Effect of pantoprazole versus other proton pump inhibitors on 24-hour intragastric pH and basal acid output in Zollinger-Ellison syndrome

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SUMMARY

Aim — In this open prospective study, the efficacy of pantoprazole in reducing gastric acid secretion in Zollinger-Ellison syndrome patients was compared to that obtained previously with other proton pump inhibitors.

Methods — Eleven male patients previously treated with omeprazole (n = 7, mean dosage: 63 mg/day; range: 20-100 mg/day) or lansoprazole (n = 4, mean dosage: 75 mg/day; range: 30-120 mg/day) were included. These patients underwent a 24-hour intragastric pH-metry, measurement of basal acid output and of serum gastrin first while receiving their usual therapy and second after 7 to 10 days of pantoprazole treatment at a mean dosage of 116 mg/day (range: 40-200 mg/day). Basal acid output was evaluated after each intragastric pH-metry, one hour before the next intake of proton pump inhibitor and a serum gastrin curve was determined according to 9 fixed time points.

Results — One patient dropped out before the second intragastric pH-metry due to an adverse event (varicella) unrelated to pantoprazole and was reinvestigated thereafter. The median 24-h intragastric pH with pantoprazole was not significantly different than that with the other proton pump inhibitors (5.3 versus 4.6, respectively; P = 0.90). Neither the median basal acid output values nor the median serum gastrin levels were significantly different between pantoprazole and the other proton pump inhibitors.

Conclusion — In these patients with the Zollinger-Ellison syndrome, pantoprazole was well tolerated and equally effective to the other proton pump inhibitors in terms of antisecretory potency.

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Zollinger-Ellison Syndrome (ZES) is a rare disease. Less than 0.1% of patients with a duodenal ulcer have a gastrinoma. In the French population, the number of patients with the ZES is about 500, with approximately 50 to 60 new patients per year. Because the symptoms of ZES are not specific, the dynamic secretin test is necessary for the diagnosis [1-3].

Proton pump inhibitors (PPIs) are the drugs of choice for the treatment of the gastric acid hypersecretion in patients with the ZES or other hypersecretory conditions [4]. It has been shown in 9 patients with the ZES that the effects of omeprazole and lansoprazole on the 24-hour intragastric pH profiles and basal acid output (BAO) were not significantly different [5]. Like omeprazole and lansoprazole, pantoprazole belongs chemically to the class of the substituted benzimidazoles (PPIs). It is an acid-activated inhibitor of the H+K+-ATPase within the gastric

RÉSUMÉ

Effet du pantoprazole comparé aux autres inhibiteurs de la pompe à protons sur le pH intragastrique des 24 heures et le débit acide basal dans le syndrome de Zollinger-Ellison

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Objectifs — Le but de cette étude prospective ouverte était de comparer l’efficacité antisécrétoire du pantoprazole chez des malades atteints du syndrome de Zollinger-Ellison par rapport à celle observée avec leur traitement habituel par d’autres inhibiteurs de la pompe à protons.

Méthodes — Onze malades de sexe masculin précédemment traités par oméprazole (n = 7, dose moyenne: 63 mg/jour; extrêmes : 20-100 mg/jour) ou par lansoprazole (n = 4, dose moyenne: 75 mg/jour; extrêmes : 30-120 mg/jour) ont été inclus dans l’essai. Une pH-métrie intragastrique des 24 heures, une mesure du débit acide basal et des dosages de gastrinémie ont été faits pendant le traitement habituel, puis après 7 à 10 jours de traitement par pantoprazole à la dose moyenne de 116 mg/jour (extrêmes : 40-200 mg/jour). Le débit acide basal a été mesuré après chaque pH-mètre des 24 heures, une heure avant la prise de l’inhibiteur de la pompe à protons et la courbe de gastrinémie a été déterminée grâce à 9 prélèvements successifs entre 8 h et 23 h.

Résultats — Un malade a été exclu de l’essai avant sa deuxième pH-mètre pour événement indésirable (varicelle) non lié au traitement par pantoprazole et a été inclus à nouveau. Le pH médian intragastrique des 24 heures sous pantoprazole n’était pas significativement différent de celui avec les autres inhibiteurs de la pompe à protons (respectivement 5,3 versus 4,6, P = 0,90). Le débit acide basal médian et la gastrinémie médiane n’étaient pas significativement différents entre les traitements par pantoprazole et par les autres inhibiteurs de la pompe à protons.

Conclusion — Chez ces malades atteints du syndrome de Zollinger-Ellison, le pantoprazole a été bien toléré et son effet antisécrétoire a été non significativement différent de celui de l’oméprazole et du lansoprazole.

ABBREVIATIONS :

BAO : Basal Acid Output
MEN-1 : Multiple Endocrine Neoplasia- type 1
PPIs : Proton Pump Inhibitors
ZES : Zollinger-Ellison Syndrome
acid secreting parietal cells. Pantoprazole is a potent inhibitor of gastric acid secretion in humans. In extended clinical trials its healing capacity was superior to that of ranitidine in peptic ulcer and reflux esophagitis patients, and comparable to that of the other PPIs [6].

The aim of the present study was to evaluate the efficacy of pantoprazole on the reduction of intragastric acid secretion during 24 hours in patients with a ZES: the effects of pantoprazole on BAO and 24-hour intragastric pH profiles were compared to those obtained with omeprazole and lansoprazole, administered to the same patients prior to the pantoprazole treatment.

Patients and methods

ZES patients of both genders, aged over 18 years, treated with a proton pump inhibitor (omeprazole or lansoprazole) not exceeding a daily dose regimen of 6 capsules for at least 6 months with a BAO of less than 10 mmol H+ /h and who gave their written informed consent prior to inclusion, were considered to be eligible in this open prospective study. Patients with a history of gastric surgery or malignancy, except ZES associated or not with the multiple endocrine neoplasia-type 1 syndrome (MEN-1), psychiatric disorders and clinical evidence of significant unstable disease of any body system, were not eligible. Also patients with a history or suspicion of alcohol abuse or drug addiction were not included in the study.

Patients were hospitalised for 2 days in a first period where a general examination and laboratory tests were performed including 9 serum gastrin determinations at fixed hours on day 1. A continuous 24-hour pH-metry was performed from 8.00 am at day 1 to 8.00 am at day 2. Intragastric pH was monitored using a glass electrode (Radiometer GK 290B), connected to a pH-meter (Radiometer, Copenhagen) and an external recorder on paper (REC G1 Serograph). A speed of 2 cm.min⁻¹ and a sensitivity of 3.5 cm.(pH unit)-¹ were chosen. The calibration was tested before and after each experiment with buffers of pH = 1 and pH = 7. An increase of pH from 1 to 7 was noted by 21 cm of range variation. The equipment drift compared to the initial calibration never exceeded 3 mm for a 24-hour period. Ninety % of the response to a pH variation was obtained in less than one second. After calibration, the electrode was positioned through the nose in the fundic area 7 to 10 cm below the gastro-oesophageal junction, determined in each subject by pH step-up across the cardia when the electrode was withdrawn from the stomach to the oesophagus.

During the pH-metry recording period, patients should not smoke or drink alcohol. Normal sleep period was respected. Meals were standardised with a caloric load amounting to 10,500 KJ/day split as follows:

- a) breakfast (8.00 am): coffee with milk (200 g), sugar (10 g), 4 rusks with butter (20 g), jam (30 g) and water (300 mL),
- b) lunch (1.00 pm): liver pate (30 g), mixed hamburger (150 g), mashed potatoes (100 g), milk (100 g), butter (15 g), yoghurt and apple jam (150 g), coffee with sugar (10 g), water (500 mL),
- c) dinner (8.00 pm) was identical to lunch.

At the end of each pH-metry monitoring period, the electrode was removed and BAO was measured during one hour through a naso-gastric tube inserted at the most dependent part of the stomach. The correct position of the tube was checked by the water recovery test. Patients layed in a semi-recumbent position on their left side. Gastric secretion was aspirated continuously by gentle manual suction and collected in 15-minute samples after discarding the first 15-minute collection corresponding to the emptying of the stomach.

The concentration of H⁺ ions was determined on each sample by a titrimetric method with NaOH 0.1N and expressed in millimoles H⁺ per litre. BAO is the sum of the four 15-minute outputs and is expressed in mmol H⁺/h.

At day 1 the patients were treated with their usual PPI therapy (omeprazole or lansoprazole), then they started the treatment with pantoprazole on day 2, for 7 to 10 days, after the BAO measurement. The patients were hospitalised once again for 2 days in a second period where all examinations and tests were repeated. The pH probe was inserted at the same position as in the first period experiment. At the end of the study, patients were asked to continue their previous treatment.

Pantoprazole enteric-coated tablets of 40 mg were taken once in the morning or twice daily (morning and evening) according to the daily dose regimen of the previous proton pump inhibitor, i.e. 30 mg lansoprazole or 20 mg omeprazole corresponded to 40 mg pantoprazole.

Before inclusion, the patients were given an oral and written information. The study was approved by the Ethics Committee of Bichat-Claude Bernard hospital on November 2nd, 1995.

Statistical analysis

The primary efficacy criterion was related to the inhibition of gastric acid secretion over 24 hours. The evaluation was performed using a 24-hour pH-metry. Results were expressed as:

- a) median pH according to different time periods: total recording time, during the day time (from 08.00 am to 22.00 pm) and during the night time (from 22.00 pm to 08.00 am),
- b) percentage of time at/or below pH 3, 4, 5 and 6 during the total recording time, during the day time (from 08.00 am to 22.00 pm) and during the night time (from 22.00 pm to 08.00 am).

The secondary criterion was the BAO measurement.

The evaluation of the tolerability was based on the recording of adverse events and/or laboratory parameters during the course of the trial.

The comparisons between the medians were analysed by a non parametric test (Wilcoxon test) with a statistical significance level of P = 0.05.

Results

Efficacy

Eleven male patients were included from January, 1996 to February, 1997. Patients’ median age was 52 years (range: 31-74 years); their median body mass index was 24.0 kg.m⁻² (range: 21.3-39.5). One patient participated twice in the trial. He was included a first time and a pH-metry was performed. Due to a varicella infection, the second pH-metry monitoring was not carried out. Because of the rareness of the disease and due to the fact that the patient was withdrawn from the study for an adverse event not related to the protocol or to the study drug, this patient was reinvestigated once again 9 months later.

At entry in the study 4 patients had a non-gastric surgery history: parathyroidectomy, hypophysectomy, pancreatectomy and/or thyroid lobectomy, triple coronary bypass grafting. Six patients were treated for at least one concomitant disease. All the 11 patients had a ZES history for at least 6 months. Seven out of 11 patients were treated with omeprazole and the 4 others with lansoprazole at daily mean dosages of 63 mg (range: 20-100 mg) and 75 mg (range: 30-120 mg), respectively. The 11 patients were then treated with pantoprazole at a daily mean dosage of 116 mg (40-200 mg). The patients’ individual data of the median pH by 24-hour period are shown in table I.

The median 24-hour intragastric pH with pantoprazole was slightly higher than with lansoprazole or omeprazole (5.3 versus 4.6), but the difference was not statistically significant (P=0.90).

The median BAO values determined within the hour preceding the next intake of proton pump inhibitor were similar: 1.71 (0 - 14.7) mmol H⁺/h for pantoprazole and 1.4 (0 - 16.2) mmol H⁺/h for the other PPIs (table II). One patient in each group had BAO > 10 mmol H⁺/h.
The pH profiles with respect to day time and night time periods and pH thresholds, as well as the median serum gastrin levels were not significantly different between both treatment periods, with pantoprazole and with other PPIs (figures 1, 2, 3).

Safety/tolerability

One non serious adverse event (varicella) was observed, 6 days after starting the treatment with pantoprazole. The causal relationship between the adverse event and the treatment has been estimated as “unrelated”. There were no clinically relevant changes in the laboratory parameters.

Discussion

For ethical and safety reasons the study was performed without prior washout of the ongoing antisecretory treatment and without randomisation of the treatment order. Both omeprazole and lansoprazole are available in France for the treatment of ZES and thus are valid comparative drugs.

The mean daily omeprazole dose of 63 mg/day (range: 20-100 mg/day) was given to the 7 patients, who were previously treated with omeprazole, in the range of published mean omeprazole dosages in patients with ZES. In the study by Mc Tavish et al. a median omeprazole dosage of 60 to 70 mg/day (range: 20-360 mg) reduced and maintained BAO at target levels of less than 10 mmol H⁺/h in ZES patients and also relieved acid-related symptoms [7].

The mean daily lansoprazole dose of 75 mg (range: 30-120 mg/day) given to the 4 patients treated with lansoprazole was also a standard dosage for ZES patients. In a previous study with lansoprazole, BAO was reduced in a dose-related manner by 5 days treatment with lansoprazole 30, 60, 90 and 120 mg/day in 4 patients, with ultimate BAO reduction of 87% (range: 75-99%) [8].

Several studies with pantoprazole in ZES patients have been performed and oral pantoprazole in daily doses of 40 mg to 240 mg have been shown to effectively control BAO and clinical symptoms in ZES patients [9-11]. In a recent study, it was demonstrated that intravenous pantoprazole, 160 to 240 mg/day administered in divided doses via 15-minute infusion, rapidly and effectively controlled acid output within 1 hour and maintained control for up to 7 days in 21 patients with ZES [12].

In our study the acid secretion was adequately controlled with a mean dose of 116 mg/day (range: 40-200 mg/day) of pantoprazole. Thus, the switch from the previous PPIs to pantoprazole on the basis of a corresponding daily dose regimen is confirmed to be effective in terms of acid secretion control.

Table I – Median pH according to 24-hour period. Patients’ individual data.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Pantoprazole</th>
<th>Other PPIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>4.9</td>
</tr>
<tr>
<td>3</td>
<td>5.3</td>
<td>3.7</td>
</tr>
<tr>
<td>4</td>
<td>5.5</td>
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<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>10</td>
<td>5.8</td>
<td>4.5</td>
</tr>
<tr>
<td>11</td>
<td>4.5</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Due to a varicella infection, patient No 6 was withdrawn from the study before the end of the pantoprazole period treatment and was excluded from the analysis.

Table II – Median 24-hour intragastric pH and median 1-hour BAO measured before next dosing in the pantoprazole and the other PPIs groups.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Pantoprazole n=11</th>
<th>Other PPIs n=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour intragastric pH</td>
<td>(2.0-6.3)</td>
<td>(2.1-7.0)</td>
</tr>
<tr>
<td>BAO (mmol H⁺/h)</td>
<td>(0.14-7)</td>
<td>(0.16-2)</td>
</tr>
</tbody>
</table>

a BAO reference value for control of efficacy in ZES patients: < 10 mmol H⁺/h.

Fig. 1 – Median percentage of time with respect to different pH thresholds during the diurnal period under pantoprazole and the other PPIs. Numbers in parentheses represent the range. Pourcentage médian de temps passé au-dessous de différents seuils de pH pendant la période diurne sous pantoprazole et sous les autres inhibiteurs de la pompe à protons. Les chiffres entre parenthèses indiquent les extrêmes.
In this study pantoprazole has been shown to be as effective and safe as omeprazole and lansoprazole in the treatment of ZES patients. It is noteworthy, indeed, that 24-hour intragastric pH profiles obtained in these patients with pantoprazole dosages appropriate to maintain 1-hour BAO before next dosing in the therapeutic range (< 10 mmol H+/h, with the exception of one patient in both groups), are predictive of a therapeutic success as shown by previous studies in ZES patients [5,13].

RÉFÉRENCES


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