Title: Codeine delays gastric emptying through inhibition of gastric motility as assessed with a novel diagnostic intragastric balloon catheter

Running head: Codeine impairs gastric motility and emptying

Authors: Nick Goelen[1], Jan de Hoon[2], John Fredy Morales Tellez[3,4], Carolina Varon[3,4], Sabine Van Huffel[3,4], Patrick Augustijns[5], Raf Mols[5], Marissa Herbots[2], Kristin Verbeke[1], Tim Vanuytsel[1,6], Jan Tack[1] and Pieter Janssen[1]

Affiliations:

[1]Translational Research Center for Gastrointestinal Disorders, KU Leuven, Leuven, Belgium.

[2]Center for Clinical Pharmacology, Leuven University Hospital, Leuven, Belgium

[3]Department of Electrical Engineering-ESAT, STADIUS Center for Dynamical Systems, Signal Processing and Data Analytics, KU Leuven, Leuven, Belgium

[4]Imec, Leuven, Belgium

[5]Drug Delivery and Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

[6]Leuven Intestinal Failure and Transplantation (LIFT), Leuven University Hospital, Leuven, Belgium

Corresponding author contact details: Nick Goelen, Herestraat 49, bus 701, BE-3000 Leuven, E-mail: nick.goelen@kuleuven.be Tel.: +32 (0)16 372342, Fax: +32 (0)16 345939

Abstract

Background: The use of opioids as analgesic is on the rise, despite their inhibitory effect on gastric emptying. A novel feeding catheter with integrated intragastric balloon was developed to continuously assess gastric motility, enabling to investigate the effect of opioids on motility and emptying simultaneously. We aimed to discriminate normal and pharmacologically-impaired gastric motility and its impact on gastric emptying in healthy adults.

Methods: The VIPUN Gastric Monitoring System comprises a nasogastric balloon catheter and a monitoring unit. In a four-way randomized cross-over design, subjects received either placebo or 58.8 mg codeine phosphate in combination with either an uninflated or inflated balloon catheter (180 mL). Motility-induced pressure changes were recorded for 6 hours. During the first 2 hours, nutrients were infused (225 kcal, 75 $mL.h^{-1}$). Gastric emptying was assessed with a ^{13}C-octanoate breath test and expressed as gastric half-emptying time (GET½). An algorithm, designed to detect phasic contractility, converted pressure changes to a gastric balloon motility index (GBMI). Results are presented as mean(SD).

Key Results: Eighteen subjects completed the investigation (32(13) years, 22(2) $kg.m^{-2}$). After codeine treatment, GBMI was lower (0.31(0.16)) and GET½ was longer (233(57) minutes) compared to placebo (GBMI: 0.48(0.15), $p<0.01$ and GET½: 172(12) minutes, $p<0.001$). Within-subject ΔGET½ correlated significantly with ΔGBMI ($r=-0.77$, $p<0.001$).

Conclusions & Inferences: The VIPUN Gastric Monitoring System allowed to assess gastric motility safely and continuously. The correlation between pharmacologically-decreased gastric emptying and motility indicates a strong link between both. Gastric motility, measured with this innovative device, can be an indicator for gastrointestinal intolerance.

Keywords: Gastric motility, gastric emptying, codeine, medical device, VIPUN GMS

Key Points:

WHAT IS CURRENT KNOWLEDGE

- Opioids impair gastrointestinal function thereby contributing to feed intolerance in critically ill patients.
- Gastric motility is currently difficult to monitor.

WHAT IS NEW HERE

- The VIPUN Gastric Monitoring System is a novel, minimally invasive technique to assess phasic gastric motility continuously.
- Codeine-induced inhibition of phasic gastric motility correlated well with delayed gastric emptying

TRANSLATIONAL IMPACT

- The VIPUN Gastric Monitoring System has the potential to guide and optimize enteral nutrition therapy in critically ill patients.

Introduction

Gastric emptying relies on a complex interplay between the major motility patterns of the stomach.[1,2] Gastric motility in the fasted state is characterized by a recurrent pattern of phasic contractions, the migrating motor complex.[3] Upon food intake, the proximal stomach relaxes and contractility of the distal stomach diminishes. Following this initial reflex relaxation, tonic contraction of the proximal stomach propels gastric contents forward, providing a first driving force for gastric emptying.[2] Simultaneously, peristaltic contractions emerging from the mid-corpus grind and sieve solid food.[4] This peristaltic motor pattern forms a second drive that pushes gastric contents distally. A third factor in the regulation of gastric emptying is opening and closure of the pyloric sphincter. The pylorus periodically opens to allow a constant flow of chyme with a caloric content of approximately 1-3 kcal.min^{-1} into the duodenum.[2,5,6] Activation of duodenal receptors, sensitive to different aspects of the chyme, initiates a complex neurohumoral feedback to finely tune gastric motility.[2] This feedback mechanism ideally results in a gastric emptying rate that matches the absorptive capacity of the small intestine.[7]

Although the use of opioids is on the rise worldwide for a plethora of indications,[8] it is associated with gastrointestinal (GI) discomfort, malfunction and intolerance,[7,9,10] exemplified by opioid-induced constipation and enteral feeding intolerance in the intensive care unit.[7,9,10] δ-, κ- and μ-opioid receptors are present throughout the central and enteric nervous system.[11] Activation of the μ-opioid-receptor in smooth muscles of the GI tract has heterogeneous effects on GI motility.[11] Overall, it is assumed that opioids inhibit gastric emptying through inhibition of propulsive gastric contractility and stimulation of distal resistance at the antrum and pylorus.[12–15] Even though it is well-known that opioids decrease gastric emptying,[16–19] their effect on gastric motility is less clear and contradicting results have been reported.[13,18–24] One factor hampering insight is the paucity of robust research tools.[25] Barostat experiments showed contradictory effects on proximal gastric tone and its impact on gastric emptying.[18,22–24] Studies using

manometry and wireless motility capsules report both inhibition and stimulation of contractility following opioid administration.[15,20] Even though, these techniques require lumen-occluding contractions, as seen in the esophagus and distal stomach. Until recently, no direct bedside measure of phasic contractility of the entire stomach was available to be used in clinical practice.

We recently developed a novel technique for continuous measurement of gastric contractility. The novel device, referred to as the VIPUN Gastric Monitoring System (VIPUN GMS) comprises a double lumen nasogastric balloon catheter and a control unit (Figure 1). The widest lumen provides a route for liquid nutrient and drug administration. A second lumen connects the intragastric balloon to an external control unit with a pressure sensor and analysis software. Once positioned, the balloon is inflated to a constant volume of 180 mL. Consequently, intraballoon pressure fluctuations, evoked by gastric muscle activity, provide a direct measure of phasic gastric contractility.[26] The optimal balloon shape and size were determined and published previously.[26] Impaired motility and emptying are important pathophysiological factors in multiple GI diseases, disorders and food intolerance in general and more specifically in critically ill patients.[27–30]

We aimed to discriminate physiological and pharmacologically-impaired gastric motility and its impact on gastric emptying in healthy subjects.

We hypothesized that a codeine-induced delay in gastric emptying is accompanied by decreased phasic gastric motility, as quantifiable with the VIPUN GMS. A secondary hypothesis was that balloon inflation could promote gastric contractility.

Materials and methods

Investigational medical device

The investigational medical device studied in this study, the VIPUN™ Balloon Catheter (Figure 1), was a single-use nasogastric balloon catheter consisting of a standard 12 French nasogastric double lumen Sump catheter (Vygon, Ecouen, France) and a polyurethane balloon (Via Biomedical, Maple Grove, MN, USA) attached to it. Deflated, the balloon catheter allows easy positioning through the nose. Once in the stomach, the balloon could be inflated. The balloon pressure was measured with a custom-made control unit connected to the catheter at the proximal ending. The control unit consisted of a pressure sensor (MPX2050DP, NXP Freescale™, Munich, Germany) and data acquisition unit (DI-245, DATAQ™ Instruments, Akron, OH, USA) that was in turn connected to a personal computer (Dell Latitude™ E5540, Round Rock, TX, USA). WinDaq™ data acquisition software (DATAQ™ Instruments, Akron, OH, USA) was used to record pressure data at 10 Hz with a resolution of 0.1 mmHg. The balloon catheter was designed to allow intragastric infusion of liquids while simultaneously recording intraballoon pressure.

Study design

In this monocentric, single-blinded, placebo-controlled, four-way cross-over investigation, healthy volunteers were randomly assigned to a treatment sequence consisting of 4 arms: 1) placebo + uninflated balloon, 2) codeine + uninflated balloon, 3) placebo + inflated balloon and 4) codeine + inflated balloon. Following a screening visit, four study visits were performed at least one week apart from each other.

Recruitment

Healthy adults with a body mass index between 18 and 25, without gastrointestinal symptoms or medical history, were recruited. Chronic dyspeptic symptoms were assessed using the PAGI-SYM questionnaire.[31] Subjects were eligible for participation if they were not pregnant (as confirmed by a urine pregnancy test) or breast feeding and had no known contra-indications for

the insertion of a nasogastric tube, no intolerance for any of the study products and no relevant medical history or concomitant drug use that could influence normal gastric function.

Study procedures

Subjects fasted and refrained from alcohol and caffeine for at least 12 hours prior to each study visit. Ad libitum water intake was allowed until 2 hours prior to each visit. Subjects were randomized during the first study visit by means of randomization envelopes containing a random treatment sequence.

The balloon catheter was inserted transnasally into the proximal stomach. Local anesthetic spray (Xylocaine 10 %, NV AstraZeneca, Dilbeek, Belgium) and a water-based lubricant (Endo Gel, RMS Home Care, Roosdaal, Belgium) were used to ease intubation. Subjects were placed in a semi-recumbent position. The balloon lumen of the catheter was connected to the control unit. The nutrient lumen of the catheter was attached via an ENFit™ connection to an enteral feeding pump. See Figure 2 for a schematic overview of the study procedures.

Codeine or placebo syrup was infused intragastrically as a bolus 25 minutes prior to nutrient infusion. Codeine was administered as 30 mL Bronchodine® (60 kcal; Laboratoria Sterop, Brussels, Belgium), containing 58.8 mg codeine phosphate. This dose of codeine was shown to delay GI motility.[32] The placebo consisted of 18.3 mL sirupus simplex (60 kcal; Fagron, Nazareth, Belgium) to match the calories in the codeine arm. After syrup administration, the balloon was either inflated manually with a syringe to 180 mL or remained uninflated, according to the randomization. Subjects were blinded throughout the investigation to the given treatment (placebo or codeine) and the intraballoon volume.

Intraballoon pressure was recorded continuously for 375 minutes, from the moment the balloon was inflated until deflation. The pressure data recorded with the uninflated balloon were not suitable for analysis.

A ^{13}C-octanoate breath test was used to quantify gastric emptying rate.[33] 1-^{13}C sodium octanoate (Cambridge Isotope Laboratories, Tewksbury, MA, USA) was mixed with Fortimel® Energy (150 kcal, 6 g proteins, 18.9 g carbohydrates and 5.8 g lipids per 100 mL; Nutricia, Utrecht, The Netherlands) to a final concentration of 0.5 mg.mL^{-1}. This nutrient mixture was infused intragastrically over a period of 2 hours at 75 mL.h^{-1} through the widest lumen of the balloon catheter. Prior to nutrient infusion, two baseline breath samples were collected by blowing through a straw in a 12 mL glass Exetainer® (Labco, Lampeter, Wales). During and after nutrient infusion, breath samples were collected at a 15-minute interval up to 6 hours. Gastric evacuation, followed by small intestinal absorption, is the rate-limiting step of $^{13}CO_2$ appearance in exhaled breath.

Venous blood samples were collected in 6 mL lithium-heparin Vacutainers® (95 USP units, BD Diagnostics, Franklin Lakes, NJ, USA) before, 90 and 180 minutes after syrup administration. Blood samples were immediately centrifuged (3000 g at 4°C for 10 minutes). Plasma samples were put on dry ice and stored at -80°C until analysis.

Hunger, nausea and upper-abdominal bloating were surveyed at baseline, 20 minutes after syrup administration and at the end of the nutrient infusion on a 100 mm visual analogue scales (VAS) (0 = absent, 100 = worst possible sensation). At the same time points, epigastric sensation or pain was graded on a 10-point scale with verbal descriptors (0 = no sensation, 5 = pain threshold, 10 = excruciating pain).

The study was performed at the Center for Clinical Pharmacology of the University Hospital Leuven, independently from the research group that developed the technique to allow an objective and independent evaluation of feasibility.

Analysis

Gastric motility

A custom-made algorithm was applied to calculate a gastric balloon motility index (GBMI) for each 30 minute-window. Pressure data was analyzed for a period of 6 hours, starting at the initiation of nutrient infusion. To pre-process the signals, an interpolation filter was first applied to remove high amplitude artefacts (gagging and coughing). Secondly, high frequency contractions (> 0.1 Hz) were discarded with a low pass filter. Finally, the signal was smoothed with a moving averaging filter with a window of 2 samples.

After pre-processing, pressure peaks were detected in the filtered signal. The start of a peak was defined as the first change in the direction of the slope to the left of a detected peak, the end of a peak was defined as the first change of the slope direction to the right of a detected peak. To decide whether a peak was produced by gastric activity or not, the separation between the peaks, the peak prominence and the time separation between the start and end of a peak were taken into account. Peaks that were not considered as produced by gastric contractions were discarded.

To calculate the GBMI, periods of gastric activity were defined as the time from the start to the end of a peak corresponding to a gastric contraction. Subsequently, the GBMI was calculated as the percentage of time in which the stomach is active in windows of 30 minutes. This can be denoted as follows:

$$GBMI = \frac{\sum_{i=1}^{n}(t_{(i)_finish} - t_{(i)_start})}{t_{total}} * 100$$

Where *n* = number of contractions, $_{(i)_start}$ = time in which the ith contraction starts and $t_{(i)_finish}$ = time in which the ith contraction ends.

Motility data were analyzed in a paired-wise fashion. Motility was only quantified for those conditions with an inflated balloon.

Since GBMI is calculated for 30 minute time periods, GBMI at 150 min is still influenced by pressure fluctuations occurring during nutrient administration. A transition margin of 60 minutes was applied to clearly differentiate between the period of nutrient infusion (t = 0-120 min) and the postprandial phase (t = 180-330 min).The period t = 330-360 min was discarded for the analysis due to the abundancy of movement artefacts.

Gastric emptying

The ^{13}C-content in breath samples was analyzed with continuous flow isotope ratio mass spectrometry (ABCA, Sercon, Crewe, UK). The ^{13}C-content was compared to an external standard [Pee Dee Belemnite (PDB) Limestone] and expressed in a Δ^{13} value in per mill (‰), after a correction for the oxygen isotope effect. CO_2-production rate was assumed to be 300 mmol.m^{-2} body surface area per hour[34]. Breath samples containing < 0.6 % CO_2 were excluded from analysis. The % dose per hour was calculated based on the % recovery of the ^{13}C dose given at a certain time. Non-linear regression analysis was performed on the % dose per hour values (MatLab® R2017b, The MathWorks®, Natick, MA, USA). The resulting half-excretion time ($GET½ = 60 \times [{}^{-1}/_{k} \times \ln(1 - 2^{-1/\beta}]$) was expressed in minutes.[33] Whereby m, k and beta are regression-estimated constants with m the % dose recovered when time is infinite. The mean peak hourly ^{13}C recovery was derived from the maxima of the individual fitted curves.

Codeine and morphine plasmaconcentration

The plasma codeine-morphine ratio was measured by reverse phase high performance liquid chromatography with mass spectrometry detection (Acquity H-class UPLC, Waters, Milford, MA, USA and Xevo TQ-S micro Waters, Milford, MA, USA). Details are provided in the supporting Information.

Safety and feasibility

Feasibility was assessed based on protocol deviations with regard to the use of the device.

Statistics

Continuous data were summarized by their mean, standard deviation (SD) and/or 95 % confidence intervals. Motility was analyzed using a two-way repeated measures analysis of variance (RM ANOVA) to test codeine-induced changes while a one-way RM ANOVA was used to investigate the breath test results, followed by paired t-tests with Bonferroni correction. Changes in GET½ were studied using generalized mixed effect models with random intercept for each subject. Relations between motility and emptying were explored using linear regression and Pearson's correlation coefficient. Categorical data were summarized by frequencies and percentages. A p-value < 0.05 was considered as statistically significant. Missing data were not imputed. Symptom scores were explored descriptively. Safety and feasibility analysis were based on the intention to treat population (all enrolled subjects). Gastric function was analyzed for those subjects who had completed all four visits (full analysis (FA) dataset).

Regulatory

This study was approved by the ethics committee of the University Hospitals Leuven (S60320, Belgian registration number: B322201733283) and the Federal Agency for Medicines and Health Products (AFMPS/80M0687). The study was registered on clinicaltrials.gov (NCT03239821) and the EUDAMED reference is CIV-BE-18-01-022724.

Results

Population

A total of 29 volunteers were screened and 23 were enrolled (intention to treat population) of whom 18 completed the four visits (13 females, age 31.5 (13.3) year, body mass index 22.4 (1.8)

kg.m^{-2}). Eighty-three visits were initiated and 75 completed according to protocol. The Full Analysis (FA) dataset comprised 72 visits. Subject disposition is shown in Figure 3. The procedures were well tolerated, except for three subjects who experienced discomfort from the nasogastric catheter. No serious adverse events or serious adverse device effects occurred. One subject was classified as a poor metabolizer based on morphine plasma concentrations after codeine administration (< 1 nM). Exclusion of this subject did not affect the outcome nor the conclusions in any of the analyses.

Motility

When the intragastric balloon was inflated, phasic motility could be observed in all subjects. Representative motility recordings are shown in Figure 4. There was a significant main effect of pharmacological condition, $F(1,17) = 15.1$, $p = 0.001$. There was also a significant main effect of time, $F(11,187) = 17.7$, $p < 0.001$ (two-way RM ANOVA). Over the entire recording period, the GBMI was significantly lower after codeine administration compared to placebo with on average 0.17 units difference (95 % CI: 0.08 to 0.26, $p = 0.001$, Figure **5**). During nutrient infusion, GBMI was significantly lower after codeine administration compared to placebo (0.12 (0.04) vs. 0.29 (0.04), $p = 0.008$, paired t-test). This difference was also observed in the postprandial phase (0.40 (0.11) vs 0.57 (0.09), $p = 0.004$, paired t-test). Moreover, GBMI was significantly lower during nutrient infusion (t = 30-120 min) compared with the postprandial phase (t = 180-330 min), irrespective of the pharmacological condition [mean GBMI codeine: 0.12 (0.11) during infusion vs. 0.42 (0.27) postprandially, placebo: 0.29 (0.26) during infusion vs. 0.60 (0.16) postprandially, both $p < 0.001$ (paired t-tests)].

Gastric emptying

The total recovered dose ^{13}C was not different in any condition ($p = 0.68$, One-way RM ANOVA). Overall, the maximum hourly recovered ^{13}C value was lower after codeine treatment, a

difference that reached significance between placebo and codeine in the conditions with an inflated balloon (12.21 (1.41) vs. 10.84 (2.21) $mg.h^{-1}$, adjusted p = 0.02, one-way RM ANOVA), however not in the conditions with an uninflated balloon (11.59 (1.49) vs. 10.75 (2.41) $mg.h^{-1}$, adjusted p = 0.41); see Figure 6. In the placebo condition, the maximum hourly ^{13}C recovery was numerically lower in the uninflated condition compared to the inflated condition (p = 0.71), whereas no difference was found between the codeine arms (p > 0.99).

Gastric half-emptying time (GET½) for each subject per treatment is shown in Figure 6. The GET½ was significantly higher after codeine administration, irrespective of the balloon volume (mean GET½ uninflated: 240 (63) min and inflated: 233 (57) min) when compared to the placebo arms (mean GET½ uninflated: 189 (40) min and inflated: 172 (12) min) for the uninflated and inflated balloon, respectively (p < 0.001, generalized linear mixed-effects model, Figure 6).

Relation between gastric motility and emptying

The relation between gastric emptying and motility both during infusion and post-infusion is shown in Figure 7. Codeine treatment resulted in a significant negative correlation between GBMI and GET½. This relation was more pronounced post-infusion (Pearson's r = -0.83, p < 0.001) compared to during infusion (Pearson's r = -0.53, p = 0.02). No such relation was found for the placebo treatment (r = -0.42, p = 0.08 during infusion and r = -0.34, p = 0.17 post-infusion). Pooling both pharmacological conditions, GBMI and GET½ were correlated well during (Pearson's r = -0.45, p = 0.006) and after nutrient infusion (Pearson's r = -0.78, p < 0.001).

A significant negative relation was observed between ΔGBMI post-infusion [codeine – placebo] and ΔGET½ [codeine –placebo] (Pearson's r = -0.77, p < 0.001), shown in Figure 8. ΔGET½ was not correlated with codeine-induced ΔGBMI during nutrient infusion (Pearson's r = -0.06, p = 0.84).

Plasma concentration of opioids

Based on plasma analysis, all but one subject readily converted codeine into morphine. Morphine plasma concentrations of this one poor metabolizer remained below the threshold of 1 nM at all sampling time points. The mean plasma codeine concentration was 363.7 (135.1) nM. The mean plasma morphine concentration was 6.0 (3.9) nM, which corresponded to a conversion of 1.8(1.2) % of codeine into morphine. There was no significant correlation ($p > 0.05$) between [morphine] and codeine-induced changes in GBMI (neither during infusion or post-infusion) and changes in GET ½.

Exclusion of the poor metabolizer in any of the analysis did not affect the outcome nor the conclusions. Therefore, the poor metabolizer was included in the FA population.

Safety and feasibility

Over the course of the investigation five subjects dropped out and were replaced. In one subject, the balloon catheter could not be placed, two subjects could not tolerate the procedures and two subjects withdrew their consent due to a lack of time. Nurses who were not involved in the development of the device achieved successful placement and removal of the balloon catheter without any remarks in 93.4 % of the procedures. Epigastric symptoms (bloating, nausea and sensation/pain) were surveyed with 100 mm VAS at baseline and 5 minutes and 125 minutes after the start of the procedure. Symptom scores were generally low. Mild nausea was associated with codeine and the inflated balloon. Mild bloating was associated with the inflated balloon. Epigastric sensation scores remained below the pain threshold. Details and figures are provided in the supporting information.

Discussion

In this study, the novel VIPUN Gastric Monitoring System was used to assess the influence of codeine on gastric motility. We hypothesized that the codeine-induced inhibition of gastric emptying is closely correlated with decreased motility. The effect of codeine on gastric emptying and motility could successfully be examined in 18 healthy subjects. It was indeed demonstrated that codeine-induced delay in gastric emptying correlated well with decreased gastric motility. The paired cross-over placebo-controlled study design enabled us to assess the effect of a single dose of 58.8 mg codeine phosphate on intraindividual differences in gastric emptying and motility. Even though the effect of opioids on gastric emptying is well-recognized, their effect on gastric motility is much less clear.[11,13–15,18,21–24] In this study, we provide strong indication that opioid-induced delayed gastric emptying is closely related to decreased phasic contractility of the stomach.

The use of the balloon catheter was found to be safe and well tolerated. Epigastric symptom scores were generally low. Mild nausea was associated with codeine administration, whereas mild bloating was associated with the inflation of the intragastric balloon. Besides their deleterious effects on GI function, opioids are indeed known to act on the chemoreceptor trigger zone as well, thereby inducing nausea and vomiting.[35]

Both codeine and nutrient infusion had a significant inhibitory effect on gastric motility. Duodenal nutrient sensing triggers a feedback loop that inhibits gastric motility, thereby facilitating gastric accommodation and limiting gastric outflow.[2,36] Opioids, on the other hand, exert their inhibitory effect on GI transit and secretion mainly by activation of peripheral μ- and δ- receptors.[14,32] A substantial confounder and important limitation of this study is the temporal overlap of the nutrient infusion and the peak pharmacological effect of codeine as both were found to reduce phasic motility. Both inhibitory effects might add to the bi-phasic motility pattern observed in both treatment arms. Codeine and morphine both reach a maximum plasma

concentration after 30 to 60 minutes, hence during meal infusion.[32] The terminal half-life in extensive metabolizers is 2 hours and 3.6 hours for codeine and morphine, respectively.[32] Both after codeine and placebo treatment, gastric motility was low during nutrient infusion and gradually increased in the postprandial period. It could be inferred that the inhibitory effect of a relatively limited nutrient exposure (60 kcal in syrup bolus and 225 kcal infused over 2 hour) diminished shortly after cessation of the infusion.[37,38] Gastric emptying in health ranges from 1 to 4 kcal/min.[6] We used a rather limited infusion rate of 1.875 kcal/min, which reflects the routine practice of nutrient delivery at the intensive care unit. This infusion rate thus matches physiological emptying rates, which probably contributes to the limited variability in the placebo conditions. In a portion of the subjects, codeine did result in a substantial inhibition of gastric motility and consequently emptying. A higher infusion rate might have delayed gastric emptying in a larger fraction of subjects.

The lower hourly ^{13}C recovery, lower peak ^{13}C recovery and longer GET½ all demonstrate that codeine administration resulted in a slower gastric emptying compared to placebo, irrespective of the balloon volume. Gastric emptying of liquids is the net effect of propulsive forces, mainly from the proximal stomach in combination with distal resistance at the antro-pyloro-duodenal region.[39] Previous research has shown that opioids increase this distal resistance.[11,13–15,40] The current study strongly indicates that opioids also inhibit the propulsive gastric forces. The ^{13}C-octanoate breath test is a semi-quantitative test, relying on preserved small intestinal absorption. Mathematical parameters are not easily translated to physiological events. The current study design does not allow to exclude the possibility that the stomach was completely empty shortly after cessation of nutrient infusion, despite the shortest calculated half-emptying time of 153 min. Nevertheless, the crossover design allows a reliable relative comparison of gastric emptying. In an ongoing follow-up study, more direct measures of gastric emptying should confirm the current observations. The GET½ reported in this study differs from other

studies given that our meal (continuous infusion of a liquid meal at 75 $ml.h^{-1}$) differs from the standard meals consumed as bolus in most other studies.[41,42]

It has previously been shown that inflation of intragastric balloons can evoke phase-III contractions.[26,43] We hypothesized that the inflated balloon might trigger contractility as seen with a solid meal.[4] Contrary to our expectations, inflation of the balloon was not able to overcome the pharmacological inhibition of gastric emptying, relative to the control condition in which the balloon was not inflated.

A significant negative correlation between GBMI and GET½ was found in the codeine arm. This relation was more pronounced in the post-infusion period (r = -0.83) compared with the period during infusion (r = -0.53). A plausible explanation is that during nutrient infusion, the combined inhibitory effect of nutrient exposure and codeine resulted in a weaker correlation between motility and emptying (Figure 7). In the postprandial period, motility was most likely less affected by the meal-induced neurohumoral feedback loop. Under physiological conditions, the variability in gastric emptying rate was small compared to the codeine arms, as expected. Consequently, no significant linear relation was found between motility and emptying in the placebo arm. A type II error cannot be excluded. The study was not designed to confirm whether opioids or a nutrient stimulus is the more potent inhibitor of propulsive contractility. Nevertheless, codeine administration and nutrient infusion were important temporal confounders, which should be taken into account in future research.

Most importantly, a significant strong negative correlation between the intraindividual codeine-induced changes in motility and codeine-induced changes in emptying rate was found. It was inferred that a substantial delay in gastric emptying rate is associated with low gastric motility. Conversely, preserved normal motility was never associated with slow gastric emptying. Further research in patient populations is imperative to define clinically relevant thresholds.

399 Codeine is a pro-drug, which is oxidized by the hepatic enzyme cytochrome P450 2D6 into its
400 active metabolite morphine.[44] Morphine is responsible for the analgesic effect of codeine, as
401 well as for the inhibitory effect on the gut.[32,45] Approximately 3 % to 10 % of the Caucasian
402 population are so-called poor metabolizers due a genetic polymorphism of the *CYP2D6* gene.[44,46]
403 In such poor metabolizers, codeine does not prolong whole-gut transit time.[32] Subjects were not
404 genetically screened *a priori*, since plasma measurements provide a more direct readout of
405 codeine absorption and oxidation into morphine. One poor metabolizer was enrolled in our
406 study, in accordance with the expected prevalence of 5.5 % as cited in the literature.[44] Exclusion
407 of this subject did not affect the outcome nor the conclusions in any of the analyses. Plasma
408 morphine concentrations did not correlate with the inhibitory effects on gastric function.
409 Multiple receptors and pathways via which opioids can interact with GI function have been
410 described.[14,21,44,47] It is conceivable that inter-individual differences in any of these pathways
411 result in heterogeneous pharmacodynamics and thus GI effects.

412 Impaired motility and emptying are important pathophysiological factors in an array of GI
413 diseases, disorders and food intolerance in general.[27,28] Feeding intolerance and stasis are major
414 issues in the intensive care unit, which affect about 50 % of all critically ill patients on nasogastric
415 tube feeding.[29] Nevertheless, the gut remains a black box for the intensive care provider.
416 Nowadays, the provision of enteral nutrition is hampered by fear of intolerance, resulting in
417 cautious feeding protocols.[48–54] Accurate, real-time bedside monitoring of gastric motility could
418 increase the efficacy and safety of enteral nutrition and decrease complications and the length
419 of stay.[30] The presented investigational medical device, the VIPUN Gastric Monitoring System
420 has the potential to guide personalized nutritional support. The infusion rate used in this study
421 reflects clinical practice at the intensive care unit. A first study using the VIPUN catheter in the
422 intensive care unit is ongoing.

The investigation was performed by nurses, who were not linked to the gastroenterology department, to allow an independent evaluation of feasibility. No hurdles were encountered that might prevent implementation in clinical practice. Apart from recording gastric contractility, the device allows simultaneous intragastric delivery of nutrients or drugs without any extra burden for the patient or the nursing staff.

Furthermore, the device can be exploited as a research tool in functional gastric motility disorders, which pose an important burden to the patients' quality of life and the healthcare system.[55] In ongoing studies, the intragastric position of the balloon catheter is being assessed by direct imaging.

We conclude that the use of the VIPUN Balloon Catheter is safe and feasible in healthy adults, and that it allows to continuously assess gastric motility during and after infusion of a liquid nutrient meal. This study provided proof-of-concept that the VIPUN Gastric Monitoring System can be used to quantify gastric motility and that phasic gastric motility is related to gastric emptying. Both nutrients and codeine were found to decrease motility while codeine was also able to decrease gastric emptying. The effect of codeine on gastric emptying was well correlated with decreased motility. Inflation of the balloon did not affect gastric emptying. These positive results support the further development of the VIPUN Gastric Monitoring System for its intended use in a clinical setting, which will conceivably contribute to a better therapeutic and nutritional management of patients with impaired gastric motility.

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457 All authors were involved in the conceptualization of the study, execution of the experiments,
458 and/or interpretation of the results. JdH was the principal investigator. JT, CV, SVH and PJ
459 designed the analysis algorithm. The manuscript was drafted by NG and PJ, and reviewed by all
460 co-authors.

461 Competing interests: NG and PJ own shares in VIPUN Medical, the other authors have no
462 competing interests.

463

464 **Abbreviations:**

465 GBMI: Gastric Balloon Motility Index, GET½: Gastric half-emptying time, VAS: Visual
466 Analogue Scale, VIPUN GMS: VIPUN Gastric Monitoring System.

467

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Figure legends

Figure 1: Schematic overview of the VIPUN Gastric Monitoring System. The proximal end of the widest lumen is fitted with an ENFit connector to enable nutrient and drug infusion. Nutrient outlets are positioned distally from the balloon (gray arrows) at 4.5 and 6 cm from the distal tip. Distal from the balloon, the tube has a length of 7 cm. The thinner balloon lumen is connected to a differential pressure transducer, which, in turn, is connected via a data acquisition unit to a standard stand-alone laptop with visualization and analysis software. Inflated balloon dimensions are approximately 14 cm by 5 cm. Artist's impression of dimensions.

Figure 2: Timeline study procedures during a single visit. After a baseline check of eligibility, an intravenous (IV) cannula was inserted. After positioning of the balloon

650 catheter, placebo or codeine syrup was administered through the nasogastric catheter
651 (10 minutes prior to balloon inflation). Two baseline breath samples were collected prior
652 to infusion of the ^{13}C-enriched liquid nutrients (120 minutes at 75 mL.h^{-1}). Afterwards,
653 breath samples were collected at a 15-minute interval. Three blood samples were
654 collected for codeine and morphine plasma analysis. Visual analogue scales (VAS) for
655 epigastric symptoms were completed at three time points. After a recording period
656 (inflated balloon) of 6 hours, the balloon was deflated and the catheter and cannula
657 were removed.

658 **Figure 3:** Subject disposition. NG: nasogastric. BMI: Body Mass Index.

659 **Figure 4: T**racings of intraballoon pressure of a single subject. Raw pressure data, prior
660 to artefact filtering, is shown for a single subject in the placebo-inflated balloon
661 condition (top, gray) and codeine-inflated balloon condition (bottom, black). The
662 corresponding Gastric Balloon Motility Index per 30 minutes and gastric half-emptying
663 time (GET½ in minutes) are shown in the table. Timing of syrup and nutrient
664 administration are indicated.

665 **Figure 5:** Mean gastric balloon motility index (GBMI) profiles per treatment. The GBMI,
666 calculated in 30-minute time windows, was significantly lower after codeine
667 administration vs. placebo ($p = 0.001$, two-way repeated measures ANOVA). Boxplots
668 show median, minimum and maximum value. Full Analysis population. Black/white:
669 codeine, grey: placebo. A.U.: Arbitrary unit.

670 **Figure 6:** Gastric emptying. Left: The fitted mean hourly ^{13}C recovery per sample is
671 plotted over time for all treatment conditions. Mean peak hourly ^{13}C recovery and

672 standard deviation are indicated as diamonds and vertical error bars. In the conditions
673 with an inflated balloon, the peak hourly recovery was significantly lower in the codeine
674 condition compared to placebo (adjusted p = 0.02, One-way repeated measures ANOVA
675 and follow-up paired t-tests). The filled circles and horizontal error bars represent the
676 mean gastric half-emptying time (GET½) and standard deviation. GET½ was significantly
677 shorter in the placebo conditions, irrespective of the balloon volume (inflated conditions
678 p = 0.001, uninflated conditions p = 0.01). Right: Gastric half-emptying time per
679 treatment arm. Black: codeine, grey: placebo. Open circles: uninflated balloon, filled
680 symbols: inflated balloon. **p < 0.01, ***p < 0.001 (linear mixed-effects model). Full
681 Analysis population.

682 **Figure 7:** Mean gastric balloon motility index (GBMI) and gastric half-emptying time
683 (GET½, in min) are shown during nutrient infusion (left graph) and in the postprandial
684 period (right graph). Individual observations are plotted after placebo administration
685 (grey squares) and after codeine administration (black squares). In the codeine
686 condition, GET½ and mean GBMI were significantly correlated both during (Pearson's r
687 = -0.53, p = 0.02) and after (Pearson's r = -0.83, p < 0.001) nutrient infusion. Linear
688 regression line and 95 % confidence interval are plotted for the codeine condition.

689 **Figure 8:** Codeine-induced changes in postprandial motility and emptying. Individual
690 differences (codeine – placebo) in gastric half-emptying time (ΔGET½, in min) and gastric
691 motility index (ΔGBMI, Arbitrary unit) are plotted. Grey dotted line: linear regression
692 line. A negative significant correlation was found (Pearson's coefficient r = -0.77, p <
693 0.001).

694