

Interactions of pre-operative erythromycin administration with general anaesthesia

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Previous reports have demonstrated a gastric emptying effect of erythromycin due to a motilin-like mechanism. We studied 50 patients, scheduled for daycase laparoscopy, randomly assigned to one of two groups: Group P patients received 30 min before induction of anaesthesia, in a double-blind manner an infusion of 250 ml dextrose 5% while patients in Group E (n = 25) received 500 mg of erythromycin diluted in 250 ml dextrose 5%. An orogastric tube was inserted to measure both gastric pH using a pHmeter and residual gastric volume (RGV) using the phenol red dilutional technique. Six patients were excluded for surgical reasons. More patients in Group P (6/22) than in Group E (0/22) had RGV > 25 ml and more patients in Group P (17/22) presented with a gastric pH < 2.5 than in Group E (5/22), P < 0.05. Since coma and respiratory depression have been reported recently after midazolam and alfentanil administration in patients having received erythromycin, recovery conditions were assessed and were found to be comparable between groups. In conclusion, the administration of iv erythromycin before outpatient laparoscopy decreased residual gastric volume and increased gastric pH without affecting recovery from general anaesthesia.

Des études récentes ont démontré que l'érythromycine augmentait la vidange gastrique grâce à un effet semblable à la motiline. Nous avons étudié 50 patientes devant subir une coelioscopie diagnostique en conditions ambulatoires. Elles ont été rando-

misées en 2 groupes: celles du groupe P (n = 25) ont reçu 30 minutes avant l'induction de l'anesthésie générale, en double aveugle, une perfusion de 250 ml de glucosé 5% alors que celles du groupe E (n = 25) ont reçu 500 mg d'érythromycine dilués dans 250 ml de glucosé 5%. Une sonde orogastrique fut introduite après l'induction pour mesurer le pH gastrique à l'aide d'un pHmètre ainsi que le volume gastrique résiduel (RGV) en utilisant la méthode de dilution à rouge phénol. Six patientes furent exclues de l'étude pour des raisons opératoires. Nous avons trouvé plus de patientes dans le groupe P (6/22) que dans le groupe E (0/22) présentant un RGV > 25 ml. De même, il y avait plus de patientes présentant un pH < 2.5 dans le groupe P (17/22) que dans le groupe E (5/22), P < 0.05. Des cas cliniques de troubles de conscience et de dépression respiratoire ayant été rapportés dans la littérature après administration de midazolam ou d'alfentanil chez des patients qui avaient reçu de l'érythromycine, les scores de réveil ont été évalués et se sont révélés comparables dans les deux groupes. En conclusion, l'administration intraveineuse d'érythromycine avant la coelioscopie diminue le volume gastrique résiduel et augmente le pH gastrique sans altérer les conditions de réveil après anesthésie générale.

Key words

COMPLICATIONS: aspiration;
GASTROINTESTINAL TRACT: stomach, volume, pH;
PHARMACOLOGY: erythromycin.

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Erythromycin is a macrolide antibiotic which has a broad spectrum activity against gram-positive and gram-negative bacteria, mycoplasmas, chlamydiae, treponemas and rickettsiae.¹ Antibiotic prophylaxis is frequently indicated before diagnostic laparoscopy since chlamydiae remain one of the most frequent causes of tubal damage. Recent pharmacological developments have shown that the use of erythromycin may interfere with anaesthesia for two reasons. First, erythromycin is known to accelerate gastric emptying in diabetic gastroparesis² and paralytic ileus.³ Since ambulatory patients may be at risk of aspiration of gastric contents,⁴ the administration of erythromycin before day-care laparoscopy might be an advantage. Second, two cases of unconsciousness after midazolam⁵ and respiratory depression after alfentanil⁶ have been reported in surgical patients who had received erythromycin. These potentially severe events have been attributed to changes in the pharmacokinetic behaviour

of midazolam⁵ and alfentanil⁷ respectively. Thus, the goal of our study was to assess prospectively (1) the effects of preoperative erythromycin on gastric volume and pH as well as (2) the perioperative anaesthetic conditions in patients undergoing ambulatory diagnostic laparoscopy.

Methods

After Institutional approval, 50 ASA-I women, scheduled for ambulatory diagnostic laparoscopy, gave informed consent to participate in this study. All patients were premedicated with hydroxyzine 100 mg *po* with 30 ml water 90 min before induction of general anaesthesia. In the preanaesthetic room and 30 min before induction of general anaesthesia, the patients were randomly assigned to one of two groups in a double-blind manner: Group P (placebo) patients ($n = 25$) received over ten minutes an *iv* infusion of 125 ml dextrose 5% while patients in Group E (erythromycin) received ($n = 25$) an *iv* infusion of 125 ml dextrose 5% containing erythromycin (500 mg) lactobionate (Abbott France®). The occurrence of nausea and/or vomiting during the infusion was noted. Midazolam 20 $\mu\text{g} \cdot \text{kg}^{-1}$, alfentanil 15 $\mu\text{g} \cdot \text{kg}^{-1}$ and propofol 2.5 $\text{mg} \cdot \text{kg}^{-1}$ were injected to induction of anaesthesia in all patients. Tracheal intubation was performed 3 min after atracurium 0.4 $\text{mg} \cdot \text{kg}^{-1}$ *iv* and anaesthesia was maintained using oxygen-nitrous oxide ($\text{FiO}_2 = 0.4$) with isoflurane 1% using a low flow circuit. Mean arterial blood pressure (MAP) and heart rate (HR) were recorded before and after induction, after intubation, after extubation and then every 30 min in the recovery room. The tracheas of all patients were extubated at the end of surgery after reversal of neuromuscular block with neostigmine sulphate 40 $\mu\text{g} \cdot \text{kg}^{-1}$ and atropine 20 $\mu\text{g} \cdot \text{kg}^{-1}$. An orogastric tube (Salem 14G) was inserted just after tracheal intubation to measure gastric pH using a previously calibrated pHmeter (Radiometer pHM 82) and residual gastric volume (RGV) using the phenol red dilutional indicator technique.⁸

Recovery times were measured from the cessation of N_2O inhalation. Assessment of immediate recovery included time to eye opening on verbal command (TEO) and time to identify the date and location (TOR). Patients were then transferred to the recovery room where assessment of intermediate recovery was performed according to the Robertson scoring system⁹ every 30 min for 90 min (TRO, TR30, TR60, TR90). Patients were then transferred to the ward and were discharged six hours after completion of anaesthesia as usually performed in our institution. Information regarding the street fitness criteria including stability of vital signs, ability to eat and void, ability to walk and dress alone were collected.

Statistical evaluation included Student's *t* test and ANOVA followed by Neuman Keuls test for quantitative

TABLE I Demographic data, mean \pm SD.

	Placebo	Erythromycin	Statistics
Age (y)	33 \pm 5	36 \pm 9	NS
Weight (kg)	59 \pm 12	59 \pm 11	NS
Height (cm)	165 \pm 6	162 \pm 6	NS

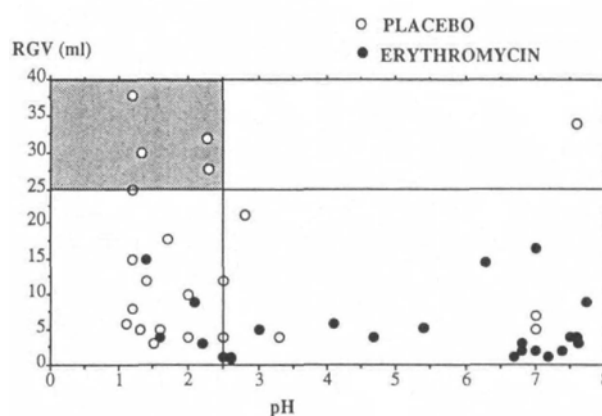


FIGURE Individual values of gastric pH and residual gastric volume (RGV).

data and a Chi square test with Yates correction when necessary for qualitative data.

Results

Demographic data were comparable between the two groups (Table I). Six patients were excluded from the study (three in each group) because laparotomy was required for surgical reasons. The incidence of nausea-vomiting during the infusion was not different in the two groups (2/22 (E) vs 1/22 (P): NS). The mean time interval between the end of the infusion and gastric sampling was comparable between the two groups: 33 \pm 6 min (E) vs 31 \pm 3 min (P). Detailed results concerning gastric pH and RGV are shown in the Figure. In brief, there were fewer patients in Group E (5/22) having a gastric pH ≤ 2.5 than in Group P (17/22), $P < 0.01$. The RGV values > 25 ml were more frequent in Group P (6/22) than in Group E (0/22), $P < 0.05$. In addition, mean RGV was lower in Group E (6.7 \pm 7 ml) than in Group P (12.2 \pm 10.7 ml) with a 95% confidence interval of the difference CI [-8.25; -2.77], $P < 0.05$. Five of the 22 patients in Group P and none of the 22 in Group E had concomitantly gastric pH ≤ 2.5 and RGV ≥ 25 ml but this difference was not statistically significant. Mean arterial pressure and heart rate were not different between the two groups at any time during the study. In addition, variables assessing immediate and

TABLE II Time interval (mean \pm SD) between infusion of erythromycin and induction of anaesthesia, the incidence of nausea-vomiting during the infusion, the duration of surgery, and isoflurane inhalation, the recovery scores and the time interval between the end of anaesthesia and discharge. TEO: time to eye opening/TOR: time to identify date and location.

	Placebo	Erythro- mycin	Statistics
Time interval infusion- induction of anesthesia (min)	31 \pm 3	33 \pm 6	NS
Nausea-vomiting	1/22	2/22	NS
Duration of surgery (min)	36 \pm 9	42 \pm 18	NS
Inhalation of isoflurane (min)	30 \pm 9	35 \pm 11	NS
<i>Immediate recovery</i>			
TEO (min)	8.2 \pm 4.7	8.2 \pm 4.4	NS
TOR	10.8 \pm 5.2	11.6 \pm 5.7	NS
<i>Robertson score</i>			
T ₀	7.5 \pm 1.6	8.1 \pm 0.7	NS
T ₃₀	8.2 \pm 0.5	8.4 \pm 0.7	NS
T ₆₀	8.5 \pm 0.5	8.7 \pm 0.6	NS
T ₉₀	8.6 \pm 0.6	8.7 \pm 0.6	NS

intermediate recovery (Table II) as well as the usual street fitness criteria assessed six hours after the end of anaesthesia were comparable between the two groups. All patients were discharged at the sixth hour after the end of anaesthesia.

Discussion

Our results are in agreement with previous studies^{2,3} demonstrating a gastric emptying effect of erythromycin. Administration of erythromycin prior to general anaesthesia for outpatient diagnostic laparoscopy induced a reduction in residual gastric volume. Indeed, since erythromycin is a motilin agonist,^{10,11} it mimics the effects of motilin on the gastric antrum and proximal duodenum and induces powerful peristaltic contractions. Moreover, a higher gastric pH was noticed in patients who had received erythromycin. This has also been demonstrated recently in postpartum patients¹² who are at high risk of aspiration. Although beneficial, the cause of this increase in pH is unexplained. The dose of 500 mg erythromycin was used because: (1) even very small doses of erythromycin (100–200 mg) are sufficient to enhance gastric emptying,^{2,13} (2) and higher doses (≥ 1000 mg) may induce an unacceptably high incidence of vomiting,¹ and (3) the usual dose of erythromycin for prophylaxis before surgery in our institution is 500–1000 mg. The time interval of 30 min from the end of the erythromycin infusion until the induction of general anaesthesia was chosen because the gastric emptying effect has been demonstrated previously to occur 30 min after its admin-

istration.² To examine the possible advantage of using erythromycin over other techniques of prophylaxis for aspiration pneumonitis, two complementary approaches are required. First, from a pharmacological point of view, the efficacy of this gastric emptying effect of erythromycin should be compared with that of metoclopramide or ondansetron in the same setting. Second, from a clinical point of view, anaesthetists have a large panel of drugs for the prophylaxis of aspiration (H₂ receptor antagonists, sodium citrate, omeprazole, metoclopramide, droperidol, low doses of erythromycin) and further comparative studies are needed to define which drug or which combination of drugs will be the most efficacious and will provide the best cost-effectiveness ratio.

The immediate and the intermediate recovery states were not affected by the administration of erythromycin. This is in disagreement with reported cases of coma or respiratory depression after erythromycin administration^{5,6} and may be because our patients received only a single dose of erythromycin and because only small doses of midazolam and alfentanil were administered. The Robertson score and other tests of recovery and discharge criteria may be insufficiently sensitive to detect minor changes of impaired recovery. Nevertheless, clinically important alterations of vigilance, which are easily detectable by these methods, did not occur. In our institution, patients undergoing outpatient diagnostic laparoscopy are arbitrarily discharged six hours after anaesthesia. All patients met the street fitness criteria at that time and did not require further monitoring, suggesting the absence of late recovery changes following erythromycin administration.

In conclusion, prophylactic administration of *iv* erythromycin before outpatient diagnostic laparoscopy decreases residual gastric volume, increases gastric pH without affecting the recovery conditions following general anaesthesia. Further studies comparing low doses of erythromycin with drugs known to be effective for the prevention of aspiration of gastric contents are warranted.

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