INTRODUCTION
1. Introduction

*Helicobacter pylori* is a small, gram-negative, curved or spiral, bacillus, microaerophilic and motile organism with multiple polar flagella (Mendall, 1995). *H. pylori* is 2.5-5 μm long and 0.5-1.0 μm wide. The bacterium is observed mainly in the spiral form, but atypical forms of *H. pylori* are also seen. A common atypical form is a spherical form, which could be a result of the bacterium minimizing content with an unfavorable environment. In the normal spiral morphology, the bacterium has 4-6 unipolar flagella. It is microaerophilic, i.e it requires oxygen but at lower levels than those contained in the atmosphere. It uses hydrogen methanogenesis as an energy source (Marshall et al., 1989). *H. pylori* (formerly called *Campylobacter pylori*) were first isolated from human gastric biopsy material in 1982 (Warren And Marshall, 1983). It excretes the enzyme urease, which converts urea into ammonia and bicarbonate. The release of ammonia is beneficial to the bacterium since it partially neutralizes the very acidic environment of the stomach including protease, catalase, and phospholipases that causes damage to those cells (Marshall et al., 1989). The pH range for survival of this bacterium is from 5.5-8.5 with an optimal pH between 6.9 and 8.0. (Rathbone and Heatley, 1992; Mendall et al., 1994).

More than 50% of the world population is colonized with *H. pylori* (Mendall, 1995 and Logan and Hiscal, 1996). *H. pylori* commonly causes peptic ulcer, a chronic inflammatory condition of stomach and duodenum. It is a major cause of morbidity in infected patients and it is associated with 90% of duodenal ulcers and 80% of gastric ulcers (Aroori, 2001). Humans appear to be the only reservoir of *H. pylori* infection and therefore human contacts remain the major mode for its transmission. Iatrogenic spread through contaminated gastrointestinal equipment has been documented (Logan and Hiscal, 1996). Contaminated water has been shown to be a source for *H. pylori*.
infection (Klein et al., 1991). Infection is mainly acquired in childhood and is usually asymptomatic (Neale and Logar, 1995).

*H. Pylori* infection probably occurs when an individual swallows the bacteria from food, fluid or perhaps from contaminated utensils. The infection remains localized to the gastric area and probably is the reason for ulcers (Lam et al., 1997; Adamek et al., 1995).

Existence of *H. pylori* has been found the world over and its prevalence in the population increases with age. In developed countries, prevalence increases about 1% per year of age while it is rare in children, and reaches 70% in the seventh decade. In developing countries, more than 50% children acquire the infection by the age of 10 years, and more than 80% of the population gets infected by the age of 20 years. In asymptomatic individuals prevalence of *H. pylori* infection varies from 31%-84%. *H. pylori* infection is chronic and once acquired remains life long, unless eradicated by antibiotics given for some other conditions. Humoral and tissue immune response by the host is usually not sufficient to clear the infection (Mendal et al., 1992; Noach et al., 1993). Colonisation of *H. pylori* occurs by producing urease and gastric acid inhibitory protein. It can colonise only in gastric type epithelium and cannot stay anywhere else in the GI tract in absence of gastric mucosa. Stimulation of the immune system of *H. pylori* contributes to host damage and it evades the immunological clearance (Noach et al., 1993). There is mounting evidence that *Helicobacter pylori* infection plays an important role in pathogenesis of carcinoma of gastric antrum and fundus. The World Health organization recently declared *Helicobacter pylori* a class I carcinogen because of the association of *H. pylori* and gastric malignancies. Most cases of chronic gastric ulcers and many cases of atrophic gastritis are due to *H. pylori* infection (Gold, 1999 and Marshall et al., 1989).
It is known that alcohol, aspirin and arthritis drugs such as ibuprofen can disturb the protective muscle layer (Lee, 1992). This allows the strong stomach acid to injure under lining stomach cells. Until the mid 1980's, it was felt that one or more of these factors working together led to the development of gastritis and ulcers (Graham, 1991). Since that time, evidences have been monitoring that *H. pylori* has major role in causing these diseases (Josenhan *et al.*, 1995).

Depending on the enzymes and toxins production, *H. pylori* strains can be divided into two groups, i.e., type 1 and type 2. Type 1 contains vacuolating toxin, encoded by the gene vacA (94-kda vacA) and cytotoxic associated protein encoded by the gene cagA (120-128- kcatA). The second group, i.e., type 2 contains non-cytotoxic vacA and cagA negative strains. It has been observed that type 1 strains cause more intensive inflammation than type 2. Such strain diversity may explain why some infected individuals do not develop diseases while some may develop peptic ulcer and gastric cancer which may be due to different type of strains (Crabtree *et al.*, 1991).

The studies have shown that 70% of strains isolated from patients with duodenal ulcer produce this toxin compared to about 30% isolated from non-ulcer dyspepsia. There is also some evidence to suggest that the degree of inflammation and subsequently clinical consequences of *H. pylori* infection are related to density of bacterial colonisation (Crabtree *et al.*, 1994 and Mobley, 1996). The enzyme produced by both types of strains plays an important role in the pathogenesis. Urease *hydrolyses* urea into ammonia and creates alkaline surroundings, thus creating a neutral microenvironment for the bacteria. It may also have a role in *H. pylori* metabolism as a part of nitrogen cycle. It has been presumed that the ammonia produced by the urease activity works with cytotoxin inducing vacuoles (Mobley, 1996).

Though *H. pylori* is strongly antigenic and leads to humoral and cellular immune
response, the human host is unable to clear the infection which may persist life long. The local inflammatory response leads to accumulation of a number of different cytokines which includes IL-8 and tumors necrosis factor alpha. These two cytokines plays an important role in the formation of inflammatory infiltrate. Type 1 *H. pylori* strains have been shown to induce significantly higher IL-8 than type 2 strains (Crabtree *et al.*, 1994 and Blaser *et al.*, 1995).

Gastrin produced by the G cells stimulates the acid secretion and has a trophic action on mucosal cells in the stomach. It has been found that *H. pylori* increases the fasting serum gastrin levels in healthy subjects and also in patients with duodenal ulcer. The main inhibitor of gastrin secretion and excretion somatostatin is produced by the D cells. Somatostatin levels are decreased in *H. pylori* positive individuals. (Harris *et al.*, 1996) *H. pylori* also decreases the gastric body mucosal histamine. There are two main opposite effects of *H. pylori* on acid secretion function of the stomach, viz., its effect on fundal histamine decreases acid output while the effect on somatostatin leading to hypergastrinaemia increases the gastric acid output (Moss *et al.*, 1992 and Moss and Calam, 1993). The basal and peak acid output changes after eradication of *H. pylori* supports the hypothesis that *H. pylori* causes impairment in the inhibitory control of gastric acid. In the early stage of infection acid output increases, leading to gastric metaplasia in duodenum, which in turn gets infected with *H. pylori* and development of duodenal ulcer. With diffuse disease the acid output falls (Moss *et al.*, 1992 and Pounder, 1996).

Dual therapy refers to the combination of Proton Pump Inhibitors (PPIs) or ranitidine bismuth citrate (RBC) and one antibiotic. Inhibition of acid secretion with a PPI or H2-receptor antagonist increases the intragastric acid level to pH 5 or more and acts synergistically with antibiotics. The first dual therapy combining omeprazole with
amoxyccillin had unpredictable efficacy ranging from 20% to 90% and thus credibility with most gastroenterologists (Laine et al., 1997 and Bayerdorffer et al., 1995). The results of dual therapy are more reproducible when amoxyccillin is replaced by clarithromycin. The PPI and clarithromycin combination, however, requires frequent dosing of clarithromycin (up to 500 mg three times daily for 2 weeks to achieve an efficacy of 63% to 81% (Harris et al., 1995; Burette et al., 1993; and Logan et al., 1994). The high doses of PPI and clarithromycin have substantially increased the cost of this regimen. Dual therapy with the RBC 400 mg and clarithromycin 500 mg twice daily for 2 weeks is another food and drug administration (FDA) approved regimen and achieves eradication rates up to 80% (Axon et al., 1997). However, the long duration of treatment and subsequent reduced compliance remain a problem.

The earlier omeprazole in combination with various antimicrobials (amoxyccillin, tetracycline, and metronidazole) against *H. pylori* have been tested and confirmed the efficacy of this 1-week regimen (Lind et al., 1996). The same results were obtained from the therapies of omeprazole, clarithromycin, and amoxyccillin or metronidazole. Their side effects are much milder than the original bismuth-based triple therapy and patient compliance is expected to improve. The role of omeprazole in these non-bismuth-based triple therapies has been substantiated by the MACH-2 study; the role appears to be a class effect of PPI (Megraud et al., 1997). Trials of regimens using other PPIs such as lansoprazole and pantoprazole showed no significant difference in their efficacy of *H. pylori* eradication (Misiewicz et al., 1997 and Labenz et al., 1997). On the other hand, the choice of antibiotics decides the efficacy of PPI-based triple therapy. The inclusion of clarithromycin in the triple therapy ensures high efficacy and reproducible results. However, the effectiveness of clarithromycin cannot be generalized to other macrolides. The use of roxithromycin and azithromycin in PPI-based triple therapy has
not been as successful as the clarithromycin combination (Cammarota et al., 1996). There have been attempts to shorten the treatment period of PPI-based triple therapy to less than 1 week, but the cure rates were markedly decreased (Kung et al., 1997). Longer treatment times of 10 to 14 days do not give superior results either (Laine et al., 1997 and Miehlke et al., 1997). Ranitidine bismuth citrate is a new amalgamated compound of ranitidine and bismuth; it combines the antisecretory activity of ranitidine with the mucoprotective and anti \textit{H. pylori} effects of bismuth. Because of its high solubility, RBC-triple therapy has proven to be highly effective in eradicating \textit{H. pylori}, with cure rates ranging from 80\% to 96\% (Savarino et al., 1997 and Laine et al., 1997). In a head-to-head comparison of RBC-triple therapy with PPI-triple therapy, no difference in the cure rate of \textit{H. pylori} infection and duodenal ulcer was found (Sung et al., 1998). One-week RBC-based triple therapy is now increasingly considered as an effective regimen for \textit{H. pylori} eradication.

The most important causes of treatment failure are poor compliance on the part of patients and the development of bacterial resistance to antimicrobial agents. Patient compliance can only be improved by choosing a simple and well-tolerated treatment regimen. The importance of the prescribing physician giving detailed instruction and explaining any possible side effects cannot be overstated.

Resistance to metronidazole is caused by a failure of bacterial reduction. The prevalence of metronidazole resistance varies from 10\% to 90\% in different countries. Triple therapy is reported to be significantly less effective against metronidazole-resistant strains of \textit{H. pylori}, with most eradication results falling between 30\% to 70\% (Ling et al., 1996; Buekley et al., 1997; Rautelin et al., 1992; and Midolo et al., 1996). It is advisable not to include metronidazole in the treatment regimen in localities where the prevalence of metronidazole resistance is high. Primary resistance to clarithromycin is
much less common than metronidazole resistance, ranging from 0% to 15% (Tompkins et al., 1997). Acquired (secondary) resistance to clarithromycin frequently develops in individuals after initial treatment failure, due to the decreased affinity of the drug for the point mutated 23 S rRNA of the bacterial ribosome (Stone et al., 1996). Performing routine pretreatment susceptibility tests is not a cost-effective option. Clinicians should choose the appropriate combination of drugs based on sensitivity patterns provided by a local reference center. However, when treatment fails, susceptibility testing should be performed to guide further therapy.

Treatment of *H. pylori* infections with a combination of proton pump inhibitor (PPI), pantoprazole plus an antibiotic has shown increased efficacy. Such combination therapy ensured increased bacterial killing and prevention of the emergence of drugs resistance (Dore et al., 1999; Louw et al., 1998). However, improper combination and selection of antibiotic for the treatment often results in failure of therapy. Failure of the therapy results in discomfort and economic loss to the patient, apart from having ethical issues of failure of treatment. The best possible solution for eradication of *H. pylori* is to use a pantoprazole and antibiotic with best efficacy. There does not exist a fixed dose combination of PPI and suitable antibiotic so far to offer best possible treatment of infection caused by *H. pylori*.

The present study was aimed at evaluating efficacy of potent fixed dose combinations of pantoprazole with antibiotics for eradicating infectious of *H. pylori*. The best antibiotic in combination with pantoprazole can be considered for clinical evaluation to establish efficacy at clinical stage.