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Erythromycin Induces Migrating Motor Complex in Human Gastrointestinal Tract

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Fifteen healthy subjects, fasted at least 8 hr, were studied by means of an infused manometric method. Twenty minutes after termination of the natural phase III activity in the duodenum, erythromycin or normal saline was administered intravenously for 15 min. When normal saline (N = 5) was infused, the next migrating motor complex (MMC) was initiated 151.2 ± 42.1 min after the infusion. On the other hand, when erythromycin was infused at a rate of 1.0 mg/kg/hr (N = 5) or 3.0 mg/kg/hr (N = 5), MMC-like contractions were initiated at shorter intervals, ie, 47.8 ± 40.9 min (P < 0.005) or 23.0 ± 13.0 min (P < 0.001), respectively. The duration, frequency, amplitude, and migrating velocity of the naturally occurring MMC (N-MMC) were not significantly different from those of the erythromycin-induced contractions except for the duration of the phase III contractions in the stomach; the duration (5.3 ± 2.2 min) of the erythromycin-induced contractions being significantly (P < 0.05) longer than that (3.2 ± 0.9 min) of the naturally occurring MMC. The immunoreactive motilin (IRM) concentration did not increase significantly after the infusion of erythromycin, when compared to that after infusion of normal saline. It is concluded that erythromycin at a dose of 1–3 mg/kg/hr for 15 min during the interdigestive state, similar to motilin, has a significant influence upon the initiation of MMC in the human gastrointestinal tract, but further investigations are required to confirm whether endogenous motilin is involved or not.

Cyclic recurring caudally migrating bands of strong contractions in the small bowel, or migrating motor complex (MMC) were first reported by Szurszewski (1) in the fasted dog and by Vantrappen et al (2) in the fasted human. The initiation of the MMC in the stomach is now postulated to be regulated at least in part by plasma motilin levels in dogs (3, 4) and humans (5–7). Recently, while studying side effects of antibiotics on the alimentary tract, we found that intravenous administration of erythromycin (EM)-induced MMC in the stomach is associated with an increase in the plasma immunoreactive motilin (IRM) concentration in fasted conscious dogs (8). In this study, we attempted to confirm whether or not EM has the same effect on human gastrointestinal motor activity as that observed in the dog.

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MATERIALS AND METHODS

Subjects. Fifteen healthy volunteers, 19–23 years old, participated in the present study. None was taking any medication or had a history of gastrointestinal symptoms or surgery. The study was approved by the Gunma University Committee (Pediatric Department) for Human Investigation on July 1, 1983, and written informed consent was obtained in each case.

Recording of Gastrointestinal Motility. The catheter is 3 mm in diameter and has four lumens, 0.8 mm in diameter, which connect to lateral orifices positioned 15 cm apart. The catheter was perfused continuously with an Arndorfer low-compliance pneumohydraulic capillary infusion pump (Arndorfer Medical Specialities, Wisconsin) at a flow rate of 0.4 ml/min. The intraluminal pressures were measured by means of pressure transducers (P23ID,

Statham Instruments) (9) and simultaneously recorded on two polygraphs (RM-6000, Nihon Kohden Kogyo, Tokyo, Japan) at high (10–25 mm/min) and low (1–5 mm/min) speed.

Procedure. All subjects were fasted for at least 8 hr before the studies. They were in the supine position throughout the recording session and were permitted to read, watch television, or sleep, as they wished. The catheter was inserted into the stomach from the nose, and, under fluoroscopic observation, the lateral orifices were positioned either in the gastric antrum, the second portion of the duodenum, the third portion of the duodenum, and the jejunum; or the gastric body, antrum, second portion of the duodenum, and the third portion of the duodenum.

Administration of EM. Erythromycin lactobionate (Erythrocin IV, 300 mg/vial, Abbott Labs, North Chicago, Illinois) was used. After at least one natural MMC (N-MMC) was confirmed to have occurred in the duodenum and an interval of 20 min from the termination of the N-MMC, EM at an infusion rate of 1.0 mg/kg/hr ($N = 5$) or 3.0 mg/kg/hr ($N = 5$) or normal saline ($N = 5$) was infused intravenously for 15 min. The choice of EM or saline was made at random.

Measurement of Plasma Immunoreactive Motilin (IRM). Collection of the blood samples began just before the infusion of test solution and continued for 30 min at 7.5-min intervals. The plasma IRM concentration was measured with a specific radioimmunoassay (RIA) for motilin developed in our laboratory as reported previously (4). Antisera for porcine motilin and synthetic porcine motilin for standard and iodination were kindly provided by Prof. N. Yanaihara, Shizuoka College of Pharmaceutical Sciences, Shizuoka, Japan. Inter- and intraassay variations in this RIA were less than 4.5 and 3.8%, respectively. The minimum detected dose was 10 pg/tube.

Data Analysis. Gastric and duodenal motor activities were classified into three phases according to Code and Marlett (10). For analysis of gastric movements, phase III was defined as the occurrence of regular contractions at a frequency of about 3/min lasting for at least 2 min. Phase III of duodenal movements was defined as regular contractions at a frequency of 10–14/min lasting for at least 2 min. Phase III activities in the stomach or the duodenum which migrated caudally were defined as MMC.

All values in the text are given as the mean ± SEM obtained from all the observations in each of the studies. Statistical analysis was performed using the Student's t test, and P values less than 0.05 were considered significantly different between paired data.

RESULTS

Initiation of MMC by EM Administration. When normal saline was infused, the next MMCs were initiated at intervals of 151.2 ± 42.1 min from the start of the infusions. Out of five examinations, the MMCs started in the stomach in one and in the duodenum in four cases. In comparison, when EM was infused at an infusion rate of 1.0 mg/kg/hr for 15 min, MMC-like contractions were initiated at intervals of 47.8 ± 40.9 min ($P < 0.005$), in the stomach in four cases and in the duodenum in one. Furthermore, when the dose of EM was increased to 3.0 mg/kg/hr, the next MMCs were initiated at intervals of 23.0 ± 13.0 min ($P < 0.001$), and all of them started in the stomach.

One MMC which was initiated 106 min after an infusion of normal saline is shown in Figure 1. Typical phase III activities occurred in the stomach and migrated caudally. EM-induced MMC is shown in Figure 2.

Comparisons were made between MMCs occurring naturally and after the infusion of EM or normal saline. The duration, frequency of contractions, and velocity of migration of phase III activity in the stomach and the duodenum are summarized in Table 1. There is no significant difference between these motor factors except for the duration of phase III activity in the stomach, the duration of the EM-induced contractions being significantly ($P < 0.05$) longer than that of the N-MMC.

Plasma IRM Concentration. Only a 6% increase in the IRM concentration above preinjection level was noticed within 30 min after EM infusion. This increase was not significant compared to the preinjection level; neither was it significant when compared to the increase (5%) after infusion of normal saline.

Side Effects during EM Infusion. There were no noticeable side effects such as nausea, vomiting, restlessness, abdominal pain, or changes in respiratory or pulse rate.

DISCUSSION

The results of this study clearly show that intravenous administration of EM at rates of 1.0 and 3.0 mg/kg/hr for 15 min significantly shortens the intervals at which the following MMCs occur. However, there are several important questions that should be discussed.

First, it is necessary to confirm that the contractions occurring after EM infusion are identical to those of the N-MMC. MMC has been well characterized by previous reports in the dog (1, 10, 12, 13) and human (5–7, 11, 14–20). The frequency of phase III contractions is constant in the gastric antrum (10–13) and the duodenum (1, 10, 13, 15, 16). The migrating velocity of phase III contractions from the stomach to the duodenum is also constant (1, 12, 17, 18), as is the duration of phase III contractions in the human duodenum (5–7, 15–17). How-

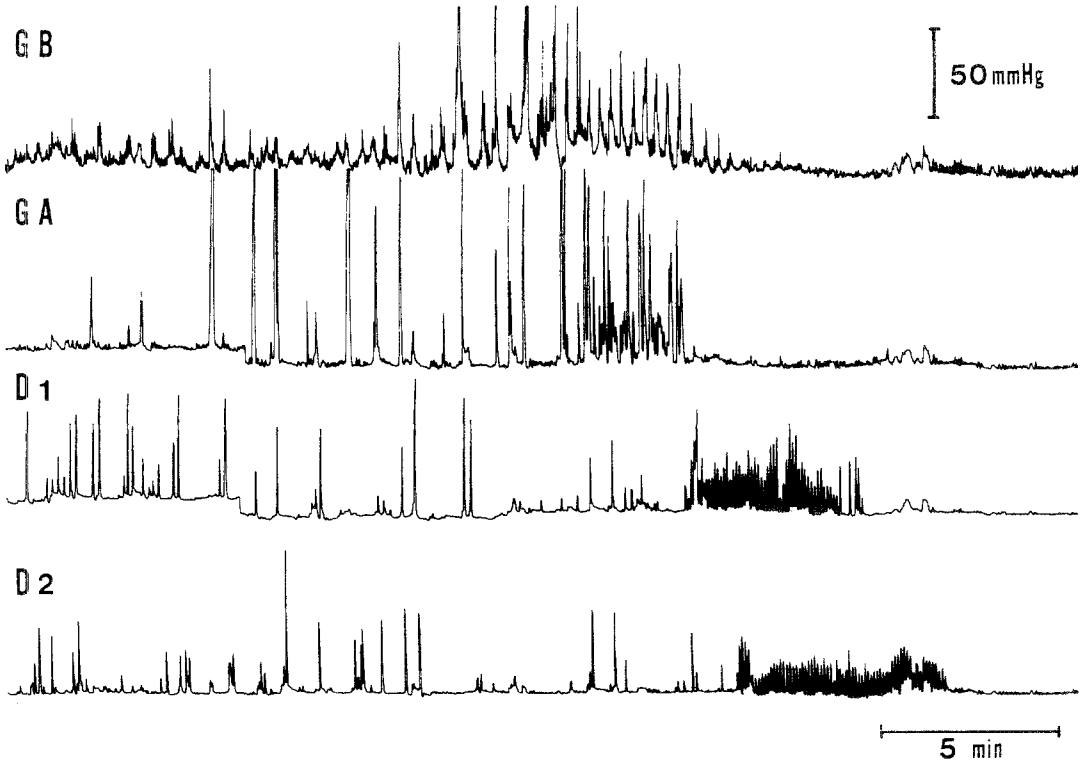

Fig 1. A typical contractile pattern of naturally occurring migrating motor complex (N-MMC) in the stomach and duodenum of a healthy 20-year-old male. In this and next figure: GB = gastric body; GA = gastric antrum; D1 and D2 = upper and lower duodenum, respectively.

ever, the duration of phase III contractions in the stomach varies to a significant extent for an unknown reason (15–18). This is also true of the canine stomach (12, 19). In humans, it has been reported that many cycles of MMC originate in the duodenum, not in the stomach (11, 15–18), when compared with studies in dogs. Analysis of our data on the motor factors in the stomach and in the duodenum clearly indicate that there is no significant difference between the N-MMC and EM-induced contractions except for the duration of phase III contractions in the stomach. Even in the N-MMC, since the duration varies considerably, as mentioned above, we concluded that EM-induced contractions are quite similar to the N-MMC originating in the stomach.

Second, are the EM-induced contractions mediated through endogenous release of motilin? In human studies, Vantrappen et al (5), Peeters et al (6), and Rees et al (7) have reported that peaks of the plasma IRM concentration coincide with the occurrence of phase III activity in MMC in the duodenum. We have also observed a similar close correlation between the plasma IRM concentration and the occurrence of phase III activity in the human (20) and canine (4) stomachs. So, at present, if MMC-like contractions are induced in the stomach by a substance other than motilin, it is necessary to confirm whether or not the occurrence of the contractions is accompanied by a rise in the plasma IRM concentration. In the dog, as mentioned above, MMC was induced by EM in association with an increase in the IRM concentration. In the present study, a 15-min intravenous infusion of EM induced phase III activities in the stomach. However, it did not increase the plasma IRM concentration when compared to the control. Therefore, it was speculated that in the human, EM induces MMC by a mechanism that is, to some extent, different from that in the dog. For example, it may be possible that EM directly has the same effect as motilin in the regulation of MMC in the human gastrointestinal tract. However, further investigations will be required to reach that conclusion.

Another significant aspect that should be emphasized in the study of the MMC is whether the MMCs are induced in the stomach or not. In this respect, there is still confusion in recent studies; the

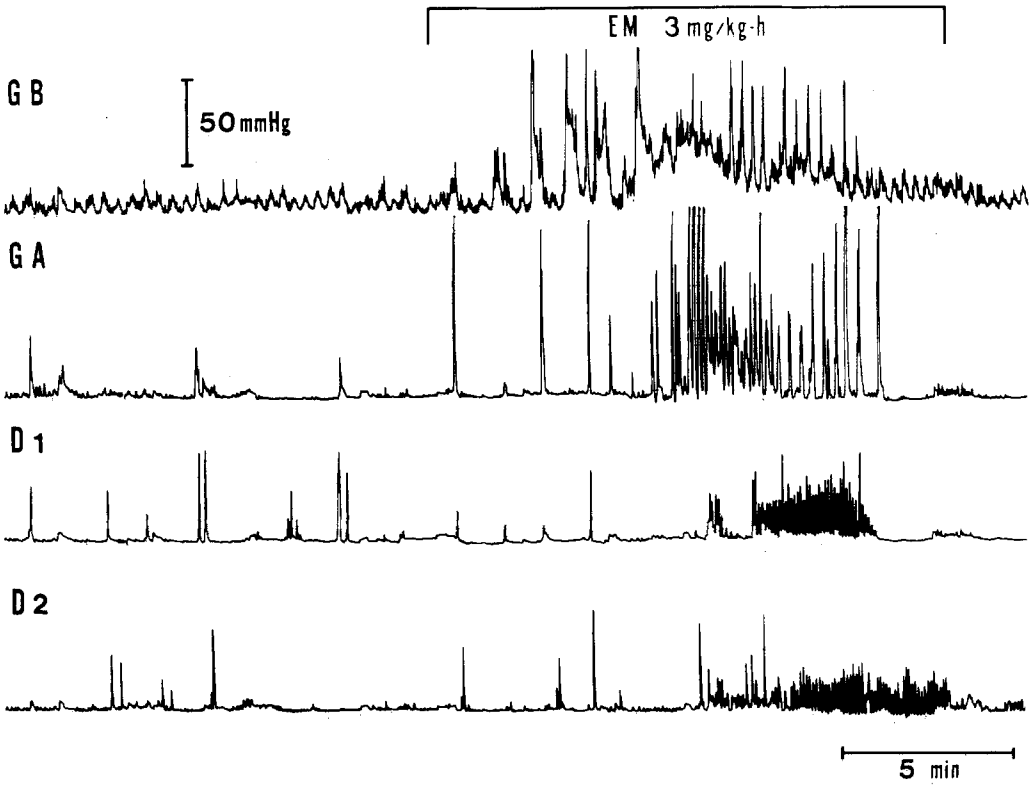

Fig 2. Erythromycin (EM)-induced contractions in the stomach and duodenum of a healthy 20-year-old male.

control mechanisms of the MMCs originating in the stomach and the upper jejunum are quite different from each other as pointed out previously (22, 23). There is no evidence to indicate that the MMCs initiated in the upper jejunum or in the more caudad small bowel are regulated by the plasma IRM concentration. A close correlation between the occurrence of the MMC and the plasma IRM peak is observed only in the MMC occurring in the stomach (6, 7, 22, 23). On the other hand, Lewis et al (24) speculated that the MMCs initiated in the duodenum are induced by a bolus of hydrochloric acid solution which is discharged from the stomach into the duodenum. Studies have suggested that morphine (24), somatostatin (25), or pancreatic polypeptide (26) are involved in the control of the initiation of MMCs in the small intestine. These factors are probably not involved in initiating EM-induced contractions which have clearly been shown to initiate in the stomach.

In the present study, we have demonstrated that a 15-min intravenous administration of EM at doses

TABLE 1. COMPARISON OF CONTRACTION FACTORS BETWEEN N-MMC AND MMC AFTER INFUSION OF NORMAL SALINE OR ERYTHROMYCIN (EM) IN HUMAN STOMACH AND DUODENUM*

Contraction factor of MMC	*Natural*	*EM*	*Normal saline*
Gastric antrum	(N = 6)	(N = 9)	(N = 1)
Duration, min	3.2 ± 0.9	5.3 ± 2.2†	4.0
Frequency, contractions/min	3.1 ± 0.4	2.9 ± 1.4	3.0
Migrating velocity to the duodenum, cm/min	7.7 ± 4.2	8.2 ± 11.7	4.3
Duodenum	(N = 15)	(N = 10)	(N = 5)
Duration, min	3.8 ± 1.8	5.5 ± 2.3	3.8 ± 2.0
Frequency, contractions/min	11.1 ± 0.3	10.9 ± 0.4	11.0 ± 0.1
Migrating velocity, cm/min	16.9 ± 19.6	6.6 ± 3.9	24.1 ± 34.0
Amplitude, mm Hg	33.3 ± 1.6	33.6 ± 2.8	33.5 ± 3.2

*All values are expressed as the mean ± SEM.
†Significantly different from natural MMC ($P < 0.05$).

of 1–3 mg/kg/hr induces MMC-like contractions in the human stomach, and that EM-induced MMCs are quite similar to the N-MMC. Further investigations will be necessary to confirm whether plasma IRM is involved or not. We believe that the use of EM is certainly helpful in studies of MMC in the human.

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