Pharmacokinetic–pharmacodynamic analysis of the role of CYP2C19 genotypes in short-term rabeprazole-based triple therapy against *Helicobacter pylori*

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**WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT**
- Asians have a higher percentage of CYP2C19 poor metabolizers (PMs) and a high percentage of *Helicobacter pylori* infection compared with Whites.
- Although rabeprazole has been suggested to be least affected by CYP2C19 genotype, the pharmacokinetic properties of rabeprazole have been shown to correlate with the CYP2C19 genotype.
- Short-term (<7 days) rabeprazole-based triple therapy has been suggested for its use in eradicating *H. pylori*, whereas the eradication rate has been reported variously as 90–27% without CYP2C19 genotyping.

**WHAT THIS STUDY ADDS**
- Population pharmacokinetic–pharmacodynamic analysis showed that the plasma rabeprazole levels, the values of $k_{eo}$ (the first-order rate constant for drug dissipation from the effect compartment), and the predicted gastrin-time profile were higher in CYP2C19 PMs than in EMs after multiple dosing.
- *Helicobacter pylori* was eradicated in all CYP2C19 PMs except in one patient infected by a resistant strain, whereas the eradication rates ranged from 58 to 85% in CYP2C19 EMs.

**AIMS**
The aim was to explore the role of CYP2C19 polymorphism in short-term rabeprazole-based triple therapy against *Helicobacter pylori* infection.

**METHODS**
Patients with *H. pylori* infection were tested for CYP2C19 genotype as poor metabolizers (PMs) or extensive metabolizers (EMs, homozygous EM or heterozygous EM) and given rabeprazole for 7 days. Antibiotics (clarithromycin and amoxicillin) were given on days 1–4, days 4–7, or days 1–7. A direct link model with an effect compartment was used in the population pharmacokinetic–pharmacodynamic analysis. The status of *H. pylori* infection was evaluated.

**RESULTS**
Rabeprazole clearance was lower in CYP2C19 PMs than in EMs (with average values of 18.7 vs. 16.8 l h$^{-1}$ in PMs and EMs, respectively), resulting in higher plasma levels in the former group. The values of EC$_{50}$ and $k_{eo}$ of gastrin response increased with multiple doses of rabeprazole. The $k_{eo}$ values were lower in CYP2C19 PMs than in EMs on day 1 (0.012 vs. 0.017 × 10$^{-4}$ min$^{-1}$), and higher than in EMs on day 4 (0.804 vs. 0.169 × 10$^{-4}$ min$^{-1}$) of rabeprazole treatment. The predicted gastrin-time profile showed a higher response in CYP2C19 PMs than in EMs on days 4 and 7. *Helicobacter pylori* was eradicated in all CYP2C19 PMs except in one patient infected by a resistant strain. In contrast, in CYP2C19 EMs the eradication rates ranged from 58 to 85%.

**CONCLUSIONS**
CYP2C19 genotypes play a role in *H. pylori* eradication therapy. Rabeprazole-based short-term triple therapy may be applicable in CYP2C19 PMs for *H. pylori* eradication.
Introduction

*Helicobacter pylori* is closely related to many gastrointestinal diseases, including chronic active gastritis, peptic ulcers, gastric carcinoma and gastric mucosa-associated lymphoid tissue lymphoma [1]. Eradication of *H. pylori* is important for reducing the relapse rate of ulcers and risk of carcinogenesis. Triple therapy with a proton pump inhibitor (PPI) and two antibiotics is considered a standard treatment for *H. pylori* infection. When the drugs are given at the recommended doses, the eradication rates range from 70 to 85% for a duration of treatment of 7–14 days [2, 3]. Few studies have compared the cost effectiveness of these different lengths of treatment [4]. Nonetheless, short-term (i.e. <7 days) triple therapy has been reported to increase patient compliance and reduce costs and adverse effects [5–7], but the evidence is limited and the rationale needs to be elucidated.

In an acidic environment, PPIs are protonated to form sulphenamides, which are covalently bound with cysteine residues in the gastric proton pump to inhibit proton secretion [8]. Most PPIs are mainly metabolized by CYP2C19, which is known to exhibit polymorphism in both its genotype and phenotype with much higher percentage of poor metabolizers (PMs) in Asians [9, 10]. Among the PPIs, rabeprazole has been demonstrated to have a high degree of activity against *H. pylori*. One reason is the higher pKa for the conversion of rabeprazole to the sulphenamide, which means it is converted at a higher pH than other PPIs, resulting in more rapid proton pump inhibition [11]. Furthermore, rabeprazole and its thio-ether metabolite inhibit the motility and urease activity of *H. pylori* [12, 13]. Given the better pharmacological profile of rabeprazole, a shorter regimen has been suggested for its use in eradicating *H. pylori*; however, the findings are controversial and the eradication rate using rabeprazole–amoxicillin–clarithromycin for 3–4 days has been reported variously as 90–27% [5]. One reason for the variation in these results could be that the CYP2C19 genotypes of the enrolled subjects were not determined in these studies. Although rabeprazole has been suggested to be the PPI least affected by CYP2C19 genotype [14], the eradication rate of a rabeprazole regimen has been shown to correlate with the CYP2C19 genotype [15]. The pharmacokinetic properties, including the area under the curve (AUC), maximal plasma concentration (Cmax) and clearance (CL) of rabeprazole were all found to be significant different between CYP2C19 PMs and CYP2C19 extensive metabolizers (EMs) [16]. Higher plasma gastrin levels were also observed in CYP2C19 PMs than in EMs after taking rabeprazole 20 mg b.i.d. for 4 days [17]. Since the extent and duration of intra-gastric acid inhibition have been proven to be important in *H. pylori* eradication and ulcer healing [14, 18], the higher plasma concentrations of rabeprazole and gastrin in CYP2C19 PMs may contribute to a better clinical outcome.

In the present study, population pharmacokinetic–pharmacodynamic (PK–PD) analysis was used to explore the role of CYP2C19 genotype in rabeprazole-based triple therapy on days 1, 4 and 7 of treatment. In addition, the clinical outcome of *H. pylori* eradication was evaluated in patients receiving rabeprazole with different antibiotic regimens for 1 week.

Materials and methods

Study design

Patients with *H. pylori*-positive ulcer or gastritis were recruited at the National Taiwan University Hospital. Patients who met any of the following conditions were excluded: (i) pregnant or nursing woman; (ii) serious concomitant illness; (iii) malignant tumour of any kind; (iv) serious bleeding during the course of this ulcer; (v) previous gastric surgery; and (vi) taking bismuth compounds or PPIs within 30 days prior to pretreatment endoscopy. Ulcer and *H. pylori* status were evaluated by endoscopy, histology, culture and the 13C-urea breath test. The study was approved by the Ethical Practices Committee of the National Taiwan University Hospital (Study ID number: 920505, NTUH93S060).

These patients were randomly assigned to one of the three study groups after giving their written informed consent. Rabeprazole 20 mg twice daily was given orally for 7 days to all three groups. Amoxicillin 1 g and clarithromycin 500 mg were also given twice daily on days 1–4 of rabeprazole treatment (group A), days 4–7 (group B), or days 1–7 (group C). The CYP2C19 genotype of each participant was analysed by the polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) method.

For PK–PD analysis, to avoid the patients having to be present all day, they were randomly assigned to one of four groups and, on days 1, 4 or 7 of rabeprazole treatment, 10-ml aliquots of venous blood were drawn 30 min before drug administration and at the time points of 0.5, 2, 4 and 8 h (group 1), 0.5, 1, 3 and 6 h (group 2), 1, 3, 6 and 10 h (group 3), or 2, 4, 8 and 10 h (group 4). The blood was centrifuged at 800 g for 10 min within 15 min of collection and 200 µl of plasma was taken for gastrin analysis and the rest of the sample placed in a storage tube containing 350 µl of a 1% aqueous solution of diethylamine for plasma rabeprazole concentration analysis. All samples were frozen at −80°C until analysis.

Endoscopy and biopsy

During each endoscopic examination, four biopsy specimens were obtained from the antrum and four from the body for histology, bacterial culture, and the Campylobacter-like organism (CLO) test. Two of the four pairs of specimens were processed with haematoxylin and eosin and Warthin–Starry silver stain. Another pair was
placed in brain heart infusion broth for transportation, then ground up and streaked onto an agar plate with selective medium [19]. The plates were incubated at 37 °C under micro-aerophilic conditions (5% O₂, 10% CO₂, 85% N₂) for 3–7 days. Helicobacter pylori was identified by its characteristic biotyping as Gram-negative, but oxidase-, catalase- and urease-positive. The fourth pair of specimens was tested using a CLO test kit (Delta West Pty Ltd., Bentley, Western Australia), the colour of which changes from yellow to purple if H. pylori is present.

**Evaluation of H. pylori status and antibiotic resistance**

Helicobacter pylori status was considered positive when (i) at least two of the above three tests were positive or (ii) only the bacterial culture test was positive. The E-test (AB Biodisk, Solna, Sweden) was used to evaluate the amoxicillin and clarithromycin resistance of H. pylori, which was considered to be resistant to antibiotics when the minimum inhibitory concentration value was ≥1 mg L⁻¹ [19]. Helicobacter pylori eradication was evaluated using a ¹³C-urea breath test before, and at 4–6 weeks after, rabeprazole treatment, performed as described previously [17].

**CYP2C19 genotyping**

DNA was isolated from peripheral leucocytes in blood samples by a standard method [20]. Genetic polymorphism of the CYP2C19*2 (CYP2C19 m1) and CYP2C19*3 (CYP2C19 m2) alleles was identified by PCR-RFLP as described previously [21, 22]. Patients were identified as homozygous extensive metabolizers (HomEM; wt/wt), heterozygous extensive metabolizers (HetEM; wt/m1 or wt/m2) or poor metabolizers (PM; m1/m1 or m1/m2) according to CYP2C19 genotypes.

**Determination of plasma concentrations of rabeprazole and gastrin**

Plasma concentrations of rabeprazole were determined by high-performance liquid chromatography as described previously [23]. Plasma gastrin concentrations were determined by radioimmunoassay using ICN kits (ICN Pharmaceuticals, Costa Mesa, CA, USA) according to the manufacturer’s protocol, as in a previous study [17].

**Population PK–PD analysis**

Population PK–PD analysis was performed using the NONMEM program (version V, level 1.1). To establish the PK and PD models, the data were analysed according to the day of rabeprazole treatment (i.e. pooled data for day 1, day 4, or day 7) given that the dosing of antibiotics is irrelevant to the PK–PD properties of rabeprazole. A naïve-pooled data analysis (i.e. pool data for all subjects and fit single ‘naïve’ individual) was performed to obtain the initial values for population PK–PD analysis. PK properties were estimated before the link to PD analysis. For PK analysis, first-order conditional estimation and a PREDPP subroutine, ADVAN2, were used for a one-compartment model with first-order absorption (kₐ) and a lag time (Aₐrog). For PD analysis, a first-order method and a PREDPP subroutine, ADVAN6, were used after the estimation of the PK parameters. On the basis of the counterclockwise hysteresis loop observed in the concentration–effect profile of rabeprazole [17], a direct link model with an effect compartment was used [24]. The concentration in the effect compartment (Cₑ) is described by Equation 1:

\[
C_e = \frac{k_{eo} k_d D}{V_d} \left[ e^{-k_{eo} t} + \frac{(k_{eo} - k) (k - k_o)}{(k_o - k_o) (k - k_o)} \right]
\]

(1)

where \( k_{eo} \) is the first-order rate constant for drug dissipation from the effect compartment, \( k_o \) the absorption constant, \( V_d \) the volume of distribution, and \( D \) the dose of rabeprazole. The PD response is described by Equation 2:

\[
E = E_0 + \left( \frac{E_m - E_0}{C_{EC_{50}} + C_d} \right)
\]

(2)

where \( E \) is the gastrin levels after dosing, \( E_0 \) the baseline gastrin levels, \( E_m \) the maximal gastrin levels, \( C_{EC_{50}} \) the rabeprazole concentration to produce half \( E_m \), and \( \gamma \) the slope factor of the concentration–response curve. The base and final models for the PK and PD analysis are listed in Table 1, in which \( \theta \) represents the predicted population mean of the parameters, \( \eta \) the random effect with a mean of zero and a variance of \( \sigma^2 \), and BSA the body surface area estimated using Mosteller’s formula [25].

**Statistical analysis**

The equivalence of demographic information among various treatment groups or genotypes was revealed by \( \chi^2 \).

**Table 1**

Parameters used in the population pharmacokinetic–pharmacodynamic (PK–PD) analysis for rabeprazole*

<table>
<thead>
<tr>
<th>Base PK model</th>
<th>Final PK model</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_d = \theta_{V_d} \times e^{\eta_{V_d}} )</td>
<td>( V_d = \theta_{V_d} \times e^{\eta_{V_d}} )</td>
</tr>
<tr>
<td>( CL = \theta_{CL} \times e^{\eta_{CL}} )</td>
<td>( CL = \theta_{CL} \times e^{\eta_{CL}} )</td>
</tr>
<tr>
<td>( k_o = \theta_{k_o} \times e^{\eta_{k_o}} )</td>
<td>( k_o = \theta_{k_o} \times e^{\eta_{k_o}} )</td>
</tr>
<tr>
<td>( A_{elag} = \theta_{A_{elag}} \times e^{\eta_{A_{elag}}} )</td>
<td>( A_{elag} = \theta_{A_{elag}} \times e^{\eta_{A_{elag}}} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Base PD model</th>
<th>Final PD model</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_0 = \theta_{E_0} \times e^{\eta_{E_0}} )</td>
<td>( E_0 = \theta_{E_0} \times e^{\eta_{E_0}} )</td>
</tr>
<tr>
<td>( E_m = \theta_{E_m} \times e^{\eta_{E_m}} )</td>
<td>( E_m = \theta_{E_m} \times e^{\eta_{E_m}} )</td>
</tr>
<tr>
<td>( EC_{50} = \theta_{EC_{50}} \times e^{\eta_{EC_{50}}} )</td>
<td>( EC_{50} = \theta_{EC_{50}} \times e^{\eta_{EC_{50}}} )</td>
</tr>
<tr>
<td>( k_{eo} = \theta_{k_{eo}} \times e^{\eta_{k_{eo}}} )</td>
<td>( k_{eo} = \theta_{k_{eo}} \times e^{\eta_{k_{eo}}} )</td>
</tr>
<tr>
<td>( \gamma = \theta_{\gamma} \times e^{\eta_{\gamma}} )</td>
<td>( \gamma = \theta_{\gamma} \times e^{\eta_{\gamma}} )</td>
</tr>
</tbody>
</table>

* \( V_d \), volume of distribution; \( CL \), clearance; \( k_o \), absorption constant; \( A_{elag} \), absorption lagged time; \( E_0 \), maximal effect; \( E_m \), baseline effect; \( EC_{50} \), concentration when half \( E_m \) achieved; \( \kappa_{eo} \), elimination constant for the effect compartment; BSA, body surface area; \( \gamma \), slope; GT, CYP2C19 genotype; \( \theta_0 \), population mean of parameter \( x \); \( \eta_{x} \), inter-subject variability of parameter \( x \).
independence test or *t*-test or ANOVA. The comparisons of predicted PK–PD parameters among various days or genotypes were analysed by the two-sided *t*-test or ANOVA. Fisher’s exact test or the \( \chi^2 \) test was used to analyse clinical outcome, only those subjects who completed the study being included in the analysis. A *P*-value < 0.05 was considered to be statistically significant.

**Results**

**Subject characteristics**

Forty-eight subjects, 33 men and 15 women, aged 18–74 years were enrolled and assigned randomly to one of the three study groups A, B and C (antibiotics on days 1–4, 4–7, or 1–7, respectively) (Table 2). Nine cases were CYP2C19 PMs and 39 EMs (including 18 HomEM and 21 HetEM). The prevalence rates of CYP2C19 HomEM, HetEM and PM were about 38, 44 and 18%, respectively. One subject with EM genotype in group B was excluded from the PK–PD analysis due to the lack of a blood sample. One subject with EM genotype in group C was excluded from the clinical outcome estimation because she failed to attend for the after-treatment \(^{13}\)C-urea breath test evaluation.

The \( \chi^2 \) independence tests revealed that the gender structure and genotype structure were not significantly different among three study groups, with \( P \)-values of 0.418 and 0.605, respectively. The gender structure was not significantly different (\( P \)-value = 0.285) between PM and EM groups. The two-way ANOVA showed that the means of age were not significantly different among three groups (\( P \)-value = 0.424) or between two genotypes (\( P \)-value = 0.962), and no significant differences on the interaction of study groups and genotypes (\( P \)-value = 0.370). There was no significant difference in the demographic data for the patients categorized by treatment group (Table 2) or CYP2C19 genotype (except the age between HomEM and HetEM on day 7) or rabeprazole treatment day (Table 3).

**Population PK–PD analysis**

In the PK analysis (Table 4), addition of the CYP2C19 genotype and the BSA of the subjects improved the fit compared with the base model, and these were therefore included in the final PK model. For the PK parameters, there was no difference among the different sampling days in subjects with the same CYP2C19 genotype (Table 4). The total clearance of rabeprazole in CYP2C19 PMs was signifi-

### Table 2

Demographic data for the patients on the different treatment protocols (groups A, B, and C)*

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>CYP2C19 (HomEM/HetEM/PM)</td>
<td>5/8/3</td>
<td>5/7/4</td>
<td>8/6/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.5 (26–73)</td>
<td>47.6 (18–72)</td>
<td>53.3 (37–74)</td>
</tr>
<tr>
<td>Gender (% M/F)</td>
<td>62.5/37.5</td>
<td>81.3/18.8</td>
<td>62.5/37.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.3 (158–180)</td>
<td>166.5 (156–176)</td>
<td>165.2 (155–174)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.1 (49–81)</td>
<td>65.2 (49–85)</td>
<td>63.3 (49–77)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.70 (1.47–1.94)</td>
<td>1.73 (1.48–2.00)</td>
<td>1.70 (1.50–1.86)</td>
</tr>
</tbody>
</table>

*Rabeprazole treatment from day 1 to day 7, antibiotics (amoxicillin and clarithromycin) being given on days 1–4 (group A), days 4–7 (group B), or days 1–7 (group C). The values in parentheses indicate the data range. HomEM, homozygous extensive metabolizers; HetEM, heterozygous extensive metabolizers; PM, poor metabolizers; BSA, body surface area.

### Table 3

Demographic data for the patients categorized according to rabeprazole treatment day

<table>
<thead>
<tr>
<th></th>
<th>Day 1 HomEM</th>
<th>HetEM</th>
<th>PM</th>
<th>Day 4 HomEM</th>
<th>HetEM</th>
<th>PM</th>
<th>Day 7 HomEM</th>
<th>HetEM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>13</td>
<td>14</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>7</td>
<td>14</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.7 (26–74)</td>
<td>51.6 (37–65)</td>
<td>52.4 (44–62)</td>
<td>54.9 (26–73)</td>
<td>46.1 (18–65)</td>
<td>53.9 (37–72)</td>
<td>57.2 (44–74)</td>
<td>44.5* (44–70)</td>
<td>48.8</td>
</tr>
<tr>
<td>Gender (% M/F)</td>
<td>69/31 (69/31)</td>
<td>63/36 (64/36)</td>
<td>50/60 (49/51)</td>
<td>82/18 (82/18)</td>
<td>73/27 (73/27)</td>
<td>57/43 (57/43)</td>
<td>69/31 (69/31)</td>
<td>77/23 (77/23)</td>
<td>67/33</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.4 (155–180)</td>
<td>165.3 (156–175)</td>
<td>165.0 (160–169)</td>
<td>166.7 (156–180)</td>
<td>165.7 (156–175)</td>
<td>165.4 (160–170)</td>
<td>164.1 (155–172.5)</td>
<td>167.7 (160–170)</td>
<td>165.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.2 (55–77.1)</td>
<td>63.2 (49–81)</td>
<td>58.2 (49.1–62)</td>
<td>66.2 (52–77.1)</td>
<td>63.1 (49.1–62)</td>
<td>63.4 (49.8–52)</td>
<td>65.0 (52–77)</td>
<td>64.9 (52–74)</td>
<td>61.2</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.73 (1.55–1.94)</td>
<td>1.70 (1.47–1.90)</td>
<td>1.63 (1.50–1.71)</td>
<td>1.75 (1.51–1.94)</td>
<td>1.70 (1.47–1.90)</td>
<td>1.70 (1.48–2.00)</td>
<td>1.72 (1.51–1.89)</td>
<td>1.74 (1.50–1.87)</td>
<td>1.67</td>
</tr>
</tbody>
</table>

*P < 0.05, day 7 HomEM vs. HetEM. The values in parentheses indicate the data range. HomEM, homozygous extensive metabolizers; HetEM, heterozygous extensive metabolizers; PM, poor metabolizers; BSA, body surface area.
Table 4
Estimated pharmacokinetic parameters for the patients categorized by rabeprazole treatment day

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HomEM</td>
<td>HetEM</td>
</tr>
<tr>
<td>CL (l h⁻¹)</td>
<td>16.8*</td>
<td>14.8*</td>
</tr>
<tr>
<td>SD</td>
<td>2.61</td>
<td>3.39</td>
</tr>
<tr>
<td>K (h⁻¹)</td>
<td>0.72</td>
<td>0.63</td>
</tr>
<tr>
<td>SD</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>V (l)</td>
<td>24.7</td>
<td>25.1</td>
</tr>
<tr>
<td>SD</td>
<td>4.71</td>
<td>3.82</td>
</tr>
<tr>
<td>Ka (l/h)</td>
<td>2.61</td>
<td>1.91</td>
</tr>
<tr>
<td>SD</td>
<td>1.33</td>
<td>2.26</td>
</tr>
</tbody>
</table>

*Significant difference (P < 0.05) from PM. HomEM, homozygous extensive metabolizers; HetEM, heterozygous extensive metabolizers; EM, extensive metabolizers; PM, poor metabolizers.

Table 5
Estimated pharmacodynamic parameters for the patients categorized by rabeprazole treatment day

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 4</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All EM</td>
<td>PM</td>
</tr>
<tr>
<td>E₀ (pg ml⁻¹)</td>
<td>42.3  (23.6)</td>
<td>40.3 (55.7)</td>
</tr>
<tr>
<td>Eₘₐₓ (pg ml⁻¹)</td>
<td>293.4 (104.0)</td>
<td>289.8 (1.8)</td>
</tr>
<tr>
<td>EC₅₀ (ng ml⁻¹)</td>
<td>0.21 (1.2)</td>
<td>56.0 (2.4)</td>
</tr>
<tr>
<td>AUC₀⁻∞ (h)</td>
<td>2.0003 (0.1)</td>
<td>2.0003 (0.0006)</td>
</tr>
</tbody>
</table>

*P < 0.05 between all EMs and PMs on day 1 and day 4, †P < 0.05 between day 1 and day 7. ‡P < 0.05 between day 1 and day 7. The values in parentheses indicate the standard deviation. EM, extensive metabolizers; PM, poor metabolizers.

Significantly lower than that in CYP2C19 EMs on days 1, 4 and 7 of treatment (P < 0.05). In all treatment days, the average values of rabeprazole clearance were 10.7 and 16.8 l h⁻¹ in PMs and all EMs, respectively. The clearance estimated in HomEM was not different from that in HetEM. The volume of distribution (V₀) and the absorption rate constant (Ka) were comparable between patients with the different CYP2C19 genotypes. Accordingly, higher plasma rabeprazole concentrations were observed in CYP2C19 PMs than in EMs after either a single dose (i.e. day 1) or multiple doses (i.e. day 4 and day 7) of rabeprazole treatment.

The baseline serum gastrin levels were 37.1 ± 26.4, 29.0 ± 22.9 and 20.8 ± 21.9 pg ml⁻¹, respectively, for HomEM, HetEM and PM (P = 0.717). Since HomEM and HetEM did not differ in their PK properties, they are pooled as EM (compared with PM) for further PD analysis (Table 5). As a result, the maximal effect (Eₘₐₓ) was decreased and the EC₅₀ increased after multiple doses of rabeprazole, indicating that a higher rabeprazole concentration may be required to achieve the same effect after multiple doses. The mean estimated keo value from the effect compartment also increased with multiple doses. It was noted that the keo value was lower in CYP2C19 PMs than in EMs on day 1, and higher than in EMs on day 4 of rabeprazole treatment. A higher keo value indicates a shorter delay before the rabeprazole-induced gastrin response. When the gastrin response of rabeprazole was predicted according to Equation 2 as a function of time, CYP2C19 PMs showed a better response than EMs on days 4 and 7, and the gastrin concentration increased after multiple doses of rabeprazole (Figure 1).

Clinical outcome (H. pylori eradication)
Forty-seven subjects completed the evaluation of eradication. Of these, H. pylori infection was successfully eradicated in 36 (Table 6). The sensitivity of H. pylori to clarithromycin played an important role in the eradication rate. Subjects infected by clarithromycin-sensitive H. pylori had significantly higher eradication rates than those infected by clarithromycin-resistant H. pylori (83.3% vs. 20%, P = 0.008; all sampling days combined). There was no significant difference in eradication rate among the different treatment groups, even after stratification for clarithromycin sensitivity (Table 6). However, we do observe the decreasing P-value (P-value decrease from 0.491 to 0.108) for the testing of equal eradication rates among three treatment groups when we considered clarithromycin sensitivity only. It was also noted that H. pylori infection was successfully eradicated in all CYP2C19 PMs, independent of the regimen, except in one patient infected by a resistant strain. In contrast, the eradication rate ranged from 71 to 80% in HomEM and from 43 to 100% in HetEM, depending on the treatments. No
significant difference was observed in HomEM and HetEM for *H. pylori* eradication in each group. Without stratification of HomEM and HetEM, the cure rate in all EMs ranged from 58 to 85%. Despite the higher cure rate in PMs, due to the limited number no statistically significant difference was observed between CYP2C19 PMs and EMs in each treatment group.

The incidence of adverse effects was 12.5, 12.5 and 25% in groups A, B and C, respectively (Table 7). Although adverse events in groups A and B were less frequent, the difference was not significant. The symptoms were mild and did not result in discontinuation of treatment. They included a bad taste, loose stools, dizziness, abdominal distress, and nausea. Drug compliance was 100% in groups A and B and 95% in group C.

### Discussion

CYP2C19 is one of the major enzymes in PPI metabolism. The PK–PD properties of PPIs such as omeprazole, lansoprazole or pantoprazole are related to the CYP2C19 genotype [9]. It is now known that the efficacy of omeprazole-based *H. pylori* therapy is dependent on the CYP2C19 genotype. Omeprazole-based therapies with duration >7 days give significantly higher eradication rates in CYP2C19 PMs than in HomEM [26]. Other studies also found a median intragastric pH <4 in CYP2C19 HomEM treated with multiple doses of omeprazole for >7 days [9, 27]. Rabeprazole is considered to be more active against *H. pylori* than most PPIs [11–13]. The ability of rabeprazole to maintain the intragastric pH above 4 in CYP2C19 HomEM is better than that of omeprazole [28]. Although rabeprazole metabolism has been considered to be less affected by the CYP2C19 genotype, CYP2C19 PMs have a significantly higher plasma rabeprazole concentration and stronger inhibitory activity on acid secretion [16, 28–31]. Furthermore, the concentration of rabeprazole thioether, the major metabolite of rabeprazole with anti-*H. pylori* activity, is higher in CYP2C19 PM [14, 32].

In the present study, the population PK analysis showed that CYP2C19 PMs had a significant lower clearance than EMs (HomEM and HetEM), resulting in higher plasma rabeprazole levels in CYP2C19 PMs. However, there was no different in PK properties of rabeprazole between HomEM and HetEM. Since the pharmacological activity of PPIs is known to be dose-dependent [14], the higher plasma concentration might result in a better response. To confirm this, a further PD analysis was performed using gastrin as a surrogate marker of the intragastric pH [33]. The results showed a correlation between plasma levels of rabeprazole and gastrin based on a direct link model. A greater and more rapid gastrin response was observed in CYP2C19 PMs on days 4 and 7 of rabeprazole treatment, reflecting stronger acid inhibition. In terms of clinical outcome,
although the sample size might limit the power for statistical analysis and clarithromycin resistance had a great effect on \textit{H. pylori} eradication, it was noted that \textit{H. pylori} was successfully eradicated in all CYP2C19 PMs infected by clarithromycin-sensitive \textit{H. pylori} regardless of the regimen they received. CYP2C19 PMs tended to have better treatment outcomes under both standard (i.e. 7 days) and short-term \textit{H. pylori} therapies.

Short-term triple therapy is not regularly used for \textit{H. pylori} treatment because of the inconsistency in the reported eradication rates; however, this may be partly due to the failure to report the CYP2C19 genotypes of the subjects [5–7, 34–36]. The successful \textit{H. pylori} eradication in CYP2C19 PMs seen in the present study suggests the possible use of short-term triple therapy in such patients. In addition, amoxicillin and clarithromycin used in triple therapy are unstable at a pH < 4 [37]. The faster and better control of the intragastric pH in CYP2C19 PMs suggests that short-term rabeprazole-based triple therapy may be useful in such patients. Our PK–PD analysis results also suggest a higher gastrin response in both CYP2C19 PMs and EMs after multiple doses of rabeprazole. This is in accordance with the potent and long-acting inhibition of gastric acid secretion by rabeprazole [38]. When the next dose is given, acid secretion is still inhibited by the previous dose and a relatively small proportion of the acid secretion inhibition is contributed by the next dose. This phenomenon is reflected by the increased EC$_{50}$ and decreased $E_{\text{max}}$ seen after multiple doses. Although CYP2C19 PMs tended to have a better response than EMs, the sufficiently high intragastric pH achieved in both groups after multiple doses of rabeprazole may partially minimize the difference in \textit{H. pylori} eradication rate, as observed with therapies longer than 7 days [26].

Taken together, the PK–PD study showed a better response in CYP2C19 PMs after multiple dosing. Also, a tendency of better clinical outcome was observed in CYP2C19 PMs along with a decrease in the number of adverse events with short-term therapy. Thus, the CYP2C19 genotype plays a role in \textit{H. pylori} eradication therapy, and short-term rabeprazole-based triple therapy may be applicable in CYP2C19 PMs for \textit{H. pylori} eradication. The possibility of the use of short-term triple therapy in CYP2C19 PMs may provide further advantages, such as increased compliance, reduced cost and less drug resistance.

**Competing interests**

None to declare.

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