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Received: 3 April 2016 | Accepted: 8 August 2016

DOI: 10.1111/nmo.12938

ORIGINAL ARTICLE

WILEY Neurogastroenterology & Motility NGM

Effect of methylnaltrexone and naloxone on esophageal motor function in man

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Funding information
This study was supported by a Methusalem grant from the University of Leuven to Prof. J. Tack

Abstract

Background: Endogenous opioids (EO) acting on μ-opiod receptors in central and enteric nervous system (ENS) control gastrointestinal motility but it is still unclear whether EO in ENS may control esophageal function in man, thus we will study the effects of methylnaltrexone (MNTX), a peripherally selective, and naloxone (NA), a non-selective μ-opiod receptor antagonist, on esophageal motility in healthy subjects.

Methods: Fifteen HV (6 M; 34.1 ± 0.6 years; BMI: 22.1 ± 0.1 kg/m^2) underwent three esophageal high-resolution manometry impedance (HRiM) studies with 10 saline swallows administered every 30 minutes: drug was administered after 30 minutes (MNTX subcutaneously/NA or saline intravenously), a solid meal after 90 minutes; measurements continued for 120 minutes postprandially.

Key Results: Methylnaltrexone did not significantly decrease the upper esophageal sphincter (UES) percentage of relaxation preprandially (72.5 ± 5 vs 66.9 ± 4.6 and 73 ± 3.8%, ANOVA between placebo, MNTX and NA, *P*=NS) and postprandially (60 minutes: 68.2 ± 5.6 vs 61 ± 5.5 and 67.1 ± 5.6%; 120 minutes: 68 ± 5.9 vs 59.3 ± 5.2 and 67.7 ± 4.7%; ANOVA between placebo, MNTX and NA, *P*=NS). MNTX and NA did not significantly alter preprandial and postprandial LES resting pressures and integrated relaxation pressure (ANOVA between placebo, MNTX and NA, all *P*=NS). Peak front velocity and distal contractile integral were not altered pre- and postprandially by MNTX and NA (ANOVA between placebo, MNTX and NA, *P*=NS). Transient lower esophageal sphincter relaxations (TLESRs') number was not altered by MNTX and NA (ANOVA between placebo, MNTX and NA, all *P*=NS).

Conclusions and Inferences: The peripheral selective and non-selective μ-opioid receptor antagonists MNTX and NA, respectively, do not alter TLESRs occurrence and esophageal peristalsis.

KEYWORDS
GERD, methylnaltrexone, naloxone, TLESRs, μ-opioid receptors

1 | INTRODUCTION

Gastro-esophageal reflux disease (GERD) is a condition where reflux of gastric contents, a physiological process after meals, is associated with symptoms such as heartburn or regurgitation or lesions.[1] Gastric acid is considered the main pathogenic agent in GERD and the predominant target for standard therapy with antisecretory compounds (proton pump inhibitors [PPIs]). However, up to 30% of the patients continue to have symptoms despite adequately dosed PPI therapy, and besides low treatment compliance, also insufficient

inhibition of acid secretion, and especially ongoing non-acid reflux episodes have been implicated.[2]

The GERD pathophysiology involves several mechanisms but failure of the esophago-gastric antireflux barrier[3] seems to play the most prominent role. In particular, transient lower esophageal sphincter relaxations (TLESRs), controlled by a vago–vagal reflex, triggered by activation of stretch receptors in the proximal stomach, and organized in the brain stem,[4] are the major mechanism underlying reflux events both in healthy and GERD subjects.[5]

Pharmacological agents inhibiting TLESRs, such as the gamma-amino butyric acid B (GABA-B) agonist baclofen, has been evaluated in GERD[6–8] but the high incidence of central side-effects with baclofen, and the low gain with newer GABA-B agonists, have hampered their successful use or drug development in GERD.[8] More recently, we demonstrated that itopride, an antidopaminergic and cholinesterase inhibitor, and rimonabant, a cannabinoid-1 receptor inhibitor, are also able to inhibit TLESRs.[9, 10] Itopride pilot studies in GERD patients are encouraging, but more extensive evaluation of its potential in GERD is lacking.[11] Rimonabant, on the other hand, has been withdrawn from use in obesity, because of an increased prevalence of depression with long-term use, making this class of agents less attractive for GERD therapy.[12] Hence, there is a persisting unmet need for novel GERD treatments targeting TLESRs.

The μ-opioid peripheral selective antagonist methylnaltrexone (MNTX) was approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of opioid-induced constipation in advanced care patients, not responding to laxative therapy.[13] Opioid nerve endings have been demonstrated in the myenteric plexus of the lower esophageal sphincter (LES) in humans[14] and opossum,[15] suggesting that they may be involved in control of LES motor function. In the opossum, μ-opioid receptor agonism inhibits LES tone and this effect is inhibited by naloxone.[15] Similarly, in humans, opioid agonists such as morphine inhibit LES relaxation induced by swallowing and by esophageal balloon distension, thereby increasing residual LES pressure.[16] In controls and GERD patients, intravenous administration of morphine inhibits the occurrence of TLESRs[17, 18] and this is completely blocked by naloxone (NA), suggesting that the actions of morphine are mainly mediated through μ-receptors. However, the effect of morphine was attributed to central actions, as the peripherally acting μ-opioid agonist loperamide did not alter the rate of TLESRs.[18] Gastric distension is one of the main triggers of TLESRs,[5] and both NA and MNTX, respectively, non-selective and selective peripheral μ-opioid receptor antagonists, are able to inhibit gastric accommodation to a meal.[19, 20] Hence, there is a potential for MNTX to also inhibit TLESR occurrence in man.

The aim of the present study was to investigate the effect of MNTX, a selective, and NA, a non-selective μ-opioid receptor antagonist, on esophageal motility and lower esophageal sphincter function in man.

Key points

- Endogenous opioids, through opioid receptors on enteric nerves, play an important role in the control of gastrointestinal motility.
- Little is known about their involvement in the control of esophageal motility.
- Using methylnaltrexone (MNTX), a peripherally selective, and naloxone (NA), a non-selective μ-opiod receptor antagonist, we found no role for endogenous opioids in the control of esophageal peristalsis and triggering of transient lower esophageal sphincter relaxations in man.

2 | MATERIALS AND METHODS

2.1 | Subjects

Studies were performed in 15 healthy volunteers (6 men; mean age, 34.1 ± 0.6 years; range 18–42 years) with a mean body mass index of 22.1 ± 0.1 kg/m^2. None of the subjects had symptoms or a history of gastrointestinal disease or upper gastrointestinal surgery, nor were they taking any medication. None of them were smokers and none had history of opioid, cannabinoid or any other drug use and/or abuse. Written informed consent was obtained from each subject and the study protocol was approved previously by the Ethics Committee of the University Hospital.

2.2 | Study design

All subjects underwent three stationary pH-high resolution impedance manometry (HRiM) studies in a single-blind, randomized, crossover design after administration of the drug or placebo (subcutaneous injection of saline or 12 mg methylnaltrexone (Relistor®; Wyeth Pharmaceuticals, Louvain-la-Neuve, Belgium; 0.6 mL) and after intravenous infusion of naloxone (0.4 mg intravenous bolus [1 mL] followed by continuous infusion 20 μg/kg/h [100 mL/h]; 'Narcan', Bristol-Myers Squibb Pharma, Braine-l'Alleud, Belgium) or intravenous infusion of saline (bolus injection of 1 mL followed by a continuous infusion of 100 mL/h), with an interval of at least 1 week. Treatment was administered on the morning of the study day during the esophageal manometry and pH measurements. This time schedule was chosen to reach a steady state plasma level of the drug.

On each day of measurements, subjects were studied after an overnight fast of at least 12 hours. Together with a water-perfused high resolution impedance manometry catheter, a pH assembly was passed through the nose under topical anesthesia and positioned with the pH electrode at 5 cm above the LES. After placement of the assembly, subjects remained in a sitting position for a habituation period of 20 minutes. This period allowed baseline assessment of esophageal peristalsis and LES function. Ten saline swallows of 5 mL of saline were administered at 1-minute interval and followed by drug or placebo according to the single-blind, randomized crossover design. During the 30 minutes after administration of the drug, esophageal and LES pressures and esophageal pH were continuously monitored. Sixty minutes after drug administration, the subjects ingested a standardized solid meal (mashed potatoes, meat loaf, apple sauce, milk, butter, 1000 kcal)[21] and recordings continued for 2 hours after the

meal. Throughout the study, 10 saline swallows of 5 mL of water were administered at 30-minute intervals. Throughout the study, the sensations of fullness, nausea, heartburn, belching, satiety, hunger, anxiety, dizziness, sleepiness, and fatigue were measured every 15 minute using validated 100-mm visual analogue scales[9, 10] (Fig. 1).

2.3 | Recording methods

Following an overnight fast, the subjects underwent an esophageal high resolution impedance manometry (HRiM) recordings. The HRiM assembly (Medical Measurement Systems, Enschede, the Netherlands) consists of 22 water perfused pressure sensors and seven impedance channels. Pressure and impedance signals were sampled at 50 Hz. The catheter was positioned with the high-definition zone in the LES region and impedance sensors, respectively, 5, 7, 9, 11, 13, 15, and 17 cm above the upper margin of the LES. Pressure signals from external transducers and impedance signals were digitized, imported to a workstation computer and saved for subsequent analysis by a dedicated software package[22] (Medical Measurement Systems).

The esophageal pH was measured with an antimony pH electrode (Synectics Medical, Stockholm, Sweden) positioned 5 cm above the proximal margin of the HRiM catheter. The pH electrode was calibrated in buffers of pH 1 and pH 7 before and after each study. During the study period, the esophageal pH was recorded continuously using an ambulatory data-logger (MicroDigitrapper; Synectics Medical, Stockholm, Sweden).

2.4 | Data analysis

2.4.1 | Esophageal motility

Standard HRiM parameters were used to characterize swallows: (i) contraction amplitudes; (ii) distal esophageal amplitude (DEA); (iii) contraction durations; (iv) peak front velocity (PFV) of esophageal contractions; (v) distal contractile integral (DCI), in mmHg/s/cm; (vi) size of any defect on the 30 mmHg isocontour plot (cm <30 ICP); (vii) resting upper esophageal sphincter (UES) and LES pressure; (viii) 4-s integrated LES relaxation pressure (IRP4), a measure of deglutitive LES relaxation.

Basal LES pressure was measured at end-expiration relative to intra-gastric pressure and was determined as means of 1-minute periods every 15 minutes, provided that the measurement was stable and no TLESR or swallow occurred. The mean LES pressure was calculated for each 30-minute period. PFV estimates the speed of contraction of the distal contractile segment referenced to a 30 mmHg isobaric contour; DCI integrates the length (cm), contractile pressure (mmHg), and duration of contraction of the 2/3 distal esophageal segment; IRP4 is a parameter that reports the lowest mean eSleeve pressure for four continuous or non-continuous seconds during the esophago-gastric junction (EGJ) relaxation.[22]

Transient lower esophageal sphincter relaxations were defined according to published criteria:[23] (i) absence of a swallowing signal for 4 seconds before to 2 seconds after the onset of LES relaxation; (ii) relaxation rate of ≥1 mmHg/s; (iii) time from onset to complete relaxation of ≤10 seconds; and (iv) nadir pressure of ≤2 mmHg. Excluding multiple swallows, LES pressure drops that fulfil the last three criteria, but have a duration of >10 seconds, can also be classified as TLESRs irrespective of the timing relative to swallowing.

2.4.2 | Gastro-esophageal reflux events and esophageal pH

Gastro-esophageal reflux on impedance was defined as a sequential orally progressing drop in impedance to less than 50% of the baseline values that starts in the most distal channel and propagates retrograde to at least the next more proximal measuring segment.[24]

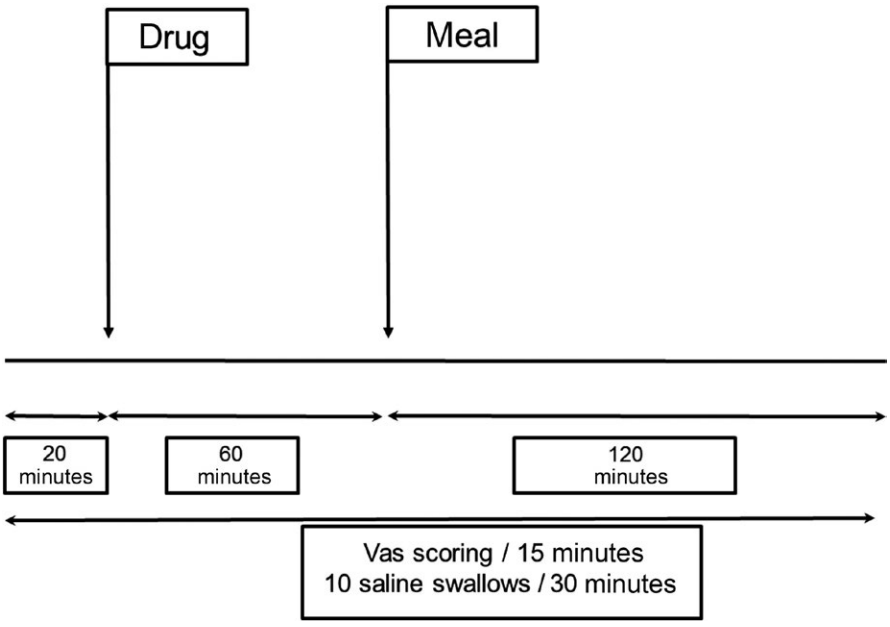

FIGURE 1 Study protocol. Healthy volunteers underwent three high resolution esophageal mano-impedance studies and pH measurement studies. After placement of the assembly 10 swallows of 5 mL of saline were administered, followed by the administration of the medication. After 60 minutes a standardized solid meal was administered and measurements continued for another 120 minutes. At 30-minute intervals, 10 saline swallows were administered. Throughout the study, at 15-minute intervals the intensity of eight epigastric symptoms was scored on visual analogue scales

The percentage of time with an esophageal pH <4 and the number of acid reflux episodes were calculated. Acid reflux episodes were defined as a decrease in esophageal pH to a value below pH 4 for at least 4 seconds or, if the basal esophageal pH was already below pH 4, as a rapid further drop in pH of at least 1 pH unit.[24]

2.5 | Statistical analysis

Data are presented as the mean ± standard error of the mean (SEM). The analysis of variance (ANOVA) was used for the comparison of the mean values of UES resting and residual pressure, PFV, DCI, TLESRs number and duration, total number of reflux episodes, between the drug and placebo studies. The changes in the basal LES pressure, IRP4, acid and non-acid reflux events number and duration between periods were evaluated using analysis of variance (ANOVA) for repeated measures. The symptom scores were compared using the Wilcoxon signed rank test. A *P*-value <.05 was considered to be statistically significant.[9,10] Bonferroni's correction for multiple testing was applied.

3 | RESULTS

3.1 | Conduct of the study

The positioning of the esophageal manometry catheters and pH probes was well-tolerated and all subjects completed all planned sessions of the study. No adverse events occurred.

3.2 | Upper esophageal sphincter function

Compared to placebo both NA and MNTX did not alter the basal UES pressure (55.1 ± 6.7 vs 57.5 ± 7.8 and 55.7 ± 8.3 mmHg ANOVA between placebo, MNTX and NA, *P*=NS). The UES resting pressure drop after the meal was not affected by drug administration (ANOVA between placebo, MNTX and NA, both *P*=NS: 60 minutes: 43.3 ± 4.2 vs 46.9 ± 6.2 and 49.4 ± 9.3 mmHg; 120 minutes: 43.1 ± 5.5 vs 42.2 ± 4.9 and 40.9 ± 8.0 mmHg). The residual UES pressure upon deglutition and the UES percentage or relaxation were also not significantly altered by MNTX or NA, both in the preprandial and postprandial period (Fig. 2A, B).

3.3 | Lower esophageal sphincter function

Compared to placebo, MNTX and NA did not affect basal and postprandial LES resting pressure (Table 1). Swallow-induced sphincter relaxation, measured as IRP4, was not significantly altered by MNTX and NA preprandially or postprandially (Table 1).

3.4 | Esophageal motility

Peak front velocity was not altered by MNTX and NA preprandially and postprandially (ANOVA between placebo, MNTX and NA, both *P*=NS) (Table 1). Similarly, DCI was also not altered by both MNTX and NA (ANOVA between placebo, MNTX and NA, both *P*=NS) (Table 2).

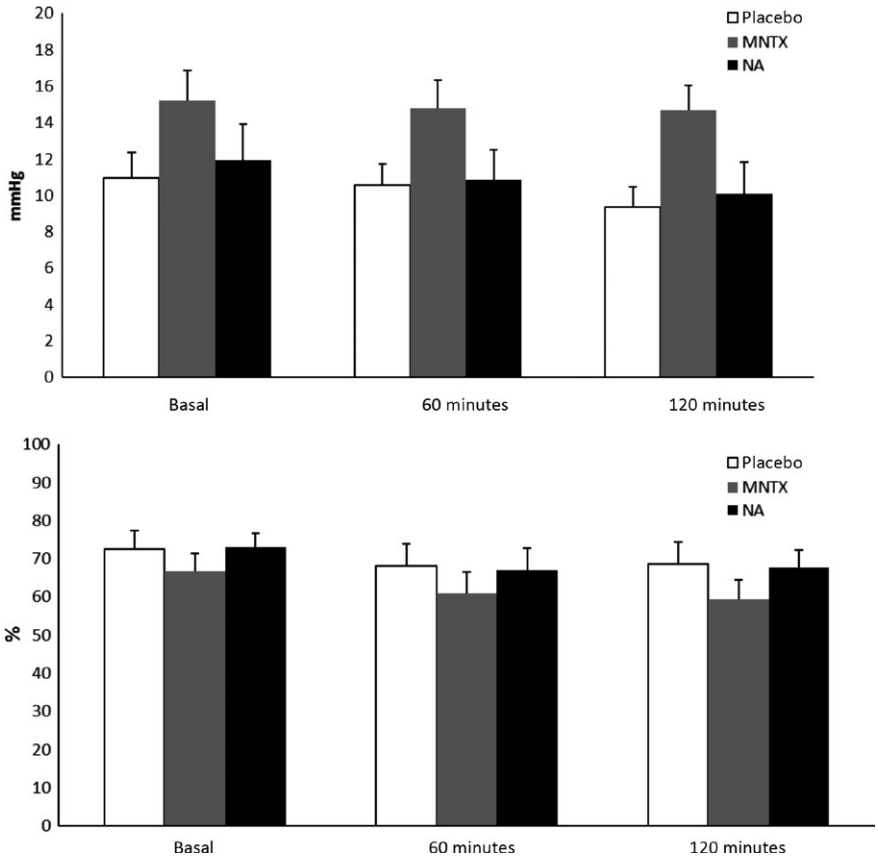

FIGURE 2 (A) UOS Residual pressure. The residual UOS pressure was not significantly altered by MNTX or NA both in the preprandial and postprandial period (ANOVA between placebo, MNTX and NA, all *P*=NS). (B) UOS percentage of relaxation. The UOS percentage of relaxation was not significantly altered by MNTX or NA, both preprandially and postprandially (ANOVA between placebo, MNTX and NA, all *P*=NS)

TABLE 1 Esophageal motility parameters measured

Parameter measured	Placebo	Methylnaltrexone	Naloxone
Preprandial LES resting pressure	41.1 ± 4.6	35.7 ± 3.4	42.7 ± 3.5 mmHg
First postprandial hour LES resting pressure	28.4 ± 2.8*	29.2 ± 3.2*	33.9 ± 3.1 *mmHg
Second postprandial hour LES resting	32.6 ± 3.4*	29.2 ± 2.3*	36.3 ± 3.2 *mmHg
Preprandial IRP4	10.7 ± 1.1	11.2 ± 1.2	13.7 ± 3.6 mmHg
First postprandial hour IRP4	6.4 ± 1.8	8.2 ± 1.1	8.8 ± 1.9 mmHg
Second postprandial hour IRP4	7.5 ± 1.1	8.6 ± 1.0	8.7 ± 2.5 mmHg
Preprandial PFV	2.4 ± 0.2	2.9 ± 0.2	2.8 ± 0.4 cm/s
Postprandial PFV	3.1 ± 0.2	3.2 ± 0.2	3.1 ± 0.2 cm/s

LES resting pressure: Compared to placebo, nor methylnaltrexone (MNTX) and naloxone (NA) increased significantly basal LES resting pressure; both drugs failed to prevent the postprandial drop in LES resting pressure as compared with placebo 60 and 120 min after the meal. *ANOVA between pre- and postprandial periods for placebo, MNTX, and NA: P=.031, P=.036, P=.030.
Integrated relaxation pressure (IRP4): The IRP4, corresponding to those of LES pressures, were not significantly altered by MNTX and NA both preprandially and postprandially. ANOVA between pre- and postprandial periods, all P=NS.
Peak front velocity (PFV) in the pre- and postprandial periods: PFV was not altered by MNTX and NA preprandially and in the postprandial period. ANOVA between placebo, MNTX and NA, P=NS.

TABLE 2 Distal contractile integral (DCI) in the pre- and postprandial period: DCI was not altered by MNTX and NA preprandially and in the postprandial period (ANOVA between placebo, MNTX and NA, both P=NS)

Treatment	Preprandial	Postprandial (mmHg/s/cm)
Placebo	1080 ± 160.1	1165 ± 192.3
Methylnaltrexone	1277 ± 169.5	1354 ± 165.7
Naloxone	1271 ± 220	1267 ± 222.1

ANOVA between placebo, MNTX and NA in the pre- and postprandial periods, both P=NS.

3.5 | Transient lower esophageal sphincter relaxations

Methylnaltrexone and NA both did not significantly affect the number of TLESRs in the fasting period or the postprandial increase in TLESR rate (Table 3).

The duration of TLESRs in the preprandial and postprandial periods was not significantly different in all treatment groups (ANOVA between placebo, MNTX and NA in pre- and postprandial periods, both P=NS) and neither MNTX nor NA prevented its postprandial increase (12.7 ± 3.8 vs 21.8 ± 3.2 seconds, for placebo; two-way ANOVA, P=.029; 11.5 ± 3.4 vs 25.8 ± 2.8 seconds and 12.4 ± 3.9 vs 19.1 ± 3.8 seconds, for MNTX and NA, respectively; two-way ANOVA, P=.033 and P=.025) (Table 4).

TABLE 3 Number of transient lower esophageal sphincter relaxations

Treatment	Preprandial	Postprandial	Total
Placebo	1.3 ± 0.4	7.3 ± 1.1*	8.6 ± 1.3
Methylnaltrexone	0.8 ± 0.4	6.3 ± 1.2*	7.2 ± 1.3
Naloxone	1.1 ± 0.5	6.2 ± 1.1*	7.3 ± 1.6

Compared with placebo, MNTX and NA did not decrease the number of transient lower esophageal sphincter relaxations (TLESRs) in the fasting period. After placebo, ingestion of the meal was associated with a significant increase in the rate of TLESRs during both the first and second postprandial hour. Neither MNTX nor NA prevented this rise in both postprandial periods (*two-way ANOVA, pre- vs postprandial periods for placebo, MNTX and NA, respectively, P=.003, P=.0031, P=.025).

TABLE 4 Duration of transient lower esophageal sphincter relaxations

Treatment	Preprandial	Postprandial
Placebo	12.7 ± 3.5 s	21.8 ± 1.2 s*
Methylnaltrexone	11.5 ± 2.8 s	25.8 ± 1.4 s*
Naloxone	12.4 ± 2.5 s	19.1 ± 0.8 s*

The duration of transient lower esophageal sphincter relaxations in the preprandial and postprandial periods was not significantly different in all the treatment groups (ANOVA between placebo, MNTX and NA in pre- and postprandial periods, both P=NS) and neither MNTX nor NA prevented its postprandial increase. *Two-way ANOVA, P=.029, P=.033 and P=.025.

3.6 | Reflux events

The time below pH 4 in the esophagus was not affected by both drugs in comparison with placebo (5.0 ± 0.5 vs 6.1 ± 0.7 and 4.4 ± 0.5 minutes, ANOVA between placebo, NA and MNTX, P=NS). Both drugs did not significantly affect the total number of reflux episodes (ANOVA between placebo, NA and MNTX, P=NS) and their postprandial increase (0.3 ± 0.2 vs 6.9 ± 1.9 for placebo; two-way ANOVA, P=.004; 0.3 ± 0.2 vs 6.3 ± 2.1 and 0.6 ± 0.3 vs 5.8 ± 2.2, for MNTX and NA, respectively, two-way ANOVA, P=.004 and P=.005).

Both drugs did not affect the number of preprandial acid and non-acid reflux episodes (ANOVA between placebo, MNTX and NA, both P=NS) and did not prevent the postprandial increase in acid reflux events (Table 5(A)); MNTX only decreased the number of non-acid

TABLE 5 (A) Acid and (B) non-acid reflux episodes. Both drugs did not prevent the postprandial increase in acid (nb) (A) and non-acid (nb) (B) reflux events

Treatment	Preprandial period (nb)	Postprandial period (nb)
(A)		
Placebo	0.1 ± 0.1	2.3 ± 0.5*
Methylnaltrexone	0.1 ± 0.1	2.4 ± 0.8*
Naloxone	0.4 ± 0.3	1.6 ± 0.4*
(B)		
Placebo	0.2 ± 0.1	1.2 ± 0.3**
Methylnaltrexone	0.2 ± 0.1	0.8 ± 0.4**
Naloxone	0.1 ± 0.1	1.2 ± 0.6**

*ANOVA between pre- and postprandial periods for placebo, MNTX, and NA: P=.029, P=.028, P=.032.
**ANOVA between pre- and postprandial periods for placebo, MNTX, and NA, respectively: P=.030, P=.032, P=.033.

reflux episodes in the postprandial period (P=.03), but this was no longer significant after correction for multiple testing (P=.08) (Table 5(B)).

3.7 | Symptoms and adverse events

No significant differences in symptom scores (calculated as area under the curve, AUC) during both the preprandial and postprandial periods were found between MNTX, NA and placebo studies except for higher hunger and appetite ratings in the fasting state after NA administration (hunger: 4015 ± 444 vs 3560 ± 478 and 3600 ± 459 mm*min; appetite: 3985 ± 447 vs 3305 ± 486 and 3555 ± 466 mm*min; NA vs placebo and MNTX, respectively, both P<.05) (Table 6). No side-effects were registered.

4 | DISCUSSION

The aim of the present study was to investigate how selective and non-selective inhibition of μ-opioid receptors would influence esophageal motility, TLESR occurrence and gastro-esophageal reflux events in healthy volunteers. Our major findings were that neither MNTX and NA alter peristaltic performance or the occurrence and duration of TLESRs preprandially and postprandially. In addition the selective and non-selective μ-opioid receptor inhibition does not lead to a significant reduction in total number of reflux events in the postprandial period as assessed by impedance and pH monitoring devices.

The impact of opioids on GI function is well-known, leading to therapeutic use of opioids as antidiarrheals. After the identification of μ-, κ-, and δ-receptors, leucine-enkephalin and methionine-enkephalin were identified in the central nervous system (CNS) and the enteric nervous system (ENS) as the first endogenous opioid receptor agonists.[25–28] The inhibitory effect of opioid receptor agonists on peristalsis, both in animal and human studies, arises from interruption of neuro-neuronal and neuroeffector transmission

TABLE 6 Upper GI symptoms before the meal

Treatment	Hunger (mm*min)	Appetite (mm*min)
Placebo	3560 ± 478	3305 ± 486
Methylnaltrexone	3600 ± 459	3555 ± 466
Naloxone	4015 ± 444*	3985 ± 447*

No significant differences in symptom scores (calculated as area under the curve, AUC) during both the preprandial and postprandial periods were found between methylnaltrexone, naloxone and placebo studies except for higher hunger and appetite ratings in the preprandial period after naloxone administration (*P<.05).
*P<.05, NA vs placebo and MNTX.

within enteric nerves,[4, 28–30] both through presynaptic and postsynaptic sites of action on enteric neurons, resulting in an attenuated release of transmitters.[31] Thus, opioid receptor agonists such as morphine can interrupt both excitatory and inhibitory neural inputs to GI muscle. More specifically, suppression of excitatory pathways inhibits the release of acetylcholine and blocks distention-induced peristaltic contractions, whereas blockade of inhibitory neural inputs results in depression of nitric oxide release from inhibitory motor neurons, disinhibition of GI muscle activity, elevation of resting muscle tone and non-propulsive motility patterns.[32, 33] Previous studies have shown that peripherally selective and non-selective (able to cross the blood-brain barrier) opioid receptor antagonists are able to influence motility in the gastrointestinal tract, especially in subjects being administered opioids.[13] In the latter case, selective antagonists such as MNTX are preferred as they do not interfere with the central analgesic effect of agonists. In the present study we observed no significant change in basal esophageal contractility patterns as assessed by HRM after administration of MNTX and NA. Hence, despite the fact that opioid nerve endings and receptors are expressed in the esophagus, as in the rest of the gastrointestinal tract, their role in esophageal body and LES motor function seems limited.[25] Similarly, UES function as assessed by manometry was not significantly altered by the opioid antagonists.

The number of TLESRs was not affected by administration of NA or MNTX, both capable of inhibiting actions of endogenous opioids. On the other hand, morphine, a synthetic opioid receptor agonist, is known to reduce the rate of TLESRs in GERD patients and to a lesser degree in healthy subjects, an effect that could be reversed by NA.[16, 17] While these studies demonstrated the ability of opioid receptor agonists to affect TLESRS, the results from our current study indicate that endogenous opioids do not play a physiological role in triggering and controlling TLESRs. This is unexpected, given the well-established effect of both NA and MNTX on gastric accommodation to a meal, which is thought to control TLESR triggering.[19, 20] However, in the study by Penagini,[16] NA, a non-selective endogenous opioids antagonist, only reversed the effect of morphine, but also did not show any "reverse agonist" effect (pharmacological effects in absence of the agonist). Also, in agreement with the findings of Penagini, in our study neither NA nor MNTX increased the LES residual pressure.[8,16] In our study both MNTX and NA failed to reduce the total number of reflux events. This is in agreement with the observation that the selective

peripheral μ-receptor agonist loperamide also did not alter the rate of reflux events in GERD patients.[18]

In summary, in this placebo-controlled, single-blind, randomized, cross-over study we observed that the specific peripheral μ-receptor antagonist, MNTX and NA do not affect esophageal body motility and LES function.

DISCLOSURE

No competing interests for any of the authors.

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