Importance of CYP2C19 genetic polymorphism in the eradication of Helicobacter pylori in north Indians

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Background & objectives: Genetic polymorphism of CYP2C19 is known to occur with a frequency of 12 per cent in north Indian population. But no study correlated CYP2C19 genetic polymorphism with eradication of Helicobacter pylori in north Indian gastritis patients positive for H. pylori and hence this study.

Methods: Ninety one consecutive patients positive for H. pylori fulfilling the study criteria were phenotyped and genotyped for CYP2C19. They were given 20 mg omeprazole (OPZ), 750 mg amoxicillin (AMC) and 500 mg tinidazole (TNZ) (bid) for 7 days followed by 20 mg OPZ (qd) for 21 days. Non eradicated extensive metabolizers (EMs) were retreated with 40 mg OPZ (bid) and 500 mg AMC (qid) for 14 days.

Results: EMs and poor metabolizers (PMs) excreted 4.26 ± 0.34 (95% CI 3.59-4.92) and 0.73 ± 0.05 (95% CI 0.63-0.82) µmol 5-OH-OPZ in 8 h, respectively. After initial therapy, EMs demonstrated 37 per cent (95% CI: 24.5-49.5) and PMs 92 per cent (95% CI: 77-107) eradication of H. pylori. Non eradicated EMs after retreatment demonstrated 90 per cent (95% CI: 79-101) eradication.

Interpretation & conclusions: This study demonstrated a direct correlation between CYP2C19 genetic polymorphism and H. pylori eradication in north Indian patients with gastritis. Knowing the CYP2C19 phenotype of a patient may help in prescribing optimum dose of proton pump inhibitor to achieve better therapeutic outcome.

Key words CYP2C19 - Genetic polymorphism - Helicobacter pylori - pharmacogenetics - proton pump inhibitors
pharmacodynamics of PPIs in the population. Frequency of CYP2C19 PMs varies in different populations\textsuperscript{4-9}. A concordance exists between in vitro activity of OPZ hydroxylase and CYP2C19 genotypes in north Indians. Heterozygote EMs (CYP2C19*1/*2) and mutant homozygote PMs (CYP2C19*2/*2) demonstrate 52 and 11 per cent activity of OPZ hydroxylase compared to normal homozygote EMs (CYP2C19*1/*1), thus demonstrating a gene dose effect\textsuperscript{10}.

Plasma concentration of different PPIs, their effect on intragastric pH and eradication of *H. pylori* depend significantly on CYP2C19 genotypes, with a better therapeutic outcome in PMs. Plasma OPZ area under curve (AUC) after a single oral dose of 20 mg OPZ was 421 ng.h/ml in normal homozygotes, 1403 ng.h/ml in heterozygotes and mutant homozygotes\textsuperscript{11}. Mean 24 h intragastric pH measured at intervals of 2 h in healthy Japanese normal homozygotes, heterozygotes and mutant homozygotes was 2.14, 3.3 and 4.47, respectively\textsuperscript{11}. Recently, Hunfeld et al\textsuperscript{12} suggested that Caucasian subjects with CYP2C19*1/*1 and CYP2C19*1/*17 genotype need stronger acid suppression therapy, especially during the first days of treatment or with on-demand therapy.

*H. pylori* positive gastric ulcer Japanese patients dual therapy results in 29, 60 and 100 per cent eradication in normal homozygotes, heterozygotes and mutant homozygotes, respectively\textsuperscript{13}. In a similar study dual therapy with 20 mg OPZ (bid) and 500 mg AMC (qid) for 1 wk demonstrated 100 per cent eradication in Japanese mutant homozygotes compared to 40 and 42 per cent in normal homozygotes and heterozygotes, respectively\textsuperscript{14}.

Hsu et al\textsuperscript{15} reported that 20 mg OPZ (bid), 1000 mg AMC (bid) and 500 mg TNZ (bid) for 14 days achieved 88 per cent (95\% CI: 79-96) eradication of *H. pylori*. Twenty mg OPZ (bid), 500 mg TNZ (bid) and 500 mg CAM (bid) for 7 days achieved 84.1 per cent (95\% CI: 73.9\textendash 91.2) eradication of *H. pylori*\textsuperscript{16}. Twenty mg OPZ (bid), 1000 mg AMC (bid) and 500 mg CAM (bid) for 7 days achieved 87.2 per cent (95\% CI: 77.9\textendash 93.8) eradication of *H. pylori*\textsuperscript{16}. Hence, eradication therapies consisting of a combination of a PPI with either TNZ-AMC, TNZ-CAM or AMC-CAM are equally effective. Information on the effect of CYP2C19 genotypes on eradication of *H. pylori* using dual\textsuperscript{13,14} or triple therapy\textsuperscript{17,18} is available in different populations but there are no data on Indian population and hence, the present study.

**Material & Methods**

**Procurement of chemicals:** Novapak C\textsubscript{8} column was supplied by Waters (India) Pvt. Ltd., Bangalore, India. E. Merck (India) Ltd., Bombay, India supplied sodium perchlorate, KH\textsubscript{2}PO\textsubscript{4}, HPLC grade acetonitrile and dichloromethane. Lomac capsules (Cipla Ltd., Bombay, India) containing 20 mg OPZ were purchased from local suppliers. Exp 31, Bst XI and Rsa I were purchased from MBI Fermentas Inc, Hanover, MD, USA. Taq DNA polymerase, *Msp* I, *Bam* HI, *Pst* I, dNTPs, primers, agarose and DNA molecular weight markers were purchased from Bangalore Genei Pvt. Ltd, Bangalore, India and 5-OH-OPZ was a gift from AstraZeneca, Molndal, Sweden.

**Selection of subjects:** Between January 2003 and December 2006 from among the patients presenting with dyspepsia and abdominal pain for >3 months to the Gastroenterology Clinic, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh for endoscopy, 91 consecutive patients were selected for the study. Inclusion criteria were age 15-65 yr, presence of endoscopic evidence of gastritis, presence of *H. pylori*, belonging to northern states of India and willing to participate in the study. Exclusion criteria were presence of gastrointestinal malignancy, presence of a potential bleeding source and significant co-morbid illness. Liver and renal function tests were carried out and those demonstrating normal biochemistry were recruited after obtaining a written consent. The Institute Ethics Committee approved the study protocol. All patients were subjected to upper gastrointestinal endoscopy (UGIE) after visualizing mucosal details. Antral biopsies were taken for rapid urease test (RUT)\textsuperscript{19}. Initial chemotherapy of the patients was started without knowing their CYP2C19 phenotype and genotype. The end point of the study was eradication of *H. pylori*.

**Study protocol:** Initial triple therapy for *H. pylori* positive patients consisted of 20 mg OPZ (bid), 750 mg AMC (bid) and 500 mg TNZ (bid) for 7 days, followed by 20 mg OPZ (qid) for 21 more days. Second UGIE was performed one month after stopping the therapy to check for eradication of *H. pylori* by rapid urease test. At each endoscopy examination a subjective impression of mucosal inflammation in the body/antrum of stomach was made and changes of hyperemia or ‘salt-and-pepper’ appearance were labelled as gastritis. Non eradicated EM patients were retreated with dual therapy consisting of 40 mg OPZ (bid) and 500 mg AMC (qid)
for 14 days. Non eradicated PM patient was re-treated with 20 mg OPZ (bid) and 500 mg AMC (qid) for 14 days. Third UGIE was performed one month after stopping the therapy to check eradication of *H. pylori*. To estimate compliance, patients were provided with a form and asked to enter the time and day at which they consumed the medicines.

**Phenotyping:** A day prior to the start of therapy each patient was asked to void the bladder before ingesting 20 mg OPZ 2 h after dinner. Urine was collected for 8 h in the glass bottles. The total volume of urine was measured and pH adjusted between 7 and 8 using 1 M Na$_2$CO$_3$. Aliquots of 30 ml were kept frozen at –20 °C until analysis. Extraction and HPLC analysis of 5-OH-OPZ from urine was performed according to the method of Kobayashi et al$^{20}$. Mean recovery of 5-OH-OPZ was 100 per cent. Intraday and interday coefficient of variation for the assay of 5-OH-OPZ was less than 2 and 8 per cent, respectively. Limit of quantitation of 5-OH-OPZ was 0.2 nmol when injected into HPLC column. Hydroxylation index (HI) was calculated by dividing the amount of OPZ ingested (57.9 µmol) by 5-OH-OPZ excreted in 8 h urine.

**Genotyping:** DNA was isolated by the method of Daly et al$^{21}$. PCR was carried on iCycler (Bio-Rad Laboratories, Hercules, CA, USA) in 50 µl reaction mixture containing 1x PCR buffer (50 mM KCl, 10 mM Tris HCl pH 8.3, 1.5 mM MgCl$_2$, and 0.01% gelatin), 0.2 mM each dNTP, 1 µM each primer, 1 µg genomic DNA and 1.5 U Taq DNA polymerase$^{22}$. PCR conditions required to amplify specific fragment for each mutation were standardized. PCR products were digested with a particular restriction endonuclease (RE) and analyzed by agarose gel electrophoresis$^{22}$. PCR conditions, primers, RE and length of expected fragments on digestion to diagnose various *CYP2C19* alleles are given in Table I$^{23-28}$. However, slight modifications were made for genotyping of *CYP2C19*4, *6 and *7. For *CYP2C19*4 forward primer was used without 6 base pair overhang$^{23}$. Primers$^{24,25}$ used for *CYP2C19*6 were the same as that of *CYP2C19*8. For *CYP2C19*7, reverse primer having a mismatch at 104,209 (*CYP2C19* Table I.

<table>
<thead>
<tr>
<th>Allele</th>
<th>Primers</th>
<th>PCR (37 cycles)</th>
<th>RE</th>
<th>DNA fragments</th>
<th>Ref</th>
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<tr>
<td>*2</td>
<td>FP 5´-AATTACAACCCAGCCTGGGC-3´</td>
<td>94 °C 60 sec</td>
<td>*Msp I</td>
<td>AF 169</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>RP 5´-TATCACTTTCCATAAAAGCAAG-3´</td>
<td>58 °C 30 sec</td>
<td>NH 120,49</td>
<td>HE 169,120,49</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>72 °C 30 sec</td>
<td>MH 169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*3</td>
<td>FP 5´-AAATGTTCCTAATTTAGCT-3´</td>
<td>94 °C 60 sec</td>
<td>*Bam HI</td>
<td>AF 271</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>RP 5´-ACTTCAGGGCTTGCTTAATA-3´</td>
<td>58 °C 30 sec</td>
<td>NH 175,96</td>
<td>HE 271,175,96</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>72 °C 60 sec</td>
<td>MH 271</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*4</td>
<td>FP 5´-TTAACAGAGGAGGAGTGA-3´</td>
<td>94 °C 60 sec</td>
<td>*Pst I</td>
<td>AF 189</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>RP 5´-TTGGTAAAGGTATTTGCA-3´</td>
<td>58 °C 15 sec</td>
<td>NH 189</td>
<td>HE 189,167,22</td>
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<td></td>
<td></td>
<td>72 °C 15 sec</td>
<td>MH 167,22</td>
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<td></td>
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<tr>
<td>*5</td>
<td>FP 5´-TCCCTATGTGGTTATTTTCCAG-3´</td>
<td>94 °C 60 sec</td>
<td>*Bst XI</td>
<td>AF 229</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>RP 5´-GAGACGCAAGGTTTGTGACA-3´</td>
<td>58 °C 30 sec</td>
<td>NH 229</td>
<td>HE 229,203,26</td>
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<td></td>
<td></td>
<td>72 °C 60 sec</td>
<td>MH 203,26</td>
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</tr>
<tr>
<td>*6</td>
<td>FP 5´-GGAGATGGAAAAAACAGACT-3´</td>
<td>94 °C 60 sec</td>
<td>*Pst I</td>
<td>AF 381</td>
<td>26,27</td>
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<tr>
<td></td>
<td>RP 5´-CAGGACTCAAATAAAAGAT-3´</td>
<td>58 °C 30 sec</td>
<td>NH 381</td>
<td>HE 381,192,189</td>
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<td></td>
<td></td>
<td>72 °C 60 sec</td>
<td>MH 192,189</td>
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<tr>
<td>*7</td>
<td>FP 5´-AAACCTGGTCTTATGGAAATG-3´</td>
<td>94 °C 60 sec</td>
<td>*Rsa I</td>
<td>AF 142</td>
<td>27</td>
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<tr>
<td></td>
<td>RP 5´-ATAACTAGTTTTGTACACT-3´</td>
<td>58 °C 30 sec</td>
<td>NH 117,25</td>
<td>HE 142,117,25</td>
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<td>72 °C 60 sec</td>
<td>MH 142</td>
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<tr>
<td>*8</td>
<td>FP 5´-GAGGATGGAAAAACAGACT-3´</td>
<td>94 °C 60 sec</td>
<td>*Esp 3I</td>
<td>AF 381</td>
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<tr>
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<td></td>
<td>72 °C 60 sec</td>
<td>MH 239,142</td>
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</table>

AF, amplified fragment; FP, forward primer; HE, heterozygote; MH, mutant homozygote; NH, normal homozygote; RE, restriction endonuclease; RP, reverse primer
gene accession number AL583836.13) was used instead of mismatch at 104,210 as described by Ibeanu et al. This created a site for Rsal instead of MaeIII.

**Statistical analysis:** Difference in mean values of phenotyping data in EMs and PMs was statistically analyzed by two-tailed student’s t test with 95 per cent confidence interval (CI). Fisher exact test was used to determine differences between counts of patients in H. pylori eradication among CYP2C19 phenotypes and \( P<0.05 \) was considered significant. The power of the study was 99.9 per cent. It was calculated using web database (www.dssresearch.com/toolkit/spcalc/power.asp) for 2 sample tests using percentage values.

**Results**

Method for phenotyping of CYP2C19 was validated by assaying 5-OH-OPZ in plasma obtained 2 h after an oral dose of 20 mg OPZ to 15 north Indian volunteers, of which 6 were EMs and 9 were PMs as assessed by urinary log HI (hydroxylation index). Analysis in plasma confirmed impaired metabolism of OPZ to 5-OH-OPZ in PMs. Urinary log HI values and plasma log metabolic ratio (MR) demonstrated a correlation coefficient of 0.83. Antimode log HI value of 1.7 separated EMs from PMs. Patients having a log HI greater than 1.7 were categorized as PMs and less than 1.7 were categorized as EMs. None of PMs demonstrated log HI value close to the cut-off value used to define PMs. Seventy seven subjects were EMs and 14 were PMs. Statistically significant difference (\( P<0.01 \)) was observed in 5-OH-OPZ excreted in 8 h by EMs and PMs viz., 4.26 ± 0.34 (95% CI 3.59-4.92) and 0.73 ± 0.05 (95% CI 0.63-0.82) µmol, respectively. Mean HI values in EMs and PMs were 17.89 ± 0.98 (95% CI 15.96-19.82) and 85.48 ± 6.78 (95% CI 72.2-98.76), respectively. Mean log HI values in EMs and PMs were 1.2 ± 0.03 (95% CI 1.15-1.25) and 1.92 ± 0.03 (95% CI 1.85-1.98), respectively.

Out of CYP2C19*2 to *8 alleles only CYP2C19*2 was present in study subjects. Forty four patients were CYP2C19*1/*1, 41 were CYP2C19*1/*2 and 6 were CYP2C19*2/*2. Of the 14 PMs, 6 were CYP2C19*2/*2, 5 were CYP2C19*1/*1 and 3 were CYP2C19*1/*2. Thus, CYP2C19*2 explained 43 per cent PMs (Table II).

None of the patients demonstrated undesirable side effects. Twenty EMs and 1 PM patient did not turn up for second UGIE and were excluded. A significant difference (\( P<0.05 \)) in eradication of H. pylori was observed between EMs and PMs. Of the 57 EMs, 21 (37%) (95% CI: 24.5-49.5) demonstrated H. pylori eradication and of the 13 PMs, 12 (92%) (95% CI: 77-107) demonstrated eradication (\( P<0.05 \)) (Fig.). Eradication rates in EMs according to intention to treat (ITT, includes dropouts) and per protocol (PP, excludes dropouts) based analysis were 27 and 37 per cent, respectively after initial triple therapy. Eradication rates in PMs according to ITT and PP based analysis were 86 and 92 per cent, respectively after initial triple therapy.

Thirty six non eradicated EMs were retreated with dual therapy. Seven EM patients were excluded as 6 did not turn up for third UGIE and 1 demonstrated poor compliance (less than 80%) to drugs. Of the 29 EMs, 26 (90%) (95% CI: 79-101) demonstrated eradication (Fig.). Eradication rates in EMs according to PP based analysis were 72 and 90 per cent, respectively after dual therapy. Endoscopic improvement of gastritis in H. pylori positive patients was also significantly different (\( P<0.05 \)) in EMs and PMs after initial triple therapy. Of the 57 EMs, 34 (60%) had endoscopic improvement compared to 13 (100%) PMs (data not shown). Twenty three non healed EMs were retreated with dual therapy. Eight EM patients were excluded as 7 did not turn up for third UGIE and 1 demonstrated poor compliance to drugs. Of the 15 EMs, 11 (73%) demonstrated endoscopic improvement of gastritis and 4 (27%) demonstrated persistence of gastritis (data not shown).

**Discussion**

Studies have correlated H. pylori eradication with CYP2C19 genotypes with respect to CYP2C19*2 and CYP2C19*3, since these mutations explain 100 per cent PMs in Orientals. This approach cannot be applied to north Indians since CYP2C19*2 could not explain all
the PMs and CYP2C19*3 was absent in north Indians. Hence, in the present study patients were phenotyped as well as genotyped for CYP2C19 to correlate with eradication of \textit{H. pylori}.

The frequency of occurrence of PMs in north Indians was intermediate as that of Caucasians (1-7%) and Orientals (15-23%)\(^4\). Since the occurrence of PMs was same in the normal healthy volunteers\(^6\) and gastritis patients in the present study, it indicated that possessing PM trait is not a risk factor for gastritis in north Indians. However, a few studies reported a correlation between CYP2C19 PM trait and gastric cancer.\(^{20,31}\)

Phenotyping data demonstrated a statistically significant difference in all parameters in EMs and PMs emphasizing the decreased ability of PM patients to metabolize OPZ compared to EM patients. Heterozygote EMs (CYP2C19*1/*2) and mutant homozygote PMs (CYP2C19*2/*2) demonstrated 35 per cent (3.36 \(\mu\)mol 5-OH-OPZ/8h) and 87 per cent (0.69 \(\mu\)mol 5-OH-OPZ/8h) reduced excretion of 5-OH-OPZ in 8 h urine compared to normal homozygotes (CYP2C19*1/*1) (5.13 \(\mu\)mol 5-OH-OPZ/8h). In PMs (CYP2C19*1/*X) both CYP2C19 alleles are mutated hence no active CYP2C19 enzyme is synthesized leading to impaired metabolism of OPZ. In contrast, normal homozygote EMs (CYP2C19*1/*1) have both the normal alleles and heterozygote EMs have one normal allele that leads to the synthesis of active CYP2C19 enzyme leading to efficient metabolism of OPZ to 5-OH-OPZ. A 50 per cent reduction in the excretion of 5-OH-OPZ was expected in CYP2C19 heterozygotes compared to normal homozygotes on the basis of gene dose phenomenon\(^32\) but heterozygotes demonstrated only 35 per cent decreased excretion of 5-OH-OPZ. This can be explained by the fact that the \textit{in vivo} metabolism of OPZ may not be dependent only on CYP2C19 activity but a variety of other pharmacokinetic parameters. Earlier studies\(^{10}\) performed in this laboratory demonstrated that a direct gene dose effect exists for the metabolism of OPZ \textit{in vitro}. The activity of OPZ hydroxylase was assayed in human liver microsomes. CYP2C19 heterozygotes demonstrated 52 per cent activity of OPZ hydroxylase compared to normal homozygotes. A 50 per cent reduction in the excretion of 5-OH-OPZ was expected in CYP2C19 heterozygotes compared to normal homozygotes on the basis of gene dose phenomenon\(^32\) but heterozygotes demonstrated only 35 per cent decreased excretion of 5-OH-OPZ. This can be explained by the fact that the \textit{in vivo} metabolism of OPZ may not be dependent only on CYP2C19 activity but a variety of other pharmacokinetic parameters. Earlier studies\(^{10}\) performed in this laboratory demonstrated that a direct gene dose effect exists for the metabolism of OPZ \textit{in vitro}. The activity of OPZ hydroxylase was assayed in human liver microsomes. CYP2C19 heterozygotes demonstrated 52 per cent activity of OPZ hydroxylase compared to normal homozygotes.\(^{10}\)

CYP2C19*1, *2 and *3 alleles occurred with frequencies of 0.709, 0.291 and 0, respectively that confirmed our earlier observations in healthy volunteers where the frequency was 0.7, 0.3 and 0, respectively.\(^9\) Allele frequency of CYP2C19*2 in north Indians is similar to that of Orientals\(^7\) and Africans is absent in north Indians. CYP2C19*2 and CYP2C19*3 accounted for all PMs in Orientals\(^7\) and Africans\(^{33}\). CYP2C19*2 could not explain all PMs and CYP2C19*3 was absent in Caucasians so more variant alleles were expected. Subsequently, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7 and CYP2C19*8 were discovered in Caucasian outlier PMs and together all these alleles explained approximately 99.74 per cent of defective alleles in Caucasians\(^4\). Similarly, CYP2C19*2 could explain only 52 per cent north Indian PMs and CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7 and CYP2C19*8 alleles are absent indicating the presence of specific single nucleotide polymorphisms (SNPs) in north Indians.

Results demonstrated that \textit{H. pylori} eradication in north Indians with standard regimens are influenced by CYP2C19 phenotypes as the number of non eradicated patients was higher in EMs as compared to PMs. Of the 29 non eradicated EMs, 26 (90%) demonstrated eradication with increased dose dual therapy. These observations are in agreement with the studies demonstrating that eradication of \textit{H. pylori} is dependent on CYP2C19 genotypes. Such studies were carried out in Orientals and Caucasians using PPI based dual, triple and quadruple therapy.\(^{34-36}\) The possible cause of higher eradication in...
PMs is decreased metabolism of OPZ, which increases the intragastric pH at which antibiotics are stable thus increasing the bioavailability of antibiotics. OPZ increases the concentration of AMC in gastric juice and OPZ per se demonstrates anti H. pylori activity.

Observations of the present study are not in agreement with studies demonstrating that CYP2C19 genotypes do not influence the eradication of H. pylori. The conflicting data in the literature about the role of pharmacogenetics of CYP2C19 in the eradication of H. pylori may be due to a variety of other factors that determine drug responses in addition to the pharmacogenetics of CYP2C19 viz., age, sex, nutritional status, liver and kidney function, concomitant diseases and medications, pharmacogenetics of CYP3A4 and interleukin-1β (IL-1β) genetic polymorphism.

In conclusion, results of the present study demonstrated that CYP2C19 genetic polymorphism is an important determinant of the efficacy of PPI based anti H. pylori therapy in north Indians. If CYP2C19 phenotype of a patient is known prior to chemotherapy, an optimal dose of the PPI can be prescribed to achieve better management of patients having H. pylori associated gastritis, gastric ulcers and duodenal ulcers.

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