The effects of nizatidine on transient lower esophageal sphincter relaxations (TLESRs) and acid reflux in healthy subjects

Katsuhiko IWAKIRI¹, Noriyuki KAWAMI¹, Hirohito SANO¹, Yuriko TANAKA¹, Mariko UMEZAWA¹, Seiji FUTAGAMI¹, Yoshio HOSHIHARA¹,² and Choitsu SAKAMOTO¹

¹Department of Medicine, Division of Gastroenterology, Nippon Medical School, Japan
²Clinic of the Ministry of Economy, Trade and Industry, Japan

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Abstract

Background: A study in Japan has found that nizatidine (NIZ) is more effective than other histamine H2 receptor agonists (H2RAs) in treating reflux esophagitis (RE), although the NIZ group included a greater number of patients with severe RE. As there was no difference in the level of acid suppression among H2RAs, it is possible that NIZ has other effects on esophageal acid exposure (EAE) besides acid suppression. In this study, the effect of NIZ on transient lower esophageal sphincter relaxations (TLESRs) and acid reflux was evaluated in healthy subjects. Methods: In 10 healthy subjects, while in a sitting position, esophageal motility and a pH study were measured for 3 hours after a meal on 2 separate days at least 2 weeks apart. Participants received an oral dose of 150 mg of NIZ, 60 min before the meal on one day and a placebo on the other. Both studies were preceded by a week of treatment with either NIZ (150 mg, bid) or a placebo and the order of treatment was randomized. Results: Basal LES pressure in the NIZ group (14.1 mmHg, median) was significantly greater than that of the placebo group (8.5 mmHg). The rate of TLESRs in the NIZ group (22.0/3 h) for the postprandial 3-hour period was significantly less than that of the placebo group (16.5/3 h) and the rate of acid reflux during TLESRs (24.7%) and the EAE (0.2%) in the NIZ group for the postprandial 3-hour period was also significantly less than that of the placebo group (74.4% and 2.8%, respectively). Conclusion: NIZ significantly reduces acid reflux by inhibiting both the rate of TLESRs and acid reflux during TLESRs.

Key words: nizatidine, transient lower esophageal sphincter relaxation, esophageal acid exposure, acid reflux

Introduction

A study carried out in Japan has found that nizatidine (NIZ) 150 mg bid, is more effective than other histamine H2 receptor agonists (H2RAs) in treating reflux esophagitis (RE), although the
NIZ group did include more subjects with severe RE compared with the famotidine group (Sekiguchi et al., 1983; Nakano et al., 1984; Sekiguchi et al., 1989). In addition, it has been reported that maintenance therapy from NIZ has a significantly higher non-recurrence rate than that of famotidine in patients with RE (Hamamoto et al., 2005). RE is characterized by excessive esophageal acid exposure, which increases significantly according to the severity of RE (Iwakiri et al., 2009). Since, as it has been reported, there is no difference in the healing rate of gastric ulcers among H2RAs (Barbara et al., 1983; Naccaratto et al., 1987; Inoue et al., 1988; Judmaier et al., 1988), it is considered that there is no significant difference in the level of acid suppression among H2RAs and it is therefore possible that NIZ has other positive effects on esophageal acid exposure besides acid suppression. Although it has been reported that NIZ enhances salivary secretion, bicarbonate output (Adachi et al., 2002) and stimulates gastric emptying (Harasawa et al., 1993; Shiomi et al., 2001), it is not clear whether or not NIZ has an effect on reflux itself.

RE is characterized by excessive esophageal acid exposure and because most acid reflux episodes, in healthy subjects and patients with RE, are caused by transient lower esophageal sphincter relaxations (TLESRs) (Iwakiri et al., 2005; Hayashi et al., 2008; Iwakiri et al., 2009), if there is a decrease in the rate of TLESRs in patients with RE, it is possible that the number of acid reflux episodes also decreases and excessive esophageal acid exposure will normalize. Since there is no difference in the rate of TLESRs in healthy subjects and patients with RE, in this study we investigated the effect of NIZ on the rate of TLESRs, the rate of acid reflux during TLESRs and esophageal acid exposure in healthy subjects.

**Methods**

**Subjects**

Studies were carried out in 10 asymptomatic, healthy volunteers, who did not have hiatus hernia, defined as when the LES-crural diaphragm separation is more than 2 cm at inspiration, using high-resolution manometry. The subjects underwent esophagogastroduodenoscopy but there were no localized lesions in the esophagus, stomach, or duodenum and none had previously undergone gastrointestinal surgery. Informed consent was obtained from every subject and the study was approved by the Ethics Committee for Human Research at the Nippon Medical School.

**Study design**

The study was carried out in single-blind fashion, where two identical tablets were administered for both NIZ and the placebo, to ensure that the subjects could not identify the treatment arm. Subjects were randomly assigned to receive either NIZ or the placebo and the order of these treatments was also randomly determined. For 7 days, subjects were given NIZ (150 mg am before breakfast and 150 mg pm before dinner) or the placebo. Subsequently, after a washout period of at least 7 days, subjects crossed over to the other arm (placebo-treatment, treatment-placebo) (Fig. 1a). After taking NIZ or the placebo for 7 days, on day 8, concurrent esophageal manometry and pH monitoring was carried out.

On the day of the study, 60 min before breakfast (6:00 am), subjects took NIZ or the placebo and thereafter food was prohibited. Subjects again took NIZ or the placebo at 1:40 pm, after which, the
manometric assembly and the pH electrode were passed via an anaesthetized nostril at 2:00 pm and positioned so that the LES was positioned 2 cm below the most proximal of the 1-cm interval side holes and the pH electrode positioned 2 cm above the proximal margin of the LES. The subjects were then allowed to adapt to the assembly for 30 min, after which recordings of LES pressure were taken for 10 min (2:30–2:40). At 2:40 pm, for a period of 20 min, the subjects were given a solid-liquid test meal, which consisted of a hamburger, ice-cream and 250 mL of mineral water (678 kcal, 34.1% fat, 17.0% protein). After the meal, if necessary, the position of the assembly was adjusted and recordings were taken for 3 h (3:00–6:00 pm) while subjects remained seated (Fig. 1b).

Recording methods

Esophageal manometry was performed with a 21-channel manometric assembly (Dentsleeve Pty Ltd., Wayville, Australia). Ten side holes, spaced at 1-cm intervals, starting at 3 cm above the distal end of the assembly, monitored pressure from the proximal stomach, LES and distal esophagus. A further 7 side holes, spaced at 2-cm intervals, monitored pressure from the distal to the proximal esophagus, and 4 side holes, at 3, 6, 10, 13 cm above the most proximal of the 2-cm interval side holes, monitored pressure from the proximal esophagus to the pharynx. Each lumen was perfused with degassed, distilled water at 0.15 mL/min by a low compliance manometric infusion pump (Dentsleeve Pty Ltd., Wayville, Australia).
Pty Ltd., Wayville, Australia). Esophageal pH was measured with an antimony electrode (Synectics Medical AB, Stockholm, Sweden) positioned at 2 cm above the proximal margin of the LES. Data were digitized with a computer and the digitized signals were displayed, stored, and analyzed, using Trace! Software (Dr. G.S Hebbard, The Royal Melbourne Hospital, Parkville, Australia).

**Data analysis**

Basal LES pressure was measured at end-expiration and referenced to end-expiratory intragastric pressure. One-minute visual means were taken for ten consecutive min and a mean basal LES pressure was calculated.

Acid reflux episodes were defined as an abrupt drop in esophageal pH below 4 for at least 4 seconds or, if basal esophageal pH was already below 4, as a further decrease in pH of at least 1 pH unit. For analysis of the occurrence of acid reflux during TLESRs, acid reflux was deemed to have occurred if there was an abrupt drop in pH of at least 1 pH unit (Holloway et al., 1991).

For each reflux episode, the mechanism of reflux was determined by the patterns of LES pressure and esophageal body activity, their relationship to swallowing, and the occurrence of abdominal straining. These mechanisms were classified as TLESR, swallow-induced LES relaxation (including multiple swallows), LES pressure drifts, absent basal LES pressure, straining and non-interpretable. For the analysis of patterns of LES pressure associated with reflux, the profile of pressure was used across the full extent of the ten 1cm-spaced side-hole array, which straddled the gastroesophageal junction. TLESRs were defined as previously described (Holloway et al., 1995). LES relaxations which lasted for more than 15 s and which were associated with a swallow, within 4 s before or 2 s after the onset of an LES relaxation, were also included as TLESRs (Kawahara et al., 1997). LES relaxations lasting <15 s, whose onset was associated with a swallow within 4 seconds before its onset until maximal relaxation had been achieved, were judged to be swallow-induced. Persistently absent basal LES pressure was defined as LES pressure of less than 2 mmHg for more than 30 s. A drift in basal LES pressure was defined as a slow fall (<1 mmHg/s) in LES pressure to a level less than 2 mmHg above intragastric pressure, maintained for less than 30 s. Abdominal strain was defined as a sharp and simultaneous increase in gastric and esophageal pressure, greater than twice the normal inspiratory increase of intragastric pressure. Straining was judged to be the principal mechanism of reflux when the onset of an acid pH deflection occurred during a strain when there was detectable (>2.0 mmHg) LES pressure, and as a possible co-factor when LES pressure at the time of reflux was < 2.0 mmHg (Penagini et al., 1996).

**Statistical analysis**

Values for the basal LES pressure, the rate of TLESRs, the rate of acid reflux during TLESRs and acid esophageal exposure were determined for each subject and from these, median values were calculated for the group as a whole. All data are presented as median (interquartile range) and were analyzed using Wilcoxon’s test. A $P$ value of <0.05 was considered significant.
**Results**

*Basal LES pressure*

Basal LES pressure in the NIZ group (14.1 mmHg [11.9–18.0]) was significantly ($P=0.0077$) greater than that in the placebo group (8.5 mmHg [7.0–9.6]).

*Mechanisms of acid reflux episodes in the NIZ group and the placebo group*

All acid reflux episodes in the NIZ group and placebo group occurred during TLESRs.
Rate of TLESRs

The rate of TLESRs in the NIZ group for the entire 3-hour period (0–3 h: 16.5/h, [16.0–19.0]) (Fig. 2), for the 0-1 hour (6.5/h, [6.0–7.0]) and for the 1–2 hour (5.0/h, [4.0–6.0]) postprandial hour (Fig. 3) were significantly less than that of the placebo group (0–3 h: 22.0/h, [17.0–22.0], \(P < 0.05\), 0–1 h: 9.0/h, [8.0–10.0], \(P = 0.0244\), 1–2 h: 6.0/h, [5.0–8.0], \(P = 0.0499\), respectively). However, for the 2–3 postprandial hour, there was no difference in the rate of TLESRs in the groups (NIZ group: 6.0/h, [5.0–6.0], placebo group: 4.5/h, [4.0–7.0]) (Fig. 3).

**Fig. 4.** The rate of acid reflux during transient lower esophageal sphincter relaxations in both the nizatidine and the placebo groups for the entire 3-hour postprandial period.

**Fig. 5.** The rate of acid reflux during transient lower esophageal sphincter relaxations in both the nizatidine and the placebo groups for each postprandial hour.
Nizatidine and TLESR

The rate of acid reflux during TLESRs in the NIZ group for the entire 3-hour period (Fig. 4) and for each postprandial hour (Fig. 5) (0–3 h: 24.7% [12.5–76.4], 0–1 h: 20.9%, [0–33.3], 1–2 h: 22.5%, [0–83.3], 2–3 h: 36.7%, [0–83.3], respectively) was significantly less than that of the placebo group (0–3 h: 74.4%, [54.2–76.9], \( P < 0.05 \), 0–1 h: 55.6%, [45.5–62.5], \( P < 0.05 \), 1–2 h: 81.7%, [75.0–100], \( P < 0.05 \), 2–3 h: 75.0%, [42.7–85.7], \( P < 0.05 \), respectively).

Esophageal acid exposure

Esophageal acid exposure in the NIZ group for the entire 3-hour period and for each postprandial hour, was significantly (\( P < 0.05 \)) less than that of the placebo group (Table 1).

Table 1. Esophageal acid exposure in the placebo group and nizatidine group

| Postprandial 3 hours | Placebo group | Nizatidine group |
|----------------------|---------------|-----------------|
| 0.2% (0.1–1.0)*      | 0.2% (0.1–1.0)* |
| Postprandial 0–1 hour| 0.3% (0–1.1)*  |                 |
| 0.2% (0–0.8)*        | 0% (0–0.7)*    |
| Postprandial 1–2 hour| 0.2% (0–0.8)*  |                 |
| 0% (0–0.7)*          |                |
| Postprandial 2–3 hour| 0% (0–0.7)*    |                 |

\( *, P < 0.05 \) vs. placebo group. Median % (interquartile range).

Discussion

In healthy subjects and patients with mild RE, most acid reflux episodes occur 0–3 hour after a meal and most are accompanied by TLESRs (Iwakiri et al., 2005). In order to investigate the effect of NIZ on TLESRs and acid reflux, we administered NIZ 60 min before a meal so that the blood concentration of NIZ would be at its maximum, approximately 80 min after having administered. As a result, in the NIZ group, compared with the placebo group, NIZ significantly increased the basal LES pressure and significantly reduced the rate of the TLESRs at 0–1 and 1–2 postprandial hours, the rate of acid reflux episodes during TLESRs at each postprandial hour and the esophageal acid exposure at each postprandial hour.

Excessive esophageal acid exposure causes RE therefore in order to reduce this, it is important to decrease gastric acid secretion, improve delayed esophageal clearance and to reduce acid reflux itself. Considering that TLESRs are the major mechanism of reflux episodes in healthy subjects and patients with gastroesophageal reflux disease (GERD) (Iwakiri et al., 2005; Hayashi et al., 2008; Iwakiri et al., 2009,), it is important to decrease the rate of TLESRs in the treatment of GERD.

At present, there are only a few pharmacological agents (morphine, cholecystokinin, atropine, baclofen) available for the treatment of acid reflux (Boulant et al., 1997; Mittal et al., 1997; Penagini et al., 1997; Boeckxstaens et al., 1998; Clavé et al., 1998,), however it is very difficult to use most of these drugs because they need to be injected and/or they have side-effects. It is possible for only baclofen to be effective in the treatment of acid reflux and it has been reported that baclofen, a gamma-aminobutyric acid B agonist, has been successful in decreasing the rate of TLESRs, as
well as decreasing the number of acid reflux episodes in healthy subjects and patients with GERD (Lidums et al., 2000; Zhang et al., 2002). Baclofen has also been effective in reducing the symptoms associated with acid reflux and non-acid reflux in the postprandial period (Vela et al., 2003). It can be used as a therapeutic option, however, its use is limited because of its side-effects and as well, the standard dose of baclofen used in Japan is half that used in Western countries. The result that NIZ decreases the rate of TLESRs, as found in this study, may be very valuable in the treatment of GERD.

Inhibition of TLESRs is theoretically feasible using either an antagonist or an agonist on the neurotransmitters and receptors, which are involved in the reflex arc underlying TLESRs (Hirsch et al., 2002). Although the mechanisms of how NIZ affects TLESRs are unknown, in view of the fact that NIZ reduces the rate of TLESRs, it is possible that NIZ participates in the reflex arc underlying TLESRs.

It is possible also that the administration of NIZ increases basal LES pressure because it has been reported that NIZ has inhibitory activity on acetylcholine esterase and as expected, basal LES pressure significantly increases after the administration of NIZ. In healthy subjects and patients with mild RE, it has been reported that acid reflux episodes occurred almost exclusively during TLESRs, therefore an increase in LES pressure after the administration of NIZ in healthy subjects, does not directly affect the number of acid reflux episodes.

In summary, NIZ significantly reduces acid reflux episodes by inhibiting both the rate of TLESRs and acid reflux during TLESRs and suppressing esophageal acid exposure time in healthy subjects.

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