Title of study:
Healing of patients suffering from gastroesophageal reflux esophagitis grade C-D according to Los Angeles classification after treatment with pantoprazole-magnesium dihydrate 80 mg o.d. in comparison to pantoprazole-sodium sesquihydrate 40 mg o.d. over 4 or 8 weeks. BY1023/M3-904.

Publication (reference): None

Principal Investigator(s):
Gudrun Gatz, M.D., ALTANA Pharma AG, Byk-Gulden-Strasse 2, 72467 Konstanz, Germany

Study center(s):
151 centers enrolled patients in Estonia, Germany, Hungary, Latvia, Lithuania, Romania, and South Africa.

Study period (years):
September 2004 – February 2005

Clinical phase: III

Objectives:
To demonstrate the superiority in healing rates of pantoprazole-Mg 80 mg (P_{Mg} group) o.d. versus pantoprazole-Na 40 mg (P_{Na} group) o.d. in patients with gastroesophageal reflux esophagitis (LA grade C-D) after 4 weeks of treatment

Methodology:
Randomized, double-blind, double dummy, multi-center, parallel-group comparison

No. of subjects (total and for each treatment):
Total patients enrolled: N = 913
Total number of safety set patients: 907 (P_{Mg} group 447, P_{Na} group 460)
Total number of full analysis set: 901 (P_{Mg} group 444, P_{Na} group 457)
Total number of per protocol set: 801 (P_{Mg} group 408, P_{Na} group 393)

Diagnosis and criteria for inclusion:
Outpatients of at least 18 years of age with gastroesophageal reflux esophagitis (LA grade C-D)

Test product/ Dose/ Mode of administration:
Pantoprazole magnesium (Mg) dihydrate 80 mg, oral administration

Batch No.: BY1023-472

Reference product/ Dose/ Mode of administration:

Pantoprazole sodium (Na) sesquihydrate 40 mg, oral administration

Batch No.: BY1023-472

Duration of treatment:

4 or 8 weeks depending on healing of gastroesophageal reflux esophagitis

Criteria for evaluation:

Primary variable:

- Endoscopically confirmed healing of gastroesophageal reflux esophagitis after 4 weeks of treatment with either pantoprazole-Mg 80 mg or pantoprazole-Na 40 mg

Secondary variables:

- Endoscopically confirmed healing of gastroesophageal reflux esophagitis after 8 weeks of treatment
- Endoscopically confirmed healing after 4 and 8 weeks depending on initial grade of gastroesophageal reflux esophagitis
- Endoscopically confirmed healing after 4 and 8 weeks depending on *H. pylori* status
- Symptom relief rates and symptom scores as assessed by ReQuest™ total score, ReQuest™ subscale GI and ReQuest™ subscale WSO
- Gastrointestinal symptoms as documented in the CRF by the investigator

Statistical methods:

Primary analysis based on the full analysis set was the comparison of healing rates after 4 weeks of treatment with either pantoprazole-Mg or pantoprazole-Na.

The following hypotheses were tested: Superiority of pantoprazole-Mg 80 mg over pantoprazole-Na 40 mg for patients with gastroesophageal reflux esophagitis LA grade C and D.

Null Hypothesis (H_0): $\psi_{Mg/Na} \leq 1$

Alternative Hypothesis (H_1): $\psi_{Mg/Na} > 1$

where $\psi_{Mg/Na}$ was the Mantel-Haenszel weighted odds ratio for healing rate adjusted for baseline LA grade. The overall level of significance was set to 5% (two-sided), which in case of one-sided hypotheses corresponded to 2.5% (one-sided). In accordance with the ICH E9 guideline (1998), this level was set to half of the conventional 5%-level in the case of one-sided tests.

Summary of Results:

The endoscopically confirmed healing rates of the reflux esophagitis after 4 weeks for the full analysis set were 39.19% (two-sided 95% exact confidence interval: [34.62%; 43.90%]) for the pantoprazole-Mg group and 38.29% (two-sided 95% exact confidence interval: [33.82%; 42.92%]) for the pantoprazole-Na group. The healing rates for the per protocol set were 39.95% (two-sided 95% exact confidence interval: [35.16%; 44.88%]) for the pantopra-

zole-Mg group and 42.24% (two-sided 95% exact confidence interval: [37.30%; 47.29%]) for the pantoprazole-Na group. The odds ratios calculated by the method of Mantel-Haenszel adjusted for baseline GERD were 1.0274 [0.7852; 1.3443] for the full analysis set and 0.9089 [0.6853; 1.2056] for the per protocol set, respectively. Superiority of pantoprazole-Mg 80 mg over pantoprazole-Na 40 mg could not been shown. This was confirmed by Fisher's exact test and analysis of the confidence intervals by means of the standard normal approximation.

The endoscopically confirmed healing rates of the reflux esophagitis after 8 weeks for the full analysis set were 78.83% for the pantoprazole-Mg group and 78.34% for the pantoprazole-Na group. The healing rates for the per protocol set were 80.64% for the pantoprazole-Mg group and 82.44% for the pantoprazole-Na group. Again superiority of pantoprazole-Mg 80 mg over pantoprazole-Na 40 mg could not been shown.

The endoscopically confirmed healing rates of the reflux esophagitis depending on the initial stage of GERD decreased with increasing GERD grades and varied between 22.92% (P_{Na}, full analysis set, GERD D after 4 weeks) and 84.12% (P_{Na}, per protocol set, GERD C after 8 weeks). However, it has to be kept in mind that for GERD grade D the number of patients was low (in total 86 patients of the full analysis set and 69 patients of the per protocol set). Within both treatment groups, differences in the healing rates between *H. pylori* negative and positive patients were not statistically significant after 4 and 8 weeks.

Symptom scores recorded by patients using the ReQuest™ questionnaire remarkably decreased from day 0 to day 28 of treatment. The overall symptom relief rates according to the ReQuest™ total score were 63.61% in the pantoprazole-Mg group versus 63.03% in the pantoprazole-Na group. After 28 days of treatment about 80% of patients were relieved from their symptoms according to the ReQuest™ total score at least one time, whereas more than 60% were finally relieved from their symptoms on day 28. Patients of the per protocol set showed a ReQuest™ total score below the threshold level on about 4 days during the last 7 days before endoscopy at visit 1 after 4 weeks and on about 5 days during the last 7 days before endoscopy at visit 2 after 8 weeks of treatment. Both treatment groups were comparable in all results concerning the patient diary ReQuest™.

In total, 23.4% of all patients in this study experienced treatment emergent adverse events (212 out of 907 patients), of which 99 patients were treated with pantoprazole-Mg 80 mg and 113 patients were treated with pantoprazole-Na 40 mg. The most frequently reported adverse event symptoms as coded by MedDRA were 'diarrhea NOS', 'headache', 'increased γ-GT', 'nasopharyngitis' and 'nausea'. Other adverse event symptoms occurred with a frequency ≤ 10 symptoms in all patients. Eleven patients prematurely discontinued the study because of an adverse event. The corresponding symptoms 'abdominal pain lower', 'headache' and 'rash NOS' were assessed as 'likely related' to the intake of pantoprazole-Na 40 mg by the investigator. All other symptoms were assessed as 'unlikely related' or 'unrelated' to the intake of study medication by the investigator. 17 treatment emergent serious adverse event symptoms occurred in 13 patients (1.4%) of the safety set during the study. Five of these patients were treated with pantoprazole-Mg 80 mg and 8 with pantoprazole-Na 40 mg. One patient died of myocardial infarction during the course of this study. All treatment emergent serious adverse events were assessed as 'unrelated' to study medication intake.

In laboratory investigations and physical examinations (including vital signs) performed after 4 and 8 weeks (for patients not healed after 4 week) of treatment, respectively, none of the parameters assessed showed systematical or clinically relevant changes during the course of the study for the two treatment groups. No relevant differences between the two treatment groups were observed.

Conclusions:

Superiority of pantoprazole-Mg 80 mg over pantoprazole-Na 40 mg with respect to the endoscopically confirmed healing rates of reflux esophagitis was not shown. Both drugs were equally efficacious in the treatment of GERD grades C to D. Both drugs were well tolerated and safe.

Date of Report: February 17, 2006