
<td>Single-dose PK study in healthy adult volunteers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Sex male</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>female</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.3 ± 7.3</td>
<td>37.5 ± 7.0</td>
<td>33.4 ± 7.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.46 ± 5.51</td>
<td>65.14 ± 8.47</td>
<td>63.73 ± 8.36</td>
</tr>
<tr>
<td>BSA (m(^2))</td>
<td>1.755 ± 0.066</td>
<td>1.769 ± 0.133</td>
<td>1.765 ± 0.133</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.794 ± 0.060</td>
<td>0.781 ± 0.141</td>
<td>0.824 ± 0.102</td>
</tr>
</tbody>
</table>

Multiple-dose PK evaluation in pediatric patients

| N                    | 6       | 15    |
| Sex male             | 3       | 8     |
| female               | 3       | 7     |
| Age (years)          | 8.2 ± 2.0 | 10.8 ± 2.0 |        |
| Weight (kg)          | 23.33 ± 3.44 | 38.63 ± 5.64 |        |
| BSA (m\(^2\))       | 0.877 ± 0.060 | 1.242 ± 0.111 |        |
| Serum creatinine (mg/dL) | 0.367 ± 0.071 | 0.424 ± 0.088 |        |

Mean ± S.D.

**Table 2. Pharmacokinetic parameters of roxatidine in pediatric patients and healthy adult volunteers**

<table>
<thead>
<tr>
<th></th>
<th>37.5 mg</th>
<th>75 mg</th>
<th>150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>354 ± 131</td>
<td>158 ± 20</td>
<td>330 ± 148</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng h/mL)</td>
<td>2.0–6.0</td>
<td>1.5–3.0</td>
<td>1.0–6.0</td>
</tr>
<tr>
<td>AUC_{0-∞} (mg h/mL)</td>
<td>1,995 ± 622</td>
<td>1,273 ± 228</td>
<td>3,513 ± 878</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>4.6 ± 1.1</td>
<td>5.6 ± 0.3</td>
<td>4.2 ± 0.9</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>19.6 ± 5.1</td>
<td>28.6 ± 5.3</td>
<td>22.4 ± 6.9</td>
</tr>
<tr>
<td>Vd/F (L)</td>
<td>134 ± 55</td>
<td>229 ± 41</td>
<td>138 ± 73</td>
</tr>
</tbody>
</table>

Mean ± S.D.

*Upper: median values, lower: range (min–max).*

---

**Fig. 1. Plasma roxatidine concentration (mean ± S.D.) in pediatric patients and healthy adult volunteers**

(a) Profiles after administration of roxatidine capsule (37.5, 75 mg) to pediatric patients. (b) Profiles after administration of roxatidine capsule (37.5, 75, 150 mg) to healthy adult volunteers.

Copyright © 2012 by the Japanese Society for the Study of Xenobiotics (JSSX)
doses were almost constant in children (Table 4). A simulation of roxatidine concentration profile after multiple doses was conducted using the superposition method with the mean plasma roxatidine concentrations in the single-dose PK study in pediatric patients. The results of the simulation were consistent with the measured Ctrough at the respective time (Fig. 4).

**Discussion**

The PK profile of roxatidine capsule in pediatric patients aged between 6 and 14 years was characterized and compared to that in healthy adult volunteers.

A number of assay methods have been developed for the determination of roxatidine in biological samples. However, blood sample volumes for pediatric studies should be minimized, and reduction of sample volumes was necessary. Therefore we developed a highly sensitive assay for the determination of roxatidine concentration. The necessary plasma volumes for each determination was reduced to 50 µL compared to 1 mL in adult trials previously performed, and our analytical method provided the advantages of high sensitivity with a limit of quantification (LOQ) of 1 ng/mL. The obtained PK parameters this time in healthy adult volunteers were comparable with those reported recently.°

Cmax and AUC0–∞ in the pediatric patients following 37.5 or 75 mg were higher than those in the healthy adult volunteers following the same doses, while Vd/F and CL/F were lower than those in the healthy adult volunteers. An investigation of the relationships of Vd/F to BSA or BW
revealed close correlation. Vd/F of roxatidine in the pediatric patients and healthy adult volunteers were comparable when adjusted by BSA or BW. Similarly, CL/F in the pediatric patients and healthy adult volunteers were comparable when adjusted by BSA or BW. The differences in Cmax and AUC0–∞ are therefore most likely attributable to differences in body size between children and adults. The absorption and elimination processes of roxatidine capsule in pediatric patients do not appear to differ substantially from the healthy adult volunteers, because Vd/F, CL/F adjusted by BSA or BW and also Tmax in the pediatric patients were similar to the adult values.

The close correlation of the Cmax and AUC0–∞ to the dose per unit BSA (mg/m²) in the pediatric patients and healthy adult volunteers shows that the PK profile of roxatidine capsule in pediatric patients is similar to the profile in healthy adult volunteers. Similar results were obtained for the dose per BW (mg/kg).

Fig. 3. The relationship between dose adjusted by BSA or BW to Cmax or AUC0–∞ in pediatric patients and healthy adult volunteers
Closed circles, pediatric patients; open circles, healthy adult volunteers; solid line, regression line. (a) Dose adjusted by BSA (mg/m²) and Cmax. Correlation coefficient = 0.8406. (b) Dose adjusted by BW (mg/kg) and Cmax. Correlation coefficient = 0.8257. (c) Dose adjusted by BSA (mg/m²) and AUC0–∞. Correlation coefficient = 0.9329. (d) Dose adjusted by BW (mg/kg) and AUC0–∞. Correlation coefficient = 0.8455.

Fig. 4. Profiles of plasma roxatidine concentrations after administration of roxatidine capsule to pediatric patients in the single-dose PK study and multiple-dose profiles simulated from single-dose PK study data
The multiple-dose data in pediatric patients were simulated with the superposition method using the mean plasma concentrations of roxatidine from the single-dose PK study in pediatric patients weighing less than 30 kg who took a 37.5 mg roxatidine capsule (n = 4) or weighing 30 kg or more who took 75 mg (n = 6). Ctrough in the multiple-dose PK evaluation in pediatric patients is shown. Solid line, 37.5 mg roxatidine capsule; broken line, 75 mg; open circles, Ctrough (mean ± S.D.) 37.5 mg at the second week (n = 1), at the 4th week (n = 5), and at the 8th week (n = 5); closed circles, Ctrough (mean ± S.D.) 75 mg at the 4th week (n = 14) and at the 8th week (n = 13).
Roxatidine excretion is dependent on renal function. $T_{1/2}$ has been reported to be prolonged, and AUC was increased in renal failure with low creatinine clearance. The dosage adjustment is necessary in renal failure. The pediatric patients with renal dysfunction were excluded in our studies, and in patients with renal dysfunction were excluded in our study.

Children aged 2 years or older is reported to be similar to that in adults. Clinical efficacy was observed in a phase 3 study with gastric pH as an endpoint was conducted (to be published elsewhere), and the results were comparable to that in other clinical studies of healthy adult volunteers.

Therefore, PK and PD profile of roxatidine in pediatric patients aged 6 years or older appears to be similar to that in adults. This is consistent with the results of our PK studies in pediatric patients and healthy adult volunteers.

The results of a simulation of plasma roxatidine concentrations after multiple doses based on the data of the single-dose PK study in pediatric patients were consistent with the measured trough levels in the multiple-dose PK evaluation in pediatric patients. This means that the steady state was reached, and that accumulation of roxatidine in plasma did not occur after multiple doses. Accumulation with roxatidine multiple doses did not occur in adults, either.

Gastric acid secretion reaches a level similar to that in adults by age 3 to 4 years. A pediatric pharmacodynamic (PD) study with gastric pH as an endpoint was conducted (to be published elsewhere), and the results were comparable to that in other clinical studies of healthy adult volunteers.

Therefore, PK and PD profile of roxatidine in pediatric patients aged 6 years or older appears to be similar to that in adults. Clinical efficacy was observed in a phase 3 study as well.

In conclusion, this investigation of the PK profile of roxatidine capsules in pediatric patients revealed the PK profile in children to be similar to that in adults when the data were adjusted by BSA or BW. This investigation also showed that the optimal roxatidine capsule dosage can be calculated according to the BSA or BW in patients aged 6 years or older. As the roxatidine capsule has a broad safety margin, the clinical dosage can be conveniently determined based on BW instead of BSA. Based on these data, the dosage of roxatidine approved by Pharmaceuticals and Medical Devices Agency for the pediatric patients with acid-related disease is 37.5 mg for those weighing less than 30 kg, and 75 mg for those weighing 30 kg or more.

Acknowledgments: The authors thank all investigators and investigators’ co-workers in the following sites. Hamamatsu University School of Medicine: Mitsuyoshi Nakashima, Saiseikai Yokohamashi Tobu Hospital: Ayano Inui, Miyagi Children’s Hospital: Daiki Abukawa, Maruyama Hospital: Shogo Sesoko, Sapporo-Kosei General Hospital: Mutsumo Konno, National Center for Child Health and Development: Katsuhiro Arai, Tokyo Metropolitan Children’s Medical Center: Yuko Hamasaki, Kanagawa Children’s Medical Center: Masato Shinkai, Eihiko Takahashi, Osaka General Medical Center: Hitoshi Tajiri, Osaka Medical Center and the Research Institute for Maternal and Child Health: Shinobu Ida.

References


