Cytochromes P450 (CYPs) are the drug metabolizing enzymes found primarily in the liver. Inter-individual variations in the metabolism of drugs have been observed in different ethnic groups due to the occurrence of genetic polymorphism of the drug metabolizing enzymes. Genetic polymorphism is the occurrence of a variant allele with a frequency of 1 per cent or greater in a population. Although various allelic forms of different CYPs have been reported, functional polymorphism has only been established for CYP2A6, CYP2C9, CYP2C19 and CYP2D6. On the basis of genetic polymorphism a population may be divided into two groups namely extensive metabolizers (EMs) demonstrating normal metabolism of the drugs and poor metabolizers (PMs) demonstrating impaired metabolism of drugs due to the deficiency of CYPs. The first PM of mephenytoin, a probe drug for CYP2C19, was reported by Kupfer et al. in 1979. Subsequently the genetic basis of CYP2C19 PM trait was demonstrated. Omeprazole (OPZ) and proguanil are the other probe drugs used to assess the activity of CYP2C19. Subjects having a log...
hydroxylation index value more than 1.7 for OPZ and a urinary proguanil to cycloguanil ratio greater than 10 are classified as PMs. CYP2C19 gene is located on long arm of chromosome 10 (10q24.1-10q24.3). It has 9 exons and 8 introns. The cDNA is 1473 bp in length. Twenty one mutant alleles of CYP2C19 have been reported (Fig.). CYP2C19*2 to CYP2C19*8 were discovered in the subjects who demonstrated decreased ability to metabolize the probe drugs, whereas CYP2C19*9 to CYP2C19*15 were reported by direct sequencing of the genomic DNA from lymphoblastoid cell lines represented by Caucasians, Asians and Africans. CYP2C19*16 was reported in a Japanese subject demonstrating a lowered capacity to hydroxylate mephobarbital. CYP2C19*17 discovered recently by direct sequencing of 5’ flanking region was shown to be the first mutant CYP2C19 allele associated with ultrarapid drug metabolism. CYP2C19*18 to CYP2C19*21 were discovered by direct sequencing of all exons of CYP2C19 in Japanese subjects. Different research groups have reported variable cure rates in patients possessing different CYP2C19 genotypes. Here we review the effect of CYP2C19 phenotypes and genotypes on the therapeutic response to proton pump inhibitors (PPIs) based upon the clinical observations reported in the literature.

Proton pump inhibitors (PPIs)

The major PPIs are OPZ, lansoprazole (LPZ), pantoprazole (PPZ) and rabeprazole (RPZ). These are used for the treatment of non ulcer dyspepsia (NUD), reflux oesophagitis, gastroesophageal reflux disease (GERD), Helicobacter pylori infection, gastric ulcers, duodenal ulcers, prevention and treatment of non steroidal anti inflammatory drugs associated damage, treatment of Zollinger-Ellison syndrome and other hyper acidic conditions. PPIs are prodrugs that, after oral administration get absorbed into the systemic circulation. After absorption, these enter the gastric parietal cells from the plasma where in the acidic milieu these are arranged non enzymatically to form active sulphenamide derivatives which then bind covalently to sulphhydryl groups of H+/K⁺ ATPase inhibiting these irreversibly. All PPIs have a common pyridinyl sulphinyl benzimidazole backbone. These are extensively metabolized in the liver by CYPs to inactive metabolites. Although both CYP3A4 and CYP2C19 are involved in the metabolism of PPIs, the major pathways are catalyzed by CYP2C19. OPZ is mainly 5-hydroxylated by CYP2C19 and partially by CYP3A4 to OPZ sulphone. LPZ is converted to 5-OH-LPZ by CYP2C19 and to LPZ sulphone by CYP3A4. PPZ is mainly converted to demethylated PPZ by CYP2C19 but a minor pathway to PPZ sulphone by CYP3A4 also exist. RPZ is mainly metabolized nonenzymatically to RPZ thioether but minor pathways to demethylated RPZ by CYP2C19 and RPZ sulfone by CYP3A4 also exists. Specifically, since CYP2C19 plays a major role in the metabolism, studies have linked genetic polymorphism of CYP2C19 with therapeutic response.

Genetic polymorphism of CYP2C19

Genetic polymorphism of CYP2C19 occurs with varying frequency among different ethnic groups viz., 15-22.5 per cent in Japanese, 12.6 per cent in

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**Fig.** Schematic picture demonstrating CYP2C19 alleles. Nine exons are depicted in the boxes. CYP2C19*2 to CYP2C19*21 are shown with the corresponding nucleotide change. CYP2C19*2 to CYP2C19*8 and CYP2C19*16 were discovered in the subjects who demonstrated decreased ability to metabolize the probe drugs whereas CYP2C19*9 to CYP2C19*15 were discovered by direct sequencing of genomic DNA from lymphoblastoid cell lines. CYP2C19*17 was discovered recently in ultra rapid metabolizers by direct sequencing of 5’ flanking region. CYP2C19*18 to CYP2C19*21 were discovered by direct sequencing of all exons of CYP2C19.
Koreans, 13-20 per cent in Chinese, 11, 12 per cent in north Indians, 14 per cent in south Indians, 2.8-5.2 per cent in Africans, 0.95 to 7 per cent in Caucasian-Europeans, 2 per cent in African-Americans, 2.4-2.6 per cent in Caucasian-Americans and 70 per cent in Vanuatu islands of Melanesia.

**CYP2C19 genotypes and pharmacokinetics and pharmacodynamics of PPIs**

It has been observed that usual doses of PPIs in EMs could not attain plasma levels that are sufficient to cause acid inhibitory effect. Hence, intragastric pH is lower in EMs. On the other hand, duration of exposure to high plasma concentration of PPIs is longer in PMs and the proton pumps in parietal cells remain inactivated for longer period resulting in higher pH and a better therapeutic outcome.

Table I summarizes different studies correlating pharmacogenetics of CYP2C19 with pharmacokinetics and pharmacodynamics of OPZ, LPZ and RPZ in various ethnic groups. The direct CYP2C19 gene dose effect is evident from the significantly different plasma area under curve (AUC) and half life values of OPZ, LPZ and RPZ after oral administration in three CYP2C19 genotype groups. CYP2C19 normal homozygotes demonstrated lowest, heterozygotes intermediate and mutant homozygotes highest AUC and plasma half life values of these PPIs. Varying plasma concentrations and half lives of PPIs in different CYP2C19 genotype groups lead to differences in inhibition of the acid secretion from the gastric parietal cells. Thus, intragastric pH after treatment with OPZ, LPZ and RPZ differed significantly between three CYP2C19 genotype groups. CYP2C19 normal homozygotes demonstrated lowest, heterozygotes intermediate and mutant homozygotes highest intragastric pH values. Gastrin AUC values also depended significantly on CYP2C19 genotypes. CYP2C19 normal homozygotes demonstrated lowest, heterozygotes intermediate and mutant homozygotes highest gastrin AUC values. Thus, majority of observations demonstrated that CYP2C19 pharmacogenetics influences the pharmacokinetics and pharmacodynamics of PPIs. Thus, the proton pumps in parietal cells are inactivated by higher concentration of PPIs and for a longer time in CYP2C19 mutant homozygotes resulting in a stronger acid inhibition and higher intragastric pH. Hence, if CYP2C19 genotypes are known prior to PPI based treatment, an optimal dose can be prescribed in order to achieve a better therapeutic outcome.

**CYP2C19 genotypes in chemotherapy of H. pylori**

*H. pylori* was discovered in the stomach of patients with gastritis and peptic ulceration. Eversince infection of mucosa of stomach and duodenum by *H. pylori* has been found to be associated with gastritis, gastric ulcers, duodenal ulcers, gastric carcinoma and other upper gastrointestinal disorders. Different treatment regimens are used to eradicate *H. pylori* but the best results are achieved by triple therapy consisting of a combination of two antibiotics [amoxicillin (AMC), clarithromycin (CAM), tinidazole (TNZ) and metronidazole (MNZ)] and one PPI. PPIs are an important part of anti *H. pylori* therapy as these increase the pH of the stomach to levels where the antibiotics are stable and thus increase the bioavailability of antibiotics. OPZ is known to increase the concentration of AMC in gastric juice. OPZ per se demonstrated anti *H. pylori* activity. A relationship between CYP2C19 genotypes and cure rates of *H. pylori* on treatment with PPI based dual, triple and quadruple therapy has been demonstrated in Orientals and Caucasians (Table II).

**CYP2C19 genotypes in PPI based dual eradication therapy:** Furuta *et al.* treated *H. pylori* positive gastric ulcer Japanese patients with 20 mg OPZ *quaef die* (qd) for 8 wk and 500 mg AMC *quarter in die* (qid) for first 2 wk and duodenal ulcer Japanese patients with 20 mg OPZ (qd) for 6 wk and 500 mg AMC (qid) for first 2 wk. They reported 29, 60 and 100 per cent *H. pylori* eradication in normal homozygotes, heterozygotes and mutant homozygotes, respectively. Higher cure rates observed in mutant homozygotes were attributed to higher plasma concentration of OPZ. Gastric pH was found to be highest in mutant homozygotes, intermediate in heterozygotes and least in normal homozygotes. Stability and antibacterial activity of AMC were maximum at high pH. High dose of OPZ may thus be required to achieve high cure rates of *H. pylori* infection in EMs who metabolize PPIs efficiently. Therapy with 20 mg OPZ *bis in die* (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. Therefore, anti *H. pylori* effect of dual therapy is efficient in PMs and hence suggests that CAM can be avoided for therapy of CYP2C19 PMs. Furuta *et al.* treated Japanese *H. pylori* positive gastritis patients with 10 mg RPZ (bid) and 500 mg AMC *ter in die* (tid) for 2 wk. A significant difference in cure rates among 3 genotypes viz., normal
homozygotes (61%), heterozygotes (92%) and mutant homozygotes (94%) was observed. The non eradicated patients consisting of normal homozygotes and heterozygotes when treated with a high RPZ dose dual therapy consisting of 10 mg RPZ (qid) and 500 mg AMC (qid) for 2 wk demonstrated 100 per cent \textit{H. pylori} eradication. Thus, \textit{H. pylori} eradication with RPZ also depends on \textit{CYP2C19} genotypes. \textit{H. pylori} infected Japanese normal homozygotes were successfully treated with high doses of dual therapy with 40 mg OPZ (tid)
and 750 mg AMC (tid) after failure to eradicate *H. pylori* with usual PPI based triple therapy\(^{48}\). Triple therapy with OPZ, AMC and CAM is not necessary in PMs as dual therapy with OPZ and AMC is highly efficient. CAM increases the plasma concentration of PPIs, since it inhibits CYP2C19 and CYP3A4, resulting in higher cure rates in EMs. Plasma concentration of OPZ in healthy Japanese PMs following CAM and OPZ co-administration was 34 times higher than normal homozygote EMs\(^{49}\). Contrary to above observations, Miyoshi *et al.*\(^ {50}\) after treatment of *H. pylori* positive Japanese patients with OPZ 20 mg (bid) and AMC 500 mg (tid) for 14 days demonstrated a statistically non significant difference in eradication *i.e.*, 71.4, 77.1 and 73.3 per cent in normal homozygotes, heterozygotes and mutant homozygotes, respectively was observed\(^ {50}\).

### Table II. CYP2C19 genotypes and eradication of *H. pylori* using different proton pump inhibitor (PPI) based therapies

<table>
<thead>
<tr>
<th>Doses</th>
<th>Ethnic group</th>
<th>Therapy</th>
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<th>*1/*X</th>
<th>*X/*X</th>
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<tr>
<td>OPZ 20 mg qd</td>
<td>Japanese</td>
<td>Dual</td>
<td>(n=28)</td>
<td>(n=25)</td>
<td>(n=9)</td>
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<tr>
<td>AMC 500 mg qid</td>
<td>8 wk</td>
<td></td>
<td>29</td>
<td>60</td>
<td>100</td>
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<tr>
<td>OPZ 20 mg bid</td>
<td>Japanese</td>
<td>Dual</td>
<td>(n=10)</td>
<td>(n=12)</td>
<td>(n=4)</td>
</tr>
<tr>
<td>AMC 500 mg qid</td>
<td>1 wk</td>
<td></td>
<td>40</td>
<td>42</td>
<td>100</td>
</tr>
<tr>
<td>RPZ 10 mg bid</td>
<td>Japanese</td>
<td>Dual</td>
<td>(n=33)</td>
<td>(n=48)</td>
<td>(n=16)</td>
</tr>
<tr>
<td>AMC 500 mg tid</td>
<td>1 wk</td>
<td></td>
<td>61</td>
<td>92</td>
<td>94</td>
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<tr>
<td>OPZ 20 mg bid</td>
<td>Japanese</td>
<td>Triple</td>
<td>(n=20)</td>
<td>(n=26)</td>
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<tr>
<td>AMC 500 mg qid</td>
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<td>88</td>
<td>100</td>
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<tr>
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<td>Triple</td>
<td>(n=88)</td>
<td>(n=127)</td>
<td>(n=46)</td>
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<tr>
<td>CAM 500 mg tid</td>
<td>1 wk</td>
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<td>92</td>
<td>98</td>
</tr>
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<td>Japanese</td>
<td>Triple</td>
<td>(n=33)</td>
<td>(n=35)</td>
<td>(n=12)</td>
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<tr>
<td>CAM 750 mg bid</td>
<td>1 wk</td>
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<td>74</td>
<td>83</td>
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<tr>
<td>LPZ 10 mg bid</td>
<td>Italian</td>
<td>Triple</td>
<td>(n=116)</td>
<td>(n=25)</td>
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</tr>
<tr>
<td>AMC 500 mg bid</td>
<td>1 wk</td>
<td></td>
<td>60</td>
<td>84</td>
<td>100</td>
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<td>LPZ 30 mg bid</td>
<td>German</td>
<td>Quadruple</td>
<td>(n=86)</td>
<td>(n=45)</td>
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<td>LPZ 30 mg bid</td>
<td>Caucasian</td>
<td>Quadruple</td>
<td>80</td>
<td>97.8</td>
<td></td>
</tr>
</tbody>
</table>

AMC, Amoxicillin; CAM, clarithromycin; LPZ, lansoprazole; MNZ, metronidazole; OPZ, omeprazole; RPZ, rabeprazole; *1/*1-normal homozygotes, *1/*X-heterozygotes and *X/*X-mutant homozygotes; n, is sample size; qd, qua die; bid, bis in die; qid, quarter in die; tid, ter in die.

CYP2C19 genotypes in PPI based triple eradication therapy: Using a triple therapy of 20 mg OPZ (bid), 500 mg AMC (qid), 200 mg CAM (qid) for 1 wk, 100 per cent eradication was achieved in PMs compared to 75 and 88 per cent in normal homozygotes, heterozygotes and mutant homozygotes, respectively was observed\(^ {50}\).
and mutant homozygotes, heterozygotes and normal homozygotes, respectively. Noneradicated group consisted of 69 per cent normal homozygotes, 28 per cent heterozygotes and 3 per cent mutant homozygotes who were then treated with higher doses of dual therapy depending on CYP2C19 genotypes. Normal homozygotes and heterozygotes were retreated with 30 mg LPZ (qid) and 500 mg AMC (qid) whereas the mutant homozygotes with 30 mg LPZ (bid) and 500 mg AMC (qid). The final eradication rate of 99.6 per cent was achieved. Therefore, by adjusting the doses according to CYP2C19 genotypes and selecting the antibiotic to which the bacteria is sensitive, dual therapy is sufficient to cure H. pylori infection. Kawabata et al. treated 80 H. pylori positive Japanese patients with triple therapy consisting of 30 mg LPZ (bid), 750 mg AMC (bid) and 400 mg CAM (bid) and observed 73, 74 and 83 per cent H. pylori eradication in normal homozygotes, heterozygotes and mutant homozygotes, respectively. Similar observations were reported in Caucasians. Saponet al. reported the first pharmacogenomic study with respect to CYP2C19 genotypes and H. pylori eradication in Italian Caucasians. Using a triple therapy of 20 mg OPZ (bid), 1000 mg AMC (bid) and 500 mg CAM (bid) for 1 wk, 60, 84 and 100 per cent eradication was observed in normal homozygotes, heterozygotes and mutant homozygotes, respectively. Fifty patients in whom H. pylori was not eradicated were either normal homozygotes (92%) or heterozygotes (8%)53. In contrast to above observations, some studies demonstrated no association between CYP2C19 polymorphism and eradication of H. pylori. No correlation was observed between CYP2C19 genotypes and eradication of H. pylori after treatment with LPZ 30 mg (bid), AMC 1000 mg (bid) and CAM 400 mg (bid) for 7 days as 100, 96 and 100 per cent eradication was observed in Japanese normal homozygotes, heterozygotes and mutant homozygotes, respectively. Similarly, after treatment with RPZ 10 mg (bid), AMC 1000 mg (bid) and CAM 400 mg (bid) for 7 days 100, 95 and 100 per cent eradication was observed in Japanese normal homozygotes, heterozygotes and mutant homozygotes, respectively indicating that CYP2C19 polymorphism did not influence H. pylori eradication. Inaba et al. treated H. pylori positive Japanese patients with OPZ 20 mg (bid), AMC 500 mg (tid) and CAM 200 mg (tid) for 7 days and demonstrated a statistically non significant difference in eradication i.e., 76.2, 88.9 and 90 per cent in normal homozygotes, heterozygotes and mutant homozygotes, respectively. Similarly after treatment with LPZ 30 mg (bid), AMC 500 mg (tid) and CAM 200 mg (tid) for 7 days a statistically non significant difference in eradication i.e., 90, 89.7 and 88.9 per cent in normal homozygotes, heterozygotes and mutant homozygotes, respectively was observed. Hokari et al. categorized H. pylori positive Japanese patients according to drug prescription into 3 groups. Group 1 was prescribed 1 wk therapy consisting of RPZ 10 mg (qd), AMC 750 mg (bid) and CAM 200 mg (bid). Group 2 was prescribed 1 wk therapy consisting of RPZ 10 mg (bid), AMC 750 mg (bid) and CAM 200 mg (bid). Group 3 was prescribed 1 wk therapy consisting of RPZ 20 mg (bid), AMC 750 mg (bid) and CAM 200 mg (bid). Data from EMs and PMs were analyzed collectively from the 3 groups. EMs and PMs demonstrated a non significant difference (86 vs 77%) in eradication of H. pylori. Dojo et al. divided H. pylori positive Japanese patients into 2 treatment groups randomly. Group 1 after treatment with 1 wk triple therapy consisting of OPZ 20 mg (bid), AMC 750 mg (bid) and CAM 400 mg (bid) demonstrated non significant eradication of 73.3, 86.1 and 85 per cent in normal homozygotes, heterozygotes and mutant homozygotes, respectively. Group 2 after treatment with 1 wk triple therapy consisting of RPZ 20 mg (bid), AMC 750 mg (bid) and CAM 400 mg (bid) demonstrated non significant eradication of 81, 82.9 and 87.5 per cent in normal homozygotes, heterozygotes and mutant homozygotes, respectively; thus demonstrating no association of CYP2C19 genetic polymorphism with H. pylori eradication.

CYP2C19 genotypes in PPI based quadruple eradication therapy: Effect of CYP2C19 polymorphism was studied in German Caucasians using quadruple therapy for H. pylori eradication consisting of 30 mg LPZ (bid), 1000 mg AMC (bid), 250 mg CAM (bid) and 400 mg MNZ (bid) for 5 days. Heterozygotes and mutant homozygotes demonstrated significantly higher eradication (97.8%) compared with normal homozygotes (80.2%)58. LPZ serum trough steady state concentrations were also significantly different viz., 78.1, 135 and 766 ng/ml in normal homozygotes, heterozygotes and mutant homozygotes, respectively. Hence, they concluded that the eradication of H. pylori is dependent on CYP2C19 genotypes when standard doses of LPZ are used in Caucasians58. Results from these studies emphasize that EMs (normal homozygotes and heterozygotes) compared to PMs (mutant homozygotes) should be prescribed higher doses of PPIs in order to achieve optimal eradication of H. pylori. Higher eradication rates observed in PMs compared to EMs is due to the impaired metabolism of PPIs in PMs. This results in the exposure of proton pumps in parietal
cells to higher concentration of PPIs and for longer duration in PMs (mutant homozygotes). This leads to higher intragastric pH at which the antibiotics are stable and thus increase the bioavailability of the antibiotics in PMs. OPZ is known to increase the concentration of AMC in the gastric juice, this effect will be pronounced in PMs. Since OPZ per se demonstrates anti \textit{H. pylori} activity, this action will also be more pronounced in PMs. Hence, if CYP2C19 genotypes are known prior to PPI based therapy, an optimal dose can be prescribed in order to achieve a better therapeutic outcome.

CYP2C19 and \textit{H. pylori} eradication in north Indian patients: Since the frequency of CYP2C19 EMs is 88 per cent in north Indians, approximately 880 million people in this country are expected to be CYP2C19 EMs, and they should be treated with increased doses of PPIs compared to PMs to achieve optimal recovery. However, correlation between CYP2C19 phenotypes, genotypes, eradication of \textit{H. pylori} and chemotherapy of gastritis has not been studied in north Indians. Since this correlation is of utmost importance for patient care, a study on the role of CYP2C19 phenotypes and genotypes in the eradication of \textit{H. pylori} and chemotherapy of gastritis in north Indians was initiated in our laboratory. Ninety one \textit{H. pylori} positive north Indian patients were phenotyped and genotyped for CYP2C19 by high performance liquid chromatography (HPLC) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), respectively. Initial \textit{H. pylori} eradication therapy consisted of 20 mg OPZ (bid), 750 mg AMC (bid) and 500 mg TNZ (bid) for 7 days. Noneradicated EMs were retreated with dual therapy consisting of 40 mg OPZ (bid) and 500 mg AMC (qid) for 14 days whereas PMs were retreated with 20 mg OPZ (bid) and 500 mg AMC (qid) for 14 days. After initial triple therapy EMs and PMs demonstrated 37 and 92 per cent eradication, respectively. Non eradicated EMs retreated with 40 mg OPZ (bid) and 500 mg AMC (qid) dual therapy demonstrated 90 per cent eradication. Non eradicated PMs retreated with 20 mg OPZ (bid) and 500 mg AMC (qid) demonstrated 100 per cent eradication, thus demonstrating a direct correlation of CYP2C19 phenotypes and genotypes with eradication of \textit{H. pylori} in north Indians.

The conflicting data in the literature about the role of pharmacogenetics of CYP2C19 in the eradication of \textit{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. Sapone et al. analyzed the combined effect of CYP2C19 and CYP3A4 polymorphisms on eradication of \textit{H. pylori} in Italian Caucasians using 20 mg OPZ (bid), 1000 mg AMC (bid) and 500 mg CAM (bid) for 7 days. The reason for this analysis was that PPIs are extensively metabolized by CYP2C19 but also metabolized by CYP3A4 to a lesser extent. CYP2C19 heterozygote patients who were also heterozygotes for CYP3A4*1B, CYP3A4*2 and CYP3A4*3 demonstrated 100 per cent eradication. Thus, there may be a possibility of existence of a positive synergism between the pharmacogenetics of CYP2C19 and CYP3A4 in eradication of \textit{H. pylori}. IL-1β C-511T genetic polymorphism also influences the effect of CYP2C19 pharmacogenetics on the eradication of \textit{H. pylori}. IL-1β is a proinflammatory cytokine with multiple biological effects, including potent inhibition of gastric acid secretion. It is 100-fold more potent inhibitor of gastric acid secretion than PPIs and is highly expressed in the gastric mucosa of \textit{H. pylori} infected patients. Since the antibiotics used for eradicating \textit{H. pylori} are acid sensitive, IL-1β genetic polymorphism can also affect the anti \textit{H. pylori} therapy. After treatment of Japanese with 750 mg AMC (bid) and 200 mg CAM (bid) together with either 20 mg OPZ (bid), 30 mg LPZ (bid) or RPZ 10 mg (bid) 78, 78 and 90 per cent eradication was observed in CYP2C19 normal homozygotes, heterozygotes and mutant homozygotes, respectively. In IL-1β C-511 C/T or T/T genotype (low acid secretion) group, there was no statistically significant difference in eradication among three CYP2C19 genotypes. In contrast, in IL-1β -511 C/C (normal acid secretion) group, the eradication rate among CYP2C19 mutant homozygotes (93.3%) was significantly higher than CYP2C19 normal homozygotes (60%) and heterozygotes (63.6%). Therefore, IL-1β genetic polymorphism in conjunction with CYP2C19 genetic polymorphism could also affect the eradication rates of \textit{H. pylori}. Studying the genetic polymorphisms of CYP2C19, CYP3A4 and IL-1β and also analysis of other confounding factors together in different populations may further enhance the understanding of the role of CYP2C19 polymorphism in the chemotherapy of \textit{H. pylori} eradication.

CYP2C19 genotypes in treatment of gastroesophageal reflux disease (GERD): Cure rates for GERD differ.
significantly in Japanese patients with different CYP2C19 genotypes. Cure rates in normal homozygotes, heterozygotes and mutant homozygotes after 8 wk treatment with 30 mg LPZ (qd) were 46, 68 and 85 per cent, respectively. Lowest cure rate observed in normal homozygotes was attributed to low plasma LPZ concentrations (312, 440 and 745 ng/ml in normal homozygotes, heterozygotes and mutant homozygotes, respectively)61. Kawamura et al62 treated 88 Japanese patients suffering from erosive reflux oesophagitis with 30 mg LPZ (qd) for 8 wk and observed 77, 95 and 100 per cent cure rates in normal homozygotes, heterozygotes and mutant homozygotes, respectively, suggesting that CYP2C19 genotypes influence the therapeutic outcome.

CYP2C19 genotypes in treatment of duodenal ulcers: A Japanese heterozygote patient with recurrent ulcer responded to 60 mg LPZ/day instead of 30 mg LPZ/day63. After treatment with 60 mg LPZ/day, pH of > 3 was maintained for 99.8 per cent time as against 88.3 per cent after treatment with 30 mg LPZ/day62. H. pylori associated refractory duodenal ulcer was cured with 40 mg OPZ (tid) and 750 mg AMC (tid) after failure to cure the ulcer with usual PPI based triple therapies in normal homozygote Japanese67. Results from these studies emphasize that EMs (normal homozygotes and heterozygotes) compared to PMs (mutant homozygotes) should be prescribed higher doses of PPIs in order to achieve optimal therapeutic outcome against GERD, reflux oesophagitis as well as duodenal ulcers.

Conclusion
Available data demonstrate that CYP2C19 pharmacogenetics influences the pharmacokinetics of PPIs. CYP2C19 mutant homozygotes demonstrate increased plasma concentration of PPIs and hence highest inhibition of proton pumps. CYP2C19 normal homozygotes, heterozygotes and mutant homozygotes demonstrated lowest, intermediate and highest H. pylori eradication, respectively using different therapies. Hence, CYP2C19 genotyping prior to treatment can help to optimize the PPI dose to achieve a better therapeutic outcome. This shall help in the better management of patients of GERD, gastritis, gastric and duodenal ulcers.

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