Erythromycin effects on gastric emptying, antral motility and plasma motilin and pancreatic polypeptide concentrations in anorexia nervosa

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Abstract

In primary anorexia nervosa, gastric motility is often impaired and ensuing symptoms further discourage eating. Prokinetic agents have been shown to accelerate gastric emptying in affected patients. This study investigated whether emptying of a radiolabelled semisolid 1168 kJ meal and antral contractility were enhanced by intravenous erythromycin. Eight women and two men with anorexia nervosa (21-46 years, 50-75% of ideal body weight) received 200 mg erythromycin or placebo under crossover double blind conditions. Gastric emptying and antral contractility were recorded scintigraphically for 90 minutes. In addition, plasma motilin and pancreatic polypeptide concentrations were determined. With placebo, antral contractions were of regular 3 cycles/minute frequency. With erythromycin, less frequent and partly arrhythmic long duration contractions set in and emptying was accelerated: after 90 minutes, the activity remaining in the stomach was markedly less than with placebo in all patients (Sign test, $p < 0.002$). Basal motilin and pancreatic polypeptide concentrations were normal and showed a normal response to the meal in all patients. Motilin concentrations decreased slightly more and pancreatic polypeptide concentrations increased markedly more with erythromycin than with placebo, possibly because the meal reached the intestine earlier. In conclusion, erythromycin accelerated emptying markedly and in most patients induced an antral motor activity characterised by long duration contractions occurring at often irregular intervals.

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antrum and the proximal duodenum,⁸ erythromycin and its derivatives may constitute a new group of agents, which could be of therapeutic value in patients with disordered gastroduodenal motor function. This is suggested also by preliminary results of studies in, albeit small, numbers of patients with such disorders. In abstract form, it has been reported that erythromycin enhanced gastric evacuation in 'many' of eight patients with delayed emptying after vagotomy and antrectomy⁹ and in four of five individuals with idiopathic or diabetic gastroparesis.¹⁰ The results of a study published in full showed that, in patients with diabetic gastroparesis, erythromycin accelerated gastric emptying not only when administered as a single intravenous dose, but also when given orally over a four week period.¹¹

The aim of the present study was to evaluate the effects of erythromycin on the impaired gastric motor function shown to prevail in patients with primary anorexia nervosa.¹²⁻¹⁷ In such patients, in whom the resumption of normal eating behaviour often is discouraged by the symptoms of gastric stasis, an acceleration of gastric emptying by erythromycin not only would provide further information on the potential prokinetic properties of the compound, but also be of major clinical importance. In addition, the study was aimed at evaluating the effects of erythromycin on the plasma concentrations of motilin and pancreatic polypeptide.

Methods

PATIENTS

Eight female and two male patients meeting the diagnostic criteria for primary anorexia nervosa as defined by DSM III-R¹⁸ and having been admitted for treatment at the Division of Psychosomatic Medicine of the Department of Psychiatry, University of Vienna, participated in the study. Their age ranged from 21 to 46 years (median, 24), their percentage of ideal body weight from 50.1 to 74.9% (median, 59.7%). None of them suffered from other diseases or took any drugs at the time of the investigation. The patients were given a short explanation of the purpose of the research and a description of the procedures to be followed. They further received a description of any reasonably foreseeable risks or discomforts. Written consent was obtained from each patient. The study was conducted in accordance with the provisions of the Declaration of Helsinki and its Tokyo Amendments. Before its initiation, the investiga-

tion had been approved by the Institutional Committee on Studies Involving Human Beings.

PROCEDURE

Each patient participated in two study sessions four days apart, in which the effects of 200 mg erythromycin (erythromycin lactobionate, Abbott, North Chicago, IL) administered by intravenous infusion on gastric emptying were compared with those of placebo under crossover double blind conditions. The patients were instructed to have their usual meal on the evenings preceding the study days but to refrain from eating after 2200 hours and not to eat or drink before coming to the laboratory at 0800 hours on the study days.

On their arrival at the laboratory, an indwelling catheter was inserted into a forearm vein and blood was drawn for the determination of basal plasma motilin and pancreatic polypeptide concentrations. Immediately thereafter, patients ingested a semisolid standard meal (for description see below), upon the completion of which another blood sample was taken. The patients now were seated between the two heads of a dual headed gamma camera and the intravenous infusion of 200 mg erythromycin dissolved in 50 ml 0.15 M saline or of 50 ml 0.15 M saline only (placebo) was started and continued over a 20 minute period using a motor pump (Unita I, Braun, Melsungen, Germany). At the same time as the infusion, the scintigraphic recording of gastric emptying commenced, which was carried out for 90 minutes. Further blood samples were taken at 20, 30, 45, 60, and 90 minutes after the start of infusion.

MEASUREMENT OF GASTRIC EMPTYING AND ANTRAL CONTRACTILE ACTIVITY

Gastric emptying was recorded by means of an isotope technique.^{16,19} A semisolid test meal was labelled with a dose of 37 MBq ^{99m}Tc-sulphur colloid diluted in 0.15 M saline. The adherence of the radiolabel to the test meal has been found to be reliable in previous *in vitro* experiments.¹⁶ The ingredients of the meal, which had a caloric content of 1168 kilo Joule and an osmolality of 558 mmol/kg, were 250 ml milk (8.75 g protein, 8.75 g fat, 12.5 g carbohydrates), 15 g sugar, 14 g maize starch (Maizena®, Knorr, Wels, Austria; 11.9 g carbohydrates) and, for flavouring, cinnamon. The meal was cooked slowly under continuous stirring until a semisolid consistency was reached. After cooling it to a temperature at which it could be ingested, it was mixed thoroughly with the radioisotope. The patients ate the test meal with a spoon.

Throughout the recording period, the patients sat in an armchair tilted at an angle of 60° backwards to avoid possible overprojection of the stomach and the small intestine. A dual headed gamma scintillation camera (Rota-Camera, Siemens AG, Erlangen, Germany) fitted with 140 keV parallel-hole collimators and interfaced to a computer system (System GAMMA-11, Digital Equipment Corporation, Marlboro, MA, USA) was used, with one camera head in an anterior and the other in a posterior position. The

patient was positioned in such a way that the stomach appeared in the centres of the fields of view of the camera heads. Geometric means of anterior and posterior camera counts were calculated to correct for changing gamma ray attenuation by the subjects' tissues resulting from the movement of the labelled meal from the fundus to the antrum and from or towards the detectors.²⁰ Data were also corrected for radionuclide decay.

Serial images of one minute frame time were acquired throughout the observation period except for minutes nine and 10, 49, and 50 as well as 89 and 90 after the start of recording, during which frame time was decreased to three seconds (s). The one minute frames were used to generate gastric emptying curves from a region of interest drawn visually around the stomach on the computer display. From these curves, background activity as counted in a region of interest drawn to the right of the gastric fundus and cranially of the antrum was subtracted, so that a falling count rate represented gastric emptying. The mean counts at each time were related to the counts at the start of recording, which were taken as 100%. In addition, the half emptying time $t_{1/2}$ was calculated from the regression line of the count rate plotted on a logarithmic scale against time on a linear scale.

On the basis of the three second frames, antral motility was evaluated employing a factor analytic method.^{21,22} Using principal component analysis and varimax rotation, this method at first identifies orthogonal factors. A subsequent oblique transformation of the factors²³ makes use of the fact that, within the area imaged by the gamma camera, regions can always be identified, in which no temporal changes of radioactivity occur. These regions are utilised as a baseline setting and permit the computation of the transformation matrix, which then is applied to the varimax factors. The results of the transformation are expressed as factor images and factor curves, the latter essentially reflecting the factor loadings. Factor images and factor curves represent the activity changes recorded over the antrum and thereby the underlying contractile activity. Each of the factor images delineates an area of uniform activity change, wherein the relative intensity in each pixel represents the contribution of that element to the total activity change. The associated factor curves depict the global variation of intensities over time. Appropriately scaled, the factor curves correspond closely to activity time curves generated for regions of interest drawn over the prominent areas of the factor images.²⁴

All computational work was done on a graphical work station (SparcStation IPC, Sun Microsystems, Mountain View, CA, USA). The software package Analyze²⁵ was used for the display of the scintigraphic images, and a version of a program package for factor analysis implemented in the programming language C++ (Todd-Pokropek A and Samal M, unpublished work) for the factor analysis. As an input, the latter program requires, apart from the image sequence to be analysed, the region in which the moving structures are to be identified – that is, a region corresponding to the anatomical bounds of the

antrum, and a background region as described above. The analysis was set to account for three factors, since previous studies have shown that three factors explain more than 95% of the total variance of a given study of antral motility. As a measure of the amplitude of antral contractions, the mean modulation depth of each factor curve was derived from the standard deviation of the mean excursion of the individual points on the curve.^{16,19} Then the autocorrelation function of the curve was computed and used to determine the frequency of antral contractions.

The total body radiation burden (0.1 mSv) resulting from one administered dose of the radionuclide as well as the dose absorbed by the stomach (1.2 mSv) were less than the radiation burden arising from a single abdominal radiograph and therefore could be regarded as acceptable for the two consecutive studies carried out in the present investigation.^{26,27}

DETERMINATION OF PLASMA MOTILIN AND PANCREATIC POLYPEPTIDE CONCENTRATIONS

At the time points specified above, blood samples of 8 ml each were drawn from a vein on the patients' forearm for the determination of plasma concentrations of motilin and pancreatic polypeptide. Blood was collected in tubes containing an appropriate amount of ethylenediamine tetra acetic acid. Fifty microlitres of aprotinin (Trasyol®, Bayer, Leverkusen, Germany; 100 000 KIU in 10 ml) per ml of blood were added and plasma separated by centrifugation. The plasma then was frozen and stored at -20°C until assayed.

Plasma concentrations of the two peptides were measured by radioimmunoassay as described previously.^{28,29} The antiserum against motilin (antiserum 106) was raised in rabbits. It is specific for motilin's N-terminus and does not cross react with other known regulatory peptides. For labelling and as a standard, porcine 13-norleucin-motilin was obtained from Novabiochem (Läufelfingen, Switzerland). The pancreatic polypeptide antibody, porcine pancreatic polypeptide for labelling and human pancreatic polypeptide as a standard were a gift from Dr E G Chance (Eli Lilly Company, Indianapolis, IN, USA). The smallest concentrations that could be distinguished with 95% confidence from zero were 4 pg/ml of motilin and 16 pg/ml of pancreatic polypeptide.

ASSESSMENT OF ADVERSE EVENTS

Unusual feelings as reported spontaneously by the patients were recorded along with the investigators' observations.

STATISTICAL ANALYSIS

The percentages of marker remaining in the stomach, the amplitude and the frequency of antral contractions as well as the plasma concentrations of motilin and pancreatic polypeptide were subjected to analyses of variance for repeated measures.³⁰ The influences of the fixed factors 'treatment' (erythromycin, placebo), 'study day' (1, 2), 'time' (the 18 five minute periods of

Figure 1: Gastric emptying of the semisolid test meal. Mean percentage of marker (SEM) remaining in the stomach over the 90 min after the start of the intravenous infusion of placebo (.....) and erythromycin (—), respectively.

recording of gastric emptying, the three periods of recording of antral motility and the seven time points at which blood samples were collected, respectively) and of the random factor 'patients' (1 to 10) were studied. As $t_{1/2}$ values usually are not normally distributed, these data were analysed using a non-parametric test – that is, the Wilcoxon's signed-rank test.³¹

Results

The analyses revealed that the sequence in which the patients received the two treatments in the two recording sessions had no significant influence on the variables measured.

GASTRIC EMPTYING

Percentage of marker remaining in the stomach

The emptying curves over time followed closely a monoexponential pattern under both experimental conditions (Fig 1). With placebo, the emptying rates were in the same range as the ones previously observed in our laboratory in patients with primary anorexia nervosa.^{11,12,16} With erythromycin, emptying was markedly faster than with placebo in all of the patients. Whereas the percentages of meal remaining in the stomach at the end of the 90 minute recording period ranged from 40.6 to 72.5% (median, 60.9%) after the infusion of placebo, they ranged from only 0.4 to 37.1% (median, 4.5%) after erythromycin. The analysis of variance revealed that the effects of the two treatments differed highly significant ($F(1,9)=104.34$, $p<0.001$).

GASTRIC HALF EMPTYING TIME

After the infusion of placebo, $t_{1/2}$ s (70.9–211.1 minutes; median, 136.7) of all patients were longer than the 75th percentile of $t_{1/2}$ s of 48 healthy subjects studied in our laboratory using the same recording technique and the same standard meal (range of $t_{1/2}$ s, 21.2–206.0 minutes, interquartile range, 41.9–64.0). After erythromycin, $t_{1/2}$ s (12.5–94.3 minutes; median, 37.2) were markedly shorter than after placebo

Figure 2: Gastric half emptying time. Half emptying times (in minutes) of the test meal after infusion of placebo and erythromycin, respectively, in the 10 individual patients.

infusion in all patients (Signed-rank test, $p < 0.002$; Fig 2). The $t_{1/2}$ s of six of the ten patients were even shorter than the 25th percentile of the $t_{1/2}$ s recorded in the 48 healthy subjects mentioned above.

ANTRAL MOTOR ACTIVITY

In the recording period nine to 10 minutes after the end of meal ingestion, all patients exhibited a rhythmic contractile antral activity at a mean frequency of 3.27 cycles/min (0.10) (SEM) when

Figure 3: Antral motor activity as depicted by three factor curves (full, broken, and dotted lines). The factor curves represent the global variations of intensity over time in three factor images – that is, areas of uniform changes of radioactivity and thereby contractile activity, along the axis of the antrum. Corresponding to the differing contraction states in the areas of the respective factor images, the factor curves are shifted in time. Upper tracing. Factor curves in minutes nine and 10 after the start of infusion of placebo in patient CP. The curves reflect rhythmic contractions occurring at a mean frequency of 2.9 cycles/minute at three points along the axis of the antrum. Lower tracing. Factor curves in minutes nine and 10 after the start of infusion of erythromycin in patient CP. Note the less rhythmic antral motor activity and the long duration of the contractions at the three points along the axis of the antrum.

placebo was infused. During erythromycin infusion, contractions occurred at a regular frequency of about three cycles/min in three patients but at less regular frequencies of 1.13 to 2.52 cycles/min in the remaining seven (Fig 3). Overall, the dominant frequency during erythromycin infusion (2.34 (0.24) cycles/min) was significantly lower ($F(1,9) = 10.10$, $p < 0.02$) than during placebo infusion. The mean amplitude of contractions during the infusion of erythromycin (7.9% modulation depth (1.2)) differed only little from the mean amplitude during placebo infusion (7.5 (0.7)%), whereas the maximal amplitudes were markedly higher with erythromycin (16.2 (4.3)%) than with placebo (9.1 (0.9)%; $F(1,9) = 3.37$, $p < 0.1$).

In the recording period 49–50 minutes after meal ingestion, antral contraction frequency remained stable when placebo had been infused (3.27 (0.23) cycles/min) and mean as well as maximal amplitudes were lower than in the first recording period (4.7 (0.5)% and 4.8 (0.8)%, respectively). After erythromycin, the partly arrhythmic pattern of contractile activity persisted; the amplitude of contractions could not reliably be quantitated any more, as the radioactivity remaining in the stomach at that time point was insufficient for these measurements in seven of the 10 patients. In the 89–90 min recording period, frequency as well as mean and maximal amplitude of contractions showed no changes from the values observed in the 49–50 minute period when placebo had been administered (3.30 (0.22) cycles/min, 4.7 (0.9)% and 5.4 (0.9)%, respectively). When erythromycin had been infused, the contractile activity could be recorded in only one patient, because there was too little radioactivity left in the antrum of the remaining nine.

PLASMA CONCENTRATIONS OF MOTILIN AND PANCREATIC POLYPEPTIDE

Motilin and pancreatic polypeptide concentrations could be determined in all studies with erythromycin administration but, because of

Figure 4: Plasma motilin concentrations. Mean motilin concentrations (SEM) in percent of values measured before (–5 min) the ingestion of the standard meal (M), after meal ingestion and anteceding the start of infusion of erythromycin or placebo (0 min), as well as 20, 30, 45, 60, and 90 minutes thereafter. Placebo studies (.....), erythromycin studies (—).

unsurmountable difficulties in obtaining blood from the emaciated patients' veins, in only eight of the 10 with placebo infusion.

Basal motilin concentrations ranged from 246 to 783 pg/ml (mean, 447.9 pg/ml (67.9) (SEM) before placebo administration and from 229 to 665 pg/ml (mean, 410.9 (57.8) pg/ml) before erythromycin. In all cases, motilin levels decreased gradually over the first 60 minutes after the start of the infusion. In the patients in whom motilin could be determined with both treatments, plasma concentrations decreased, on the mean, faster and more with erythromycin than with placebo (Fig 4). The analysis showed that the effects of the two treatments differed statistically ($F(1,7)=11.5$, $p<0.02$). The overall downwards trend of plasma concentrations resulted in a significant F value for the time factor ($F(6,42)=10.56$, $p<0.001$). At 90 minutes, motilin levels were slightly higher than at 60 minutes in seven of the 10 patients having received erythromycin and in four of the eight patients, in whom motilin concentrations could be measured after placebo administration.

Basal pancreatic polypeptide concentrations ranged from 29 pg/ml to 489 pg/ml (mean, 198.9 (54.4) pg/ml) before placebo administration and from 30 pg/ml to 382 pg/ml (mean, 152.5 (24.7) pg/ml) before infusion of erythromycin. In all patients, pancreatic polypeptide concentrations increased sharply with meal ingestion, the increases being about as high in the patients in whom subsequently erythromycin was infused as in the ones who subsequently received placebo (Fig 5). Immediately after placebo infusion, plasma concentrations were only slightly higher than before and peak levels occurred either at that time point or 10 minutes later. After the infusion of erythromycin, however, plasma concentrations were markedly higher than before the infusion in all of the patients (Fig 5). Thereafter, pancreatic polypeptide concentrations decreased again but remained on a higher level than after placebo throughout the recording time. The analysis showed that the treatment effects differed, although statistical significance was not

reached ($F(1,7)=3.78$, $p<0.1$). The overall upwards trend after meal ingestion was reflected by a significant F value for the influence of the time factor ($F(6,42)=6.33$, $p<0.001$) and the differing treatment effects over time by a significant F value for the interaction treatment $\times$ time ($F(6,42)=2.93$, $p<0.02$).

ADVERSE EFFECTS

Twenty and 25 minutes after the start of the infusion of erythromycin, respectively, two of the 10 patients reported slight nausea which lasted for about five minutes. More intense but still moderate nausea was reported by another patient at 15 minutes after the start of infusion. In this patient, as well, the feeling subsided after five minutes. In one patient, the investigators noted abdominal rumbling in the period 15 to 25 minutes after the start of erythromycin administration. No adverse events whatsoever were reported or observed during and after placebo infusion.

Discussion

The results of the present study show that erythromycin markedly accelerated gastric emptying in all of the 10 patients with primary anorexia nervosa studied. This finding is consistent with observations made in patients with diabetic^{10,11} and idiopathic gastroparesis,¹⁰ and with impaired gastric motor function after vagotomy and antrectomy.⁹ Erythromycin markedly accelerated the delayed gastric emptying not only in relation to the emptying rate prevailing with placebo, but to such an extent that, in six of the 10 patients, $t_{1/2}$ s were shorter than the 25th percentile of the $t_{1/2}$ s recorded in a group of 48 healthy individuals using the same recording technique and the same standard meal. A similar observation has been made by Janssens *et al*¹¹: in patients with diabetic gastroparesis having received erythromycin, the emptying of solid meal constituents was more rapid than in healthy untreated volunteers.

The enhanced emptying during and after erythromycin administration was associated, in the period nine to 10 minutes from the end of meal ingestion, with strong antral contractions of long duration. In contrast with the entirely rhythmic antral activity occurring at a frequency of about three cycles/minute during and after the infusion of placebo, these contractions were of lower and often irregular frequency. The induction by intravenous erythromycin of forceful antral contractions has also been reported by other authors, who had observed this phenomenon to occur not only in the postprandial period,^{32,33} but also in the interdigestive state.³³⁻³⁶ That these contractions often do not take place at the regular rate of about three cycles/minute, characteristic for the antrum after a meal, but much less frequently, has been reported earlier as well: in 13 fasted healthy subjects, erythromycin induced powerful peristaltic contractions with a mean occurrence of 0.96 per minute and, in eight fasted patients with diabetic gastroparesis, with a mean occurrence of 0.52 per minute.³⁶ Eight healthy men exhibited antral contractions of

Figure 5: Plasma pancreatic polypeptide concentrations. Mean pancreatic polypeptide concentrations (SEM) in percent of values measured before (-5 min) the ingestion of the standard meal (M), after meal ingestion and anteceding the start of infusion of erythromycin or placebo (0 min), as well as 20, 30, 45, 60, and 90 minutes thereafter. Placebo studies (.....), erythromycin studies (—).

large amplitude and long duration setting in six to nine minutes after the start of erythromycin infusion, which occurred at a mean frequency of about 2.4 cycles/minute in the fasting state and at a mean frequency of about 2.0 cycles/minute in the fed state.³³ No erythromycin induced arrhythmias have been detected in studies recording the electrogastrogram from electrodes attached to the skin of the abdomen. In 10 lightly sedated cynomolgus monkeys, erythromycin increased the amplitude and decreased the frequency of the signal, which remained rhythmic.³⁷ It has even been reported that, in four patients with gastroparesis, erythromycin converted electrogastrographically recorded arrhythmic slow waves into regularly occurring waves.³⁸ The discrepancy between these reports and the findings of the present as well as of a previous study³⁶ possibly is because the cutaneously recorded electrogastrogram reflects the slow wave activity only and not the superimposed spiking activity and thus can give no, and be it indirect, information on the contractions of the antrum.

Whether the accelerating effect of erythromycin on gastric emptying has to be attributed primarily to the induction of forceful antral contractions or to an effect on gastric tone, cannot be answered from the results of the present study. The strength of antral contractions, however, seems to play an important role. In healthy subjects, the emptying of solid, but not of liquid, meal constituents has been found to be slow with low antral motor activity and faster with a more active antrum.³⁹ Similarly, in patients with gastric stasis, a slow emptying rate for solids was found to be associated with antral hypomotility.⁴⁰ In a previous study in which the effects of the gastroprokinetic agent, cisapride, were evaluated in patients with primary anorexia nervosa and in which the same semisolid meal and the same recording technique was used as in the present investigation, the rate of emptying was related significantly to the amplitude of antral contractions.¹⁶

The fall in motilin concentrations under both experimental conditions could be related mainly to an increase in blood glucose levels, as it has been reported⁴¹ that plasma motilin declined significantly after both the ingestion and the intravenous infusion of glucose. Such a mechanism would explain the fact that the plasma concentrations of motilin decreased more and earlier when erythromycin was administered: in this condition gastric emptying was faster than with placebo thus enabling an earlier absorption of the meal constituents in the small intestine. A direct effect of erythromycin on plasma motilin levels cannot be ruled out although it has been observed that erythromycin had no such effect in fasting humans.² In fasted dogs, erythromycin induced a motilin release.¹

Plasma pancreatic polypeptide concentrations under basal conditions were within the normal range in all patients and in all experimental sessions and also exhibited the normally occurring sharp increase after meal intake. In an earlier study in patients with anorexia nervosa,⁴² the pancreatic polypeptide response to the meal did not differ from the one observed in healthy control subjects and in another it was only

slightly more accentuated.⁴³ Uhe *et al*⁴⁴ observed a significantly greater postprandial pancreatic polypeptide increase to occur in anorectic patients; this, together with the fact that low basal pancreatic polypeptide concentrations have been reported to prevail in obese subjects,⁴⁵ led them to suggest that pancreatic polypeptide might play a role in the regulation of appetite and food intake. As the control of pancreatic polypeptide release is thought to be largely under vagal cholinergic control,^{46,47} they also hypothesised that the more accentuated pancreatic polypeptide response might be the result of a high vagal drive.⁴⁴ Their data do not look very convincing, however, as the postprandial pancreatic polypeptide concentrations in their patients with anorexia show great variation, whereas those of their six healthy control subjects vary very little. Moreover, a high vagal drive should also lead to increased basal pancreatic polypeptide concentrations, a feature which was present neither in the patients of Uhe *et al*⁴⁴ nor in those of the present investigation. Further and more prolonged studies in the pancreatic polypeptide response of patients with anorexia nervosa to a meal are needed to clarify this matter. After the infusion of erythromycin, the levels of pancreatic polypeptide were much higher than after placebo infusion. This seems to be because of the acceleration of gastric emptying produced by erythromycin and the consecutive earlier onset of the intestinal phase of pancreatic polypeptide release.⁴⁸ A pronounced rise in pancreatic polypeptide concentrations has been observed to be associated also with a motilin induced enhancement of gastric emptying in patients with diabetic gastroparesis,⁴⁹ although in these patients the normally occurring early rise in pancreatic polypeptide, which is thought to result from stimuli transmitted through the vagal nerves,⁴⁸ failed to take place, probably as a result of autonomic neuropathy.⁵⁰

Adverse effects of erythromycin as observed in the present study – that is, slight to moderate nausea in three of the 10 patients and borborygmi in one, have been reported to occur also by other workers.^{32,33} The fact that the incidence of side effects was somewhat higher in the latter studies may be because the doses administered were, on a mg per kg body weight basis, at least twice as high than the dose administered in the present investigation. The same explanation might apply to the fact that 200 mg of erythromycin intravenously induced side effects in the present study but not in patients with diabetic gastroparesis¹¹: the latter may have received a lower dose on a mg per kg basis as their body weights, presumably, were in the normal range, whereas our patients had a median weight of only 59.7% of their ideal body weight.

In conclusion, erythromycin, 200 mg administered by slow intravenous infusion, markedly accelerated the slow gastric emptying of a semisolid meal in all of the 10 primary anorexia nervosa patients studied and, in seven of them, changed the entirely rhythmic antral motor activity in the immediate postprandial period into one characterised by stronger and longer lasting contractions occurring at a lower rate and at often irregular intervals. These results further

add to the evidence that erythromycin is endowed with potent gastropromkinetic properties and that related compounds, devoid of antibiotic activity, may represent promising tools in the future treatment of impaired gastric motor function in a variety of conditions.

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