JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2011, 62, 5, 521-526
www.jpp.krakow.pl

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EFFECTS OF MELATONIN AND TRYPTOPHAN ON HEALING OF GASTRIC AND DUODENAL ULCERS WITH *HELICOBACTER PYLORI* INFECTION IN HUMANS

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Melatonin (MT) and its precursor L-tryptophan (TRP) are implicated in the protection of gastric mucosa against aspirin-induced lesions and in the acceleration of healing of idiopathic gastro-duodenal ulcers, but no information is available whether these agents are also effective in healing of gastroduodenal ulcers accompanied by *Helicobacter pylori* (*H. pylori*) infection. In this study three groups A, B and C, each including 7 *H. pylori*-positive patients with gastric ulcers and 7 *H. pylori*-positive patients with duodenal ulcers, aging 28-50 years, were randomly assigned for the treatment with omeprazole 20 mg twice daily combined with placebo (group A), MT administered in a dose of 5 mg twice daily (group B) or TRP applied in a dose of 250 mg twice daily (group C). All patients underwent routine endoscopy at day 0 during which the gastric mucosa was evaluated and gastric biopsies were taken for the presence of *H. pylori* and histopathological evaluation. The rate of ulcer healing was determined by gastroduodenoscopy at day 0, 7, 14 and 21 after the initiation of the therapy. Plasma MT, gastrin, ghrelin and leptin were measured by specific RIA. At day 21, all ulcers were healed in patients of groups B and C but only 3 out of 7 in group A of gastric ulcers and 3 out of 7 in duodenal ulcers. Initial plasma MT showed similar low levels in all three groups but it increased several folds above initial values in ulcer patients at day 7, 14 and 21. Plasma gastrin and leptin levels showed a significant rise over initial values in patients treated with omeprazole and placebo, MT or TRP while plasma ghrelin levels were not significantly affected by these treatments. We conclude that MT or TRP added to omeprazole treatment, significantly accelerates healing rate of *H. pylori* infected chronic gastroduodenal ulcers over that obtained with omeprazole alone and this likely depends upon the significant rise in plasma MT and possibly also in leptin levels, both hormones involved in the mechanism of gastroprotection and ulcer healing.

Key words: *gastric ulcer, duodenal ulcer, Helicobacter pylori, gastrin, ghrelin, leptin, L-tryptophan, melatonin*

INTRODUCTION

Infection with *Helicobacter pylori* (*H. pylori*) is a substantial public health problem that affects 20-50% of people in industrialised nations and up to 80% in less developed countries. *H. pylori* is associated with many gastro-duodenal disorders, including peptic ulcer disease, gastric carcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. All international guidelines recommend eradication of *H. pylori* using the proton pump inhibitors, such as omeprazole, as well as the combinations of amoxicillin and clarithromycin.

In experimental animals as well as in humans, melatonin (MT) and L-tryptophan (TRP) are highly effective gastroprotective substances against aspirin-induced mucosal lesions (1). Our previous study has revealed that MT or TRP combined with omeprazole accelerates the healing of *H. pylori*-negative (idiopathic) gastro-duodenal ulcers when compared with placebo and this healing effect has been attributed to increments in plasma melatonin levels (2). However, no study has been performed to determine whether MT or TRP combined with omeprazole is also effective in the promotion of healing of *H. pylori*-positive gastroduodenal ulcers in humans. This study was designed to assess the efficacy of MT and TRP added to omeprazole in healing of ordinary *H. pylori*-positive gastric or duodenal ulcers and, in addition, to examine the possible mechanisms, particularly the role of some gastrointestinal hormones such as MT, gastrin, ghrelin or leptin in the mechanism of healing of gastric and duodenal ulcers. It is of interest, that we attempted to look for the effect of human ingestion of TRP to check whether this MT precursor applied orally would undergo biotransformation in the stomach leading to release of MT as documented before in mechanism of experimental ulcer healing (3).

MATERIAL AND METHODS

Patients and treatments

The study was approved by the appropriate Institutional Review Committee of the Medical University of Lublin (Poland) and patients gave written informed consent to participate in this

study prior to their inclusion. All patients underwent routine endoscopy at day 0 during which the gastric mucosa was evaluated and gastric biopsies were taken for the presence of *H. pylori* and histopathological evaluation. The standard gastroscopy was performed by one investigator (K.C.) using Olympus GIF Q 160 endoscope (Tokyo, Japan) and video recorder. The mucosal samples were taken from the lesser curvature of mid-antrum and mid-body of the stomach for the *H. pylori* determination using the rapid urease test (CLO test; Delta West, Bentley, Australia) and for histopathological examination. Three groups (A, B and C) of *H. pylori*-positive chronic gastric or duodenal ulcer patients, each group including 7 controls without ulcer (A), 7 patients with gastric ulcers (B), and 7 subjects with duodenal ulcers (C), aging 28-50 years, were randomly assigned for the treatment with omeprazole (OME) (Losec, Astra Zeneca, Poland; 20 mg twice daily combined with placebo, group A), MT (Lekam, Zakroczyn, Poland; 5 mg twice daily, group B) or TRP (Ardeydorm, Ardeypharm, Germany; 250 mg twice daily, group C).

Additionally, in order to eradicate *H. pylori* infection, each patient received Duomox (Astellas, Japan) in form of tablet of 1.0 g twice daily and metronidazole (Polpharma, Poland) in form of 2 tablets of 0.25 g ingested twice daily over the period of the first seven days.

Hormone determinations

The concentrations of plasma hormones (MT, gastrin, ghrelin and leptin) were determined at day 0 and at day 7, 14, and 21 after treatment, the blood samples were collected for determination of plasma levels of these hormones. The plasma samples were stored at -20°C.

The measurement of plasma MT levels was performed using the RIA kit from DRG Instruments GmbH in Marburg (Germany) as described before (1, 2). The MT RIA-kit utilized a specific sample preparation containing 5-metoxytryptamine-125-Bolton-Hunter-conjugate as a tracer and a specific anti-melatonin antibody. This antiserum did not show cross-reactivity with any product related to MT metabolism such as serotonin, 5-metoxytryptophan or N-acetyl-serotonin. The assay reliably detected MT concentrations as low as 1 pg/mL and the intra-assay and inter-assay variations were 7 and 8 pg/mL, respectively. The rate of ulcer healing was determined by gastro-duodenal endoscopy performed at day 0, 7, 14, and 21 of therapy, the venous blood being taken for measurements of plasma hormones; MT, gastrin, ghrelin and leptin using specific radioimmunoassay described previously (2).

Statistical analysis

Results are expressed as means ±S.D. The significance of differences between means was evaluated using analysis of variance followed by the Duncan's test or, when appropriate, by the Wilcoxon's rank sum test with a confidence level at $p<0.05$.

RESULTS

After 7 days of treatment, gastric and duodenal ulcers were healed in 2 (1 gastric and 1 duodenal ulcer) patients (14%) of group B and in 2 (1 gastric and 1 duodenal ulcer) patients (14%) of group C, but none of gastric or duodenal ulcer of group A (*Fig. 1*). At day 14th, ulcers were healed in 5 (35% of each gastric and duodenal ulcers) patients of group B and in 4 (28%) of group C, but only in 2 (14%) of group A. At day 21th, all ulcers were healed in groups B and C, and only in 7 (50%) patients with gastric and duodenal ulcer of group A. In 2 patients of group A, a duodenal ulcer was healed after 28 days, whereas in 4 patients (group A), a gastric ulcer was healed after 28 days (data not shown).

Plasma gastrin levels almost doubled over initial value at day 7th of placebo plus OME treatment of gastric ulcer (89.5±12.6 pM) and duodenal ulcer patients (76.3±20.8 pM), reaching at day 21th, the values of 32.5±7.6 pM and 79.6±15.3 pM, respectively (*Table 1, Figs. 2A* and *3A*). Plasma gastrin levels tended to decrease day 14th and 28th comparing with respective values at day 7th in the MT and TRP treated patients with gastric and duodenal ulcers (group B and C, respectively) but remained elevated above control at day 0, however, these increments were not significantly different from those observed in placebo-treated patients (*Figs. 2A* and *3A*).

As shown in *Table 1* and *Figs. 2B* and *3B*, the initial plasma MT levels at day 0 were similar in all three groups A, B and C. In patients treated with omeprazole plus placebo (group A), the plasma melatonin levels remained similar at all days of treatment. In contrast, after concurrent treatment with omeprazole and MT (group B), the plasma MT levels increased several-fold above the initial value (day 0) already at day 7th, reaching at day 14th the levels of 96.4±19.5 pg/mL in MT-treated patients with gastric ulcer and 46.8±6.5 pg/mL in those with duodenal ulcer. Similarly, plasma MT in gastric ulcer and duodenal ulcers patients treated

Table 1. Plasma concentrations of melatonin, gastrin, ghrelin and leptin in gastric or duodenal ulcer patients treated with omeprazole (OME) plus melatonin, OME plus tryptophan (TRP) or placebo plus OME. Mean ±S.D. of 7 patients with gastric ulcer and 7 patients with duodenal ulcer. Asterisk indicates significant ($P<0.05$) increase above the hormone initial level (at day 0).

	Treatment	Gastrin [pM]				Melatonin [pg/ml]				Ghrelin [pg/ml]				Leptin [ng/ml]			
		Day				Day				Day				Day			
		0	7	14	21	0	7	14	21	0	7	14	21	0	7	14	21
		Mean±S.D.				Mean±S.D.				Mean±S.D.				Mean±S.D.			
Gastric ulcers	Melatonin + OME	26.7 ±8.2	97.6± 10.5*	98.9± 12.0*	95.1± 11.3*	15.9 ±5.2	161.2 ±22.5 *	96.4± 19.5*	86.3± 14.6*	132.1 ±35.6	186.2 ±34.1	142.5 ±21.1	150.8 ±18.6	4.3± 0.9	12.6± 0.8*	16.3 ±2.7 *	14.9± 3.6*
	TRP + OME	20.8 ±7.1	148.3± 25.5*	95.7± 11.4*	98.2± 10.4*	13.0 ±3.8	78.5± 22.8*	69.4± 2.3*	73.8± 9.2*	120.4 ±13.5	95.6± 10.2	103.8 ±9.4	125.1 ±13.6	5.5± 0.9	9.5± 0.7*	9.6± 0.8*	12.6 ±1.9*
	Placebo + OME	23.3 ±4.8	89.5± 12.6*	48.6± 9.2*	32.5± 7.6*	25.3 ±6.4	20.2± 8.7	20.6± 5.1	18.8± 4.2	148.3 ±26.2	145.7 ±18.1	179.3 ±24.4	156.7 ±7.7	3.3± 0.5	6.2± 1.8	5.9± 2.1	6.6± 2.8
Duodenal ulcers	Melatonin+ OME	32.5 ±8.1	112.5± 18.1*	73.8± 22.5*	75.6± 12.3*	16.9 ±2.9	32.5± 4.7*	46.8± 6.5*	63.4± 9.8*	132.3 ±12.6	159.4 ±13.5	149.8 ±13.1	134.2 ±15.6	10.7± 1.9	27.5± 3.6*	19.9 ±2.8 *	16.2 ±2.1*
	TRP + OME	29.2 ±7.4	59.7±1 4.3*	45.4± 10.1*	42.6± 1.7*	13.3 ±4.6	41.5± 5.1*	38.3± 4.9*	32.5± 3.0*	118.3 ±8.5	128.6 ±10.1	101.3 ±7.6	15.2± 9.4	9.5±2 .6	12.6± 2.0	24.6 ±2.8 *	7.5 ± 1.8
	Placebo + OME	27.2 ±8.6	76.3± 20.8*	58.0± 9.1*	79.6± 15.3*	11.2 ±2.8	13.0± 3.5	12.6± 3.8	13.7± 3.8	128.5 ±13.6	154.9 ±16.3	169.1 ±18.2	128.1 ±23.6	11.3± 2.6	15.6± 3.1	16.3 ±3.5	17.2± 4.7

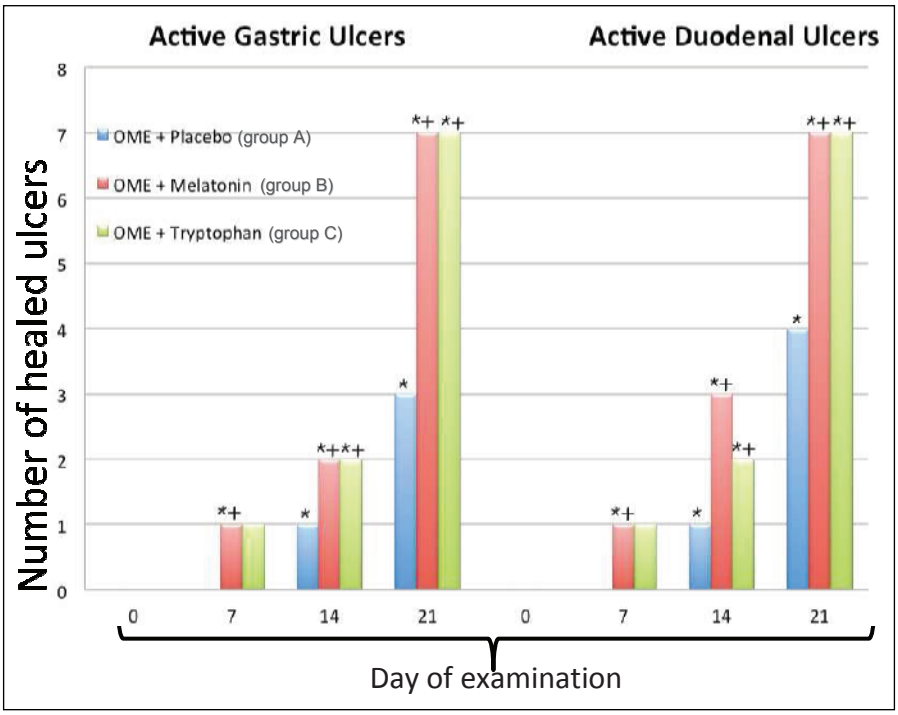

Fig. 1. Number of patients with active gastric or duodenal ulcers at the start of study (day 0) and at 7th, 14th and 21th days of treatment with omerazole (OME) + placebo (group A), OME + melatonin (group B) or OME + tryptophan (group C). Means ±S.E.M. of 7 ulcer patients in each study group. Asterisk indicates a significant increase ($p<0.05$) of healed ulcers above that observed in these patients at day 0. Asterisk and cross indicate a significant increase ($p<0.05$) compared to the value observed in ulcer patients treated with OME + placebo.

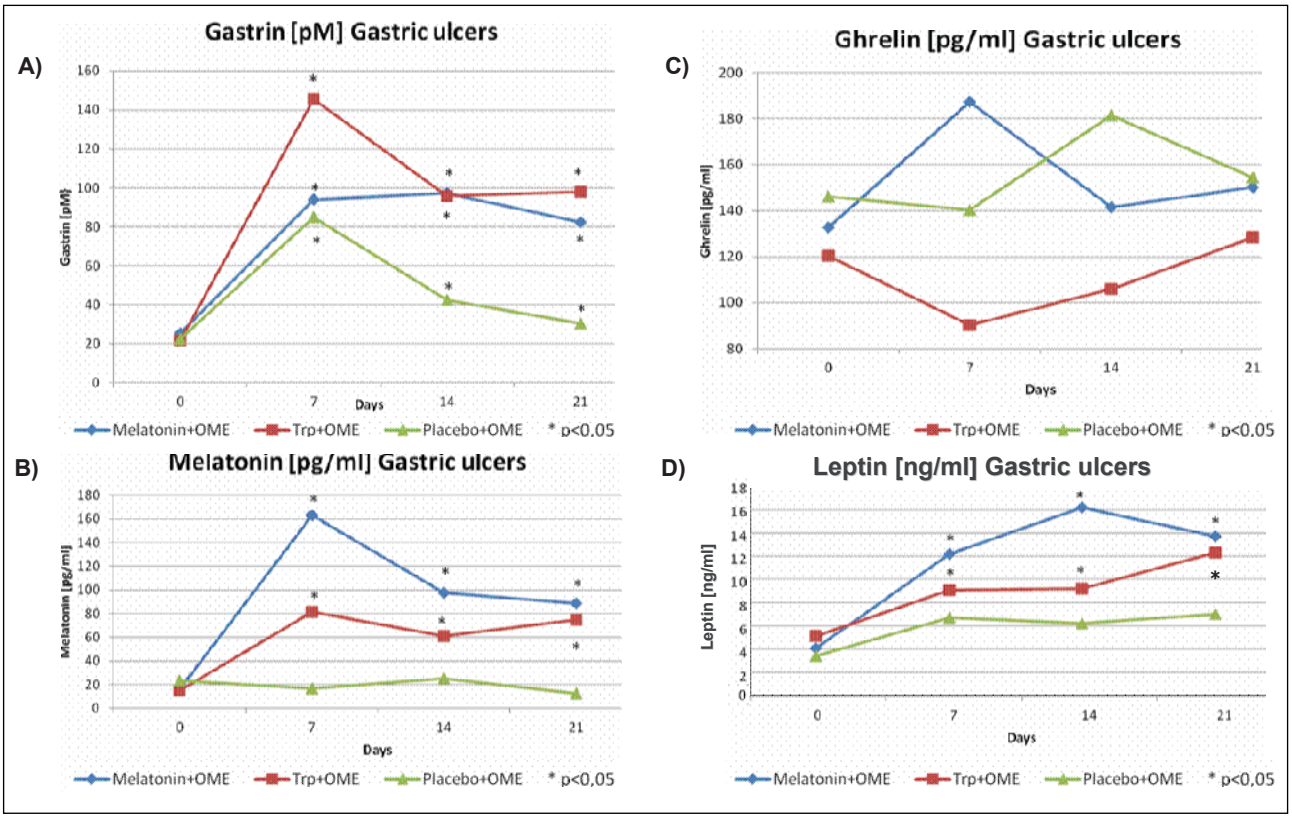

Fig. 2. Plasma levels of gastrin (panel A), melatonin (panel B), ghrelin (panel C) and leptin (panel D) in patients with active gastric ulcers at the start of study (day 0) and at day 7th, 14th and 21st of treatment with omerazole (OME) + placebo (group A), OME + melatonin (group B) or OME + tryptophan (TRP, group C). Means ±S.E.M. of 7 gastric ulcer patients. Asterisk indicates a significant increase ($p<0.05$) above the respective values at day 0 or above the respective values obtained in patients treated with placebo plus OME.

with the omeprazole combined with TRP, reached at 14th day the values of 69.4±2.3 pg/ml and 38.3±4.9 pg/mL, respectively. This significantly increased plasma MT levels over that recorded in placebo group were also observed at 21th day of treatment with OME plus MT or OME combined with TRP both, in gastric ulcer and duodenal ulcer patients (see *Table 1* and *Figs. 2B* and *3B*).

Plasma ghrelin levels were not significantly affected by the treatment with MT or TRP combined with OME as compared to

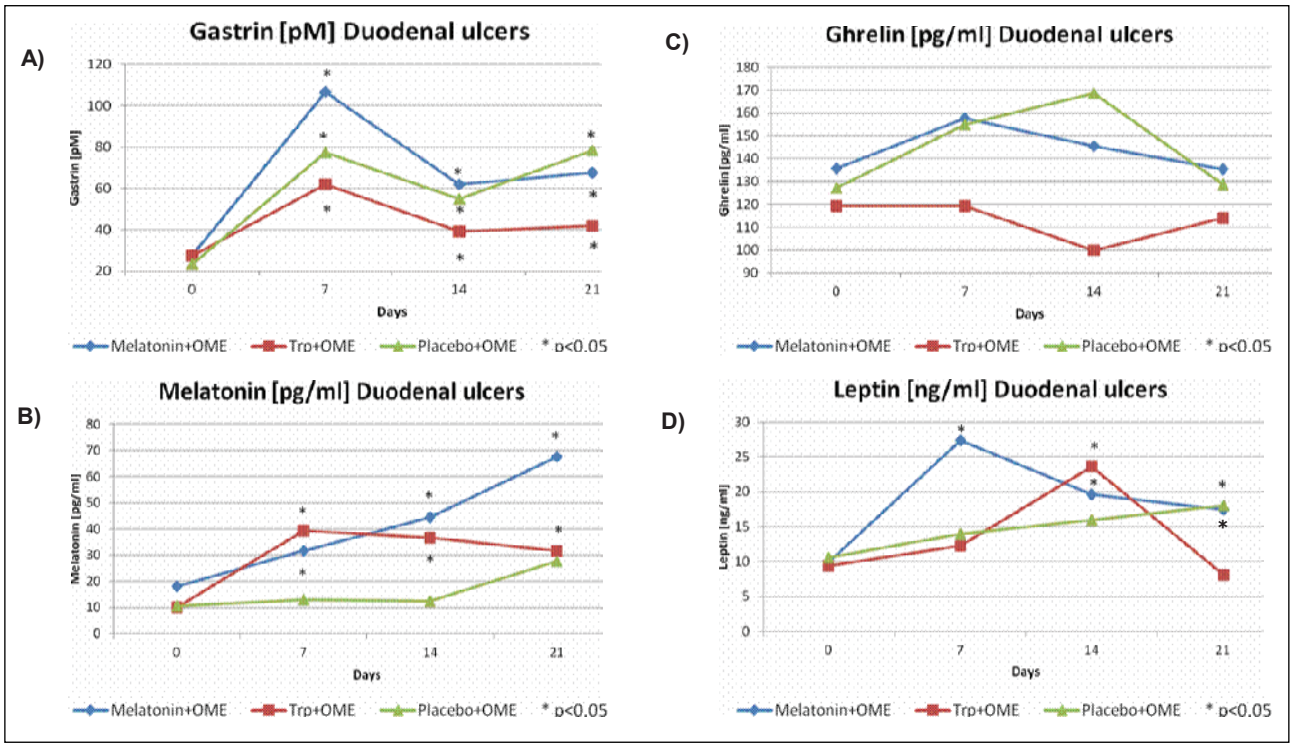

Fig. 3. Plasma levels of gastrin (panel A), melatonin (panel B), ghrelin (panel C) and leptin (panel D) in patients with active duodenal ulcers at the start of study (day 0) and at day 7th, 14th and 21st of treatment with omerazole (OME) + placebo (group A), OME + melatonin (group B) or OME + tryptophan (TRP, group C). Means of 7 duodenal ulcer patients. Asterisk indicates a significant increase above the respective values at day 0 or above the respective values obtained in patients treated with placebo plus OME.

placebo at any day of treatment tested (*Table 1*, *Figs. 2C* and *3C*). Plasma leptin levels in gastric ulcer patients showed significant increase over initial values at day 0 in both, patients treated with OME combined with MT and subjects treated with TRP combined with OME at all tested days. The duodenal ulcer patients showed significant increments of plasma leptin when treated with MT plus OME at all tested days, but when treated with TRP plus OME plasma leptin showed significant rise only at day 14th of treatment, while remaining unchanged at day 7 and 21 (*Table1*, *Figs. 2D* and *3D*). Plasma leptin in both in gastric and duodenal ulcer patients treated with placebo plus OME (group A) tended to slightly increase, especially in duodenal ulcer patients (*Fig. 3D*) but this rise over initial values did not reach statistical significance.

DISCUSSION

H. pylori infection is a substantial health problem affecting about 20-50% of individuals in industrialised countries and about 80% in less developed nations (4). The available multicenter epidemiological studies performed in Poland have indicated that about 64% of adults and 32% of children below the age of 18 years are infected with *H. pylori* (5). It is well established that *H. pylori* infection may lead to the pathological consequences in upper gastrointestinal tract including gastritis, gastric and duodenal ulcers or gastric carcinoma (6, 7). The literature data suggest that in the countries with high incidences of gastric carcinoma, the successful eradication of *H. pylori* constitutes the preventive strategy against neoplastic diseases suggesting that the eradication treatment of *H. pylori* infection should be advocated to individuals infected by this bug (8-10).

Currently, *H. pylori* elimination with triple therapy is a recognised management of treatment and prevention of gastric and duodenal ulcer diseases (7, 9-10). The disadvantage of triple therapy is the increased antibiotic resistance divergent depending on region of the world. According to the European guidelines of the Third Maastricht Consensus Conference, in the regions with resistance to clarithromycin exceeding 20%, the first-line therapy that includes PPI, amoxicillin and metronidazole should be performed (7). The resistance to clarithromycin in Poland is high because the percentage of resistant strains in adults is about 15% and in children it averages about 28% (11). Thus, according to the recent recommendations, clarithromycin should not be used for *H. pylori* eradication without initial bacterial antibiotic susceptibility testing. These tests are, however, not always feasible and therefore, amoxicillin and metronidazole are recommended for the first-line treatment. This is why we have employed in our study, this recommended regimen of drugs that was described in detail above.

Another form of management for gastric and duodenal peptic ulcer diseases is to administer agents that strengthen the gastric mucosal barrier by reducing oxidative stress caused by various topical irritants including bacterial infection. MT is a potent endogenous antioxidant which also shows anti-inflammatory action (12-14). The cytostatic effect of MT resulting from its ability to inhibit the cell proliferation, suggests that this hormone could influence exert the inhibitory effect on the process of apoptosis. According to Bubenik (14), and recent clinical observations by Chojnacki *et al.* (15) and Gonciarz *et al.* (16), MT shows the usefulness not only in the prevention but also as the supportive adjuvant to standard therapy of major gastric pathologies such as ulcerative colitis, irritable bowel syndrome (IBS), non-alcoholic steatohepatitis and even colorectal carcinoma.

The first clinical studies in humans carried out by our group (1, 17) demonstrated that the treatment with exogenous MT and

its precursor TRP attenuated the aspirin-induced gastric mucosal lesions. We documented that the beneficial effects of MT were independent of endogenous production of PGE_2 in the gastric mucosa. Moreover, our recent study in humans (2) revealed that MT applied in a dose of 5 mg twice a day or TRP administered in a dose of 250 mg twice a day added to PPI, significantly accelerated idiopathic gastric and duodenal ulcer healing in patients without *H. pylori* infection. Based on these encouraging results, we decided to determine the effects of MT on gastric and duodenal ulcer healing in *H. pylori*-positive patients. We report in present study that exogenous MT or TRP significantly accelerated healing of gastric and duodenal ulcers in *H. pylori*-infected patients compared to placebo. The comparison of MT and TRP treatment outcomes in patients with gastric or duodenal ulcers infected with *H. pylori* indicates that both treatments exerted a beneficial effects resulting in acceleration of ulcer healing, irrespective of the presence of *H. pylori* infection or bacterial eradication as observed at day 14th or 21st following eradication therapy recommended to all patients at the period of first seven days of their entrance to this study. In order to get some insight into the possible mechanism of ulcer healing induced by MT or TRP combined with OME, the plasma levels of the gut hormones including MT, gastrin, ghrelin and leptin were determined. In all patients either with gastric and duodenal ulcers treated orally with MT and TRP a marked rise in plasma levels of gastrin and MT were observed despite *H. pylori* infection similar to plasma levels of these hormones recorded in idiopathic ulcer patients reported by our group before (2). The rise in plasma gastrin in gastric and duodenal ulcers treated with the OME seems to merely reflect the inhibition of gastric acid secretion by proton pump inhibitor used, resulting in the removal of well-known inhibitory effects of somatostatin released from the D-cells in antral part of gastric mucosa on the gastrin-producing G cells to stimulate the gastric acid (18, 19). As no significant difference was observed in plasma gastrin level in ulcer patients treated with OME plus placebo and OME plus MT or TRP, we believe that the acceleration in ulcer healing could not be solely attributed to the alterations in plasma levels of gastrin. Similarly, plasma ghrelin, which has been implicated in the *H. pylori*-infected gastrointestinal mucosa and gastric cancer (19), does not seem to contribute to the observed enhancement of the ulcer healing rate following treatment with OME combined with MT or TRP because the plasma ghrelin levels was unaltered in patients with gastric and duodenal ulcer throughout the study period. In contrast to gastrin, the rise in the plasma MT levels could be involved in the healing effect of exogenous MT as proposed before (20, 21) because the improvement of gastric and duodenal ulcer healing by treatment with MT and TRP was accompanied by a significant rise in the plasma MT increments while in OME treated control patients without MT or TRP treatment, the healing of ulcers was uncompleted at the end of the study and the plasma levels of MT were unchanged throughout the study period. Besides the increment in plasma MT levels, we observed the small but significant rise in plasma leptin levels in MT- and TRP-treated patients but not in placebo-treated control patients suggesting that this hormone might be involved in ulcer healing. Experimental studies in animals including those carried out in our unit, clearly showed that leptin exhibits gastroprotective and ulcer healing activities due to its angiogenetic properties (22-26), which could also contribute to the observed stimulation of ulcer healing in our patients treated with OME combined with MT or TRP. Our results concerning leptin remains in keeping with that of Kebapcilar *et al.* (27) who reported that that plasma leptin levels in their cohort patients infected with *H. pylori* was unchanged before and after *H. pylori* eradication. Indeed, we did not observe any significant alterations in plasma leptin concentration in our control patients with gastric and duodenal ulcer treated with placebo and OME. In another report by Francois *et al.* (28), the postprandial plasma leptin level but not plasma of acylated ghrelin levels rose significantly following bacterial eradication and remained significantly correlated with BMI in these patients. None of these studies however, considered the treatment with MT which in our present study resulted in the marked increase in plasma increments of leptin. This MT-induced increase in leptin concentration during follow up of these patients in our study could explain the faster rate of healing acceleration in these patients possibly due to stimulation by leptin of NO, endogenous prostaglandins and growth factors such as transforming growth factor-alpha (TGFα) as potential mediators involved in the gastroprotection, mucosal repair and process of ulcer healing (26).

In summary, this report demonstrates for the first time that exogenous MT and that generated in the gastrointestinal tract from TRP contribute to the healing of *H. pylori* infected gastro-duodenal ulcer probably due to antioxidant and anti-inflammatory effects of both MT and leptin generated in gastric mucosa in response to treatment with MT or TRP. It is noteworthy that in our study MT and TRP were added to standard antisecretory therapy with OME and both these agents significantly accelerated ulcer healing in *H. pylori*-infected patients compared to placebo control patients treated with OME only. Based on results of our study, the mechanism of beneficial action of exogenous MT or that released endogenously after intragastric ingestion of TRP, may depend upon the enhancement of plasma of gastroprotective MT and leptin levels.

Conflict of interests: None declared.

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Received: June 15, 2011
Accepted: September 26, 2011

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