Effect of erythromycin on gastric myoelectrical activity in normal human subjects

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Chen, Jiande, Paul Yeaton, and Richard W. McCallum. Effect of erythromycin on gastric myoelectrical activity in normal human subjects. *Am. J. Physiol.* 263 (*Gastrointest. Liver Physiol.* 26): G24–G28, 1992.—While a great deal of attention has been paid to the effect of erythromycin (Ery) on gastric contractility, its effect on gastric myoelectrical activity, which controls gastric motility, remains unknown. In this study, Ery (6 mg/kg) was infused intravenously in 14 normal human subjects (placebo controlled). Gastric myoelectrical activity was recorded using the surface electrogastrographic method. The electrogastrogram (EGG) recordings were analyzed using spectral analysis methods. It was found that the presence of the 2–4 cycles/min activity (normal slow wave frequency range) in the EGG was $51 \pm 19\%$ in the first hour of the intravenous Ery infusion, which was significantly smaller ($P < 0.001$, t test) than that ($72 \pm 20\%$) during the corresponding control period (intravenous saline). This difference was, however, not quite significant ($P = 0.067$, t test) in the second hour after the infusions. The average score for nausea during Ery was 4.5 (0 for no nausea, 10 for the most severe nausea). We conclude that *1*) intravenous Ery induces irregularities in the cutaneous EGG in normal human subjects; and *2*) the noninvasive cutaneous EGG is an attractive method both for the investigation of the effects of pharmacological and prokinetic agents such as Ery on gastric myoelectrical activity in humans and for correlating clinical responses to changes in the EGG.

electrogastrogram; electrogastrography; electrical activity; stomach; slow wave; gastric motility

RECENT PUBLICATIONS have shown that erythromycin (Ery) mimics the effect of the gastrointestinal polypeptide motilin on gastrointestinal motility (14, 28). Ery induces phase III activity of the interdigestive migrating motor complex (MMC) in humans (30) and improves gastric emptying in gastroparetic patients (15, 20, 23). The effects of Ery on gastric myoelectrical activity have not been reported.

It is known that gastric myoelectrical activity controls gastric motility, thereby modulating the frequency and propagation velocity of gastric contractions. Two types of gastric myoelectrical activity have been observed: electrical control activity or slow wave and contraction related electrical response activity (ERA). The gastric slow wave is present all the time, originating in the orad part of the corpus and propagating aborally through the longitudinal muscle fiber to the pylorus. Its normal frequency in humans is ~3 cycles/min (cpm; or 0.05 Hz). When phasic contractions occur, the gastric slow wave is followed by ERA. Gastric dysrhythmias are believed to be associated with gastric dysmotility and can be induced pharmacologically by agents such as epinephrine, glucagon, met-enkephalin, prostaglandin, secretin, and insulin (1, 3, 17, 27).

Gastric myoelectrical activity can be measured serosally by sewing electrodes on the serosal surface of the stomach during laparotomy (12, 21, 24), mucosally by intubating electrodes into the stomach (13), or cutaneously by placing electrodes on the abdominal skin (2). The cutaneously recorded gastric electrical activity is referred as an electrogastrogram (EGG) (26).

The EGG is attractive because it is noninvasive. However, it is difficult to interpret because the signal is sometimes impaired by "noise" such as respiratory and motion artifacts. Comparisons of cutaneous and serosal (or mucosal) recordings (12, 13, 21, 24) and computer simulations (5) have shown that *1*) the frequency and changes of gastric myoelectrical activity are reflected in the EGG; *2*) serosal and cutaneous recordings of gastric slow wave frequency are perfectly correlated; *3*) when phasic contractions occur, ERA is reflected in the EGG as increased amplitude; *4*) spike activities are not observable in the EGG even if the high cutoff frequency of the recording equipment is set equal to 30 Hz; and *5*) the propagation direction of the gastric slow wave may be observed in the EGG (10).

The aim of this study was to examine the effect of Ery on the gastric myoelectrical activity in normal human subjects using the electrogastrographical technique.

MATERIALS AND METHODS

Subjects

Fourteen normal volunteers (9 males, 5 females, age: 26.6 ± 4.7 yr) with no history of gastrointestinal diseases participated in the study. All subjects had taken no medications with known effects on gastrointestinal tract the week before and during the study. The protocol was approved by the Human Investigation Committee at the University of Virginia Health Science Center and written consent forms were signed by all subjects.

EGG

To reliably record the myoelectrical activity from the stomach, subjects first underwent ultrasonography in the supine position to mark the vertical axis of the distal stomach on the abdomen. The EGG recording was performed in a quiet room with subjects lying supine. They were asked not to talk or move during the recording. The abdominal surface of the recording sites was cleaned with sandy skin prepping paste (OMNI PREP, Weaver) to achieve better conduction and to reduce skin-electrode motion artifacts. Four electrodes (bio potential skin electrode, In Vivo, Metric, Healdsburg, CA) filled with electrode jelly (Electrode Electrolyte, Beckman) were placed on the abdominal surface. Three active electrodes were placed along the marked vertical axis of the distal stomach at an interval of 3.5 cm, and one common reference electrode was placed 6–10 cm superior near the right breast (see Fig. 1). Three EGG signals were amplified and displayed on recording charts by a dynograph chart recorder (Beckman Instruments) and on-line digitized by a 12-bit analog/digital (A/D) convertor (MetraByte). The digitized data representing real EGG data (in μV) were stored in readable ASCII files in an IBM-AT personal computer. The low and high cutoff frequencies of the recording
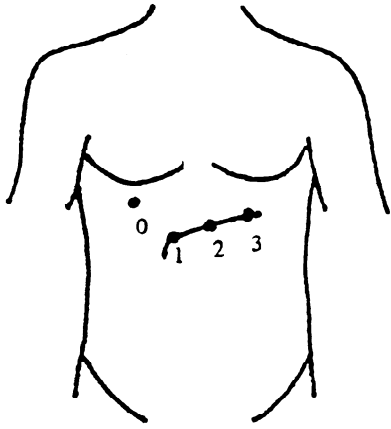
Fig. 1. Position of electrodes. *1-3*: active electrodes; *0*: reference electrode.

equipment were set at 0.02 Hz (1.2 cpm) and 0.3 (18 cpm) Hz, respectively. The paper speed was 0.5 mm/s, and the sampling frequency for the A/D conversion was 2 Hz.

Procedure

The study started at 11 A.M. by giving a standardized meal (lunch). Normal saline was intravenously infused 2 h later at 1 P.M. Another test meal (dinner) with the same nutrients was fed again at 3 P.M. followed by an intravenous Ery infusion (6 mg/kg) at 5 P.M. The subjects were blinded to the contents of the infusions. EGG recordings were made from 1 to 3 P.M. and from 5 to 7 P.M.

Two test meals were prepared to reflect a normal American diet, each having equal caloric, micronutrient, and fiber content: 733 kcal for males, 667 kcal for females, 50% carbohydrates, 30% fat, 20% protein, and 5 g fiber. The lunch meal consisted of a turkey sandwich, crackers, and a cup of skim milk. The dinner meal consisted of chicken noodles, corn, potato chips, and a cup of water.

The degree of nausea during the infusions was scored by all subjects at a range of 0-10 (0 being no nausea and 10 the most severe).

All EGG recordings were processed off-line by a comprehensive software package (6) developed in our laboratory for graphic display and spectral analysis.

Data Analysis Methods

Power spectral analysis. Because of superimposed noise such as respiratory artifacts and electrocardiogram, quantitative analysis of the EGG signal in time domain was very difficult. In this study, we applied a smoothed power spectral analysis method: the periodogram method (19, 22). The periodogram is based on the fast Fourier transform and provides a smoothed power spectrum for a time series with a large amount of data.

Adaptive spectral analysis. For an EGG recording, the periodogram method requires a large number of samples and provides only frequency information. Time of frequency changes is unavailable using the periodogram method. To investigate the effect of Ery on the EGG, specifically to examine whether Ery induces tachygastria or bradygastria of brief duration, the adaptive running spectral analysis method (11) was applied. With this method an EGG signal is modeled by a set of autoregressive moving average parameters. These parameters are initially set to zero and iteratively adjusted for each available EGG sample according to a least mean square algorithm (11). At any point in a time series, a power spectrum is calculated instantaneously from the updated parameters of the model. Similarly, the power spectrum of the signal for any particular time interval is calculated by averaging the model parameters over that time interval.

EGG Data Analysis

Difference of percentage of 2-4 cpm activity in EGG during placebo and Ery. Four 1-h EGG recordings (1st and 2nd hour after administration of intravenous saline, 1st and 2nd hour after administration of intravenous Ery) were obtained in each subject. For each 1-h EGG recording, 20 power spectra were calculated using the adaptive spectral analysis method, each representing 3-min data. The presence or absence of 2-4 cpm (normal slow wave frequency) activities was determined by inspecting spectral peaks at 2-4 cpm in the power spectrum, and the percentage of the presence of 2-4 cpm activities in each 1-h EGG recording was obtained. Student's paired t test was applied to investigate the difference of the percentage of 2-4 cpm activity during saline and Ery infusions.

Difference of EGG power during placebo and Ery. The smoothed power spectral analysis method was applied to the first 1-h EGG recording during saline and Ery infusions. An overall power spectrum was obtained from each 1-h EGG recording, and mean powers at frequency bands of 0.5-2 and 2-4 cpm were calculated. The power difference during saline and Ery infusions at each frequency band was investigated using Student's paired t test.

Distinction between tachygastria and harmonics of primary frequency. Both visual inspection of the original EGG tracing and adaptive spectral analysis were used to distinguish between tachygastria and harmonics of the primary frequency. After the running power spectra of an EGG recording was obtained, a computer program was used to detect spectral peaks in the 4- to 9-cpm range in the running power spectra. When a peak was found in that range, it was examined to see whether it was a tachygastria or a harmonic of the primary frequency. It was judged to be a tachygastria if it was the only peak in the 0.5- to 9-cpm range or if its frequency was not close to the multiples of any peak frequency in the 0.5- to 4-cpm range. It was noted in the study that sometimes the harmonics were not exactly equal to the multiples of the primary frequency due to limited frequency resolution (0.23 cpm/frequency bin). Whenever it was confusing to distinguish between tachygastria and harmonics, the original EGG tracing was visually inspected.

RESULTS

The cutaneous EGG recorded postprandially was less regular with Ery than with saline infusion as shown on Table 1. The power spectra of the EGG in the first hour after Ery infusion showed less 2- to 4-cpm activity than the corresponding control period (51 vs. 72%, $P = 0.001$, Student's t test). This difference was, however, not significant in the second hour after the infusions ($P = 0.067$, t test). The average score for nausea was 4.5 during Ery and 0.0 during saline (see Table 1).

A significant increase of low frequency (0.5-2 cpm) power was observed. The power of 0.5-2 cpm in the first hour after the infusion was 50.3 ± 3.9 (mean $\pm$ SD) dB with saline and increased to 53.0 ± 3.9 dB with Ery ($P = 0.001$). This 3-dB increase in power was equivalent to an increase of 41% in amplitude. Although the EGG showed less regular 2-4 cpm activity with Ery, an increase in power of 2-4 cpm was observed (48.4 ± 2.9 dB with saline, 50.1 ± 3.2 dB with Ery, $P < 0.05$). No evident tachygastrial activities were observed with Ery by the adaptive spectral analysis and the visual inspection of the original EGG tracing, although a similar power increase in the 4- to 9-cpm range was noted.

A typical example of the effect of Ery on the cutaneous EGG is shown in Figs. 2-4. Figure 2 presents 10-min

Table 1. *Percent of 2-4 cpm in the first hour EGG recordings after saline and Ery infusions*

	% of 2-4 cpm (1st h)		Nausea	
Subject	Saline	Ery	Saline	Ery
1	95	45	0	10†
2*	50	25	0	3
3*	80	40	0	5
4	55	75	0	0
5	70	50	0	3
6	65	35	0	4
7	90	45	0	2
8	35	25	0	4
9*	100	75	0	3
10	75	50	0	2
11*	100	70	0	10†
12	50	35	0	5
13*	50	35	0	10
14	60	60	0	2
Mean ± SE	72±5.4	51±5.0	0±0	4.5±0.9

In the 1st hour, % of 2-4 cpm was significantly smaller after erythromycin (Ery) than after saline ($P = 0.001$, t test). In the 2nd hour, % of 2-4 cpm was not significantly different after Ery and saline ($P = 0.067$, t test). * Females; † vomiting during Ery infusion

EGG tracings during saline (A) and during Ery (B). It can be seen that 1) the EGG has more regular 2- to 4-cpm activity during saline than during Ery, and 2) although the EGG is less regular during Ery, its amplitude is higher than that during saline. Figure 3 shows the running power spectra of the EGG after the infusions of saline (A) and Ery (B). It is evident that the running power spectra of the EGG has more peaks at 2-4 cpm (higher percentage of 2- to 4-cpm activity) with saline than with Ery. It is also seen that Ery induces more low frequency activities (more peaks in the 0.5- to 2-cpm range). The running power spectra of the EGG has more peaks (13 peaks) at low frequency (0.5-2 cpm) with Ery than with saline (5 peaks). Higher frequencies (>4 cpm) seen in Fig. 3 are generally harmonics of 0.5- to 4-cpm activities. Because of the limited frequency resolution, the harmonics were sometimes not exactly the multiples of the primary frequency. Power spectra of the entire 1-h EGG recordings with saline and with Ery are presented in Fig. 4. Two clear observations are made in Fig. 4. 1) The EGG becomes less regular with Ery: a peak at 2-4 cpm with saline disappears with Ery. 2) Although the power spectrum with Ery has no peak at 2-4 cpm, its power at whole frequency band including 2-4 cpm is higher than with saline.

DISCUSSION

Recently, the effect of Ery on gastric motility and gastric emptying has been investigated. Ery mimics the effect of the gastrointestinal polypeptide motilin on gastrointestinal motility. Itoh et al. found that intravenous Ery (1-3 mg·kg^{-1}·h^{-1}) induced rhythmic phase III contractile activity of the MMC in dog (14) and humans (28). Very recently, Janssens et al. (15) found that a dose of 200 mg of Ery administered intravenously during the immediate postprandial period markedly improved the severely impaired gastric emptying of both liquid and solid meals in patients with diabetic gastroparesis. In a study of acute and chronic treatment of gastroparesis with Ery, Rich-
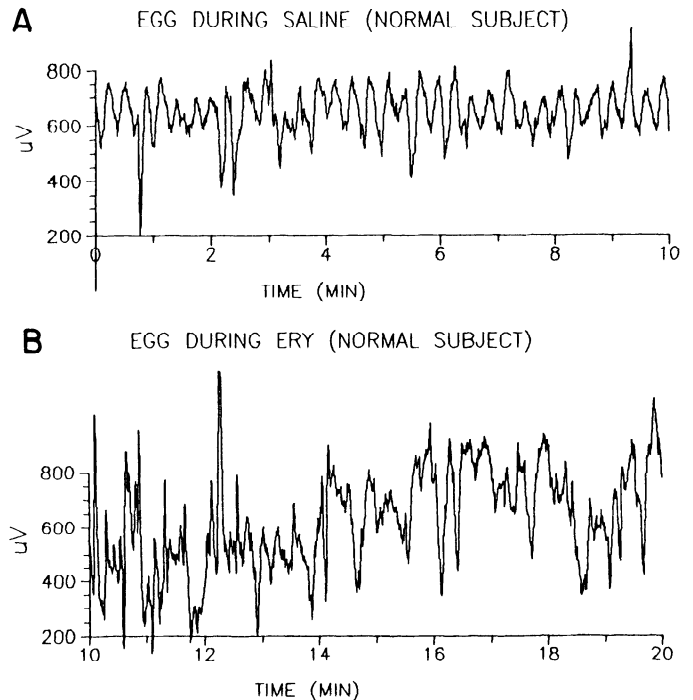

Fig. 2. Effect of erythromycin (Ery) on the electrogastrogram (EGG) in a normal subject (N1). A: 10-min EGG during placebo showing regular 2- to 4-cpm activity; B: 10-min EGG during intravenous Ery showing less regular 2- to 4-cpm activity. The patient felt severely nauseated and vomited with Ery.

ards et al. (23) in our laboratory found that acute intravenous dosing of Ery accelerated gastric emptying in most patients with gastroparesis. While a great deal of attention has been paid to the effect of Ery on gastric motility, its effect on the gastric myoelectrical activity remains unknown.

Our study findings include the following. 1) In normal human subjects, the cutaneous EGG became significantly less regular (less 2- to 4-cpm activity). The subjects felt nauseated with intravenous Ery; but the total power of the EGG at 2-4 cpm increased with intravenous Ery. 2) A significant increase of low frequency (0.5-2 cpm) activities were observed. 3) No evident tachygastrias were appreciated with intravenous Ery, although there was a power increase in the 4- to 9-cpm range. 4) The effect of intravenous Ery on the EGG was more pronounced during the first hour than during the second hour.

The increased EGG power with intravenous Ery may result from the augmented contractility of the stomach. In other words, it may be attributed to the contraction-related electrical response activity. The amplitude increase of myoelectrical activity in the postprandial EGG has frequently been observed, and several explanations have been given (4, 7, 8, 24, 25). In well-designed experiments, Smout et al. (24) examined closely the relationship between amplitude variations in the EGG and the mechanical activity of the stomach. They reported that the amplitude increase of the postprandial EGG is related to the increased contractile activity after eating. A study performed in our laboratory (7) showed that the amplitude increase of the postprandial EGG is due to gastric contractions as well as to gastric distension. Based on a sham feeding study, Stern et al. (25) indicated that the
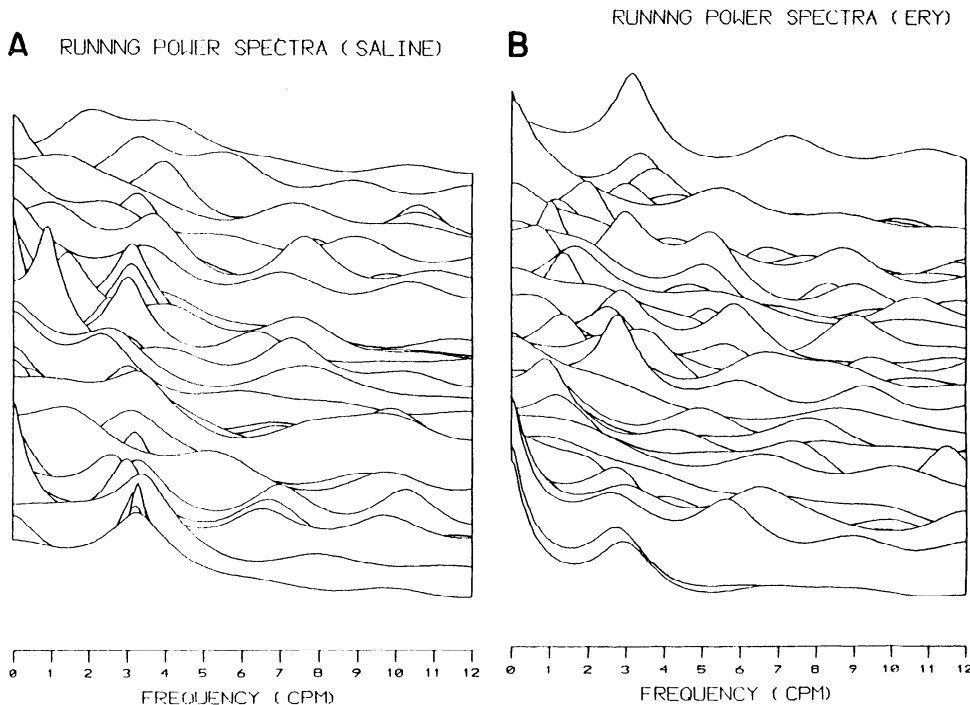
RUNNNG POWER SPECTRA (ERY)

A   RUNNNG POWER SPECTRA (SALINE)   **B**

Fig. 3. Running power spectra of EGG recordings with placebo (*A*) and Ery (*B*) in a normal subject (*N1*). Each curve (from bottom to top) represents a power spectrum of 3-min EGG data. Peaks at 2-4 cpm indicate presence of normal gastric slow wave. Fewer peaks are found at 2-4 cpm with Ery than with placebo.
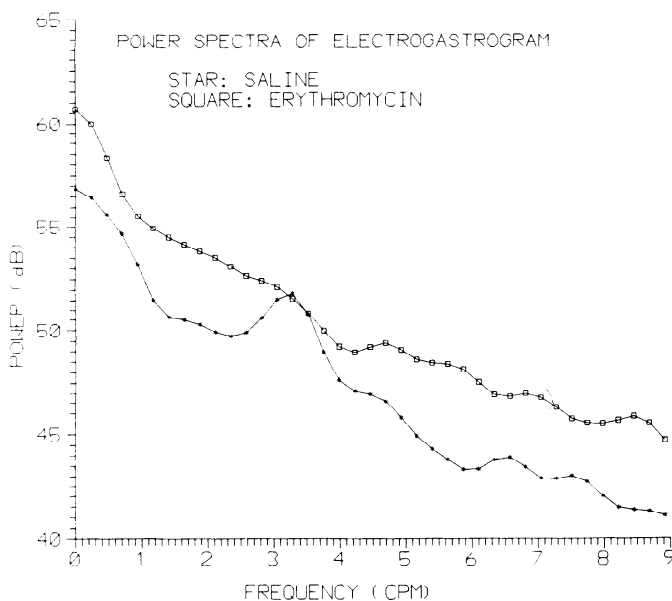
FREQUENCY (CPM)   FREQUENCY (CPM)

POWER SPECTRA OF ELECTROGASTROGRAM

STAR: SALINE
SQUARE: ERYTHROMYCIN

Fig. 4. Overall power spectra of 1st 1-h EGG recordings with placebo (star-curve) and Ery (square-curve) in a normal subject (*N1*). Peak at 2-4 cpm with placebo is absent with Ery. The power is, however, higher with Ery than with placebo.

cephalic-vagal stimulation could result in an amplitude increase during eating. We believe that the amplitude increase of the EGG with intravenous Ery infusion observed in this study was attributed to the increased contractile activity of the stomach. The relationship between the low frequency component (0.5-2 cpm) in the EGG and gastric motility has not yet been well understood. Two types of low frequency components have been reported in the literature: bradygastria and superimposed low frequency component. Bradygastria reflects an alteration of the gastric slow wave from normal frequency (3 cpm) to a lower frequency (≤2 cpm), whereas the superimposed lower frequency component is just an additional

activity with a lower frequency (0.5-2 cpm) superimposed on the normal slow wave (2-4 cpm) and is usually observed in the cutaneous recording.

Bradygastria, i.e., the alternation of the normal frequency (2-4 cpm) to a lower frequency (0.5-2 cpm), has frequently been reported in the literature and is probably associated with gastric dysmotility or motor quiescence (3, 16). The superimposed low frequency component has been observed in postprandial cutaneous EGG recordings in our laboratory. In one study, we recorded cutaneous EGGs in 10 normal subjects and 18 patients with gastroparesis with simultaneous recordings of manometric activities in the antral stomach, duodenum, and small intestine. Low frequency components were frequently observed in the postprandial EGG and found to be superimposed on the normal slow wave activity. Spectral analyses showed that these low frequency components were associated with strong antral contractions and/or duodenal contractions (9).

In this study, both types of low frequency components were observed. In some EGG recordings (or periods) bradygastrias were noted, whereas in some other recordings (or periods) the low frequency component was superimposed on the normal gastric slow wave (2-4 cpm).

The deterioration of the EGG (less 2-4 cpm activities) by intravenous Ery in normals was observed to be associated with nausea and vomiting. The absence of 2- to 4-cpm activities in the EGG with Ery may be due to impairment of the internal gastric slow wave and disturbance of strong irregular contractions at low frequency (0.5-2 cpm). As we mentioned in the previous paragraphs there is an increase in the EGG amplitude when there are strong contractions in the stomach due to contraction-related ERA. The ERA associated with strong low frequency contractions induced by Ery result in 0.5- to 2-cpm activities in the EGG, which may be so strong that the normal 2- to 4-cpm activities in the EGG are obscured.

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