

Electrogastrography in experimental pigs: the influence of gastrointestinal injury induced by dextran sodium sulphate on porcine gastric erythromycin-stimulated myoelectric activity

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Submitted: 2011-05-20 *Accepted:* 2011-08-25 *Published online:* 2011-11-05

Key words: **dextran sodium sulphate; electrogastrography; erythromycin; experimental pigs; gastrointestinal motility**

Neuroendocrinol Lett 2011;32(Suppl.1):131–136 PMID: 22167215 NEL32S111A17 ©2011 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVES: Electrogastrography (EGG) is a non-invasive investigation of gastric myoelectrical activity. The aim of study was to evaluate the impact of erythromycin on EGG in gastrointestinal toxic injury induced by dextran sodium sulphate (DSS) in experimental pigs. **METHODS:** The experiments were carried out on 12 adult pigs (weighing 30–35 kg). EGG was recorded using Digitrapper equipment (Synectics Medical AB, Stockholm). Running spectrum activity was used for EGG evaluation. There were two groups of animals: Group I: 6 controls with erythromycin administration (1,600 mg intragastrically); Group II: 6 animals treated with DSS (for 5 days, 0.25 g/kg per day in a dietary bolus) followed by erythromycin administration. Baseline and subsequent six separate 30-minute EGG-recordings (from time 0 to 360 min) were accomplished in each animal. **RESULTS AND CONCLUSION:** A total of 84 records were analysed. Baseline dominant frequency of slow waves was fully comparable in both groups. In Group I, there was a significant increase in dominant frequency after erythromycin administration (maximum between 240–360 min). There was a flat non-significant and delayed increase in dominant frequency after erythromycin administration in Group II. The difference between Group I and II at particular time intervals was not significant but a diverse trend was evident. EGG recording enables us to register a gastric myoelectrical effect of prokinetic drugs. Erythromycin induced a significant increase in the dominant frequency of slow waves. DSS caused toxic injury to the porcine gastrointestinal tract responsible for the delayed and weaker myoelectrical effect of erythromycin in experimental animals.

INTRODUCTION

Gastrointestinal motility is controlled by a complex multifactorial system based on electromechanical and neuro-endocrine function. The myoelectric activity of the gastrointestinal tract consists of two kinds of potentials: slow waves and spike activity organised in myoelectric migrating complex (Thor *et al.* 2007). The slow wave of the gastrointestinal tract mainly functions to trigger the onset of spike to elicit smooth muscle contraction, which provides the essential power of motility. Smooth muscle myogenic control activity or slow wave is believed to originate in the interstitial cells of Cajal. The electrical coupling promotes interaction between muscle cells and the interstitial cells of Cajal additionally contribute to slow wave rhythmicity (Chang 2005; Chen *et al.* 1994).

Surface electrogastrography (EGG) is a non-invasive method for clinical assessment of gastric myoelectrical activity. Our group demonstrated for the first time in our previous studies that EGG is reliable and feasible in experimental pigs too (Varayil *et al.* 2009; Květina *et al.* 2010; Ali *et al.* in press). Porcine EGG is fully comparable with that recorded in healthy humans (Varayil *et al.* 2009; Parkman *et al.* 2003).

Macrolides with lactone ring containing 14 atoms as erythromycin and clarithromycin have prokinetic effect on the gastrointestinal tract by acting as motilin receptor agonists (Hawkyard *et al.* 2007). Erythromycin, currently the most potent prokinetic drug, has been shown to initiate gastric interdigestive migrating motor complexes which are the motor events responsible for gastric emptying (Prather *et al.* 1993; Keshavarzian *et al.* 1993; Curry *et al.* 2001).

In humans, inflammatory bowel disease is associated with altered myoelectric activity and gastric emptying, both in Crohn's disease and ulcerative colitis (Gryboski *et al.* 1992; Bracci *et al.* 2003; Kohno *et al.* 2006). Dextran sodium sulphate (DSS) has been widely used for experimental models of colitis, including porcine ones (Mackenzie *et al.* 2003; Bassaganya-Riera *et al.* 2006).

The aim of this study was to assess the influence of gastrointestinal injury induced by DSS on porcine gastric myoelectric activity stimulated by intragastrically administrated erythromycin. The results allow us to organize further experimental studies concentrated on the gastric motility disorders and its treatment in the inflammatory bowel disease patients.

MATERIAL AND METHODS

Animals

Twelve healthy mature female pigs (*Sus scrofa f. domestica*, hybrids of Czech White and Landrace breeds; 4–5 months old, weighing 30–35 kg) were included into the study. The animals were fed twice a day (standard assorted food A1) and had allowed free access to water.

Experimental design

All EGG recordings were accomplished in the morning after 24-hour fasting. The animals were divided into the two groups. The 6 control animals (Group I) received no pre-treatment. A 30-minute baseline EGG was recorded. Afterwards, 1,600 mg of erythromycin was administrated intragastrically. Subsequent six separate 30-minute EGG-recordings (from time 0 to 360 min) were accomplished in each animal. Another six animals (Group II) were treated with DSS (molecular weight 36–50 kDa; MP Biomedicals, Solon, OH, USA) for 5 days: 0.25 g/kg per day in a dietary bolus every morning. The next day after the last dose of DSS, a 30-minute baseline EGG was recorded. Afterwards, 1,600 mg of erythromycin was administrated intragastrically. Subsequent six separate 30-minute EGG-recordings (from time 0 to 360 min) were accomplished in each animal in the same manner as in Group I.

After accomplishment of EGG recording, the pigs were sacrificed by means of pharmacological euthanasia (T61, Intervet International BV, Boxmeer, the Netherlands; dose of 2 mL/kg). Immediate autopsy was performed to exclude direct toxic injury to the porcine stomach by DSS.

Electrogastrography

Surface cutaneous EGG was recorded using a Digi-trapper (Synectics Medical AB, Stockholm, Sweden). All EGGs were carried out under general anaesthesia. Intramuscular injection of ketamine (20 mg per kg; Narkamon, Spofa, Prague, Czech Republic) was used as an introduction. Repeated doses of thiopental were administrated intravenously when appropriate. Intravenous infusions of 0.9% saline solution were chosen to secure basal hydration (1,000 mL/8 hours).

All animals were lying in a right lateral position during EGG recording. The epigastric area was shaved before application of electrodes to decrease impedance in signal conduction through the skin. Electrode placement always began with placing the first electrode within 5 cm of the xiphoid process in the centre and then subsequently placing the other two at a distance of 15 cm from the central electrode in the left and right hypochondrium respectively.

Running spectral analysis (based on Fourier transform) was used for the evaluation of the EGG. The results were expressed as running spectrum percent activity and dominant frequency of slow waves was set at all intervals of EGG recordings (according to Varayil *et al.* 2009).

Ethics

The Project was approved by the Institutional Review Board of the Animal Care Committee of the Institute of Experimental Biopharmaceutics, Academy of Sciences of the Czech Republic, Protocol Number 149/2006. Animals were held and treated in accordance with the European Convention for the Protection of Vertebrate

Animals Used for Experimental and Other Scientific Purposes (Council of Europe 1986).

Statistical analysis

Data were statistically treated by means of descriptive statistics, non-paired t-test and Mann-Whitney rank sum test using SigmaStat software (Version 3.1, Jandel Corp., Erkrath, Germany).

RESULTS

EGG recording was successfully accomplished in all animals. A total of 84 records were analysed. Baseline dominant frequency of slow waves was fully comparable in both groups (see Table 1). In Group I, there was a significant increase in dominant frequency after erythromycin administration from basal mean values 4.57 ± 1.28 to its maximum between 240–360 min with mean values 6.61 ± 0.56 and 6.63 ± 1.16 cycles per minute, respectively, $p=0.005$ and $p=0.015$ (see Table 1 and Figure 1 for details). There was a flat non-significant and delayed increase in dominant frequency after erythromycin administration in Group II (see Figure 2). The difference between Group I and II at particular time intervals was not significant but a diverse trend was evident (see Table 1 for details).

Autopsy found a normal gastrointestinal tract in all animals in Group I. In Group II, severe colitis was found in all animals especially in the caecum and right hemi-colon (with ulcers, bleeding erosions and muco-

sal erythema). The stomach and small intestine were macroscopically and histologically normal in all animals in Group II.

DISCUSSION

Our current study set two major aims, firstly to evaluate the gastric myoelectric effect of erythromycin, a potent prokinetic drug; and secondly to assess the consequences of toxic DSS on the functioning of the porcine stomach. Both parts were successfully accomplished. Nevertheless, our initial results must be evaluated and interpreted with caution, we are fully aware of the possible limits of this study.

Pigs can be used in various preclinical experiments (Květina *et al.* 2008; Kuneš *et al.* 2010) as a representative of the omnivore due to their relatively very similar gastrointestinal functions in comparison to man (Kararli 1995). However, there are some distinct differences in the anatomy and physiology of the stomach between humans and pigs (Bureš *et al.* 2009; Kopáčová *et al.* 2010; Tachecí *et al.* 2010). The porcine stomach is pouch-shaped, gastric cardia is close to the pylorus, and a special transverse pyloric fold serves as a “gate-keeper”. Gastric emptying of pigs is much slower, there are significant remnants of food in the porcine stomach even after 36–48 hours of fasting found at gastroscopy (Kopáčová *et al.* 2010; Tachecí *et al.* 2010).

Erythromycin induced a significant increase in the dominant frequency of slow waves in our current

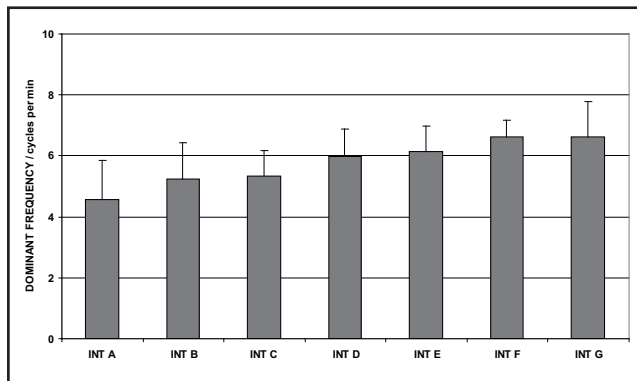


Fig. 1. Electrogastrography in control experimental pigs (Group I).

Mean dominant frequency of slow waves before and after erythromycin administration. See text for details of the study design.

INT A: a 30-minute basal EGG recording before the administration of erythromycin

INT B: EGG recording after erythromycin administration in time 0 to 30 min

INT C: time interval 30–60 min after erythromycin administration

INT D: time interval 60–90 min after erythromycin administration

INT E: time interval 90–120 min after erythromycin administration

INT F: time interval 240–270 min after erythromycin administration

INT G: time interval 330–360 min after erythromycin administration

Statistically significant difference: INT A vs. INT D: $p=0.048$; INT A vs. INT E: $p=0.031$; INT A vs. INT F: $p=0.005$; INT A vs. INT G: $p=0.015$; INT B vs. INT F: $p=0.029$.

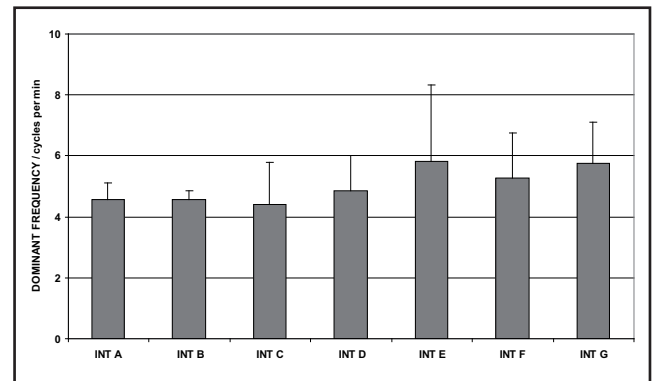


Fig. 2. Electrogastrography in experimental pigs pre-treated with dextran sodium sulphate for five days (Group II).

Mean dominant frequency of slow waves before and after erythromycin administration. See text for details of the study design.

INT A: a 30-minute basal EGG recording before administration of erythromycin

INT B: EGG recording after erythromycin administration in time 0 to 30 min

INT C: time interval 30–60 min after erythromycin administration

INT D: time interval 60–90 min after erythromycin administration

INT E: time interval 90–120 min after erythromycin administration

INT F: time interval 240–270 min after erythromycin administration

INT G: time interval 330–360 min after erythromycin administration

There was no statistically significant difference between particular intervals.

Tab. 1. Electrogastrography in experimental pigs. Dominant frequency of slow waves (cycles per minute). See text for details of the study design.

Interval	Group I.		Group II.		p-value
	Mean ± Std Dev	Median IQR	Mean ± Std Dev	Median IQR	
A	4.57 ±1.28	4.46 3.39–5.16	4.57 ±0.55	4.32 4.21–5.23	NS (<i>p</i> =0.991)
B	5.23 ±1.20	5.40 4.69–5.70	4.56 ±0.30	4.48 4.44–4.54	NS (<i>p</i> =0.215)
C	5.33 ±0.83	5.23 4.63–5.83	4.41 ±1.39	4.19 3.53–4.72	NS (<i>p</i> =0.195)
D	5.99 ±0.88	6.21 5.79–6.62	4.85 ±1.15	4.46 4.04–5.23	NS (<i>p</i> =0.081)
E	6.14 ±0.84	6.33 5.90–6.77	5.83 ±2.50	4.85 4.68–5.63	NS (<i>p</i> =0.240)
F	6.61 ±0.56	6.49 6.21–6.90	5.28 ±1.46	5.30 4.01–6.70	NS (<i>p</i> =0.180)
G	6.63 ±1.16	6.42 5.70–6.84	5.76 ±1.36	6.24 4.53–6.90	NS (<i>p</i> =0.258)

Interval A: a 30-minute basal EGG recording before administration of erythromycin

Interval B: EGG recording after erythromycin administration in time 0 to 30 min.

Interval C: time interval 30–60 min. after erythromycin administration

Interval D: time interval 60–90 min. after erythromycin administration

Interval E: time interval 90–120 min. after erythromycin administration

Interval F: time interval 240–270 min. after erythromycin administration

Interval G: time interval 330–360 min. after erythromycin administration

Std Dev: standard deviation

IQR: inter-quartile range

NS: statistically non-significant difference

study. These findings were consistent in all animals. To the best of our knowledge there are no available published data so far to evaluate the impact of erythromycin on porcine electrogastrography. In humans, erythromycin was studied both in healthy volunteers and patients with gastroparesis (characterised by tachygastria in EGG). DiBaise *et al.* evaluated the effect of low dose erythromycin (50 mg or 100 mg i.v. infusion in adult healthy volunteers). A two-hour EGG recording showed a decrease of three cycles per minute rhythm and corresponding increase of tachygastria after 100 mg infusion (DiBaise *et al.* 2001). Faure *et al.* administered erythromycin (3 mg/kg i.v.) to ill children and found no correlation between increased antral motor index (number of waves × sum of amplitudes) and running total spectrum power ratio, regardless of diagnosis (chronic intestinal pseudo-obstruction, chronic vomiting or abdominal distension) (Faure *et al.* 2000). Chen *et al.* studied the effect of erythromycin (100 mg i.v.) in gastroparesis. A 30-minute EGG recording revealed a significant increase in the dominant power of EGG

together with an improvement in the regularity of gastric slow waves (Chen *et al.* 1998). We used the intragastric delivery of erythromycin in pigs as an equivalent of the oral route in humans. The oral route may be preferred because erythromycin-related, fatal cardiac complications (published formerly) have been associated with parenteral administration only (Farrar *et al.* 1993; Gouyon *et al.* 1994).

The doses of erythromycin used in our study were relatively high (1,600 mg) for several reasons. Oral administration of a low dose might result in inadequate serum concentrations with no prokinetic effect and the peak serum drug concentration after this type of administration is 4–10 times lower than when the drug is administered by the intravenous route in humans (Parsons *et al.* 1980; Houin *et al.* 1980). And last but not least, there is still a lack of data on erythromycin pharmacokinetics in experimental pigs.

All our porcine EGGs were acquired under general anaesthesia just for practical reasons, although both general and epidural anaesthesia may affect the myoelectrical activity of the stomach in humans (Cheng *et al.* 1999; Lombardo *et al.* 2009; Oshima 2009). Delayed gastric emptying and start of intestinal absorption of erythromycin might participated on delayed effect of erythromycin observed during EGG recording (see below).

However, the most important factor is the time of the EGG recording. We accomplished a 6-hour EGG in all animals and revealed an increase in dominant frequency with its maximum between 240–360 min after erythromycin administration. These changes might be missed in case of shorter recording. Most human studies found erythromycin-induced changes of dominant power in particular. Our previous porcine study demonstrated that the running spectrum percent activity is superior to the power analysis in an experimental setting (Ali *et al.*, in press). Andreis *et al.* evaluated EGG in conscious and anaesthetised dogs. Erythromycin induced an increased power ratio, the amplitude increased whereas frequency decreased (Andreis *et al.* 2008).

DSS, a sulphated polysaccharide, reproducibly induces experimental acute and chronic colitis. DSS is thought to induce mucosal injury and inflammation initially through a direct toxic effect on epithelial cells with subsequent activation of macrophages and T lymphocytes resulting in cytokine mediated cytotoxicity (Ni *et al.* 1996; Leung *et al.* 2000). There are several ways to explain the impact of DSS on porcine erythromycin-induced myoelectric changes. Despite the normal gross appearance of the stomach at autopsy, DSS might exert its direct toxic effect on the porcine myoelectric function. In our current study, the baseline dominant frequency of slow waves was fully comparable in both groups, with and without pre-treatment with DSS. However, the DSS group failed to increase myoelectric activity after erythromycin stimulation. The possible explanation is an analogy with inflammatory bowel

disease, human colitis could be associated with altered myoelectric activity of the uninvolved stomach (Gryboski *et al.* 1992; Bracci *et al.* 2003; Kohno *et al.* 2006). This possible explanation has been supported by an experimental study by Aube *et al.* They found altered myoelectrical activity in the non-inflamed ileum of rats with experimental colitis induced by trinitrobenzene sulphonic acid (Aube *et al.* 1999).

In conclusion, EGG recording enables us to register a significant gastric myoelectric effect of prokinetic drugs in experimental pigs. Erythromycin induced a significant increase in the dominant frequency of slow waves in our setting. DSS caused toxic injury to the porcine gastrointestinal tract that was responsible for delayed and weak myoelectric effect of erythromycin in experimental pigs. Additional studies are warranted to further clarify this phenomenon. Our settings allow set up further experimental studies on gastric motility disorders in inflammatory bowel diseases.

ACKNOWLEDGEMENTS

The study was supported by research project MZO 00179906 from the Ministry of Health and by grant GACR 305/08/0535. The authors would like to thank to Dr. Jarmila Klusáková for her kind histopathological analyses.

Conflicts of interests

The authors disclose no conflicts.

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