A Retrospective Study on Efficacy of Proton-Pump Inhibitor-based Triple Therapy for Eradication of *Helicobacter pylori* in Patients with Chronic Renal Failure

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ABSTRACT

Objective: The efficacy of short-course triple eradication therapy has been documented in patients with *Helicobacter pylori* infection and normal renal function. We have evaluated a one-week proton-pump inhibitor-based triple therapy for *Helicobacter pylori* eradication in a retrospective review of patients with chronic renal failure.

Methods: We studied 25 patients (mean age 65.1 ± 2.4 years) with creatinine clearance <30 ml/min/1.73 m² or serum creatinine level >200 μmol/L (13 on dialysis), who had *Helicobacter pylori* infection, documented by histological examination or rapid urease test, together with either peptic ulcer disease or severe gastritis. The combination of Omeprazole 20 mg BID or Lansoprazole 30 mg BID, amoxicillin 1 gm BID and clarithromycin 500 mg BID was given for one week, in addition to therapy for peptic ulcers. All patients were re-endoscoped four weeks later.

Results: All but one patient (96%) had successful eradication. On repeat endoscopy, all 13 patients with peptic ulcers had healed ulcers. For the 12 gastritis patients, three became normal and nine had persistent gastritis. For patients not on dialysis, the serum creatinine level and creatinine clearance remained stable at two weeks after treatment (303 ± 37 vs. 330 ± 36 μmol/L, *p*=ns; 23.6 ± 3.4 vs. 26.0 ± 3.9 ml/min/1.73 m², *p*=ns, respectively).

Conclusion: The short course triple therapy was highly efficacious for *Helicobacter pylori* eradication in patients with chronic renal failure, with no adverse effect on renal function.

Keywords: Chronic renal failure, Eradication, *Helicobacter pylori*, Triple therapy

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INTRODUCTION

Infection with *Helicobacter pylori* has been recognised to have a pathogenetic role in chronic active gastritis and peptic ulcer disease[1]. In view of the high serum and gastric juice urea concentrations in uraemic patients, the increased utilisation of urea by the urease of *Helicobacter pylori* can lead to an elevated concentration of gastric juice ammonia, a substance that has been incriminated in the development of chronic gastritis[2].

There is a great variation in the reported prevalence (17-63.5%) of *Helicobacter pylori* infection in uraemic patients[3-5]. Studies on patients with normal renal function have shown that successful eradication of *Helicobacter pylori* led to healing of ulcers[6], significant reduction of ulcer relapse rate[1,7], and a reduction of recurrence of intestinal type gastric cancer after endoscopic resection[8]. It is expected that patients with impaired renal function could share these benefits. Various antimicrobial agents have been used in different combinations for eradication of *Helicobacter pylori* including amoxicillin, clarithromycin, tetracycline and metronidazole[9-10]. The optimal regimen in any particular region may be affected by the development of resistant strains to various antimicrobials, the incidence of side effects and compliance to the regimens[9-10]. The MACH2 (metronidazole, amoxicillin, clarithromycin, *H. pylori*) study showed that the addition of omeprazole to two antimicrobials increased the efficacy of *Helicobacter pylori* eradication whether an amoxicillin/clarithromycin combination (OAC, 94% eradication rate) or a metronidazole/clarithromycin combination (OMC, 87% eradication rate) was used[11]. Lansoprazole is reportedly more effective than omeprazole as for growth inhibitory and bactericidal activity against *Helicobacter pylori* in vitro[12]. The acid-suppressive effect of lansoprazole seems to be stronger, because of superior bioavailability[13]. However, the efficacy of the short-course proton pump inhibitor-based triple therapy has not been documented in patients with renal failure. Eradication rates of 78.6 to 82.6% were obtained using long courses from four to 24 weeks of other combinations in patients with end-stage renal failure[4,14]. We retrospectively evaluated the efficacy and safety, including adverse effects on renal function, of a one-week therapy with proton

Table I. Outcome of 25 patients with ulcers and gastritis after *H. pylori* eradication therapy.

	First endoscopy			Repeat endoscopy
	Symptoms (anaemia: pain: GIB)	CRF: on dialysis	Endoscopic and histological findings	
Rapid urease test (+ve : -ve)			23 : 2	
Ulcers	5 : 6 : 2	6 : 7	8 GU; 4 DU; 1 combined*	all healed†
Chronic active gastritis	3 : 3 : 3	5 : 4	9 chronic active gastritis*	2 healed 3 chronic inactive gastritis 4 persistent lesion
Chronic gastritis	1 : 1 : 1	1 : 2	3 chronic gastritis	1 healed 2 persistent lesion
HP eradication (+ve : -ve)				24 : 1

*: one patient with negative rapid urease test
†: one GU patient with failed eradication
CRF, chronic renal failure; DU, duodenal ulcer; GIB, gastrointestinal bleeding; GU, gastric ulcer.

pump inhibitor in combination with amoxicillin and clarithromycin for the eradication of *Helicobacter pylori* in patients with chronic renal failure.

METHODS

Patients

Patients with chronic renal failure with a creatinine clearance below 30 ml/min/1.73 m^2 or serum creatinine level greater than 200 μmol/L, who had *Helicobacter pylori* infection together with either peptic ulcer disease or severe gastritis, were recruited for the study. They were serial patients with renal impairment referred to have endoscopic examination at our department during the period from July 1996 to December 1998. They were enrolled when they had the infection documented by histological examination or rapid urease test (RUT) as described below. The group composed of 25 patients (six women, 19 men), 13 of whom were on dialysis treatment (four haemodialysis and nine continuous ambulatory peritoneal dialysis). Their mean age was 65.1 ± 2.4 years. The causes of renal impairment were unknown in 11 patients, diabetes mellitus in six, hypertension in three, chronic glomerulonephritis in three, polycystic kidney disease in one and renal stone in one patient. The baseline serum creatinine level was 637 ± 59 μmol/L (range, 203-1,435). The baseline proteinuria and creatinine clearance among the patients not on dialysis were 1.9 ± 0.6 gm/d (range, 0.09-6.5) and 23.6 ± 3.4 ml/min/1.73 m^2 (range, 11.8-51), respectively.

Nine patients were referred to have endoscopic examination for anaemia that was thought unaccountable by the degree of renal impairment (Table I). Ten had epigastric pain or discomfort while six had a recent gastrointestinal bleeding episode.

Methods

Gastroduodenal endoscopy was performed on entry and at four weeks after eradication treatment. At each examination, two pieces of biopsy specimens from the antrum were obtained for a rapid urease test. Another two pairs of biopsy specimens were obtained from the antrum and the gastric body for histological examination. Gastric mucosa biopsies were examined by light microscopy with hematoxylin and eosin staining. All biopsies were found suitable for a definitive diagnosis as reviewed by the pathologists who were unaware of the RUT results. The histological assessment was negative for *Helicobacter pylori* in two patients who had positive RUT results. Thirteen patients had ulcer disease – four had duodenal ulcers, eight had gastric ulcers and one combined (Table I). Twelve patients had isolated gastritis, of which histological assessment revealed chronic gastritis, defined by infiltration of lamina propria by predominantly lymphocytes and plasma cells, in three and chronic active gastritis, with marked infiltration of neutrophils in addition to lymphocytes and plasma cells[15], in nine. The rapid urease test was performed using a homemade kit. A gastric antral biopsy specimen was placed in the pre-prepared well on the slide (containing urea), and if *Helicobacter pylori* is present, the ammonia generated produced a change in the colour of a pH indicator. The slide was inspected for any colour change after 20 minutes and again after 24 hours of incubation at room temperature. The sensitivity and specificity of the test in our centre were 90.6 and 100%, respectively[16]. The rapid urease test was positive in all but two patients (one with fundal gastritis and one with combined gastric and duodenal ulcer). *Helicobacter pylori* infection was deemed to be present if either the biopsy urease test or histology was positive.

None of the patients had allergy history to any of the components of the regimen, had previous attempts of *Helicobacter pylori* eradication, or had used antibiotics for other indications within two weeks prior to study.

The following data were collected: reason and findings of endoscopic examination, diagnosis of the renal failure, serum creatinine level, 24-h proteinuria and creatinine clearance.

***Helicobacter pylori* eradication treatment**

Indications for *Helicobacter pylori* eradication included peptic ulcer disease and severe gastritis. The combination of omeprazole 20 mg BID (19 patients, OAC) or lansoprazole 30 mg BID (six patients, LAC), amoxicillin 1 gm BID and clarithromycin 500 mg BID was given for one week. The choice of the proton pump inhibitors was determined by the attending physicians. On completion of treatment, the presence of side effects was noted and compliance checked. In addition to the eradication treatment, patients with peptic ulcer were given famotidine 40 mg at night for four weeks to promote ulcer healing, reduced to 20 mg at night for patients with creatinine clearance below 20 ml/min/1.73 m^2.

Four weeks upon completion of the eradication treatment, all patients were re-endoscoped. Ulcer healing was defined as endoscopically complete re-epithelialisation. Two pairs of biopsy specimens were taken from the antrum and the corpus for histological assessment of *Helicobacter pylori* infection. The pathologists were unaware of the eradication treatment given. Successful eradication of the bacterium was defined as no histological evidence of *Helicobacter pylori* infection on all four biopsy specimens.

Apart from patients on dialysis treatment, all patients had serum creatinine level and creatinine clearance measured at two weeks after completion of eradication treatment. Creatinine clearance was calculated from 24-h urine creatinine excretion and the serum creatinine level, normalised to 1.73 m^2 surface area.

All patients gave informed consent.

Statistics

The values of parameters are given as mean (± standard error of mean) where appropriate. Differences in renal function between baseline and follow-up values were compared by paired Wilcoxon's test. Compliance was assessed as consumption of more than 90% of the medications. The cut-off level for statistical significance was taken as p=0.05 (two-tailed).

RESULTS

***Helicobacter pylori* eradication**

All patients completed the one-week eradication treatment without any major side effects. All but one patient (from LAC group) had successful eradication of *Helicobacter pylori* infection as assessed by histological examination at four weeks after treatment (96%, Table I). This patient had healed gastric ulcer and antral gastritis on the second endoscopy. Further eradication treatment was not given in view of the poor baseline serum creatinine level (301 μmol/L).

Follow-up of gastritis, ulcer healing and symptoms

On repeat endoscopy at four weeks after completion of the eradication treatment, all fourteen patients with peptic ulcers, including the patient with persistent *Helicobacter pylori* infection, had healed ulcers (Table I).

For the nine patients with chronic active gastritis on the initial biopsy, two had normal endoscopic findings as well as histology on repeat endoscopy; three had normal endoscopy findings and chronic inactive gastritis on biopsy (Table I). There were four patients with persistent gastritis (antral or diffuse) on both endoscopy and biopsy. For the three patients with chronic gastritis on the initial biopsy, one became normal while two had persistent gastritis.

Successful *Helicobacter pylori* eradication was always associated with clinical improvement with disappearance of epigastric pain and control of gastrointestinal bleeding.

Renal function

For patients not on dialysis, the serum creatinine and creatinine clearance remained stable after the eradication therapy (303 ± 37 vs. 330 ± 36 μmol/L, p=ns; 23.6 ± 3.4 vs. 26.0 ± 3.9 ml/min/1.73 m^2, p=ns, respectively).

DISCUSSION

With the exception of patients with gastrinoma and those taking nonsteroidal anti-inflammatory drugs, more than 95 percent of patients with duodenal ulcers and more than 80 percent of patients with gastric ulcers are infected with *Helicobacter pylori*[17]. The International Agency for Research on Cancer has categorised *Helicobacter pylori* infection as a class I carcinogen and a definite cause of human gastric cancer[18]. While upper gastrointestinal upset including nausea, loss of appetite and dyspepsia are symptoms experienced by many uraemic patients, studies have found a significant proportion of these patients suffering from peptic ulcer diseases or chronic gastritis. Milito et al. performed upper gastrointestinal endoscopy for 95 patients on long-term haemodialysis and identified superficial gastritis in 66% of patients, with signs of activity in 19%[19]. Atrophic gastritis was seen in 15% and intestinal metaplasia in 3% of the cases[19]. In contrast, active peptic ulcer did not appear to be more common in patients on haemodialysis than in the general population[20]. Among uraemic patients, *Helicobacter pylori* infection has been reported to have a prevalence of 17-63.5%[3-5]. The European *Helicobacter pylori* Study Group has suggested that all *Helicobacter*

pylori positive patients with peptic ulcer disease, patients with functional dyspepsia in whom no other possible causes of symptoms are identified after full investigation, patients with low-grade gastric mucosa associated lymphoid tissue lymphoma and those having gastritis with severe macroscopic or microscopic abnormalities should receive eradication therapy[21]. The American College of Gastroenterology has not included gastritis in the recommended list of conditions for *Helicobacter pylori* eradication[22], but in view of the high prevalence of severe gastritis in uraemic patients[19] and the possible long-term sequelae, we tend to go for eradication therapy for patients with severe gastritis. The pattern of presentation did not differ between patients with peptic ulcer and gastritis in the present series (Table I) and the eradication rates were equally high for both groups of patients. However, while ulcer healing was documented in all patients, gastritis persisted in nine of the twelve patients, though in a milder form in general (Table I).

It has been found that the urease-based tests including the urease slide test remained reliable in determining *Helicobacter pylori* status, despite the markedly increased concentrations of urea in the gastric juice among chronic renal failure patients. Rowe et al found no false-positive or false-negative results after 20 minutes and 24 hours of incubation[5]. We have thus used both rapid urease test on antral biopsy and a careful microscopic examination of the antral and gastric body biopsies[23] to determine *Helicobacter pylori* status. In 23 of 25 patients judged infected with *Helicobacter pylori*, the RUT was clearly positive after 20 minutes of incubation.

In patients with normal renal function, the combination of proton pump inhibitor (omeprazole 20 mg BID or lansoprazole 30 mg BID) with amoxicillin 1 gm BID and clarithromycin 500 mg BID for one week have been found to be superior to other proton pump inhibitor-based combination therapy[11,24]. Besides achieving an eradication rate of 85-95%, it is simple to use with twice-daily dosing and has few side effects. Cure rate of more than 90% has been reported with the combination of a proton pump inhibitor, amoxicillin and metronidazole against metronidazole-sensitive *Helicobacter pylori* strains[25]. However, eradication rate may decrease by 15 to 20% in the presence of metronidazole resistance[25]. Locally, the overall metronidazole resistance rate was 53.5% among Chinese peptic ulcer patients in Hong Kong[26]. There is evidence that metronidazole resistance can be treated successfully with a triple therapy including clarithromycin[27] and thus, we have chosen the triple therapy with clarithromycin and not a nitroimidazole. To date, there are few reports on *Helicobacter pylori* eradication in patients with chronic renal failure. Tamura et al used the combination of lansoprazole 30 mg daily (eight weeks), amoxicillin 500 mg daily (three weeks) and plaunotol 80 mg TDS (24 weeks) in 14 patients with end-stage renal failure and achieved an eradication rate of 78.6% four weeks after the completion of amoxicillin therapy[14]. This is a rather prolonged treatment course and compliance is therefore of concern. Muñoz de Bustillo et al reported an eradication rate of 60.8% among 33 haemodialysis patients with omeprazole 20 mg BD and amoxicillin 500 mg TDS for two weeks[4]. The rate went up to 82.6% after a second cycle with omeprazole 20 mg BD plus clarithromycin 500 mg BD for another two weeks.

The main role of the proton pump inhibitor is to increase the antibacterial effectiveness of antibiotics by increasing the pH of gastric juice through acid suppression. At high concentrations, the proton pump inhibitors have antimicrobial or even bactericidal activity[12,13]. Furthermore, they can inhibit *Helicobacter pylori* urease activity[28]. The proton pump inhibitors are primarily eliminated by the hepatic route with negligible amounts of unchanged drugs recovered in the urine[29]. Pharmacokinetic data of omeprazole in patients with renal insufficiency and those on dialysis suggested that the drug absorption and pharmacokinetics profiles were not affected[29]. However, the elimination of the total pool of metabolites of omeprazole was decreased[30]. Renal failure also did not change the pharmacokinetics of lansoprazole, but the renal elimination of the drug's principal metabolites was decreased[31]. As almost all amoxicillin is excreted by the kidneys, prolonged plasma half-lives is seen in patients with impaired renal function[32]. Clarithromycin is metabolised in the liver and the excretion of the drug and the 14-OH metabolite is by renal mechanisms[33].

These pharmacokinetic properties of the three drugs might have contributed to the high eradication rate achieved in the present study (96%), when compared to the 78.6-82.6% using long courses of other combinations in patients with end-stage renal failure[4,14]. Presumably the serum drug levels would have been higher than in patients with normal renal function. However, the current regimen is considered very safe without any major side effects. The other factor for the successful outcome is the excellent compliance to the treatment regimen in the studied patients. Irregular therapy compliance is currently considered the main reason for treatment failure[10].

With the results of this study, we believe that a proton pump inhibitor-based triple therapy using omeprazole 20 mg BID or lansoprazole 30 mg BID, amoxicillin 1 gm BID and clarithromycin

500 mg BID for one week is highly efficacious for *Helicobacter pylori* eradication in patients with chronic renal failure. Without a control group and a prospective design, we have limitations in concluding the true efficacy of this regimen.

For patients with normal renal function, if first-line therapies like a proton pump inhibitor-based one-week triple therapy fail, one option is to add bismuth to the triple therapy, resulting in so-called quadruple therapy[34]. However, bismuth salts in general should be avoided in renal failure due to the accumulation of their cations that can be toxic[29]. Tetracycline, another agent commonly used in quadruple therapy, is also contraindicated in patients with renal impairment as the plasma half-life is markedly prolonged and the potential nephrotoxicity may worsen the existing renal function or any residual renal function. The other option is to switch between clarithromycin and metronidazole. There is at present no recommendation on what would be the next step if this fails for patients with chronic renal failure. Viable options include increasing the dose of the proton pump inhibitor and amoxicillin to tackle the problem of antibiotic resistance and the use of newer therapeutic agents like rifabutin[34].

REFERENCES

1. Graham DY, Lew GM, Klein PD, Evans DG, Evans DJ Jr, Saeed ZA, et al. Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric or duodenal ulcer. Ann Intern Med 1992; 116:705-8.
2. Triebling AT, Korsten MA, Dlugosz JW, Paronetto F, Lieber CS. Severity of Helicobacter-induced gastric injury correlates with gastric juice ammonia. Dig Dis Sci 1991; 36:1089-96.
3. Ala-Kaila K, Vaajalahti P, Karvonen AL, Kokki M. Gastric Helicobacter and upper gastrointestinal symptoms in chronic renal failure. Ann Med 1991; 23:403-6.
4. Mu oz de Bustillo E, S nchez Tomero JA, Sanz JC, Moreno JA, Jim nez I, L pez-Brea M, et al. Eradication and follow-up of *Helicobacter pylori* infection in hemodialysis patients. Nephron 1998; 79:55-60.
5. Rowe PA, El Nujumi AM, Williams C, Dahill S, Briggs JD, McColl KEL. The diagnosis of *Helicobacter pylori* infection in uremic patients. Am J Kidney Dis 1992; 20:574-9.
6. Lam SK, Ching CK, Lai KC, Wong BC, Lai CL, Chan CK, et al. Does treatment of *Helicobacter pylori* with antibiotics alone heal duodenal ulcer? A randomised double blind placebo controlled study. Gut 1997; 41:43-8.
7. Labenz J, B rsch G. Highly significant change of the clinical course of relapsing and complicated peptic ulcer disease after cure of *Helicobacter pylori* infection. Am J Gastroenterol 1994; 89:1785-8.
8. Uemura N, Mukai T, Okamoto S, Yamaguchi S, Mashiba H, Taniyama K, et al. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev 1997; 6:639-42.
9. Burette A, Glupczynski Y, De Prez C. Evaluation of various multi-drug eradication regimens for *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1992; 4:817-23.
10. Graham DY, Lew GM, Malaty HM, Evans DG, Evans DJ Jr, Klein PD, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 1992; 102:493-6.
11. Lind T, M graud F , Unge P, Bayerd rf fer E, O Morain C, Spiller R, et al. The MACH2 study: role of omeprazole in eradication of Helicobacter pylori with 1-week triple therapies. Gastroenterology 1999; 116:248-53.
12. Nakao M, Malfertheiner P. Growth inhibitory and bactericidal activities of lansoprazole compared with those of omeprazole and pantoprazole against *Helicobacter pylori*. Helicobacter 1998; 3:21-7.
13. Timmer W, Ripke H, Kleist P, Ehrlich A, Wieckhorst G, Lucker PW, et al. Effect of four lansoprazole dose levels and one dosage regimen of omeprazole on 24-hour intragastric pH in healthy subjects. Methods Find Exp Clin Pharmacol 1995; 17:489-95.
14. Tamura H, Tokushima H, Murakawa M, Matsumura O, Itoyama S, Sekine S, et al. Eradication of *Helicobacter pylori* in patients with end-stage renal disease under dialysis treatment. Am J Kidney Dis 1997; 29:86-90.
15. Price AB. The Sydney System: Histological division. J Gastroenterol Hepatol 1991; 6:209-22.
16. Lau CF, Wong MC, Yee KS, Loo CK, Lam KM. Evaluation of an economical, home-made rapid urease test for the detection of *Helicobacter pylori* infection in an ex-subvented hospital. Proceedings of the Tenth Asian-Pacific Congress of Gastroenterology, Yokohama, Japan, 1996; p188.
17. Peterson WL. *Helicobacter pylori* and peptic ulcer disease. N Engl J Med 1991; 324:1043-8.
18. Forman D. *Helicobacter pylori* and gastric cancer. Scand J Gastroenterol 1996; 31 (Suppl 220):23-6.
19. Milito G, Taccone-Gallucci M, Brancaleone C, Nardi F, Cesca D, Boffo V, et al. The gastrointestinal tract in uremic patients on long-term hemodialysis. Kidney Int 1985; 28 (Suppl 17):S157-60.
20. Andriulli A, Malfi B, Recchia S, Ponti V, Triolo G, Segoloni G. Patients with chronic renal failure are not at a risk of developing chronic peptic ulcers. Clin Nephrol 1985; 23:245-8.
21. The European *Helicobacter Pylori* Study Group. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. Gut 1997; 41:8-13.
22. Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Am J Gastroenterol 1998; 93:2330-8.
23. Logan RPH, Polson RJ, Misiewicz JJ, Rao G, Karim NQ, Newell D, et al. Simplified single sample ^{13}Carbon urea breath test for *Helicobacter pylori*: comparison with histology, culture and ELISA serology. Gut 1991; 32:1461-4.
24. Labenz J, Stolte M, Peitz U, Tillenburg B, Becker T, Borsch G. One-week triple therapy with omeprazole, amoxicillin, and either clarithromycin or metronidazole for cure of *Helicobacter pylori* infection. Aliment Pharmacol Ther 1996; 10:207-10.
25. Lerang F, Moum B, Haug JB, Tol s P, Breder O, Aubert E, et al. Highly effective twice-daily triple therapies for Helicobacter infection and peptic ulcer disease: does in vitro metronidazole resistance have any clinical relevance? Am J Gastroenterology 1997; 92:248-53.
26. Ching CK, Leung KP, Yung RWH, Lam SK, Wong BCY, Lai KC, et al. Prevalence of metronidazole resistant *Helicobacter pylori* strains among Chinese peptic ulcer disease patients and normal controls in Hong Kong. Gut 1996; 38:675-8.
27. Adamek RJ, Suerbaum S, Pfaffenbach B, Opferkuch W. Primary and acquired *Helicobacter pylori* resistance to clarithromycin, metronidazole, and amoxicillin — influence on treatment outcome. Am J Gastroenterol 1998; 93:386-9.
28. M graud F. Adjuvant therapy for *Helicobacter pylori* eradication: Role of lansoprazole shown in vitro. J Clin Gastroenterol 1995; 20 (Suppl 1):S24-7.
29. Gladziwa U, Koltz U. Pharmacokinetic optimisation of the treatment of peptic ulcer in patients with renal failure. Clin Pharmacokinet 1994; 27:393-408.
30. Naesdal J, Andersson T, Bodemar G, Larsson R, Reg rdh CG, Sk nberg I, et al. Pharmacokinetics of [^{14}C] omeprazole in patients with impaired renal function. Clin Pharmacol Ther 1986; 40:344-51.
31. Delhotal-Landes B, Flouvat B, Duchier J, Molinie P, Dellatolas F, Lemaire M. Pharmacokinetics of Lansoprazole in patients with renal or liver disease of varying severity. Eur J Clin Pharmacol 1993; 45:367-71.
32. Arancibia A, Droguett MT, Fuentes G, Gonzalez G, Gonzalez C, Thambo S, et al. Pharmacokinetics of amoxicillin in subjects with normal and impaired renal function. Int J Clin Pharmacol Ther Toxicol 1982; 20:447-53.
33. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, and azithromycin. Mayo Clin Proc 1999; 74:613-34.
34. Sung JJY. Where are we with current therapy? Helicobacter 2000; 5 (Suppl 1):S17-21.