Clinical Trial Protocol

The effect of intravenous erythromycin on gastric emptying in patients undergoing rapid sequence intubation for full stomach.
A randomized, placebo-controlled, double-blind study (ErythroEmerge-Study)
6th revision-1st amendment 10.5.2012

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Signature Page

I, the undersigned, have reviewed this Protocol, including Appendices. I will conduct the clinical study as described and I will adhere to GCP/ICH and all the ethical and regulatory considerations stated. I have read and understood the contents of the Investigators' Brochure.

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1 Introduction

Urgent or emergency surgery requires that fasting rules observed in elective settings are not respected. Patients who are anesthetized in such conditions are at risk for regurgitation and subsequent broncho-aspiration during induction of anesthesia due to a full stomach; they often have ingested food or liquids before the injury, or they may have swallowed blood from oral or nasal injuries. Also, gastric emptying is delayed in these patients due to the stress of trauma.[1] Already in 1946, Mendelson described the consequences of bronchoaspiration.[2] Since, anesthetists and emergency physicians have tried to avoid broncho-aspiration in emergency patients using premedication with pro-kinetic drugs (for instance, metoclopramide) or its complications with antacid substances, and through the use of a rapid sequence intubation procedure with cricoid pressure. The incidence of aspiration is low, about 1.4 to 6 in 10'000 anesthetics.[3] About 6 in 100'000 anesthetics will lead to a pulmonary complication due to broncho-aspiration and about 1 in 100'000 patients is likely to die due to aspiration.[4] Thus, although episodes of broncho-aspiration are rare, efficacious prevention of this potentially lethal complication is important. One method to reduce the risk of broncho-aspiration during induction of anesthesia is the pharmacological reduction of the gastric content (i.e. pre-treatment). The intention of this study is to investigate the efficacy of erythromycine in emptying the stomach of non-fasted surgical patients before induction of anesthesia in the emergency setting.

2 Study objectives

2.1 Primary objective

To investigate gastric emptying, in adults scheduled for rapid sequence intubation for full stomach, the effect of a short intravenous infusion of erythromycin 3 mg/kg, administered 20 min before intubation,

2.2 Secondary objectives

To assess tolerability and safety of a single intravenous dose of preoperative erythromycin in surgical patients.

3 Study design

Single centre, stratified (according to emergency setting), randomized, placebo-controlled, double-blinded study.

4 Subject selection

4.1 Inclusion criteria

Subjects must satisfy the following criteria to be enrolled into the study:

- Adult, age ≥18 years, male or female.
- American Society of Anesthesiology [ASA] status I, II or III.
- Non-starving patient presenting for surgery.
- Patient is able to read and understand the information sheet and to sign and date the consent form.
- If the patient is female and of childbearing potential, she must have a negative pregnancy test (serum hCG or urine dipstick).

4.2 Non-inclusion criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

- A history of allergy or hypersensitivity to erythromycin or other macrolides.
- Concomitant use of terfenadine, astemizole, cisapride, pimozid, cyclosporine, clarithromycine, ergotamine, dihydroergotamine.
- Acute intermittent porphyria.
- Acute or subacute necrosis of the liver, acute or subacute hepatitis, acute liver trauma
    - Bilirubin >1.5 x upper limit normal (ULN)
    - Alanine aminotransferase (ALAT) >2.5 x ULN
    - Aspartate aminotransferase (ASAT) >2.5 x ULN
    - Anamnestically (in absence of laboratory tests).
- Acute renal failure, acute glomerulonephritis, nephritic syndrome, chronic renal failure with electrolyte disorders, uremia
    - Creatinine >1.5 x ULN
    - Anamnestically (in absence of laboratory tests).
- Exacerbated asthma, exacerbated chronic obstructive lung disease, acute pulmonary infection.
- Coronary heart disease (unstable angina, myocardial infarction within the last 6 months), decompensated cardiac insufficiency, aortic aneurysm.
- Polyneuropathy (for instance, due to diabetes mellitus)
    - Anamnestically (in absence of laboratory tests).
- Patients with esophageal and pharyngeal disease (i.e. esophageal varices, esophageal and pharyngeal cancer, Zenker's diverticulum).
- Status after gastric surgery, gastric bypass surgery, Nissen operation.
- Patients with life-threatening illness or injury needing immediate surgery.
- Patients with moderate to severe head trauma (Glasgow Coma Scale <13 on admission).
- Psychological or psychiatric disorders.
- Dementia or inability to understand the study protocol.
- Patient scheduled for ileus surgery.
- Women who are pregnant, breast feeding, or planning to breast feed within 7 days of administration of study drug.

4.3 Subject recruitment, screening and laboratory tests

The emergency team will screen eligible patients and will obtain written informed consent. If pathologic conditions such as acute or sub-acute necrosis of the liver, acute or sub-acute hepatitis, acute liver trauma, acute renal failure, acute glomerulonephritis, nephritic syndrome, chronic renal failure with electrolyte disorders or uremia are suspected or can not be excluded anamnestically, specific blood test will be performed. In female patients of childbearing potential, samples will be taken for pregnancy tests (serum hCG or urine dipstick).

5 Treatments

5.1 Investigational agent

5.1.1 Drug description

Erythromycin is a well-known antibiotic of the macrolide group and commercialized since 1952. It is produced by a strain of *Streptomyces erythraeus*. It is basic and readily forms salts with acids.

Erythromycin lactobionate is a soluble salt of erythromycin suitable for intravenous administration. It is available as a sterile, lyophilized powder in vials containing the equivalent of 1 g of erythromycin activity (Erythrocine® i.v.). It is prepared as a solution

and lyophilized in its final container.
Erythromycin lactobionate is chemically known as erythromycin mono (4-0-β-D-galactopyranosyl-D-gluconate) (salt). The structural formula is:

5.1.2 Indications

Intravenous erythromycin is used as an antibiotic for many infections such as moderate to severe infections of the upper and lower respiratory tract, skin infections, acute pelvic inflammatory disease, prevention of rheumatic fever and others. For the treatment of severe infections in adult and pediatric patients, the recommended intravenous dose of erythromycin lactobionate is 15 to 20 mg/kg/day. Higher doses, up to 4 g/day, may be administered for severe infections.
Beside its antibiotic effect, erythromycin is an agonist at the motilin receptor and it has cholinergic stimulatory properties.[5] In animal experiments, erythromycin has been shown to accelerate gastric emptying by inducing powerful antral contractions which are capable of forcing coin-sized indigestibles out of the stomach.[6] Erythromycin also increases lower esophageal sphincter tone by stimulating cholinergic receptors.[7] Thus, this drug exerts two potentially useful effects that may decrease the risk of regurgitation in patients with full stomach.
Janssens et al.[8] were the first to show that in patients with diabetes mellitus and delayed gastric emptying, intravenous administration of erythromycin 200 mg before a test meal could normalize the gastric emptying rate of both liquids and solids. After oral administration of erythromycin 250 mg three times a day for 4 weeks, the gastric emptying was improved but not to the same extent as in the initial experiments with intravenous administration. The observations by the Leuven group were subsequently confirmed in several studies in patients with gastroparesis.[9,10,11]
Finally, erythromycin is used for the treatment of gastric dysmotility in the critically ill,[12] in the treatment of gastrointestinal dysmotility in preterm infants,[13] and also to enhance gastric emptying in patients after esophagectomy.[14]

5.1.3 Adverse effects

Adverse effects following the use of intravenous erythromycin are rare. Occasional venous irritation has been encountered, but if the infusion is given slowly, in dilute solution, pain and vessel trauma are minimized.
Life-threatening episodes of ventricular tachycardia associated with prolonged QT interval (*torsades de pointes*) have been reported in some patients after intravenous administration of erythromycin lactobionate.
Susceptibility to the development of *torsades de pointes* arrhythmia, a rare but serious cardiac condition, is related to electrolyte imbalance (hypokalaemia and hypomagnesaemia), hepatic dysfunction, myocardial ischemia, left ventricular dysfunction, idiopathic Q-T prolongation, and concurrent antiarrhythmic therapy. Elderly patients exhibit a greater frequency of decreased hepatic function, cardiac function, and of concomitant disease and other drug therapy, and therefore should be monitored carefully during erythromycin therapy.
Allergic reactions ranging from urticaria to anaphylaxis have occurred. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely.
There have been isolated reports of reversible hearing loss occurring mainly in patients with renal insufficiency and in patients receiving high doses of erythromycin.
Occasionally patients present epigastric cramps, nausea and vomiting, diarrhea and an increased intestinal motility after intravenous erythromycin.

5.1.4 Drug interactions

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. Concomitant use of erythromycin and ergotamine or dihydroergotamine may lead to ergotamine toxicity with vascular spasm and ischemia of the extremities and

other tissues, including the central nervous system.
There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly.
Erythromycin has been reported to significantly alter the metabolism of the non-sedating antihistamines, terfenadine and astemizole, when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QTc interval prolongation, cardiac arrest, *torsades de pointes*, and other ventricular arrhythmias, have been observed. In addition, deaths have been reported with concomitant administration of terfenadine and erythromycin.
The use of erythromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, bromocriptine, valproate, terfenadine, and astemizole. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin. Doses should be reduced in cases of severe renal insufficiency (creatinine clearance < 10 ml/min). Erythromycin is predominantly excreted by the liver; erythromycin should be administered carefully in patients with hepatic insufficiency. Patients with myasthenia gravis can present increased muscle weakness under erythromycin treatment. Patients with acute intermittent porphyria may develop an acute crisis if erythromycin is given.

5.1.6 Contraindications

- Hypersensitivity to erythromycin.
- Severe hepatic insufficiency.
- Patients with concomitant use of ergotamine or dihydroergotamine.

5.1.7 Pregnancy and nursing

There is no evidence of teratogenicity or any other adverse effect on reproduction in animal studies. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.
Erythromycin is excreted in breast milk. Caution should be exercised when erythromycin is administered to a nursing woman.

5.2 Dose rationale

Doses of erythromycin to enhance gastric emptying are much smaller than those needed for antibiotic therapy.
In a randomized trial, a single intravenous bolus dose of erythromycin 250 mg, 20 min prior to emergency endoscopy for upper gastrointestinal bleeding, was shown to clear the stomach from any content in 82% of the treated patients compared with 33% of the patients receiving a placebo ($P<0.001$).[15] No adverse effects were reported in that trial.
In the anesthesia literature there are several randomized controlled trials investigating the effect of erythromycin on volume and acidity of gastric contents in surgical patients. Patients were always low risk (ASA I to II), and fasting (i.e. scheduled for elective surgery). In one study, an intravenous infusion of 500 mg erythromycin was compared with placebo.[16] The two other studies compared a 200 mg oral dose with placebo.[17, 18] In all studies, pretreatment with erythromycin effectively and significantly decreased residual gastric volume and acidity, without relevant adverse effects.
In the emergency setting, there is one relevant case report only. Kopp et al. reported on a young patient undergoing emergency esophagogastroduodenoscopy.[19] He had upper gastrointestinal bleeding and had had a complete meal 2.5 hours before induction of anesthesia. He received a premedication with intravenous erythromycin lactobionat 100 mg, 80 minutes before induction of anesthesia. After induction of anesthesia, endoscopy revealed a completely empty stomach.
In volunteers it was shown that erythromycin promoted gastric emptying even during episodes of acute pain. Intravenous erythromycin 250 mg or placebo were administered

during painful stimuli without significant side effects.[20]
Boivin et al.[21] attested for dose-responsiveness of erythromycin in healthy volunteers. They compared intravenous erythromycin 0.75 mg/kg, erythromycin 3.0 mg/kg, metoclopramide 10 mg and placebo. They concluded that erythromycin 3.0 mg/kg most effectively promoted gastric emptying with an acceptable adverse effect profile (stomach cramping and nausea).
Based on these studies, and in agreement with a previous trial that was performed in our institution,[15] we will test erythromycin as a single intravenous dose of 3 mg/kg (maximum dose 300 mg).

5.3 Risks and benefits

Erythromycin has been associated with adverse effects, specifically in patients with hepatic disorders and in those using concomitant drugs.
Considering relevant information from The Compendium Suisse (edition 2008) and from the published literature, we estimate the risk of drug-related adverse effects as extremely low in our study, since we will follow strict definitions of non-inclusion criteria (see, 3.2.2), and we will test one single dose that is similar to the doses that were studied in previous trials.[16, 17, 18] The additional risk of an esophagogastroduodenoscopy, in this setting and performed by an experienced gastroenterologist is very low. Complications of upper gastrointestinal endoscopy are cardio-respiratory, infectious and rarely instrumental. Perforations were 8/10.000 and cardiorespiratory complications were 7/1000 in a prospective series of 250.000 patients. The perforations are extremely rare in the absence of a therapeutic procedure. Hemorrhages are infrequent and mainly due to accidental biopsy of a vascular lesion. The infectious risk linked to gastroscopy is very low because new techniques of washing with automatic washing machines, using potent disinfectants such as peracetic acid, are now adopted. The most important factors associated with endoscopy-induced morbidity are inexperience and incompetence of the investigator, and over-sedation of the patient.[30] Our patients will be anaesthetized and curarized before endoscopy will start. All three investigators are experienced staff members of the gastroenterology unit of our hospital.

5.4 Study drug preparation, randomization, stratification, blinding

The hospital pharmacy will be responsible for study drug preparation and randomization. Randomization will be in a 1:1 ratio to erythromycin treatment or placebo. Identical 10 ml syringes of erythromycin 3% and placebo (0.9% saline) will be prepared every two weeks and stored at 2-8oC. Patients, care givers (anesthetists), and observers (gastroenterologists) will be unaware of study drug assignment. Study drugs will be stratified to "Trauma" and "Non-Trauma".

5.5 Study drug administration and compliance

For all patients, a standardized volume of 10 ml of the study drug (see, point 5.4.) will be diluted in 90 ml NaCl 0.9% (total volume, 100 ml). Both, the study drug and the 90 ml NaCl bag will be prepared by the pharmacy. Using sterile syringes, the investigator will withdraw from this solution as many milliliters as necessary to obtain a volume that corresponds to 1 ml per kg bodyweight of the patient (i.e. for a 67 kg patient, 33 ml would be with withdrawn). Thus, the maximum volume that can be administered to a patient will be 100 ml (i.e. for a patient weighing ≥100 kg). Both the volume of the withdrawn solution and the volume of the eventually administered study drug solution will be recorded in the CRF. The withdrawn solution will be disposed as usual for pharmaceutical products. Twenty minutes prior to the scheduled induction of anesthesia, patients will receive their study drug solution as an intravenous infusion during 5 min. The regimen corresponds to 3 mg/kg of erythromycin.

5.6 Induction and maintenance of anesthesia

No premedication will be given (as is usual practice in emergency cases in our institution). Monitoring will be standard (ECG, SaO_2, $ETCO_2$, invasive or non-invasive

blood pressure). Induction will be with a classic "rapid sequence" procedure with an intravenous hypnotic (thiopental 5 mg/kg, propofol 2 mg/kg or etomidate 0.2 mg/kg) and a neuromuscular blocking agent (succinylcholine 1 to 1.5 mg/kg or rocuronium 1.2 mg/kg [i.e. 4xED95]). Cricoid pressure will be applied at the discretion of the responsible anaesthetist. Maintenance will be with intravenous sufentanil 0.2 µg/kg or fentanyl 2 µg/kg, and with propofol or 1 to 1.5 MAC isoflurane, sevoflurane or desflurane, with or without N_2O.

5.7 Gastroscopy – technique and instruments

Gastroscopy, or upper gastrointestinal endoscopy, permits the exploration of the upper gastrointestinal tract up to the second part of the duodenum. The diameter of the endoscopes varies between 5 and 13 mm. The gastroscopy is generally well tolerated and is performed without sedation in 60% of the cases. The lack of tolerance to this procedure is generally due to nausea and vomiting provoked by the gag reflex, when the endoscope is in the region of the retropalate. Annually, about 3,000 gastroscopies are performed in our hospital.

6 Study evaluations

6.1 Baseline data

For non-trauma patients, the following baseline data will be recorded:

- Solid food and or liquids: time of last oral intake.
- Baseline pain (if any) before induction (Visual Analogue Scale, ranging from 0=least possible pain to 100=maximum possible pain).
- Any opioids during the last six hours before induction (yes/no).
- Diabetes (yes/no).
- Intake of antacid drugs during the last 24 hours.

For trauma patients, the following baseline data will be recorded: Solid food: delay between last oral intake and the accident.

- Liquids: delay between last oral intake and the accident.
- Baseline pain before induction (Visual Analogue Scale, ranging from 0=least possible pain to 100=maximum possible pain).
- Any opioids during the last six hours before induction (yes/no).
- Diabetes (yes/no).
- Injury severity score.[22]
- Intake of antacid drugs during the last 24 hours.

6.2 Efficacy evaluations

6.2.1 Primary endpoint

Immediately after intubation, one of three senior gastroenterologists (JLF, EG, LS) will perform an upper GI endoscopy.
The following primary endpoint will be recorded:

- Stomach clear from any content: yes/no (dichotomous)

6.2.2 Secondary endpoints

- Estimation of the volume of gastric content if stomach not empty (ml).
- Acidity of gastric content if stomach not empty (pH).

6.2.3 Safety evaluations

The following symptoms are to be evaluated systematically

- Drug-related allergic reactions
- Gastrointestinal cramps after study drug administration but before intubation
- Nausea or vomiting after study drug administration but before intubation
- Arrhythmia

- Regurgitation with or without broncho-aspiration at induction.

6.2.4 Additional measurements

- Blood glucose before administration of study drug. Acute hyperglycemia reduces the erythromycin-induced acceleration of gastric emptying in healthy subjects[23] and in diabetic patients.[24] Emergency patients are likely to have stress- induced hyperglycemia. However, unequal distribution of high blood glucose levels among treatment groups may be a confounding factor.
- Intubation score according to Cormack scale.[25]

7 Adverse event reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and sponsor, and is mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements to ensure appropriate reporting.

7.1 Definitions

7.1.1 Adverse event

An adverse event (AE) as defined by the International Conference on Harmonization (ICH) is any untoward medical occurrence in a clinical study subject that is administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medical (investigational) product, whether or not related to the medicinal (investigational) product.
This includes any occurrence that is new in onset, or aggravated in severity or frequency, from the baseline condition, or abnormal results of diagnostic procedures including laboratory test abnormalities.
The sponsor collects adverse events starting with the first study-related procedure (not with signing the informed consent).
For the purpose of this study, an AE is relevant if it occurs within 24 hours after study drug administration.

7.1.2 Serious adverse event

A serious adverse event (SAE) as defined by the ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening (the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires or prolongs hospital stay
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect
- Is an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical relevance. They may jeopardize the subject, and may require an intervention to prevent one of the other serious outcomes noted above.
For the purpose of this study, an SAE is relevant if it occurs within 24 hours after study drug administration.

7.1.3 Unlisted (unexpected) adverse event

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product information (e.g. the package insert/summary of product

characteristics) (ICH).

7.1.4 Associated with the use of the drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable or very likely by the definitions listed below:

Not related
An adverse event, which is not related to the use of the drug.

Doubtful
An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or (?) is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Possible
An adverse event, which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable
An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by de-challenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very likely
An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

7.2 Recording of adverse events

At each contact with the subject, the investigator must seek information on adverse events (AE) by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results shall be recorded in the source document, though should be grouped under one diagnosis.
All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events (SAE) that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.
Regularly evaluated symptoms as listed under paragraph 6.2.3 (Safety evaluations) are not considered as adverse events unless they fulfill the criteria of a serious adverse event (definition see paragraph 7.1.2).

7.3 Duration of adverse event recording

Adverse events (AE, SAE) will be recorded up to 24 hours after study drug administration.

7.4 Reporting of serious adverse events

Reports of serious adverse events (SAE) will be submitted to the Ethics Committee (investigator) and Swissmedic (sponsor) as soon as possible but no later than 15 days for the Suspected Unexpected Serious Adverse Reactions (SUSAR) and as soon as possible but no later than 7 days for a death.
The non-SUSAR SAE will be reported by the way of annual reports.
A register containing all the AE occurring during the study must be made and kept by the sponsor and made available to the Regulatory Authorities.

7.5 Medical monitoring

The Principal Investigator will oversee the safety of the study. This safety monitoring will include a regular assessment of the number and type of serious adverse events and appropriate reporting of adverse events as noted above. The intensity of adverse events will be graded on a three-point scale (mild, moderate, or severe) and described in detail, along with the investigator's assessment of the relationship of the event to treatment.

8 Statistics

8.1 Sample size determination

The degree of efficacy we are expecting is based on a previously published randomized trial that was performed in our hospital and that investigated the efficacy of erythromycin in patients undergoing emergency gastroscopy for gastrointestinal bleeding.[15] In that trial, 42 of 51 (82%) patients receiving intravenous erythromycin 250 mg and 18 of 54 (33%) controls receiving saline 20 minutes before gastroscopy had an empty stomach. This difference was statistically significant (P<0.001). Thus, about 65% of patients with gastrointestinal bleeding who did not receive a prokinetic treatment had a significant amount of blood in their stomach.

The incidence of patients who have a non-empty stomach while undergoing emergency surgery remains unknown. However, if we assume (as previously reported[15]) that there is a 50% absolute risk difference in having an empty stomach when receiving erythromycin compared with placebo, we need to randomize 18 patients into each group to show a statistically significant difference (alpha = 0.05, beta = 0.2) (InStat 2.01). Since we stratify patients into "Trauma" and "Non-trauma", and to account for possible drop-outs we shall randomize 100 patients (i.e. 2 x 25 for "Trauma" plus 2 x 25 for "Non-trauma").

8.2 Recalculation of sample size after inclusion of 100 patients

After inclusion of 100 patients, without opening the randomization code, we realized that the incidence of patients with "full stomach" in our study was lower than the 65% initially expected. In fact, only 24 of 100 patients were found to have a "full stomach", meaning that the theoretical maximum baseline risk of "full stomach" would be of 24/50, 48%. Therefore, the aim of reaching a 50% absolute risk reduction of having a "full stomach" with erythromycin could not be used anymore for the sample size estimation.

In relative terms, based on the previously published study[15] and on clinical grounds, we decided that a clinically relevant degree of efficacy would be established if erythromycin was shown to decrease the incidence of "full stomach" by 60% (RR: 0.4). Based on our data, if erythromycin showed this degree of efficacy, the estimated incidence of "full stomach" in the placebo group would be about 34%, and in the erythromycin group 14%.

In this context, the sample size needed to reach 80% power to detect a difference of this magnitude, using a one-sided test (we do not expect erythromycin to increase the incidence of "full stomach"; alpha=0.05) is 65 patients per group, which represents 15 additional patients receiving placebo, and 15 receiving erythromycin. In order to ensure a balanced distribution of patients among the 4 sub-groups, we decided to include 32 additional patients (2 x 8 patients for "Trauma" and 2 x 8 patients for "Non-Trauma").

8.3 Statistical methods

Baseline characteristics will be compared using Mann-Whitney or Pearson chi squared test as required. A two-sided P value <0.05 will be considered statistically significant. Dichotomous data (primary endpoint, drug related adverse effects) will be analyzed using relative risk with 95% confidence interval. When the 95% confidence interval exclude 1, we assume that the difference is statistically significant at the 5% level.

9 Data handling and record keeping

9.1 Source documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.1.1 Direct recording in the Case report Forms

The injury severity score will be recorded in the case report form (CRF) only. It will be calculated after inclusion of the patient. All other baseline data, such as delay between last oral intake of solid food and liquids and the accident, and baseline pain before induction, must be recorded on the anesthesia protocol or on other source documents.

9.2 Case Report Form (CRF)

The CRF is the primary data collection instrument for the study. All data requested on the CRF will be recorded and all missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, we will write "N/D". If the item is not applicable to the individual case, "N/A" will be written. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All changes will be initialed and dated. Errors will not be erased or whited out. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

9.3 Data Quality Control and Quality Assurance

Throughout the study, a quality control and quality assurance will be performed to check the strict application of the protocol and conformity of the data entered on the CRF with the source documents and ensures its correct completion.

10 Ethical considerations

10.1 Investigators responsibilities

The investigators are responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.
GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have originated in the Declaration of Helsinki, and that the clinical study data are credible.

10.2 Independent ethics committee (IEC)

This study will be undertaken after the research protocol, information letter, and informed consent have obtained approval from our Institutional Trial Review Board (Comité de Recherche, CoRe, Service d'Anesthésiologie), the Ethics Committee of Geneva University Hospitals, and Swissmedic.
During the study, the investigators will send the following documents to the Ethics Committee, if necessary:

- Protocol amendments.
- Revisions to informed consent form and any other written materials that are provided to the patients.
- Summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC).
- Reports of adverse events that are serious, unlisted, and associated with the investigational drug.
- New information that may affect adversely the safety of the patient or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.
- Report of deaths under the investigator's care.

At the end of the study, the investigators will notify the Ethics Committee about study completion.

10.3 Informed consent

10.3.1 Written informed consent before study procedure

Before the study, each patient will be evaluated by a physician (emergency physician, anesthetist, gastroenterologist) who will be responsible for ensuring that the study is performed in accordance with the protocol, current guidelines on Good clinical Practice (GCP), and applicable regulatory requirements.
Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form will be signed before performance of any-study related activity. The consent form that is used has been approved by the reviewing Ethical Committee and Swissmedic. The informed consent is in accordance with the principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines and applicable regulatory requirements.
Before entry into the study, the investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his/her disease. Subjects will be told that refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be assessed by competent authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the subject is authorizing such access.
The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry to the study, consent should be appropriately recorded by means of the subject's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.
Patients with life-threatening illness or injury needing immediate surgery will not be included because there will be not sufficient time to obtain informed and written consent.

10.3.2 Post intervention visit

Patients will be visited by one of the principal investigators 24 hours after the intervention and will be re-informed about the study procedure ("debriefing"). They will be asked if they still agree to participate in the study and if the data collected can be used for analysis.

10.4 Privacy of personal data

The collection and processing of personal data from subjects enrolled in this study will be limited to those that are necessary to investigate the efficacy, safety, quality, and utility

of the investigational product used in this study.
These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

10.5 The role of a placebo group

The role of placebos in clinical trials has been discussed repeatedly.[26-29] For the present project, there are several arguments in favour of placebos:

- There is no gold-standard prokinetic drugs against which erythromycin could be compared. In absence of a gold standard treatment, the best comparator remains a placebo.
- Event rates for empty stomach in non-starving patients vary widely. The inclusion of a placebo group allows estimation of the true underlying risk (for instance, in the Frossard study,[15] only 67% of the control patients who did not receive any prokinetic drug had blood in their stomach).
- In an active-controlled comparison there is the possibility of equivalence; without a placebo control, internal sensitivity of the trial would not be proven.

10.6 Feasibility of the study

About 1,500 emergency surgeries are performed in the HUG each year (excluding maternity and pediatrics). There are no major logistic constraints; for instance, during week-ends and during night-time, the collaborating gastroenterologists are always available. We assume that half of all patients undergoing emergency surgery are eligible, and one third of those eligible may potentially be included into our study. These are 250 patients each year. If 50% of those accept to participate in our study and can be randomized, we may recruit 125 patients during a one year period. Consequently, our study should be finished within one year.

10.7 Implication, clinical relevance

Regurgitation of gastric content with subsequent broncho-aspiration during induction of general anesthesia is a rare but major adverse event. Broncho-aspiration may lead to pneumonia with subsequent ARDS and eventually death. Duration of hospitalization is likely to be prolonged in these patients. Prevention of this life-threatening adverse event of anesthesia is important.
"Stomach clear from any content" may be regarded as a surrogate endpoint. However, we may assume that a patient with a completely empty stomach cannot regurgitate and therefore cannot aspirate gastric contents into the lungs. Also, a study that aims to investigate the potentially beneficial effect of a pro-kinetic drug on the incidence of broncho- aspiration itself needs to be very large.
If a simple and inexpensive pretreatment with a single dose erythromycin regimen proofs to effectively empty a patient's stomach empty before intubation, and without unacceptable adverse effects, clinical practice is likely to change.
Subsequent clinical studies could be designed to evaluate:

- The optimal dose of erythromycin and the optimal timing of drug administration;
- Efficacy and safety of erythromycin in other patient populations (for instance, children or patients with overt ileus);
- Efficacy and safety of alternative motilin agonists (for instance, Atilmotin).

11 Financing and insurance

11.1 Funding source

This study will be financed by a "Fonds de service APSI" grant attributed to Dr Czarnetzki.

11.2 Conflict of interest
None of the investigators has any conflict of interest.

11.3 Insurance
A special insurance for clinical studies will be provided by the University Hospitals of Geneva.

12 Publication policy
Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the study sponsor.
The results of the study will be subject to abstract presentations at international and national congresses and the results will be submitted to publication in a peer-reviewed journal.

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