EVALUATION OF THERAPIES IN THE TREATMENT OF *HELICOBACTER PYLORI* ASSOCIATED NON-ULCER DYSPEPSIA

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ABSTRACT

This randomised double blind placebo controlled study evaluated the effectiveness of colloidal bismuth subcitrate (CBS), ampicillin and their combination in the treatment of Helicobacter Pylori in non-ulcer dyspepsia (NUD) and assessed if elimination of this organism is associated with improvement of gastritis and the symptoms. Forty-eight NUD patients with H. pylori and histologic gastritis were randomly allocated to one of the three regimens for 28 days. Symptoms were assessed before and after treatment. Forty-three patients completed the trial. Repeat endoscopy within 48 hours of completing treatment showed suppression of H. pylori in 6 of 7 patients (85.7%) on combined therapy and one of 8 patients (12.5%) on CBS therapy (p=0.0205). There was no suppression of the bacteria in patients treated with ampicillin. Repeat endoscopy performed 2 weeks after completing treatment showed suppression of H. pylori in 3 of 7 patients (42.9%) on combined therapy and none in the other two groups. Patients on combined therapy who had suppression of H. pylori, 48 hours or 2 weeks after completing treatment were noted to have historical improvement of their gastritis (p=0.0001 and p=0.05 respectively). This was also associated with improvement of symptoms in these patients.

Keywords: Helicobacter Pylori, non-ulcer dyspepsia, gastritis, suppression, colloidal bismuth subcitrate.

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INTRODUCTION

Bismuth compounds were introduced in medicine in the 18th century. They were first advocated for the treatment of dyspepsia by Chambers in England and Kussmaul in Germany[1]. They are being evaluated for their antibacterial activity against *Helicobacter pylori*[2], an organism associated with duodenal ulcerations and non-ulcer dyspepsia[3]. *H. pylori*, a gram negative spiral organism was first isolated from the gastric mucosa in 1982, and is almost always present in patients with histological gastritis but rarely on normal mucosa[4]. It has been suggested by Marshall et al to have a pathogenic role in gastritis[4].

Non-ulcer dyspepsia (NUD) is a symptom complex of uncertain etiology . In Malaysia NUD is a common diagnosis in patients investigated for dyspepsia[5] and about a third are associated with *H. pylori*[6]. The significance of this association and the benefits from treatment are still doubtful. In this study, we evaluated the efficacy of different treatment regimens in eliminating *H. pylori* from the gastric mucosa and determined if elimination was associated with histological or symptomatic improvements.

METHODS

Patients

Forty-eight NUD patients with confirmed *H. pylori* infection (23 males, 25 females, mean age 42.3 years, range 18-70 years) participated in the trial over a period of 18 months. These patients were chosen from patients who had symptoms of dyspepsia and required endoscopic examination. Dyspepsia was defined as upper abdominal pain or discomfort, heartburn, nausea, vomiting or other symptoms considered to be referable to the proximal alimentary tract[7].

Non-ulcer dyspepsia (NUD) was defined as dyspepsia where clinical evaluation and basic laboratory tests failed to reveal any obvious structural cause for the symptoms and in which endoscopy was normal or there was visual evidence of non-erosive gastritis or non-erosive duodenitis[5].

Patients with esophageal ulcers, reflux esophagitis, cancer of the esophagus, gastric and duodenal ulcer disease,

gastrectomy and cancer of the stomach or duodenum were excluded. Patients with a history of biliary disease were excluded but ultrasound was not done to confirm or detect such in any patient. Patients who had recent treatment (4 weeks prior to endoscopy) with nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, corticosteroids, or patients who were pregnant, lactating, or had liver or kidney impairment were also excluded.

Informed written consent was obtained from all patients. The study was approved by the Ethical Committee of the Faculty of Medicine, Universiti Kebangsaan Malaysia.

Study Design

Patients with dyspepsia for 3 months or more and in whom *H. pylori* and histological gastritis was detected in the antrum qualified for the trial. They were given a symptom assessment sheet which they were required to fill for 14 consecutive days before treatment began. The symptom sheet inquired about the presence of epigastric pain, flatulence and post-prandial belching. Presence of a symptom within a day was given a score of 1. The symptom scores were added for each patient giving a possible score ranging from 0 to 14 for each symptom. Patients were randomised to receive one of the three treatment regimens that is (a) CBS (two tablets twice daily ie 480 mg) for 28 days and ampicillin (2 capsules four times/day ie 2000 mg) for the first 10 days of treatment, (b) CBS for 28 days and placebo matched to ampicillin for the first 10 days of treatment and (c) ampicillin for the first 10 days of treatment and placebo matched to CBS for 28 days. Blindness was also preserved by providing all three regimens in identical dispensing envelops with similar instructions. All medications were dispensed by the UKM dispensary unit. Patients were allowed to take gelusil for symptom relief throughout the trial and were asked to record the number of gelusil tablets consumed 2 weeks before and after treatment. Patients who required NSAIDs, antibiotics or H_2 antagonist anytime during the trial were excluded .

Side effects were assessed 2 weeks after commencement of treatment. At the follow-up visit patients were given a second similar symptom assessment sheet to fill for 14 consecutive days until the end of treatment. Patients were divided into two groups; in one group repeat biopsy was done within 48 hours of completing treatment and the other, 2 weeks after treatment. Failure to detect the organism within 48 hours or 2 weeks after completion of treatment was considered as suppression of the bacteria. At endoscopy, biopsies were taken from the prepyloric antral mucosa, body and duodenal bulb for histopathological examination. When the mucosa appeared inflammed, the specimens were taken from the red areas, otherwise any part of the mucosa. The biopsy forceps was washed in saline in between biopsies at different sites from the same patient. After each patient the biopsy forceps was sterilized with glutaraldehyde and then rinsed with saline. Endoscopies were done by three gastroenterologists.

Histopathology

Hematoxylin and eosin staining was used to study the gastric mucosal biopsy section for gastritis and *H. pylori*. In cases where presence of the organism was doubtful, Warthin-Starry stain was used for confirmation. The presence of *H. pylori* and histological gastritis refers to the antrum. Antral gastritis (AG) was graded from 0 to 3 according to the modified Whitehead classification[8]. The same histopathologist who was blinded to the type of treatment the patient had received, examined the slides before and after treatment.

Of the 197 patients with non-ulcer dyspepsia that were screened, 66 (33.5%) were *H. pylori* positive. All patients in whom *H. pylori* was detected in the antrum also had histological gastritis of this region. Forty-eight of the 66 *H. pylori* patients qualified and agreed to enter the trial.

Statistical Analysis

Results were expressed as mean (S.E.M.). The t-test, Chi-square test with Yates correction and Wilcoxon's rank-sum tests were used appropriately. A p value of less than or equal to 0.05 was considered significant.

RESULTS

Forty-three patients completed the trial. One patient on combined therapy developed rashes. Two patients on monotherapy with CBS were excluded, one due to non-compliance and the other chose not to continue with the trial as he felt his flatulence worsened on commencement of treatment. Two patients (one on combined therapy and the other on ampicillin) did not come for repeat endoscopy and were not contactable.

Of the 43 patients who completed the trial, 14 were treated with combined therapy; 14 with CBS and 15 with ampicillin. There was no significant difference among the patients in the three groups with respect to age, sex, race, grades of *H. pylori* infection, grades of gastritis and symptoms before treatment (Table I).

Table I - Characteristics of 43 patients randomised into 3 treatment groups.

Characteristics	Groups			Statistical significance
	CBS & ampicillin	CBS	Ampicillin	
Patients (n)	14	14	15	NS
*Age (years)	48.1 (4.78)	37.2 (3.61)	38.9 (3.28)	NS
Sex (M:F)	8:6	6:9	7:7	NS
Race (M:C:I)	1:7:6	2:12:2	0:10:3	NS
*Symptom score	110.3 (6.68)	88.3 (31.46)	88.7 (21.39)	NS
*Duration of symptoms(days)	7.9 (1.93)	6.4 (1.70)	7.6 (1.97)	NS
*Antacid consumption (tablet)	24.6 (2.7)	20.7 (3.6)	29.7 (4.0)	NS
*Grades of infection	2.07 (0.22)	2.40 (0.19)	2.50 (0.17)	NS
*Grades of gastritis	1.93 (0.07)	2.0 (0.10)	2.07 (0.03)	NS

Race (M:C:I) - Race (Malays : Chinese : Indians)

NS - Not significant.

* Figures expressed as mean (SEM).

Patients in all treatment group had *H. pylori* and histological gastritis in their antrum, and had experienced dyspepsia for at least 3 months.

Elimination of *H. pylori* with Treatment

All patients were positive for *H. pylori* before treatment. When gastric mucosal biopsies were studied within 48 hours of completing treatment, the combined therapy succeeded in suppressing *H. pylori* in 6 of 7 patients (85.7%), whilst therapy with CBS suppressed *H. pylori* in one of 8 patients (12.5%) (Table II). The combined therapy was found to have a significantly better HP suppression rate compared to the latter (x^2=5.37, p=0.0205). Ampicillin did not suppress *H. pylori* from any of the 7 patients treated with it.

In the group of patients assessed 2 weeks after completing treatment the combined therapy succeeded in suppressing *H. pylori* in 3 of 7 patients (42.9%) (Table III). In contrast, *H. pylori* persisted in patients treated with the other two regimens (Table III).

Table II - Detection of *H. pylori* in the antrum and assessment of antral gastritis (AG) in three treatment groups within 48 hours of completing treatment.

Treatment Groups	No. of H. pylori -ve patients(%)	AG before treatment vs after treatment Mean (SEM)
* CBS & Ampicillin (n=7)	6 (85.7)	1.86 (0.14) vs 0.86 (0.14)
* *CBS (n=8)	1 (12.5)	2.0 (0.1) vs 1.5 (0.1)
Ampicillin (n=7)	0	2.0 (0.22) vs 2.29 (0.81)

* CBS & Ampicillin: supression more effective than CBS alone: p=0.0205; AG of whole group improved: p=0.0038; AG *H. pylori* negative patients improved: p=0.0001

** CBS: AG of all patients improved significantly: p=0.03

Table III - Detection of *H. pylori* in the antrum and assessment of antral gastritis (AG) in 3 treatment groups 2 weeks after completing treatment.

Treatment Groups	No. of H. pylori -ve patients	AG before treatment vs after treatment Mean (SEM)
* CBS & Ampicillin (n=7)	3 (42.9%)	2.0 (0) vs 1.43 (0.30)
CBS (n=6)	0	2.2 (0.17) vs 2.0 (0.26)
Ampicillin (n=8)	0	2.0 (0) vs 1.88 (0.23)

* CBS & Ampicillin: more effective in suppressing *H. pylori*; AG of *H. pylori* negative patients improved: p=0.05.

Histological Response

Patients in all treatment groups had microscopic evidence of antral gastritis before starting treatment.

The Combined Therapy Group

Overall, of the 14 patients treated with combined therapy, 9 were *H. pylori* free and had improvements of their histological antral gastritis (Table IV). The rest of the patients who remained positive for the *H. pylori* had no significant improvement of their histological gastritis.

The histological gastritis of 7 patients studied within 48 hours of completing treatment improved significantly (p=0.0038) after completion of treatment (Table II). One of these 7 patients (14%) had complete morphological restoration of the gastric histology and 5 (71%) had significant improvement. The only patient whose gastritis remained unchanged was the one with persistent infection .

In patients assessed 2 weeks after completing treatment there was significant improvement of the gastritis in 3 patients who were freed of the organism (p=0.05) (Table III) . However when patients who remained *H. pylori* positive were included, no significant improvement in the gastritis was noted (p=0.10) .

The CBS Group

There was significant improvement of the gastritis in all patients assessed within 48 hours of completing treatment (p=0.03) (Table II). Despite this significant improvement *H. pylori* was suppressed only in one of 8 patients. In those assessed 2 weeks after completion of treatment, there was no significant improvement of their gastritis (p=0.61) (Table III) .

The Ampicillin Group

There were no significant improvement of the gastritis in all patients in this group, whether assessed within 48 hours (p=0.17) or 2 weeks after completing treatment (p=0.6) (Tables II and III).

Symptomatic Response

In all patients, symptomatic response was evaluated by comparing various parameters 2 weeks before and 2 weeks after starting treatment. The three parameters which were used to gauge the symptomatic response in patients eliminated of *H. pylori* or not (whether 48 hours or 2 weeks after treatment) were symptom scores, antacid consumption and the number of pain-free days.

Symptom Score

Patients on combined therapy and in whom *H. pylori* were eliminated had significant improvements in the severity of epigastric pain, flatulence and belching. Patients with persistent infection had improvement of flatulence only (Table V).

Patients treated with CBS experienced improvements in flatulence and epigastric pain but belching persisted with no significant improvement (Table V).

There was no improvements of all the three symptoms in patients treated with ampicillin (Table V).

Antacid Consumption

Patients in all treatment groups had comparable antacid consumption before trial (Table I). In the combined therapy group the mean number of gelusil tablets consumed by patients who were eliminated of *H. pylori* was 20.0 (6.67) before treatment vs 4.0 (1.33) after treatment (p=0.003). For patients who continued to have the organism after treatment, the mean number of gelusil tablets consumed was 32.80 (3.87) vs 16.8 (7.62) after treatment (p=0.343).

Table IV - Assessment of antral gastritis (AG) in patients freed of *H. pylori* after treatment.

Treatment Groups	AG before treatment vs after treatment Mean (SEM)
* CBS & Ampicillin (n=14)	* 2.0 (0) vs 0.78 (0.15) (n=9)
CBS (n=14)	2.0 vs 1.0 (n=1)
Ampicillin (n=5)	no. *H. pylori* free patients

* CBS & Ampicillin: Significant improvement of AG in all *H. pylori* negative patients; $p < 0.05$.

Table V - Mean symptoms scores of patients on different treatments

Treatment	Before treatment vs after treatment Mean (SEM)		
	Epigastric pain	Flatulence	Belching
CBS & Ampicillin (HP -ve) (n=9)	4.89 (0.82) vs *0.89 (0.26)	6.33 (0.93) vs *1.22 (0.41)	11.01 (1.09) vs *1.56 (0.77)
CBS & Ampicillin (HP +ve) (n=5)	13.4 (1.13) vs 9.8 (2.25)	7.6 (2.50) vs 5.0 (2.24)	5.2 (2.44) vs 3.2 (2.72)
CBS (n=14)	10.8 (2.38) vs *6.3 (1.85)	5.1 (1.42) vs **2.5 (1.18)	3.8 (1.41) vs 1.9 (0.88)
Ampicillin (n=15)	8.1 (1.35) vs 7.4 (1.23)	3.2 (1.13) vs 3.2 (1.31)	5.5 (1.56) vs 6.5 (1.82)

Significant improvement of all three symptoms in H. pylori -ve patients on combination therapy. Duration of symptoms among the three groups were comparable (Table I).

* $p < 0.01$
** $p < 0.05$

The mean number of gelusil tablets consumed by the patients on CBS reduced significantly after treatment (p=0.0007). In contrast, patients treated with ampicillin had no significant change in their antacid consumption (p=0.101).

Number of Pain-free Days

In the combined therapy group the mean number of pain-free days experienced by patients eliminated of *H. pylori* was 5.44 (1.81) before treatment vs 9.70 (3.26) after treatment (p=0.003). However, patients with persistence of the organism did not show such a benefit (p=0.089).

The mean number of pain-free days in patients on CBS also increased significantly from 3.14 (0.99) before treatment vs 8.0 (1.20) after treatment (p=0.0007).

The number of pain-free days in patients treated with ampicillin did not change significantly before and after treatment (p=0.2948).

DISCUSSION

In this study we found the combined therapy to be the most effective regimen in suppressing *H. pylori* in the gastric mucosa of patients with NUD. A high suppression rate obtained with treatment combining CBS and an antibiotic has also been reported by other investigators[2,9]. The suppression rate achieved was much higher within 48 hours (85.7%) compared to 2 weeks after completing treatment (42.9%). The time interval between the end of treatment and repeat biopsy is an important factor when evaluating the effectiveness of treatment. Patients assessed soon after completion of treatment show a higher suppression rate but this would not truly reflect the actual elimination rate of *H. pylori*.

The other two regimens were ineffective. The low suppression rate obtained with CBS therapy were in discordance with previous studies which achieved 83.3% suppression rate[10] as opposed to our 12.5% . This may be due to the longer period of treatment administered by the investigator.

Treatment with ampicillin failed to suppress *H. pylori* from any patients. A study by Glupczynski et al initially indicated that amoxycillin administered as monotherapy was effective in achieving a 91% clearance rate but unfortunately the relapse rate after 14 days of completion of treatment was 100%[2]. The author attributed the relapse to incomplete elimination and persistence of the organism in the gastric mucosa, thus allowing the organism to proliferate once treatment has stopped. In our study of patients treated with ampicillin and CBS placebo, when repeat biopsy was done at 48 hours and 2 weeks after treatment it would actually be about three to five weeks consecutively after the course of ampicillin as ampicillin was given only for the first 10 days of treatment and here the organisms persisted in all the patients. This supports the above finding which shows that monotherapy with an antibiotic is ineffective.

All patients in whom *H. pylori* were suppressed had improved gastric histology whilst that of patients with persistence of the organism remained unchanged. At 48 hours, in the CBS treated group, there was a significant improvement in the mean AG score when all the patients were considered but this significance did not hold true if the *H. pylori* negative patient was excluded. Nevertheless, in the CBS treated group, it is not surprising to find some patients with improvement of AG despite persistence of the organism as CBS is known to exert cytoprotective and anti-inflammatory actions on the gastric mucosa[2, 11, 12]. It is not entirely clear to what extent the antibacterial activity and the local effects of bismuth contribute to the efficacy in treating gastritis. However in the combination therapy group, it was quite clear that suppression of *H. pylori* was associated with improvement of AG and persistence of it lacks such improvement. This strenghtened the possibility of a pathogenic role for *H. pylori* causing gastric inflammation. This finding is similar to that observed by other investigators[2,10,13]. Ampicillin, unlike bismuth, does not have any direct effects on the gastric mucosa. Hence, the absence of improvement of gastritis in the ampicillin treated patients which remained positive for the organism.

The outcome of this trial suggests that an initial antibiotic therapy aided by CBS is required to wipe the majority of the bacterial population present at the beginning of therapy. Continuing the administration of CBS after cessation of antibiotic therapy helps to clear residual bacteria present on the gastric mucosa whilst restoring normal gastric histology which is probably achieved through an interplay of both factors - the bactericidal actions and the direct effects of CBS. From this study, it is also clear that CBS alone is not adequate to suppress the bacteria and the improvements of gastritis in patients with persistence of *H. pylori* is a consequence of its direct local effects but whether or not this improvement is long lasting or otherwise is unknown. In an effort to study if eradication of *H. pylori* improves gastritis, it is perhaps better to employ agents devoid of direct effects on the gastric mucosa.

We also found that patients in the combined therapy group and the CBS group achieved good symptomatic responses. On the whole the combined therapy group experienced significant symptom relief. However it is interesting to note that patients cleared of the bacteria had a greater reduction in symptom score, consumed less antacid and had increased number of pain-free days after treatment. This was experienced to a lesser extent by the patients with persistent infection. This observation suggests that to a certain degree *H. pylori* may be responsible for the symptoms of dyspepsia.

Although the bacterial suppression rate was low in the CBS group these patients also had a significant improvement of some symptoms. Here again the direct effects of bismuth could be responsible. Bismuth compounds have been known to be effective in alleviating symptoms of dyspepsia by their ability to bind to mucus glycoproteins and may reduce acid attack on the mucosa[14,15]. This could account for the improvement of symptoms to some degree in patients with persistent infection.

The bactericidal action of CBS against *H. pylori* in vivo has previously been demonstrated[16]. Despite this, eradication rates achieved with it is poor. Data from different studies show that a 4-week course of CBS eradicates *H. pylori* in only 20% of individuals[17]. A successful therapeutic agent would be one that is able to kill all the organisms present in the gastric mucosa, thus minimising relapses due to recrudescence. This would be possible if the bactericidal agent is able to reach all areas colonised by the organism. A detailed study on the distribution and localisation of CBS in the gastric mucosa may provide us some answers. However, studies on the pharmacokinetics of CBS in the gastric mucosa is limited. It has been shown that CBS is taken up by the antral and fundal mucosa but it was not within the aims of the study to show the distribution of CBS within the gastric mucosa[18]. An electron microscopy study by Coghill et al[19] suggests that CBS does not penetrate the mucus barrier of the stomach as opposed to the findings of other investigators[17,18]. It may be possible that organisms deep within the gastric crypts are spared from the bactericidal action of CBS. Hence, a thorough investigation of the localisation of CBS throughout the mucosal surface is needed.

CONCLUSION

In conclusion, our study supports the evidence that *H. pylori* is a pathogen causing histologic gastritis in NUD. Clearly, elimination of *H. pylori* results in resolution or improvement of histologic gastritis whereas persistent infection results in persistent inflammation. A short term combination therapy is suc-

cessful in suppressing *H. pylori* with associated improvement of gastritis but these effects may not be long lasting. In our community, NUD is a common cause of discomfort and there would be considerable impact if elimination of *H. pylori* brings relief to even a small proportion of our NUD patients.

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REFERENCES

1. Winship KA. Toxicity of bismuth salts. Adv Drug React Ac Pois Rev 1983;2:103-21.
2. Glupczynski Y, Burette A, Labbe M, Deprez C, De Reuck M, Deltenre M. Campylobacter pylori - Associated gastritis: A Double Blind Placebo - Controlled Trial with Amoxycillin. Am J Gastroenterol 1988; 83: 365-72.
3. Dooley CD, Cohen H. The Clinical Significance of Campylobacter pylori. Ann Intern Med 1988; 108: 70-9.
4. Marshall BJ, McGechie DB, Rogers PA, Glancy RJ. Pyloric campylobacter infection and gastroduodenal disease. Med J Aust 1985; 142: 439-44.
5. Kudva MV, Thein-Htut. Upper gastrointestinal endoscopy as an initial investigation in dyspepsia - A Malaysian experience. Med J Malaysia 1988, 43: 311-7.
6. Colin-Jones DG, Bloom B, Bodemar G et al. Management of dyspepsia: Report of a working party. Lancet 1988; i: 576-9.
7. Nafeeza MI, Shahimi MM, Kudva MV, Mazlam MZ, Isa MR. Campylobacter pylori, non ulcer dyspepsia and race in Malaysia (Letter). Lancet 1989; i: 1018.
8. Whitehead R. Mucosal biopsy of the gastrointestinal tract. In: Bennington JL.ed. Major problems in Pathology. Vol III, 2nd ed. Philadelphia: WS Saunders, 1979: 15.
9. Marshall BJ, Goodwin CS, Warren JR et al. Long term healing of gastritis and low duodenal ulcer relapse after eradication of Campylobacter pyloridis. A prospective double blind study. Gastroenterology 1987; 92 (part 2): 1518 (abstract).
10. Rokkas T, Pursey C, Uzocchina E et al. Non-ulcer dyspepsia and short term De-Nol therapy: a placebo controlled trial with particular reference to the role of Campylobacter pylori. Gut 1988; 29: 1386-91.
11. Toukon AU, Kamal MF, Amr SS, Arnaout MA, Abu Romiyeh AS: Gastroduodenal inflammation in patients with non-ulcer dyspepsia. Am J Gastroenterol 1987; 82: 1149-52.
12. Barron JH, Bar J, Batten J, Sidebotham R, Spencer J. Acid, pepsin, and mucus secretion in patients with gastric acid and duodenal ulcer before and after colloidal bismuth subcitrate (De-Nol). Gut 1986; 27: 486-90.
13. Mc Nulty CAM, Gearty JC, Crump B et al. Campylobacter pyloridis and associated gastritis: Investigator blind, placebo-controlled trial of bismuth salicylate and erythromycin ethylsuccinate. Br Med J 1986; 293: 645-9.
14. Hollanders D, Morrisey SM, Mehta J. Mucus secretion in gastric ulcer patients treated tripotassium dicitrate bismuthate (De-Nol). Br J Clin Pract 1983; 37: 112-4.
15. Shallcross TM, Rathbone BJ, Heatley RV. Campylobacter pylori and non-ulcer dyspepsia. In : Rathbone BJ, Heatley RV. eds. Campylobacter pylori and Gastroduodenal Disease. Blackwel Scientific Publications 1979: 155-66.
16. Marshall BJ, Armstrong JA, McGechie DB, Francis GJ. The antibacterial action of bismuth: early results of antibacterial regimens in the treatment of duodenal ulcer. In: Pearson AD, Skirrow MB, Lior IT, Rowe B. eds. Campylobacter III: Proceedings of the third international workshop on Campylobacter infections. London: Public Health Laboratory Service, 1985: 165-6.
17. Tytgat GNJ, Axon ATR, Dixon MF, Graham DY, Lee A, Marshall BJ. Helicobacter Pylori : Causal agent in peptic ulcer disease. J Gastroenterol and Hepatol: Working Party Reports to the World Congress of Gastroenterology Sydney; 1990: 36-45.
18. Stiel D, Murray DJ, Peters TJ. Uptake and subcellular localisation of bismuth in the gastrointestinal mucosa of rats after short term administration of colloidal bismuth subcitrate. Gut 1985; 26: 364-8.
19. Coghill SB, Hopwood D, McPherson S, Hislop S. The ultrastructural localisation of De-Nol (colloidal tripotassium dicitrato bismuthate - TDB) in the upper gastrointestinal tract of man and rodents following oral and instrumental administration. J Pathol 1983; 139: 105-14.