Pre-operative oral erythromycin reduces residual gastric volume and acidity

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We investigated whether low-dose erythromycin (200 mg) given as an oral premedicant altered the residual gastric volume and its acidity in fasted patients at induction of anaesthesia in a single-blinded study. Sixty patients were allocated randomly to receive either an erythromycin tablet (200 mg) or nothing with 10 ml water 3 h before induction of anaesthesia, and another 60 patients 1 h before induction of anaesthesia. Oral erythromycin significantly reduced residual gastric volume when it was given approximately 3 h ($P<0.05$; 95% CI for median difference: 0.1–17 ml) or 1 h ($P<0.0005$; 95% CI for median difference: 6–24 ml) before induction of anaesthesia. Erythromycin significantly reduced gastric acidity when it was given 1 h before induction of anaesthesia ($P<0.02$; 95% CI for median pH difference: 0.1–1.7). In contrast, when given 3 h before induction of anaesthesia, erythromycin did not significantly alter acidity.

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Pulmonary aspiration of gastric contents remains one of the major causes of death related to anaesthesia. Although routine use of aspiration prophylaxis is unnecessary, it may be performed in certain groups of patients, such as pregnant women undergoing Caesarean section.1

Erythromycin, a macrolide antibiotic, at therapeutic doses (500–1000 mg), induces strong and continuous gastric contractions2 3 and may often cause gastrointestinal symptoms.4 5 In contrast, at lower doses (up to about 200 mg), it induces intermittent contractions in the stomach, and the contractions migrate into the intestine.2 3 6 Several studies have shown that a sub-therapeutic dose of erythromycin accelerates gastric emptying of both solids and liquids in healthy volunteers7 as well as in patients with delayed gastric emptying due to several pathological reasons.7 8 Erythromycin also has other gastrointestinal prokinetic effects.9

Mechanisms for gastric emptying during the fed and the fasted state differ considerably. Therefore, drugs, which accelerate gastric emptying of ingested food, may not reduce residual gastric juice during the fasted state.10 There has been only one report regarding the effect of erythromycin on residual gastric volume and its acidity.11 In that study, a therapeutic dose of erythromycin (500 mg) injected intravenously significantly decreased residual gastric volume and acidity.11 Erythromycin could be used as a premedicant for prophylaxis of aspiration pneumonitis if erythromycin at a sub-therapeutic dose produces a similar effect by oral administration. It is not known if this regimen is effective, since erythromycin can easily be inactivated by gastric juice.12 Therefore, we studied if a sub-therapeutic dose of erythromycin 200 mg given as an oral premedicant altered the residual gastric volume and its acidity in fasted patients scheduled for elective surgery.

Patients and methods

We studied two sets of 60 patients (total 120 patients), ASA physical status I or II, undergoing elective surgery, in whom tracheal intubation was indicated. Patients were excluded if they had any pathology of the upper respiratory or upper alimentary tract, were at risk of pulmonary aspiration of gastric contents, or if they were taking drugs which were known to alter gastric motility. Institutional Research Ethics Committee approved the study and written informed consent was obtained from all patients.

The patient was asked not to eat solid food for at least 5 h and not to drink liquids for 3 h before the start of the study. No premedicants were given. In the first set of 60 patients, we studied if oral erythromycin, given approximately 3 h before induction of anaesthesia, reduced gastric volume. In this set of patients we decided to give erythromycin 3 h later
preoperatively so that any untoward gastrointestinal symptoms could be identified and treated before induction of anaesthesia. We planned to give erythromycin 1 h before the induction of anaesthesia, if erythromycin significantly reduced residual gastric juice without producing gastrointestinal symptoms in this first set of patients.

Patients were allocated randomly to one of two groups. Block randomization (in blocks of 12) was used for allocation, and cards indicating allocations were placed in serially numbered, sealed opaque envelopes. In one group, an erythromycin stearate tablet 200 mg (Erythrocin, Dainippon Pharmaceuticals, Japan) with 10 ml water were given orally, whereas in the other group, only 10 ml water was given. We did not blind the patients from allocation, since placebo tablets were not available.

Since we found that erythromycin tablet given approximately 3 h before induction of anaesthesia significantly reduced residual gastric juice without producing gastrointestinal symptoms (see Results), we decided to study the effect of erythromycin given approximately 1 h before induction of anaesthesia. The second set of 60 patients were allocated randomly to one of two groups, and 10 ml water with and without a 200 mg erythromycin tablet was given orally approximately 1 h before induction of anaesthesia.

In the operating theatre, anaesthesia was induced with propofol and neuromuscular blockade produced with vecuronium; anaesthesia was maintained with sevoflurane and nitrous oxide in oxygen. After the patient’s trachea was intubated, residual gastric contents were collected via a gastric tube by a researcher who was blinded. A 18-Fr multi-orificed Salem Sump gastric tube (Argyle, St Louis, Missouri, USA) was inserted orally and correct placement was confirmed by auscultation of bubbling sounds over the epigastrium during insufflation of air through the catheter. Residual gastric contents were collected using a syringe, and its volume and acidity were measured. Gastric acid was measured using a set of pH test papers (Toyo Roshi Kaisha, Tokyo, Japan) which consist of two-step indicators: one test paper indicated pH with a sensitivity of 1 (1±11) and the second set with a sensitivity of 0.2 for the order of 0.1.

Table 1 Patients’ characteristics (mean (sd) [range]). In the first set of patients, either water 10 ml (group W3) or an erythromycin tablet 200 mg with 10 ml water (group E3) was given 3 h before induction of anaesthesia. In the second set of patients, either water 10 ml (group W1) or an erythromycin tablet 200 mg with 10 ml water (group E1) was given 1 h before induction of anaesthesia

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Male/female</th>
</tr>
</thead>
<tbody>
<tr>
<td>W3</td>
<td>46 (14) [20-65]</td>
<td>162 (8) [148-176]</td>
<td>61 (12) [41-95]</td>
<td>18/12</td>
</tr>
<tr>
<td>E3</td>
<td>43 (16) [20-68]</td>
<td>166 (8) [150-179]</td>
<td>61 (10) [45-94]</td>
<td>20/10</td>
</tr>
<tr>
<td>W1</td>
<td>50 (12) [24-65]</td>
<td>162 (9) [148-183]</td>
<td>62 (11) [44-86]</td>
<td>15/15</td>
</tr>
<tr>
<td>E1</td>
<td>48 (13) [26-70]</td>
<td>166 (9) [147-183]</td>
<td>66 (12) [47-96]</td>
<td>18/12</td>
</tr>
</tbody>
</table>

Table 2 Residual gastric volume (ml) and its acidity (pH) (median [95% CL]). In the first set of patients, either water 10 ml (group W3) or an erythromycin tablet 200 mg with 10 ml water (group E3) was given 3 h before induction of anaesthesia. In the second set of patients, either water 10 ml (group W1) or an erythromycin tablet 200 mg with 10 ml water (group E1) was given 1 h before induction of anaesthesia

<table>
<thead>
<tr>
<th>Group</th>
<th>Volume (ml)</th>
<th>P</th>
<th>Acidity (pH)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>W3</td>
<td>26.5 [15.5, 35.8]</td>
<td>–</td>
<td>1.8 [1.8, 2.0]</td>
<td>–</td>
</tr>
<tr>
<td>E3</td>
<td>10.0 [5.2, 14.8]</td>
<td>–</td>
<td>2.8 [2.0, 4.0]</td>
<td>–</td>
</tr>
<tr>
<td>W1</td>
<td>27.5 [18.0, 32.0]</td>
<td>–</td>
<td>2.0 [2.0, 2.8]</td>
<td>–</td>
</tr>
</tbody>
</table>

Differences between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Volume difference</th>
<th>P</th>
<th>Acidity difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1-W1</td>
<td>−9 [−17, 0]</td>
<td>&lt;0.05</td>
<td>0.1 [0, 1.0]</td>
<td>0.29</td>
</tr>
<tr>
<td>E3-W3</td>
<td>−14 [−24, −6]</td>
<td>&lt;0.0005</td>
<td>0.4 [0.1, 1.7]</td>
<td>&lt; 0.02</td>
</tr>
</tbody>
</table>

Statistical analysis

The normal plot and Shapiro-Francia W’ test showed that the volume and pH of residual gastric contents were not normally distributed. Therefore, the Mann-Whitney U test was used to compare the volume or acidity between the two groups in each set of groups. P<0.05 was considered significant.

The 95% confidence limits (CL) for medians for the volume and pH in each group were calculated using the SINTERVAL commend (sign test) in Minitab release. CLs for the median differences between groups were also calculated.

From previously reported studies and a preliminary study, the mean residual gastric volume at induction of anaesthesia in fasted patients would be about 25 ml (with standard deviation (SD) of approximately 15). We considered that a 50% reduction (i.e. 12.5 ml) in residual gastric volume would be clinically relevant difference. Sixty patients would be required to detect this difference, with a power of 90% and P=0.05.
Results

The ages, weights and sex ratios of groups were generally similar (Table 1).

Oral erythromycin significantly reduced residual gastric volume when it was given approximately 3 h ($P<0.05$; 95% CI for median difference: 0–17 ml) or 1 h ($P<0.0005$; 95% CI for median difference: 6–24 ml) before induction of anaesthesia (Table 2).

Erythromycin significantly reduced gastric acidity when it was given 1 h before induction of anaesthesia ($P<0.02$; 95% CI for median pH difference: 0.1–1.7). In contrast, when given 3 h before induction of anaesthesia, erythromycin did not significantly alter acidity (Table 2).

No patients complained of abdominal discomfort, nausea or vomiting preoperatively.

Discussion

We found that a sub-therapeutic dose of erythromycin (200 mg) given orally either 1 or 3 h preoperatively significantly reduced residual gastric volume and it also significantly decreased gastric acidity when given 1 h preoperatively.

The mechanism of gastric emptying of ingested food differs markedly from that of emptying of residual gastric contents during the fasting state. During the fed state, the stomach empties its contents by continuous irregular motility, whereas during the fastest state gastric motility is not constant and increases and decreases at a fixed cycle, which is regulated by the interdigestive migrating motor complex. The complex, a typical gastrointestinal activity that occurs during the interdigestive (fasting) state, is a cyclical motor pattern which usually originates in either the stomach or duodenum, and migrates to the terminal ileum. The motor complex consists of three main phases: after a period of quiescence (phase 1), an irregular spiking activity occurs (phase 2), which is taken over by intense bursts of action potentials (phase 3 or activity front). Gastric juice accumulates during phase 1 and 2, but during phase 3 the stomach strongly contracts and empties the residual gastric contents. In man, this strong contraction occurs every 1.5 to 2 h.

Motilin, a 22-amino acid gastrointestinal peptide whose receptors are abundant in the stomach, is likely to be involved in initiating the migrating motor complex. Injection of exogenous motilin induces gastric contractions which migrate to the intestine. In addition, injection of a motilin antiserum disrupts the natural migrating motor complex until plasma motilin concentration returns to the physiological level. Furthermore, during the interdigestive state, plasma motilin concentration fluctuates, and there is a close correlation between the peak plasma motilin concentration and motor complex cycle.

Erythromycin is considered to induce the phase 3 of the migrating motor complex, even during the fed state, as a motilin receptor agonist. First, binding studies have confirmed that erythromycin displaces the binding of a radiolabelled motilin. Second, the stimulatory effect of erythromycin is decreased in animals tolerant to motilin. Third, injection of erythromycin increases plasma motilin concentration in dogs. Therefore, it was likely that erythromycin significantly decreased residual gastric contents by inducing phase 3 in our patients.

A sub-therapeutic dose of oral erythromycin decreased gastric acidity in our study. This result is consistent with a previous study of the effect of erythromycin injected intravenously during fasting state or during continuous enteric feeding. The mechanisms for the inhibitory effect of erythromycin is not known. One possibility is that gastric acidity decreased by emptying of gastric juice. However, this is unlikely, since one study showed that residual gastric contents decreased during hunger contractions (without any medication), but gastric acidity increased. More likely possibility is that erythromycin decreased gastric acidity by direct action, possibly through motilin receptors. First, motilin also inhibits gastric acid secretion in animals. Second, infusion of acid solution into the stomach inhibits phase 3 of the migrating motor complex and decreases plasma motilin concentration, indicating that there is a relation between plasma motilin concentration and intragastric acidity. Third, erythromycin has a direct action to the stomach, since both erythromycin and motilin stimulate pepsinogen secretion from the chief cell of the isolated guinea-pig stomach.

The H2 histamine receptor antagonists inhibit secretion of gastric juice and acid, and has no influence on the volume and acidity of gastric juice that is already in the stomach. Therefore, these drugs may not effectively reduce gastric volume and acidity within 60–90 min. In contrast, erythromycin can reduce residual gastric juice by stimulating gastric emptying and, thus, it is possible that residual gastric juice would be reduced shortly after administration of erythromycin. Therefore, we were interested to see if erythromycin could reduce gastric volume and acidity 1 h after oral administration. Time to reach peak plasma concentration after oral administration of an erythromycin tablet has been reported to be 2–3 h (manufacturer’s information sheet). Therefore, it can be deduced that erythromycin can reduce gastric volume and acidity at much lower plasma concentration than a therapeutic concentration as an antibiotic.

One major complication of erythromycin is gastrointestinal symptoms. Most subjects experience gastric discomfort, and some of them nausea and vomiting if a therapeutic dose of erythromycin is infused intravenously. In contrast, in our study, no patient had such symptoms after oral administration of a sub-therapeutic dose. It has been shown that there is a significant correlation between severity of symptoms and infusion rate or between symptoms and plasma erythromycin concentration.
References


8 Fiorucci S, Distrett E, Gerli R, Morelli A. Effect of erythromycin on gastric and gallbladder emptying and gastrointestinal symptoms in scleroderma patients is maintained medium term. Am J Gastroenterol 1994; 89: 550–5


21 Lee KY, Chang T, Chey WY. Effect of rabbit antimotilin serum on myoelectric activity and plasma motilin concentration in fasting dog. Am J Physiol 1983; 245: G547–53

22 Christofides ND, Nodlin IM, Fitzpatrick ML, Bloom SR. Effect of motilin on the rate of gastric emptying and gut hormone release during breakfast. Gastroenterology 1979; 76: 903–7


30 Fiorucci S, Morelli A. Motilin and erythromycin stimulate pepsinogen secretion by chief cells isolated from guinea pig stomach. Gastroenterology 1993; 104: 1030–6