ENDOTOXIN IN THE CONSCIOUS PIGLET: ITS EFFECTS ON SOME GENERAL AND GASTROINTESTINAL MYOELECTRICAL PARAMETERS

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ABSTRACT

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The effect of an intravenous bolus injection of endotoxin, 0.1, 1 or 10 $\mu\text{g/kg}$, on rectal temperature, clinical appearance, haematological parameters, and on gastrointestinal electrical activity was examined in 11 conscious piglets of 4-5 weeks of age, with implanted electrodes in the *antrum pylori*, duodenum, jejunum and ileum. All doses resulted in a significant and dose-dependent increase in rectal temperature, in pronounced clinical signs and in distinct changes in haematological values. These included shivering, depression, respiratory distress, a leukopenia (0.1 $\mu\text{g/kg}$) or a leukocytosis (1 $\mu\text{g/kg}$) with a shift to the left, an accelerated sedimentation rate and a decreased packed cell volume. Doses of 1 and 10 $\mu\text{g/kg}$ induced a transient inhibition of gastroduodenal electrical activity. These results suggest that, in the piglet, endotoxin primarily manifests general clinical signs and that the gastrointestinal effects coincide with these.

Keywords: endotoxin, *Escherichia coli*, gastrointestinal, pig, myoelectrical activity

INTRODUCTION

Important economic losses are caused by colibacillary toxemia in piglets. A variety of stresses, such as changes in food and environment, can trigger off enteric colibacillosis, resulting in weanling diarrhoea and oedema disease (Morris, 1984). An important component in weanling diarrhoea is enterotoxigenic *E. coli* (ETEC) induced hypersecretion, resulting from fluid secretion from the crypt cells and inhibition of absorption from the villous cells (Cox *et al.*, 1988). What may also be important in the pathogenesis of ETEC diarrhoea, however, is a change in intestinal motility. In rabbits, an alteration in small-intestinal myoelectric activity and motility was observed after intraluminal application of live ETEC bacteria or enterotoxin (Burns *et al.*, 1978, 1980).

In human medicine, lipopolysaccharide (LPS) or endotoxin, a constituent of the outer membrane of Gram-negative bacteria like *E. coli*, has been implicated in several clinical conditions such as septic shock, inflammatory bowel disease, adult respiratory distress syndrome (ARDS) and acute renal and multiple organ failure (Bayston and Cohen, 1990). In the pig, also, several pathological conditions, such as shock, oedema disease and *post partum* lactation failure, are associated with the presence of endotoxin (Morkoç *et al.*, 1983; Morris, 1984).

Diarrhoea can be induced in mice by intravenous (i.v.) injection of 0.4 mg/kg LPS

(Doherty, 1981). In conscious goats, sheep and rabbits, several hours of inhibition of gastrointestinal motility has been described following i.v. injection of a low dose ($0.1 \mu\text{g/kg}$) of endotoxin (Van Miert, 1971; Duranton and Buéno, 1984; Fioramonti *et al.*, 1984). This disturbance of the motility pattern may result in retching and profuse diarrhoea in animals suffering from shock (Lohuis *et al.*, 1988). Infusion of high doses ($2.5 \text{ mg kg}^{-1} \text{ h}^{-1}$) of endotoxin in piglets resulted in death from shock and disseminated intravascular coagulation (DIC) within 8–22 h following the start of the experiment in 6 out of 9 animals, without the occurrence of diarrhoea. Of the three surviving piglets one developed diarrhoea (Schrauwen *et al.*, 1986).

The aim of the present study, therefore, was to examine the primary signs of disease in the conscious piglet after i.v. bolus injection of low and moderate doses of LPS (0.1 , 1 and $10 \mu\text{g/kg}$) by measurement of rectal temperature, clinical appearance and some haematological parameters and to compare the timing of these with observations of gastrointestinal myoelectrical activity.

MATERIALS AND METHODS

Experiments were performed on 11 conventionally raised, female piglets from the same farm, 4 to 5 weeks old and weaned at the age of 3 weeks. The animals were individually housed and supplied with a 17.5% protein commercial diet and water *ad libitum* throughout the experimental period.

The piglets were anaesthetized with methomidate (Hypnodil, Janssen), 15 mg/kg , and azaperone (Stressnil, Janssen), 2 mg/kg , and sets of nichrome electrodes ($110 \mu\text{m}$ in diameter) were implanted, via an abdominal incision, into the walls of the *antrum pylori* about 4 cm from the pylorus, of the duodenum about 12 cm from the pylorus, and of the midjejunum and caudal ileum near the apex of the caecum. The electrodes were tunnelled subcutaneously and exteriorized on the back of the neck. During the same operation, a Silastic catheter (Dow Corning) was implanted in the jugular vein for LPS injection and blood sampling and similarly exteriorized on the back of the neck. Patency of the catheter was maintained by daily flushing with saline and refilling with a heparin solution (5000 U/ml).

About 5 days after implantation, gastrointestinal electromyographic (EMG) activity was recorded daily over 8 h using a multichannel recorder (SensorMedics) with a time constant of 1 s for gastric recordings and 0.03 s for small-intestinal recordings. Spike activity was simultaneously integrated at 20 s intervals by means of a linear integrator and a potentiometric recorder.

Endotoxin (LPS; *E. coli*, $\text{O}_{111}:\text{B}_4$, Westphal, Difco) was injected i.v. as a bolus in doses of 0.1 , 1 and $10 \mu\text{g kg}^{-1}$ (0.5 ml) $^{-1}$ saline. In each experiment only one dose of LPS was administered and, to avoid the development of tolerance, each pig received only two doses with an interval of 1 week between the respective administrations.

The LPS-induced effects on clinical appearance and on gastrointestinal EMG activity were measured for 6.5 h after the injection. At 30-min intervals during the experimental period and just prior to and at 24 h after LPS administration, the rectal temperature was measured and blood samples were taken.

Estimated blood parameters included the total white blood cell and platelet counts, differential leukocyte count, packed cell volume (PCV) and 24-h sedimentation rate. These parameters were compared with control values prior to

LPS administration and analysed by means of a two-way analysis of variance (ANOVA). Simple contrasts were used to differentiate between control values and those at different experimental time intervals.

Phasic EMG activity during the experiment was compared with time-matched values on proximate control days. The integrated activity was evaluated by planimetry of half-hourly segments and also compared with time-matched segments on control days. For the small-intestinal activity, planimetry included the total integrated activity and the peaks resulting from the regular spiking activity (phase III). Irregular spiking activity (phase II) was then calculated as the difference between the total and phase III integrated activity.

Both phasic and integrated antral and small-intestinal activities were analysed using a two-way ANOVA. When appropriate, control values with no significant differences between time segments were pooled. Simple contrasts were used to differentiate between control and different time segments.

All statistical analyses were performed using the computer program SPSS/PC (SPSS Inc., Chicago, IL, USA). The results are expressed as mean $\pm$ SEM. Significance was accepted at $p \leq 0.05$.

RESULTS

Rectal temperature and clinical appearance

The control rectal temperature was $39.4 \pm 0.2^\circ\text{C}$. Injection of $0.1 \mu\text{g/kg}$ endotoxin resulted in a transient temperature increase to $40.5 \pm 0.4^\circ\text{C}$ at 1 h after injection. LPS, $1 \mu\text{g/kg}$, induced a more pronounced febrile response from 0.5 h until 4 h after injection with a maximal value of $41.0 \pm 0.1^\circ\text{C}$ at 2 h after injection. Following injection of $10 \mu\text{g/kg}$, hyperthermia was maintained until 5 h with a peak value of $41.3 \pm 0.2^\circ\text{C}$ at 2.5 h (Figure 1).

The temperature increase was accompanied by shivering, and different degrees and durations of depression and anorexia were observed.

Following injection of $0.1 \mu\text{g/kg}$ LPS, moderate respiratory distress with hyperpnoea and dyspnoea was noticed in 1 out of 8 piglets. Endotoxin, $1 \mu\text{g/kg}$, resulted in dyspnoea in 7 out of 8 animals and in nausea and vomiting within 20 min after injection in 3 out of 8. Following injection of $10 \mu\text{g/kg}$ LPS, the dyspnoea and vomiting were complicated in two pigs by the additional development of acrocyanosis and coughing. In a third pig, severe excitation followed by pronounced depression was observed. Therefore, experiments with $10 \mu\text{g/kg}$ were restricted to these three animals.

None of the doses studied induced diarrhoea within 24 h after injection.

Haematological parameters

Control values for leukocyte counts were $13\,500 \pm 1500 \text{ cells/mm}^3$. The leukocyte formula comprised $15 \pm 5\%$ band neutrophils, $18 \pm 5\%$ segment neutrophils and $58 \pm 6\%$ lymphocytes. PVC control values were $32 \pm 2\%$, the control sedimentation rate was $75 \pm 26 \text{ mm/24 h}$ and the thrombocyte count was $338 \pm 82 \times 10^3 \text{ cells/mm}^3$.

Figure 1. Rectal temperature before (control) and at different intervals after injection of LPS, 0.1, 1 and 10 $\mu\text{g/kg}$, in the conscious piglet. Significantly different from control value at * $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$

LPS, 0.1 $\mu\text{g/kg}$, induced an increase in leukocyte count for 2.5 h, starting 1.5 h after the injection (Table I). Monitoring the leukocyte formula revealed significant changes with a decrease in lymphocytes and an increase in band neutrophils, with a ratio of $19 \pm 3\%$ lymphocytes to $64 \pm 7\%$ band neutrophils 2.5 h after injection.

Half an hour after the injection of 1 $\mu\text{g/kg}$, a leukopenia occurred, which remained significant until 2 h later (Table I). The effects on the leukocyte formula were an even more pronounced decrease in lymphocytes and a substantial increase in band neutrophils with a concomitant decrease in segment neutrophils (Figure 2).

Both doses resulted in a decrease in PCV and an accelerated sedimentation rate (Table I). No significant effect was observed on the thrombocyte counts, although there was a tendency towards a decrease.

Because of the increased blood coagulability following injection of 10 $\mu\text{g/kg}$, the catheter occasionally clogged and blood parameters could not be determined at all in one piglet and were incomplete in two piglets. No statistical analysis was performed therefore. The individual values are presented in Table I but these reveal inconsistent results: one pig did not manifest an obvious effect on its leukocyte count, whereas the other one displayed a severe leukopenia. As regards their leukocyte formula, both animals showed a pronounced increase in band neutrophils and a decrease in lymphocytes, with a maximal ratio for individual piglets of 81/7 and 75/17 at 4 and 5 h after injection, respectively. In one pig, an increase in PCV was observed, whereas the other one displayed a decrease. In both animals the sedimentation rate was clearly accelerated (Table I) and the thrombocyte counts were decreased.

Twenty-four hours after LPS administration nearly all the haematological parameters were again within control values.

TABLE I
The effect of endotoxin on some blood parameters in the conscious piglet

Parameters	Control values	1	2	3	Time after injection (hours)	5	6	24
<i>Endotoxin, 0.1 µg/kg (mean ± SEM)</i>								
Leukocytes/mm ³ × 100	134.0 ± 13.1 (8)	123.5 ± 14.0 (8)	231.1 ± 38.4 (8) ^a	227.4 ± 33.7 (8) ^a	279.4 ± 87.3 (8) ^c	163.8 ± 22.6 (7)	126.5 ± 15.7 (6)	149.5 ± 15.4 (8)
PCV (%)	32.0 ± 2.1 (4)	30.3 ± 1.4 (4)	29.3 ± 1.4 (4) ^b	29.8 ± 0.6 (4) ^a	28.5 ± 1.7 (4) ^c	29.0 ± 1.2 (4) ^b	28.5 ± 1.1 (4) ^c	31.0 ± 1.6 (4)
Sedimentation rate (mm/24 h)	74.7 ± 25.8 (3)	100.3 ± 13.9 (4) ^b	89.0 ± 13.8 (4)	96.0 ± 13.4 (4) ^a	102.8 ± 11.2 (4) ^b	104.0 ± 10.7 (4) ^b	107.0 ± 13.9 (3) ^b	117 ± 48 (2)
<i>Endotoxin, 1.0 µg/kg (mean ± SEM)</i>								
Leukocytes/mm ³ × 100	137.6 ± 15.5 (8)	87.1 ± 14.2 (8) ^b	98.3 ± 19.1 (8) ^a	109.0 ± 23.0 (8)	117.8 ± 22.1 (8)	99.4 ± 15.9 (7)	118.2 ± 13.4 (6)	133.7 ± 10.8 (8)
PCV (%)	31.2 ± 0.8 (5)	30.8 ± 0.2 (5)	30.2 ± 0.9 (5)	30.0 ± 0.7 (5)	29.0 ± 1.3 (5) ^a	27.4 ± 0.7 (5) ^c	27.0 ± 0.6 (5) ^c	31.0 ± 1.2 (5)
Sedimentation rate (mm/24 h)	57.8 ± 18.7 (5)	54.2 ± 18.9 (5)	48.6 ± 19.7 (5)	60.0 ± 18.1 (5)	80.2 ± 16.8 (5) ^a	90.0 ± 15.9 (5) ^b	99.8 ± 16.6 (5) ^c	65.4 ± 19.8 (5)
<i>Endotoxin, 10.0 µg/kg (individual values)</i>								
Leukocytes/mm ³ × 100	274 182 (2)	149 71 (2)	214 (1)	219 (1)	216 71 (2)	256 93 (2)	242 86 (2)	236 134 (2)
PCV (%)	28 30 (2)	31 24 (2)	30 (1)	31 (1)	30 28 (2)	26 (1)	27 (1)	27 27 (2)
Sedimentation rate (mm/24 h)	121 68 (2)	124 (1)	118 (1)	129 (1)	137 118 (2)	141 (1)	144 (1)	84 47 (2)

Significantly different from control values at ^a, $p \leq 0.05$; ^b, $p \leq 0.01$; ^c, $p \leq 0.001$; (n) - numbers of observations; individual results are given for $n = 1$ and 2

Figure 2. Leukocyte formula before (control) and at different intervals after injection of LPS, 1 $\mu\text{g}/\text{kg}$, in the conscious piglet. Significantly different from control value at * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Figure 3. Half-hourly integrated antral activity on a control day and on the day of injection of 1 $\mu\text{g}/\text{kg}$ LPS in the conscious piglet. Significantly different from pooled control value at * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Electromyography

The control antral EMG activity was composed of the electrical control activity (ECA) and the electrical response activity (ERA) with superimposed fast oscillations. ECA occurred at a mean frequency of $4.54 \pm 0.04/\text{min}$ but with significant differences between pigs and times. Fast oscillations were observed at an interburst frequency of $2.43 \pm 0.08/\text{min}$, about 50% of the ECA. Control small-intestinal recordings displayed the normal pattern of migrating myoelectrical complexes (MMC), consisting of phase I, phase II and phase III activities. Duodenal, jejunal and ileal MMC recycled at 59 ± 1 , 63 ± 1 and 78 ± 1 min intervals, respectively. However, significant differences between pigs were observed. Following a duodenal phase III, complete (abolition of ECA and ERA) or partial (abolition of ERA) inhibition of antral myoelectrical activity was observed.

Figure 4. Frequency of electrical control activity (ECA) and fast oscillations (f.osc.) on the antrum on the control day (pooled values of all measurements over the equivalent 4-h period) and at different intervals following injection of LPS, $1 \mu\text{g}/\text{kg}$, in the conscious piglet. Significantly different from pooled control value at $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$

During the period of hyperthermia following the injection of $0.1 \mu\text{g}/\text{kg}$ endotoxin, there was no significant alteration in the control pattern of antral phasic activity, nor in its integrated value. The phasic recordings from the duodenum showed a significant prolongation of phase I for 3 h following injection, with a maximum of 18.9 ± 12.4 min during the second hour as compared with a control value of 5.8 ± 1.3 min, but this was apparently insufficiently pronounced to induce a significant change in the integrated activity.

Administration of 1 and $10 \mu\text{g}/\text{kg}$ LPS resulted in a significant diminution of

antral integrated activity. From 30 min after injection of $1 \mu\text{g/kg}$, there was significant decrease in the area under the curve (AUC), which was sustained until 4 h after injection (Figure 3). Analysis of phasic recordings revealed prolongation of the phase of complete inhibition following phase III in the duodenum for 3 and 4 h respectively after injection of 1 and $10 \mu\text{g/kg}$. The inhibition times for $1 \mu\text{g/kg}$ rose from 3.4 ± 0.7 min for the control to 19.5 ± 6.3 , 9.7 ± 3.1 and 10.5 ± 2.2 min during the first, second and third hour after injection respectively; for $10 \mu\text{g/kg}$: from 4.1 ± 0.9 min to 26.0 ± 6.6 , 19.7 ± 0.9 , 24.7 ± 6.7 and 14.3 ± 3.3 min during the first, second, third and fourth hour respectively. In addition there was also a significant decrease in the frequency of fast oscillations accompanying the ECA until 3.5 h after injection (Figure 4). Vomiting occurred during this inhibitory phase in the antrum.

Figure 5. Half-hourly integrated irregular spiking activity in the duodenum on control day and on day of injection of LPS, $1 \mu\text{g/kg}$, in the conscious piglet. Significantly different from pooled control value at $*p \leq 0.05$, $**p \leq 0.01$, $***p \leq 0.001$

Following administration of LPS at $1 \mu\text{g/kg}$, duodenal EMG integrations revealed a significant decrease in AUC within the first half hour, which lasted until 6 hours after injection. This decrease could be attributed to a decrease in phase II activity, which followed the same pattern (Figure 5). Phasic recordings demonstrated a significant prolongation of phase I until 3 h after the injection, with a maximum duration of 21.5 ± 2.6 min during the second hour after injection as compared with 6.0 ± 1.2 min for the control.

Administration of $10 \mu\text{g/kg}$ to the three piglets did not produce a similar consistent effect on duodenal integrated activity but resulted in sporadic significant decreases over the whole recording time. The same applied to the phase II integrated curve. Analysis of phasic recordings revealed an increase in the duration of phase I for 3 h but only after the first hour had passed. Furthermore, in one pig, a different phase

II pattern was observed at 10 $\mu\text{g}/\text{kg}$. This consisted of intermittent periods of activity resembling the phases of regular spiking activity but of much shorter duration (≤ 2 min), with a higher frequency of occurrence, and delineated by periods of quiescence or irregular activity.

Jejunal and ileal phasic recordings and integrations revealed no significant changes in EMG activity.

DISCUSSION

The clinical signs manifested after i.v. administration of LPS are well known and have been documented in various animal species. These effects include: (a) general depression; (b) respiratory distress; (c) vasomotor disturbances, possibly terminating in shock; (d) fever, sometimes followed by hypothermia; (e) disturbance of the motility pattern of the gastrointestinal tract, resulting in retching and profuse diarrhoea in animals suffering from shock; (f) extreme polymorphonuclear leukopenia followed by leukocytosis; (g) metabolic disturbances (Lohuis *et al.*, 1988). The gravity of the developing signs depends largely on the species involved, the dose administered and the route and rate of administration. Furthermore, within each species, individual susceptibility and age influence the degree of distress.

Comparable clinical manifestations to the present observations in the pig were reported after an i.v. bolus injection of 0.5–3 $\mu\text{g}/\text{kg}$ in pregnant gilts (Cort, 1985) and in boars (Wallgren, 1989). Infusion of 11–12.1 $\mu\text{g kg}^{-1} \text{ h}^{-1}$ for 48 h in pigs of approximately 30 kg also induces almost identical signs (Kurtz and Quast, 1982).

As reviewed by Bayston and Cohen (1990), these signs are generated by triggering a complex of endogenous substances rather than by the endotoxin itself.

Interleukin-1 or endogenous pyrogen (EP) stimulates thermoregulatory centres in the hypothalamus by inducing local PGE₂ synthesis, resulting in fever (Lohuis *et al.*, 1988).

Lung injury following endotoxin is probably mediated through platelet activating factor (PAF), which in turn stimulates eicosanoid release (Olson *et al.*, 1990) and may lead to pulmonary hypertension, increased pulmonary vascular resistance and permeability, pulmonary oedema and bronchoconstriction (Orr *et al.*, 1977; Schrauwen *et al.*, 1986; Olson *et al.*, 1987, 1990).

Alterations in the leukocyte count are probably induced by a balance between tumour necrosis factor, interleukin-1 and interleukin-6 stimulating neutrophil release from the bone marrow into the peripheral circulation (Van Miert, 1990) and the sequestration of white blood cells, in particular from the pulmonary circulation (Grisham *et al.*, 1988).

Endotoxin furthermore causes platelet agglutination and increased coagulability of the blood, eventually resulting in disseminated intravascular coagulation (DIC) in several organs (see, e.g., Bayston and Cohen, 1990). This enhanced coagulability complicated the course of our experiments at 10 $\mu\text{g}/\text{kg}$ LPS.

The unexplainable decrease in PCV, observed in our study following bolus injection of LPS, has also been described in pigs of approximately 4 months of age following i.v. injection of 4 $\mu\text{g}/\text{kg}$ endotoxin (Orr *et al.*, 1977).

Considering the gastrointestinal effects, i.v. injection of 0.1 $\mu\text{g}/\text{kg}$ endotoxin in sheep and rabbits (Duranton and Buéno, 1984; Fioramonti *et al.*, 1984) was reported

to induce complete inhibition of antral activity lasting up to several hours. The basic electrical rhythm or ECA only remained in the sheep. These authors, however, make no mention of the time constant used in their gastric recordings. Applying the same constant as that used for intestinal recordings (0.03 s) may cause filtering out of part of the ECA, ERA and smaller fast oscillations. In this way, following LPS injection, only elimination of larger fast oscillations could be detected. The absence of fast oscillations, however, is no sure indication of the absence of a contraction, for which ERA are the best indicators (Laplace and Roman, 1979; Laplace, 1980). However, ERA are more difficult to identify and an acceptable relationship between the presence and amplitude of fast oscillations and contractions has been reported (Ruckebusch *et al.*, 1981). Therefore we evaluated fast oscillations, so giving an estimate of the minimal contraction frequency present. Following i.v. injection of the higher doses of LPS, 1 and 10 $\mu\text{g}/\text{kg}$, we observed only partial inhibition of antral EMG activity, especially of the fast oscillations which were superimposed on ERA.

The concurrence of the antral inhibition with the rectal temperature increase suggests a causal relationship. Lohuis and colleagues (1988) concluded that the inhibition of forestomach motility in ruminants after i.v. injection of endotoxin is likely to be the combined result of two different mechanisms: one of which is prostaglandin mediated and one resulting from an unknown temperature-independent mechanism.

In the intestine, i.v. bolus administration of LPS at 0.1 $\mu\text{g}/\text{kg}$ in the rabbit has been said to inhibit strongly the spiking activity of the duodenum, jejunum and ileum for 4–6 h, with propagating spike bursts of large amplitude appearing instead (Fioramonti *et al.*, 1984). Identical doses in the sheep replaced the jejunal pattern of MMC by periods of intense activity of about 13 min (Duranton and Buéno, 1984).

In the present experiments, a possible altered pattern of duodenal activity was observed in only one of the three pigs at the dose of 10 $\mu\text{g}/\text{kg}$. However, to our knowledge this did not resemble any of the previously described alterations. Particular altered patterns of small-intestinal electrical activity have been described as characteristic of a diarrhoeal state (Laplace, 1984) and as resembling the effect of *Vibrio cholerae* as well as of *E. coli* enterotoxins (Mathias *et al.*, 1976, 1982; Burns *et al.*, 1978, 1980; Koch *et al.*, 1983). Our results agree with the absence of diarrhoea after the administration of any dose of LPS. Kurtz and Quast (1982), on the other hand, reported the development of severe diarrhoea in pigs of 30 kg within 2–6 h of the start of a 48-h infusion of sublethal doses of LPS, 15.4–16.5 $\mu\text{g kg}^{-1} \text{ h}^{-1}$. In those animals, necropsy revealed oedema and infarction of the gastrointestinal wall due to intravascular thrombi. The question therefore arises whether possible alterations of EMG activity and/or diarrhoea following high doses of endotoxin in the pig could not result from ischaemia and/or release of mediators such as PAF (Hsueh *et al.*, 1987; Whittle *et al.*, 1987; Esplugues and Whittle, 1989) or eicosanoids, preceding and/or following DIC in the intestinal circulation.

In conclusion, low and moderate doses of endotoxin result in variable general effects in the piglet, which coincide with a transient inhibition of gastroduodenal activity, without prominent changes in the recurrence of phase III activity of the MMCs.

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