A Comparison of the Effect of Regular Eno® and Placebo on Intragastric pH

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Background: Eno® (sodium bicarbonate + citric acid, active moiety sodium citrate) is a non-prescription antacid that is used for relief of heartburn, sour stomach, and acid indigestion.

Objective: The primary objective of this trial was to determine the time required for regular Eno® to induce a significant acid neutralization effect compared to placebo.

Methods: We conducted a randomized, open, crossover study in healthy fasting subjects. Subjects received either regular Eno or placebo (water), with a two-day washout between crossover periods. Changes in gastric pH were measured with a nasogastric pH probe and recorded using a Mark I Gastrograph.

Results: Twenty-four subjects completed the study. Eno showed a significant increase in pH within 6 seconds compared to 18 seconds for placebo.

Conclusions: Our study suggests that Eno can create a significantly greater and faster neutralization effect when compared to placebo in healthy, fasting individuals. Eno was well tolerated in this study.
pH within minutes (3). Its duration of action, like other antacids, is subject to the rate of gastric emptying. This study was conducted according to the Declaration of Helsinki and relevant Good Clinical Practice and Guidelines for Conduct of Clinical Investigations. Written and dated informed consent was obtained from all subjects.

**METHODS**

This was a randomized open crossover study in healthy subjects. The study was conducted at KEM hospital in Mumbai, India between January and May 2000.

**Subjects**

Twenty-nine healthy fasting subjects were recruited for this study. Subjects’ suitability for entry into the study was confirmed according to the criteria for inclusion and exclusion. Subjects who met all of the following criteria were eligible for inclusion into the study. Male or female between the ages of 18–55 years of age; had clinically normal physical findings at the time of pre-entry physical examination; had laboratory values within appropriate reference limits at the time of the pre-entry evaluation. The following rendered subject ineligible for inclusion in the study: an immunocompromised subject or those suffering from any serious or debilitating medical condition; current drug or alcohol abuse; history of diabetes; treatment with any medication which could alter or influence stomach acidity or test drug/placebo activity; significant abnormalities of pre-trial laboratory studies; subjects who were known to have been non-compliant or whom the investigator felt may have been unreliable or unsuitable to participate in a clinical trial, participation in a clinical trial during the previous 30 days and the presence of any disease/condition or physical defect which could preclude the subject from complying with study procedures. Subjects could be withdrawn from the trial for any of the following reasons: requirement of changes to any medications that might influence the outcome of the study treatments; at the discretion of the physician; or choosing to withdraw him-or herself from the trial.

**Randomization**

The subjects were randomized to a predetermined medication sequence provided by Quintiles ClinData. Subject numbers were allocated according to the subjects’ chronological enrollment into the study. After a subject had been given a subject number, the sequence group was read from the randomization list. The randomization was balanced for the two treatment sequences, and a block size of 4 was used.

**Study Design**

The following assessments were carried out before subjects were entered into the study: complete medical history, physical examination, clinical laboratory evaluation and pregnancy test, where applicable. These assessments were to be completed within 14 days before entering the study. Subjects who fulfilled the eligibility criteria were randomized to a predetermined medication sequence of Eno/water or water/Eno, orally, once at Visit 2 and the alternative at Visit 3, with a washout period of 36 to 48 hours between doses. During the study period subjects were not permitted to use any concomitant medication. On study days, subjects were to refrain from smoking. Subjects were instructed not to drink alcoholic beverages for at least 24 hours prior to, and during each session. Additionally, coffee, tea and chocolate were prohibited for 24 hours prior to the study. While in the trial, subjects were not to take any medications which might influence the outcome of study treatments. Any medication ingested by a subject during the course of the trial was to be recorded in detail on the case record form (CRF). Antacid was not permitted within 24 hours of the start of the study day. On each study day following an 8-hour (overnight) fast, each subject was to present him/herself at the study unit where he/she was to be weighed and examined. A nasogastric probe was positioned in the antral region of the stomach about 60 minutes before dosing, using standard technique. After a stabilization period of between 20 to 45 minutes, gastric pH data were to be recorded for a 15-minute baseline. After baseline recording, subjects were to be instructed to completely swallow test product. The dose was to be consumed as quickly as possible, i.e., within 30 seconds. The dose of Eno was one sachet
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prepared according to the directions on the package label. Once swallowed, the timing for the 60-minute test period recording was to begin.

Safety and Efficacy Measurements

Laboratory evaluations were obtained at Visits 1 and 3 and adverse events and concomitant medication were reviewed at Visits 2 and 3. A microelectrode probe (Ingold 440 M-4 combined glass electrode) was used for the pH recording. A 2-point calibration of the electrode, using standard buffers of pH 7.0 and pH 1.7 was performed prior to insertion. Entry of the electrode into the stomach was confirmed by a sharp fall in pH to less than 2.5. This position was to be measured during the first intragastric assessment and positioning and verification of pH was to be repeated at the second study period. Intragastric pH was monitored and recorded every 6 seconds via a portable data-logger (Mark-I Gastrograph® MIC AG, Solothurn, Switzerland).

Statistical Considerations

A difference in time-to-pH $> 3.5$ of 200 seconds between treatments and a standard deviation of 300 seconds was assumed, yielding an effect size (ratio) of 0.67. The sample size of 24 completed subjects was sufficient to assure $>80\%$ power to detect this effect size when using the $2 \times 2$ Latin square design at the significance level of 0.05. Baseline pH at each session was used as a covariate. A suitable multiple-comparisons test was used to define which means were significantly different, if any. Fisher’s exact test was done on the “preference” data to obtain a p-value for the differences between treatments. A t-test was carried out by treatment to compare the mean of the pre-baseline medians with the mean of the medians calculated during the first 18 seconds after treatment.

The pH values were smoothed by using a rolling median with a window width of 3 values (18 seconds). All calculations on pH were done using this rolling median. The pH values over time were summarized using descriptive statistics for the rolling medians for each 1-minute interval, and graphed using the median value for each treatment group at each (6-second) time-point. The beginning of the time interval for which a statistically significant difference between baseline and post-treatment was observed, was considered to be the time required for the treatment to induce a statistically significant acid neutralization effect. The time to a one pH unit change was calculated as the first time after baseline when the rolling median of the pH level reached a value one pH unit larger than the median recorded during baseline. The time needed to achieve a pH of 3.5 or greater was the first time the rolling median of the pH was above 3.5 after baseline. The time needed to achieve a pH of 3.5 or to demonstrate a one pH unit change was analyzed in terms of subject “preferences,” e.g., a subject was said to “prefer” Eno if he had achieved a one pH unit change sooner with Eno than placebo. Subjects who had not achieved a one pH unit change and subjects who dropped out of the study before the change was achieved were treated as censored observations.

RESULTS

Subjects

Twenty-nine subjects were enrolled in the study. The intent-to-treat (ITT) and per-protocol (PP) populations only differed by one subject, therefore only the ITT population was analyzed. Twelve subjects in the Eno/Water sequence and 12 subjects in the Water/Eno sequence completed the study.

Baseline Characteristics

Baseline was calculated for each subject as the median pH value over the 15-minute baseline period. All subjects in both sequence groups were male Asians/Indians. No previous medication was reported for either group. Demographic data is presented in Table 1.

Protocol Deviations

Three protocol violations were reported. One subject from each group had significant laboratory abnormalities at baseline and was not randomized to study drug. One subject took longer than 30 seconds to swallow the placebo medication at Visit 3.
pH Results

Dosing with Eno resulted in a statistically significant change in pH from the baseline pH at the first available time point (6 seconds). Dosing with water resulted in a lesser pH change (pH 2.35 increasing to pH 2.65), compared to Eno (pH 2.20 increasing to pH 3.11); and the change occurred at a slightly later time (18 seconds post-dosing). The median time required to achieve a pH $\geq 3.5$ was 40.5 seconds for Eno and 1960.0 seconds (32 minutes) for water. When comparing treatments, a statistically significant difference was found indicating Eno to be better than water in achieving this clinically meaningful level of neutralization. When comparing

<table>
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<th>Variable</th>
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<th>Water</th>
<th>Eno</th>
<th>p-value</th>
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<tr>
<td>Time to significant change in pH (seconds)</td>
<td>18</td>
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<tr>
<td>Time to pH $\geq 3.5$ (seconds)</td>
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<td>1.000</td>
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</tr>
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</table>

Table 2

Results
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Figure 2. Mean pH values over time (rolling medians).

treatments for time to achieve a pH change of 1 unit, no statistically significant difference was found (Figure 2).

Adverse Events
Five subjects reported adverse events. The adverse event mentioned most frequently was anemia. All adverse events were determined by the investigator as unlikely to be related to the study drug. No deaths or serious adverse events were reported by any subject during the study.

DISCUSSION
The results of this study provide evidence to support the hypothesis that regular Eno is more effective than placebo (water) in neutralizing gastric acid. It was seen in this study that Eno was well tolerated in the study population. A limitation of this study was that the measurement equipment did not permit a continuous recording of gastric pH, which could have resulted in more precise timings. Also, the study only included males; however, there is no reason to believe that females would give different results. The quick increase in pH seen with Eno suggests that it would be a successful therapy for patients suffering from symptoms of heartburn or indigestion. Eno is more effective in neutralizing gastric acid and has a faster onset of action than water. This study shows that Eno provides faster onset of action compared to water which is of great value to the consumer who is looking for quick relief.

Acknowledgment
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References