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Published in:
Neurogastroenterology and Motility

DOI (link to publication from Publisher):
10.1111/nmo.13753

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

Ambulatory assessment of colonic motility using the electromagnetic capsule tracking system: effect of opioids

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Short running title: Colonic motility and opioids

Trial registration: The two included clinical trials were registered at www.clinicaltrialsregister.eu (Trial A EudraCT no. 2013-001540-60; Trial B EudraCT no. 2015-000419-42)

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Key Points

- Opioid treatment often induces constipation, while co-administration with opioid antagonists counteracts opioid-induced constipation. The impact of opioids and opioid antagonists on colonic motility is poorly documented.
- Oxycodone increases colonic transit time mainly by reducing the number of long and fast contractions. Naloxegol in co-administration with oxycodone restores most of the opioid-induced effects on colonic motility.
- Detailed information of colonic motility may help us understand the mechanisms underlying opioid-induced constipation and other gastrointestinal diseases.

ABSTRACT

Background: Opioid treatment often causes debilitating constipation. However, it is not well described how opioids affect colonic motility and whether opioid-induced constipation is due to either a decrease of powerful peristaltic contractions or 'uncoordinated' peristalsis. The present study aims to investigate the effect of oxycodone on parameters of colonic motility and to determine if motility is normalized by the opioid antagonist naloxegol.

Methods: In two randomized, double-blind crossover trials, oxycodone or placebo were administered to 25 healthy males (Trial A), while another 24 healthy males were administered oxycodone with naloxegol or placebo (Trial B). Colonic motility was assessed by tracking the progression of an electromagnetic capsule throughout the large intestine. Segmental colonic transit times and capsule movements were calculated using displacement distance and velocity.

Key Results: In Trial A, colonic transit time increased during oxycodone treatment compared with placebo (39 vs. 18 hours, $P<0.01$). Displacement during long fast antegrade movements was shorter during oxycodone treatment than with placebo (10 vs. 20 cm, $P=0.03$). In Trial B, colonic transit time was faster during oxycodone+naloxegol than during oxycodone+placebo (40 vs. 55 hours, $P=0.049$), mainly caused by an increase of the percentwise fraction of distance covered by fast movements in the left colon ($P=0.001$).

Conclusion & Inferences: Oxycodone treatment impaired colonic motility, manifested as increased transit time, specifically decreased long fast antegrade movements, and addition of naloxegol improved motility dynamics. In humans the increased transit time during opioid treatment is caused by a decrease in long fast movements rather than uncoordinated peristalsis.

Key words: Colon, Electromagnetic capsule, motility, opioids, opioid antagonists

INTRODUCTION

Opioids are the most frequently prescribed drugs to treat moderate to severe pain and the use is increasing in most countries.[1,2] Unfortunately, opioids have multiple adverse effects. In the bowel wall, opioids bind to opioid μ-receptors and gives abnormal motility, decreased secretion of fluids and increased sphincter tone.[3,4] This may cause a cluster of gastrointestinal (GI) symptoms referred to as opioid-induced bowel dysfunction, which embraces symptoms like gastroesophageal reflux, abdominal discomfort, vomiting, bloating, borborygmi, and constipation. Opioid-induced constipation (OIC) is the most burdensome and common adverse effect of opioid treatment and affects around 40-70% of patients taking opioids continuously; symptoms typically manifest as infrequent bowel movements or defecation difficulties.[5,6] It is well-known that colonic transit time increases during opioid use, and the opioid antagonist naloxone reduces opioid-induced slow transit.[7,8] However, the pathophysiology underlying OIC is not completely clear. Because opioid receptor agonists can influence both excitatory and inhibitory activity, as well as activate the interstitial cell–muscle network, their effects on GI motility and secretion can be complex.[9] However, most of our current knowledge is obtained from preclinical studies or isolated muscle strips, and in humans it remains to be determined how opioids affect the colon in vivo. The most important parameters to study are whether opioids lengthen transit by decreasing the number of powerful, prolonged peristatic colonic contractions called 'mass movements',[10] or by inducing uncoordinated and non-propulsive peristalsis.[11]

High-resolution manometry is the gold standard for assessment of colonic motor function.[12] Unfortunately, catheter placement during colonoscopy requires an empty colon which disturbs normal physiology. The wireless motility capsule (WMC) is a less invasive method for investigating the whole GI tract in one examination. It allows assessment of transit times through the stomach, the small intestine and the colorectum, as well as an estimate of contractile activity. Unfortunately, the WMC does not determine the precise position of the capsule within each GI segment, which is a prerequisite for detailed description of progression patterns.[13]

The Motilis 3D-Transit system is an electromagnetic wireless capsule system which can be used in an ambulatory setting, is minimally invasive, and enables examination of the GI tract under conditions very close to the normal daily routines of the subject under study.[14] 3D-Transit recordings provide

detailed information on total and regional GI transit times. Recently, further software development for postprocessing of data allows detailed description of movement patterns within the colon.[15]

OIC can be studied in different patient groups. However, manifestations of OIC in patients are often difficult to distinguish from comorbidities and concomitant drug use, which complicates identification of the underlying pathophysiological mechanisms.[16] To circumvent these bias during the study of opioid effects in the gut we have previously developed an experimental model to induce OIC in healthy volunteers using oxycodone, an opioid that is associated with OIC and often used in pain treatment.[16,17] We hypothesized that oxycodone would decrease fast colonic propulsion and increase uncoordinated activity, while the selective peripherally acting opioid antagonist naloxegol would reverse the effect of oxycodone on colonic motility.

The present study aims to use this model to investigate the effects of oxycodone and oxycodone co-administered with naloxegol on colonic motility and transit using the 3D-Transit system.

MATERIAL AND METHODS

Data was collected from two previously published clinical trials, both approved by The North Denmark Region Committee on Health Research Ethics (reference numbers: N-20130030 and N-20150014) and the Danish Health and Medicines Authority (reference numbers: 2013070299 and 2015021429).[7,18] The experiments took place at the research facilities of Mech-Sense, Aalborg University Hospital, Department of Gastroenterology & Hepatology, Aalborg, Denmark. Conventional transit times from the two trials have previously been published.[7,18]

Experimental design

Trial A included 25 healthy volunteers studied in a randomized, double-blinded crossover design of two study periods each of 5 days separated by 52±10 days.[7] Trial B included 24 healthy volunteers studied in a randomized, double-blinded crossover design of two study periods each of 6 days, this time separated by 52±80 days.[18] None of the included subjects took any medication that affected GI motility, nor did any volunteer have current symptoms or a history of GI disease. No volunteer participated in both trials.

In both studies, healthy volunteers arrived at the research facility in the morning after an overnight fast. The electromagnetic capsule was swallowed on the first study day in Trial A and the second study day in Trial B after ingestion of a standardized meal (375 kcal, 11.4 g fat, and 1.8 g fiber) and a glass of water. Participants were instructed not to eat again until 6 hours after ingestion of the capsule. No further instructions on meals were given. Subjects were instructed to refrain from sports or other hard physical efforts and, furthermore, to keep a minimum of 40 cm between recording equipment and large electronic devices like laptops to ensure adequate signal strength. Experiments were continued until capsule expulsion or return of equipment on the last study day.

Dosing

Subjects in Trial A were randomly treated with either oral prolonged-release oxycodone (5 mg twice on the first study day, 10 mg twice on study days 2-4, and 10 mg once on the last study day) or matching placebo tablets. Subjects in Trial B were treated with oral prolonged-release oxycodone (10 mg twice

on the first study day, 15 mg twice on study days 2-5, and 15 mg once on the last study day) in both study periods, plus either naloxegol (25 mg once on study days 2-6) or matching placebo tablets in the two treatment arms. An overview of study medication is shown in Figure 1.

---------- Figure 1 ----------

Motilis 3D-Transit System

The ambulatory 3D-Transit system (Motilis Medica SA, Lausanne, Switzerland) consists of an ingestible electromagnetic capsule (dimensions: 21 x 8 millimeters, density 1.6 gram per cubic cm) and a belt-worn detector plate. Capsule position in three directions (x, y, z) and angular rotation in two directions (Φ and θ) are estimated from the capsule's emitted electromagnetic field and are post-processed using dedicated computer software. Battery lifetime is approximately 100 hours with a sampling frequency of 5 Hz. The study period length in the two trials were longer than the capsule battery life (120 hours) and was chosen to ensure maximum recording length and allow for other study endpoints not reported in the present study. The subjects' posture changes and physical movements are recorded with an accelerometer in the detector plate. A respiratory belt worn around the chest helped to identify respiratory artefacts.

Self-assessed bowel habits

Subjects filled in The Bristol Stool Form Scale for evaluation of the number of spontaneous bowel movement and stool consistency at each study day in Trial A and Trial B.[19]

Data analysis

The present study focuses solely on colonic recordings. Ileocecal passage was determined by the capsule's two-dimensional location in the lower right abdomen and a decrease in contraction frequency from six to three contractions per minute.[7,20,21] Prior to classification of movement patterns, all fast capsule movements (> 4 cm with a mean velocity > 4 cm/min) were identified using an automated

algorithm (Motilis Medica SA, Lausanne, Switzerland).[22] Non-physiological movements and artifacts were included in these fast capsule movements, and were then manually discarded based upon accelerometer readings and changes in location. To avoid large breathing artefacts and to simplify analysis, data were down sampled to one data point per 3 minutes of recording, or 5 millimeters progression. The capsule movements were divided into five types of motor patterns as previously described;[15,22] 1) long fast antegrade movement (>10 cm and >10 cm/min), 2) fast antegrade movement (>4 cm, <10 cm, and >4 cm/min), 3) slow antegrade movement (>4 cm, <4 cm/min, and >4 cm/h), 4) slow retrograde movement (<-4 cm, <4 cm/min, and >4 cm/h), and 5) fast retrograde movement (<-4 cm and >4 cm/min). Parameters of capsule progression including distance, number and velocity of all motor patterns were computed. The fraction of no capsule movement (fraction of colonic transit time not classified as specific movement excluding missing data), and the amount of missing data (the fraction of transit time, that has not been recorded due to technical issues like battery change and electrical interference) were also computed. Velocities for capsule movements in both antegrade and retrograde direction were divided in histogram bins in a logarithmic scale.[22] The colonic trajectory was estimated as previously proposed and divided into four segments: cecum/ascending colon; transverse colon; descending colon; and rectosigmoid.[23] Examples of colonic progression during oxycodone treatment and placebo are shown in Figure 2. Data analysis was performed in MATLAB (MathWorks Inc., Natick, MA, USA) version R2016a.

---------- Figure 2 ----------

Statistical analysis

Data were assessed for normality and analyzed accordingly. Parametric data are presented in means and standard deviations and non-parametric data are presented in medians and interquartile ranges (IQR). The number of capsule movements in each colonic segment is presented as the sum of all movements starting in, passing through or ending in the segment. Motility parameters were analyzed with a repeated measure mixed model using colonic segment and treatment as factors and adjusted for multiple

comparisons with Bonferroni *post hoc* analysis. Correlation between bowel habits (frequency of spontaneous bowel movements and stool consistency) and motility parameters were tested with the Pearson correlation statistics and adjusted for multiple comparisons using Bonferroni *post hoc* analysis. The velocity distributions were likewise compared using a mixed model with velocity and treatment as factors and Bonferroni *post hoc* analysis. Two-tailed *P*-values < 0.05 were regarded as statistically significant. Statistical analyses were performed in Stata (Version 15; StataCorp LP, College Station, TX, USA).

RESULTS

Healthy volunteers

In Trial A, colonic motility data from 36 out of the 50 (72%) recordings were available for analysis with 18 recordings in each arm. Fourteen recordings were not analyzed due to malfunctioning capsules (n=4) or frequent loss of transmission signal and poor recording quality (n=10). Median age of subjects was 24 years [range: 21-56]; median BMI was 23.9 kg/m^2 [range: 22.9-25.0]. In Trial B, colonic motility patterns were analyzed in 38 out of the 48 (79%) recordings with 20 and 18 recordings in the oxycodone/naloxegol and oxycodone/placebo arms, respectively. Ten recordings were not analyzed due to frequent loss of transmission signal resulting in poor recording quality. Median age of subjects was 25 years [range: 20-46]; median BMI was 23.1 kg/m^2 [range: 20.9-31.5].

Oxycodone vs. placebo, Trial A

Colonic motility parameters are shown in Table 1. Oxycodone treatment slowed both total colonic transit (median 39.1 hours [IQR: 19.4-67.9] vs. 18.2 hours [IQR: 15.2-27.0], *P*=0.002) and ascending colon transit (median 9.1 hours [IQR: 3.9-33.2] vs. 7.8 hours [IQR: 3.9-11.5], *P*=0.03) compared with placebo. The number of long fast antegrade movements was higher in the placebo group (median 2 movements [IQR: 1-4] vs. 1 movement [IQR: 0-2], *P*<0.001), with the highest segmental difference in the descending colon (median 1 movement [IQR: 0-1] vs. 0 movement [IQR: 0-0], *P*=0.04). The total distance covered by long fast antegrade movements was higher in the placebo group than in the oxycodone group (median 20.4 cm [range 0-93.4] vs. 10.2 cm [range 0-72.0], *P*=0.03). No differences in retrograde movements were seen between the oxycodone group compared to the placebo group (median 3 movements [IQR: 2-5] vs. 2 movements [IQR: 1-4], *P*=0.6). Conversely, oxycodone treatment increased the number of slow antegrade movements compared with placebo (median 10 movements [IQR: 7-13] vs. 6 movements [IQR: 4-10], *P*=0.002). The total distance covered by slow antegrade movements was higher in the oxycodone group than in the placebo group (median 41.5 cm [range 16.3-97.0] vs. 26.6 cm [range 8.1-63.0], *P*=0.001). Overall, the percentwise fraction of distance covered in fast movements was highest in the placebo group (median 54.2% [IQR: 41.3-69.2] vs. 32.1%

[IQR: 27.9-51.8], *P*<0.001), with the largest differences in the ascending colon (median 43.4% [IQR: 19.2-67.7] vs. 0.0% [IQR 0.0-28.4], *P*=0.03).

The analysis of capsule movement time showed that there was no difference in the fraction of time when the capsule did not move between oxycodone treatment and placebo (median 81.3% [IQR: 75.7-85.9] vs. 78.4% [IQR: 68.3-86.1], *P*=0.41).

Velocities of capsule progression were decreased during oxycodone treatment compared with placebo treatment (*P*=0.04) with longer distance covered at very slow velocities (≈ 0.5 cm/min) and shorter distance at very fast velocities (≈50 cm/min) in the oxycodone group compared with the placebo group (Figure 3).

---------- Table 1 ----------

---------- Figure 3 ----------

Oxycodone and naloxegol vs. oxycodone and placebo, Trial B

Colonic motility parameters are shown in Table 2. In general, naloxegol treatment improved the impaired motility effect caused by oxycodone. Total colonic transit time (median 40.1 hours [IQR: 25.3-54.4] vs. 54.7 hours [IQR: 37.2-72.0], *P*=0.049) and rectosigmoid transit time (median 5.0 hours [IQR: 1.7-19.5] vs. 21.2 hours [IQR: 13.0-30.9], *P*<0.001) were faster during oxycodone/naloxegol treatment than during oxycodone/placebo treatment. No differences in retrograde movements were seen (median 2 movements [IQR: 1-4] vs. median 2 movements [IQR: 1-4], *P*=0.2). There was an increased number of slow antegrade movements in the oxycodone+placebo group compared with the oxycodone+naloxegol group (median 10 movements [IQR: 8-14] vs. median 8 movements [IQR: 6-10], *P*=0.03). The total distance covered by fast antegrade movements was longer during oxycodone+naloxegol treatment than during oxycodone+placebo treatment (median 13.1 cm [range 4.2-50.9] vs. 8.9 cm [range 0-18.6], *P*=0.04). Overall, the percentwise fraction of distance covered by fast movements was higher during oxycodone+naloxegol treatment (median 29.4% [IQR: 21.9-51.9] vs. 23.2% [IQR: 14.9-35.0], *P*=0.001), with largest differences in the descending colon (median 16.8% [IQR: 0.0-59.2] vs. 0.0% [IQR: 0.0-0.0], *P*=0.013) and in the sigmoid/rectum (median 47.5% [IQR:

36.9-100] vs. 19.3% [IQR: 0.0-37.0], *P*=0.001). A graphical overview of study results is shown in Figure 4.

The analysis of capsule movement time showed that there was a non-significant trend between treatment arms where the oxycodone+naloxegol recordings had relative less time with movements than the oxycodone+placebo recordings (median 90.1% [IQR: 85.0-94.5] vs 88.6% [IQR: 86.7-92.8], P=0.07).

---------- Table 2 ----------

---------- Figure 4 ----------

Motility measures and bowel habits

No significant correlations between the number of spontaneous bowel movements or stool consistency and motility measures were found when investigated separately for each of the four treatment arms (all *P*>0.05). However, if all 74 recordings from the two trials are combined (allowing for 34 subjects to be tested twice), there is a significant correlation between the number of bowel movements and the colonic transit time with a Pearson's correlation coefficient of -0.45 (*P*<0.001), clearly showing that higher colonic transit time is negative correlated with the frequency of bowel movements.

Dose-response effect of oxycodone

The administered dose of oxycodone was higher in Trial B (oxycodone+placebo arm) than in Trial A (oxycodone arm). The dose-response effect of oxycodone was investigated by comparing the motility results between the two trials. Colonic transit times were not increased in Trial B compared to Trial A (median 54.7 hours [IQR: 37.2-72.0] vs. 39.1 hours [IQR: 19.4-67.9], *P*=0.22). There was fewer fast antegrade movements in Trial B compared to Trial A (median 2 movements [IQR: 1-3] vs. 3 movements [IQR: 2-5], *P*=0.01). Less activity at fast velocity was observed in Trial B compared to trial A (median 23.2% [IQR: 14.9-35.0] vs. 32.1% [IQR: 27.9-51.8], *P*=0.02). There was observed more time of capsule non-movement in Trial B compared to Trial A (median 88.6% [IQR: 86.7-92.8] vs. 81.3% [IQR: 75.7-

85.9], $P<0.01$). All other comparisons between motility measures in Trial A and Trial B showed no differences (All $P>0.05$).

DISCUSSION

The main finding of this study was that oxycodone increased colonic transit time by reducing the efficacy of antegrade movement and number of long fast antegrade movements and slowed the progression velocity. Another important finding was that oxycodone increased the number of slow antegrade movements while the number of retrograde movements remained unchanged. Thus, our findings suggest that oxycodone slowed and shortened propulsive contractions rather than increasing retrograde activity. When naloxone was added to oxycodone, it did not restore long fast movements, but rather reduced colonic transit time by significantly increasing the distance covered by short fast movements and by reducing the number of slow antegrade movements evoked by oxycodone. Naloxegol restored displacement distance associated with fast movements mainly in the descending colon and sigmoid part of colon.

The pathophysiological mechanisms underlying OIC is complex, and colonic dysmotility is believed to have an essential contribution.[3] This makes colonic motility especially important when describing the GI side effects of opioids. It is well known that opioids cause prolonged colonic transit time.[7,24–26] It is, however, debatable whether this is due to reduced propulsive contractility or uncoordinated contractions. The present findings suggest that increased transit time during opioid treatment can be attributed to a decrease in long fast movements, even though number of slower antegrade movements increased.

The capsule continuously progressed at a slower velocity through the colon during oxycodone treatment. The velocity distribution of slow and very fast movements in the placebo group is similar to that reported in previous studies of healthy volunteers, including results obtained with a previous version of the system.[22,27] Hence, no major placebo effect in colonic movement velocities was seen.

Detailed differentiation of various colonic movements has not previously been described in OIC. However, Dinning et al. studied colonic motor patterns in patients with slow-transit constipation using high-resolution colonic manometry.[28] They observed that retrograde colonic movements were far less prevalent in patients with severe constipation compared with healthy controls. The same study also reported that motor patterns with a frequency of 2-6 cycles per minute were commonly observed in slow transit constipation, although they were rarely coordinated as propagating activity.[28]

No significant difference in retrograde movements between placebo and oxycodone was found in the present study. This finding proposes that the mechanisms behind OIC and slow-transit constipation are not the same, although results obtained with high-resolution manometry and 3D-Transit cannot be directly compared. It is not entirely clear whether this discrepancy was due to unchanged physiology (i.e. lack of bowel preparation) or the present method of analysis. High-resolution manometry studies have shown that retrograde propagating pressure waves can occur in both longer movements, and in shorter cyclic movements that can propagate antegrade as well as retrograde.[29] The analytic method applied to the present data favors progressive movements over cyclic movements that move the capsule back and forth within a short period; accordingly, this motor pattern may be underestimated.

Long fast antegrade movements, likely the correlate of high-amplitude propagating sequences shown manometrically, may be impaired during oxycodone treatment akin to that seen in slow transit constipation,[28,30] where build-up of feces in the proximal parts of the colon is the result.[16] Severe constipation with excess fecal matter in the colon may compromise colonic peristalsis, slow down propulsion of feces, increase water reabsorption and harden stools in a vicious circle.[31] Survey results from our study, previously reported by Nilsson et al. and Grønlund et al., also confirm that stools are hardened during oxycodone treatment compared with placebo,[16] and are softened again after treatment with naloxegol.[32] When investigating how the motility measures relate to the frequency of bowel movements or stool consistency, no significant correlations were found in each of the four study arms. This was not an unexpected finding as objective measurements of motility rarely correlate to clinical parameters.[33]

Study limitations

The main limitation of the current study is the high number of excluded capsule recordings due to failed examinations, where poor recording quality was the largest contributor to failure. A total of 24 of 98 recordings (24%) were excluded from analysis. The high failure rate has likewise been observed in previous studies using the system,[15] why design of future studies have to take this into consideration.

It is a limitation that the capsule only describes its own movement. Hence, the length of a given contraction will be underestimated if the capsule is not located where the contraction starts or entirely

missed if the contraction occurs at a location away from the capsule. Colonic manometry does not have this limitation, but the placement of a catheter in an empty colon does not allow examination under normal physiological conditions. Indeed, colonic manometry in the cleansed bowel may underestimate the number of high-amplitude propagating sequences,[34] which likely occur more frequently in the non-prepared bowel.

The study design may not mirror clinical OIC. The number of subjects and the duration of treatment with opioids were limited by ethical considerations. However, a great advantage in using the model in healthy volunteers is that co-morbidity, concomitant medication, immobility and psychiatric disorders can be avoided.[16]

Another considerable limitation of the present study is that it only included males. However, there is no evidence that the pathophysiology of OIC should differ between genders. Male participants were the preferred choice in the current study to avoid alterations in gut function during the female menstruation cycle.[35]

The administered opioid doses were chosen to be ethically justifiable with a hypothesized constipating effect. However, longer treatments or higher dosages would plausibly cause more severe GI symptoms. The opioid dose was highest in Trial B compared to Trial A and resulted in changed motility measures when compared. The magnitude of colonic transit times seemed longer during the higher oxycodone dose; however, they were not significantly different. This may be in line with findings from epidemiological studies, which have shown that both low and high dose opioids can give constipation.[36] Animal studies have previous shown that there exist a dose-response effect of opioids on gastrointestinal motility,[37] akin to clinical practice. Our results contribute to the finding of a dose-response effect, but the connection must be investigated further in studies designed for this endpoint. Like the opioid dose, the dose of naloxegol is crucial to its effect. Van Malderen et al. evaluated the dose of naloxegol in opioid-naïve volunteers and in chronic opioid-treated patients, and showed that patients needed a lower dose of naloxegol to reverse symptoms of constipation than healthy volunteers treated with opioids.[38] In another healthy volunteer study by Halawi et al, 25 mg naloxegol (recommended dose for treating OIC) did not reverse transit times after receiving codeine.[39] In our study, participants were likewise treated daily with 25 mg naloxegol, which may have been inadequate to

reverse all motility disturbances caused by opioids. Naloxegol did enhance colonic motility, although the relatively low dose may have us underestimate its potential treatment effect.

In conclusion, our study demonstrates the effects of oxycodone and naloxegol on detailed colonic motility in healthy volunteers. Our findings show that oxycodone causes increased colonic transit time with fewer long fast movements than placebo. Naloxegol restored some fast movements and reversed the prolonged transit, but did not completely normalize colonic motility. This implies that the Motilis 3D-Transit system has a promising future in motility assessment studies. However, recording quality, data interpretation and analysis need further improvement and simplification before the system can be widely adopted in clinical practice.

Acknowledgements: This study was partly funded by an unrestricted research grant from The Svend Andersen foundation.

Disclosures: Vincent Schlageter is co-owner of Motilis Medica SA. The other authors have no conflicts of interest.

Author contributions: All authors have made substantial contributions to the study. EBM designed the study, acquired data, analyzed and interpreted data, drafted the manuscript and implemented algorithms; MWK drafted the manuscript and revised the manuscript for important intellectual content; DG and JLP acquired data and revised the manuscript for important intellectual content; VS provided technical support and technical review; KK, SMS and AMD designed the study, interpreted data, and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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TABLES

Table 1. Colonic motility parameters in healthy volunteers during oxycodone or placebo treatment (n=18)

	Treatment		Cecum & ascending	Transverse	Descending	Sigmoid & rectum	All colon
Capsule transit characteristics							
Colonic transit time (hours)	Oxycodone		*9.1 (3.9-33.2)	4.4 (2.7-9.5)	1.2 (0.6-7.5)	8.4 (1.7-23.8)	*39.1 (19.4-67.9)
	Placebo		7.8 (3.9-11.5)	3.9 (1.9-6.0)	0.9 (0.3-2.5)	5.2 (1.4-8.9)	18.2 (15.2-27.0)
Total velocity (cm hour^{-1})	Oxycodone		1.6 (1.0-3.6)	4.4 2.1-8.3	7.0 (1.6-28.0)	2.4 (1.4-10.8)	2.4 (1.7-3.2)
	Placebo		2.0 (1.7-5.4)	7.6 (3.3-10.1)	22.2 (4.2-44.8)	4.6 (1.4-8.9)	4.2 (2.6-6.0)
Displacement at fast velocity (% of length)	Oxycodone		0.0 (0.0-28.4)	30.1 (0.0-50.9)	25.6 (0.0-79.3)	41.4 (0.0-77.0)	32.1 (27.9-51.8)
	Placebo		*43.4 (19.2-67.7)	46.0 (12.7-55.4)	76.9 (23.8-100)	70.7 (41.7-87.1)	*54.2 (41.3-69.2)
No capsule movement (% of time)	Oxycodone		79.7 (68.8-86.3)	78.9 (70.2-89.5)	76.3 (45.8-89.8)	84.4 (80.0-90.3)	81.3 (75.7-85.9)
	Placebo		79.1 (73.1-86.5)	74.7 (67.2-84.9)	81.8 (37.5-91.7)	83.8 (75.9-92.4)	78.4 (68.3-86.1)
Missing data (% of time)	Oxycodone		0.11 (0.07-0.13)	0.06 (0.03-0.10)	0.01 (0.00-0.06)	0.05 (0.00-0.08)	0.09 (0.05-0.13)
	Placebo		0.09 (0.05-0.15)	0.07 (0.02-0.14)	0.00 (0.00-0.03)	0.04 (0.01-0.12)	0.09 (0.06-0.15)
Movement patterns							
Long fast antegrade (no)	Oxycodone	*N*	*2*	*6*	*5*	*8*	*21*
			0 (0-0)	0 (0-1)	0 (0-0)	0 (0-1)	1 (0-2)
	Placebo	*N*	*8*	*13*	**14*	*11*	**46*
			0 (0-1)	1 (0-1)	1 (0-1)	1 (0-1)	2 (1-4)
Fast antegrade (no)	Oxycodone	*N*	*12*	*22*	*11*	*15*	*60*
			0 (0-1)	1 (0-2)	0 (0-1)	1 (0-1)	3 (2-5)
	Placebo	*N*	*12*	*18*	*13*	*15*	*58*
			1 (0-1)	1 (0-1)	1 (0-1)	1 (0-1)	3 (2-5)
Slow antegrade (no)	Oxycodone	*N*	*46*	*59*	*43*	*45*	**193*
			3 (2-4)	3 (2-5)	2 (1-3)	2 (1-3)	10 (7-13)
	Placebo	*N*	*35*	*46*	*25*	*20*	*126*
			2 (1-2)	2 (2-3)	1 (0-2)	1 (0-2)	6 (4-10)
Slow retrograde (no)	Oxycodone	*N*	*27*	*11*	*15*	*16*	*69*
			1 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)	3 (2-5)
	Placebo	*N*	*14*	*13*	*8*	*11*	*46*
			1 (0-1)	0 (0-1)	0 (0-0)	0 (0-1)	2 (1-4)

Data are presented as medians (interquartile range). Comparisons were made using repeated measures mixed models with the two factors segment and treatment. The P-value for "All colon" is for the overall mixed model, and segmental P-values are Bonferroni post-hoc corrected. N=total number of movements. (*) indicates *P*-values < 0.05.

Table 2. Colonic motility parameters in healthy volunteers during oxycodone+naloxegol (n=20) or oxycodone+placebo treatment (n=18)

	Treatment		Cecum & ascending	Transverse	Descending	Sigmoid & rectum	All colon
Capsule transit characteristics							
Colonic transit time (hours)	Oxy+Nal		7.7 (3.6-31.2)	6.4 (5.2-13.3)	1.9 (0.9-8.6)	5.0 (1.7-19.5)	40.1 (25.3-54.4)
	Oxy+Pla		7.3 (6.0-13.9)	9.5 (4.2-15.3)	6.7 (3.2-13.2)	*21.2 (13.0-30.9)	*54.7 (37.2-72.0)
Total velocity (cm hour^{-1})	Oxy+Nal		1.6 (0.6-4.1)	2.6 (1.6-3.6)	4.4 (0.9-14.1)	3.8 (1.4-11.1)	2.0 (1.4-2.7)
	Oxy+Pla		1.4 (1.1-2.3)	1.7 (1.0-3.5)	1.5 (1.1-3.9)	0.9 (0.7-1.7)	1.4 (1.2-1.7)
Displacement at fast velocity (% of length)	Oxy+Nal		25.7 (0.0-44.5)	9.0 (0.0-46.6)	*16.8 (0.0-59.2)	*47.5 (36.9-100)	*29.4 (21.9-51.9)
	Oxy+Pla		28.9 (0.0-51.7)	0.0 (0.0-25.5)	0.0 (0.0-0.0)	19.3 (0.0-37.0)	23.2 (14.9-35.0)
No capsule movement (% of time)	Oxy+Nal		92.5 (82.5-96.2)	90.3 (76.0-95.3)	83.9 (71.1-93.6)	87.2 (64.9-92.1)	90.1 (85.0-94.5)
	Oxy+Pla		88.0 (83.3-96.1)	84.0 (75.8-92.3)	82.7 (76.1-92.6)	92.9 (86.2-94.8)	88.6 (86.7-92.8)
Missing data (% of time)	Oxy+Nal		0.02 (0.01-0.03)	0.02 (0.01-0.04)	0.01 (0.00-0.04)	0.02 (0.00-0.05)	0.02 (0.01-0.04)
	Oxy+Pla		0.01 (0.00-0.04)	0.04 (0.02-0.07)	0.01 (0.00-0.06)	0.02 (0.01-0.07)	0.03 (0.02-0.06)
Movement patterns							
Long fast antegrade (no)	Oxy+Nal	*N*	*4*	*3*	*5*	*10*	*22*
			0 (0-0)	0 (0-0)	0 (0-0)	1 (0-1)	1 (0-2)
	Oxy+Pla	*N*	*4*	*5*	*1*	*4*	*14*
			0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-2)
Fast antegrade (no)	Oxy+Nal	*N*	*12*	*9*	*8*	*17*	*46*
			1 (0-1)	0 (0-1)	0 (0-1)	1 (0-1)	3 (1-3)
	Oxy+Pla	*N*	*10*	*6*	*2*	*13*	*31*
			0 (0-1)	0 (0-1)	0 (0-0)	0 (0-1)	2 (1-3)
Slow antegrade (no)	Oxy+Nal	*N*	*32*	*47*	*38*	*32*	*149*
			2 (1-3)	3 (1-3)	2 (1-3)	2 (0-3)	8 (6-10)
	Oxy+Pla	*N*	*42*	*56*	*40*	*48*	**186*
			2 (1-3)	3 (2-4)	3 (2-3)	2 (1-3)	10 (8-14)
Slow retrograde (no)	Oxy+Nal	*N*	*11*	*10*	*5*	*12*	*38*
			0 (0-1)	0 (0-1)	0 (0-0)	0 (0-1)	2 (1-4)
	Oxy+Pla	*N*	*15*	*7*	*6*	*27*	*55*
			0 (0-1)	0 (0-0)	0 (0-1)	1 (0-3)	2 (1-4)

Data are presented as medians (interquartile range). Comparisons were made using repeated measures mixed models with the two factors segment and treatment. The P-value for "All colon" is for the overall mixed model, and segmental P-values are Bonferroni post-hoc corrected. Abbreviations: Oxy=Oxycodone treatment; Nal=Naloxegol treatment; Pla=Placebo treatment; N=total number of movements. (*) indicates *P*-values < 0.05.

Figure legends

Figure 1. Overview of study medication in Trial A and Trial B. The active arms in both trials are marked with white boxes, and the placebo arms are marked with gray boxes.

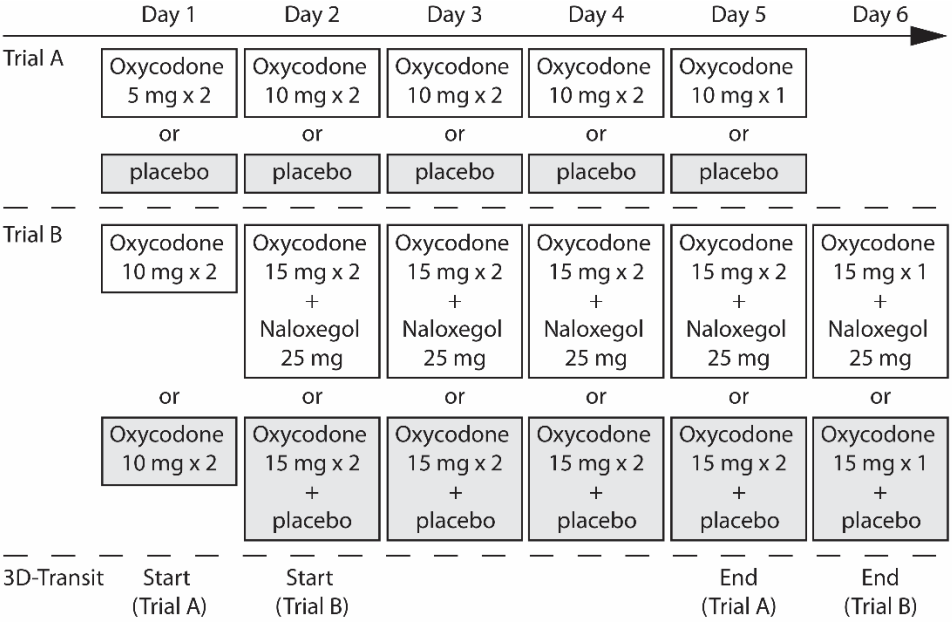
Figure 2. Colonic progression patterns during oxycodone and placebo in the same subject. Anatomical position in the colon is represented by the distance in cm from cecum to the rectum (Y-axis). (a): Recording during placebo treatment. The capsule stands still in the ascending colon for 20 hours. (b): Recording during oxycodone treatment. Colonic transit time is longer, and the capsule stays in the ascending colon in 34 hours. The capsule is moved from mid descending colon to the rectum in one long fast movement.

Figure 3. Analysis of propulsive velocities in the colon. Bar chart of mean and standard error of means of the distribution of capsule displacements at all velocities in colonic recordings during oxycodone and placebo treatment. The x-axis is logarithmic. The total distance covered by the capsule (the sum of all bins in the figure) was longer during oxycodone treatment compared to placebo (mean±SD 139±54 cm vs. 120±46 cm, P=0.04). Comparisons were made using a repeated measures mixed models with the two factors velocity bin and treatment. Differences between treatments at each velocity were investigated with a Bonferroni post hoc test. Differences at slow and very fast velocities indicated by asterisks (*).

Figure 4. Graphical presentation of findings. Displacement distance is illustrated by arrow length. (a): Oxycodone compared with placebo mainly affected fast movement displacements and reduced the number of fast movements. Conversely it increased the number and distance covered by slow antegrade movements. Oxycodone did not change retrograde activity. (b): Naloxegol compared with placebo (co-administered with oxycodone) increased fast movement displacement mainly in the right colon due to an increase in the number of fast movements covering short distance.

Figures for:

Ambulatory assessment of colonic motility using the electromagnetic capsule tracking system: effect of opioids



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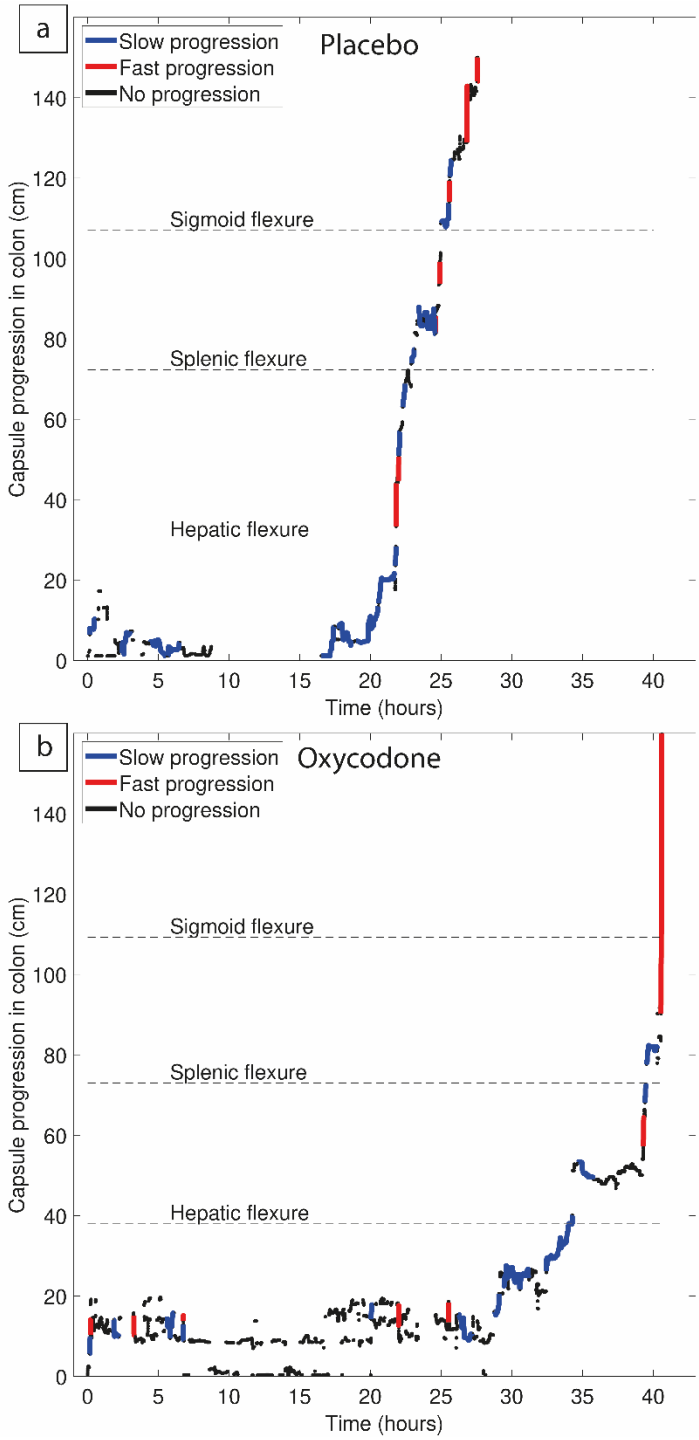

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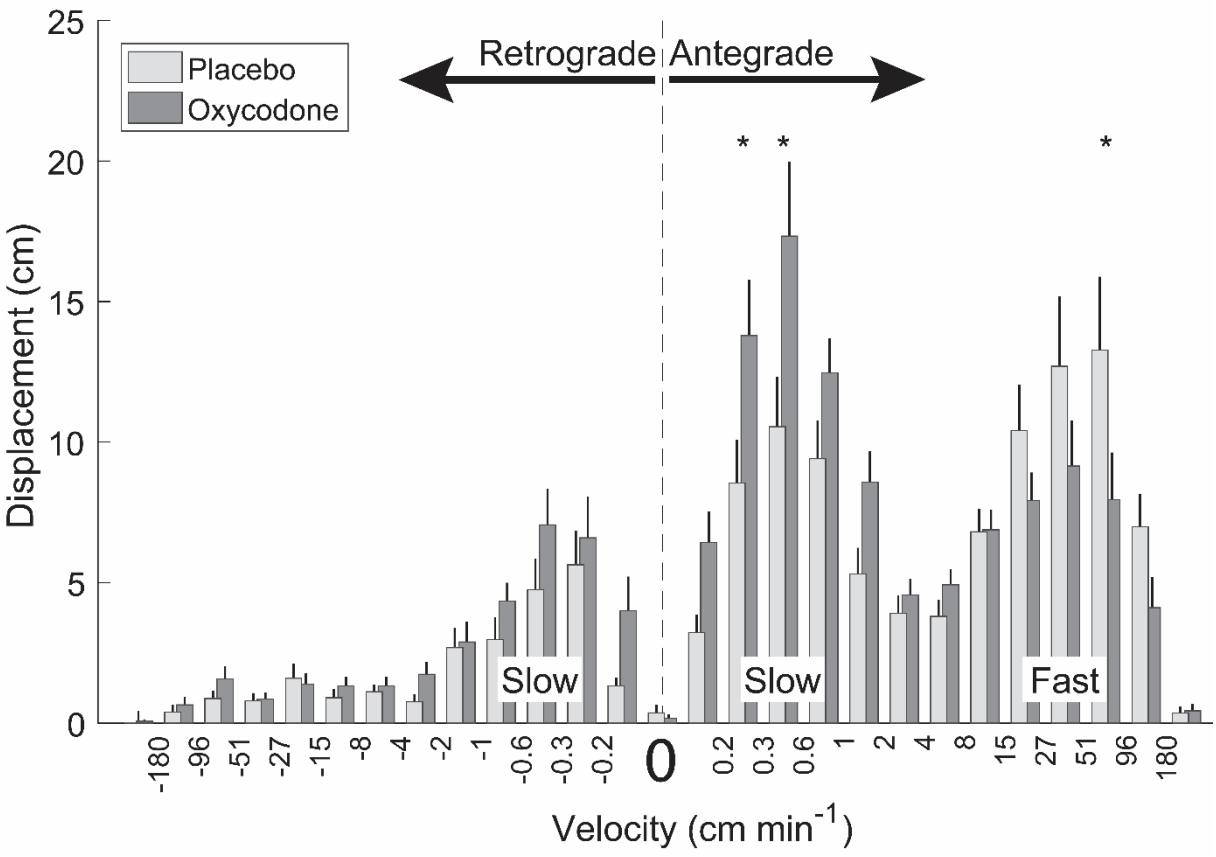

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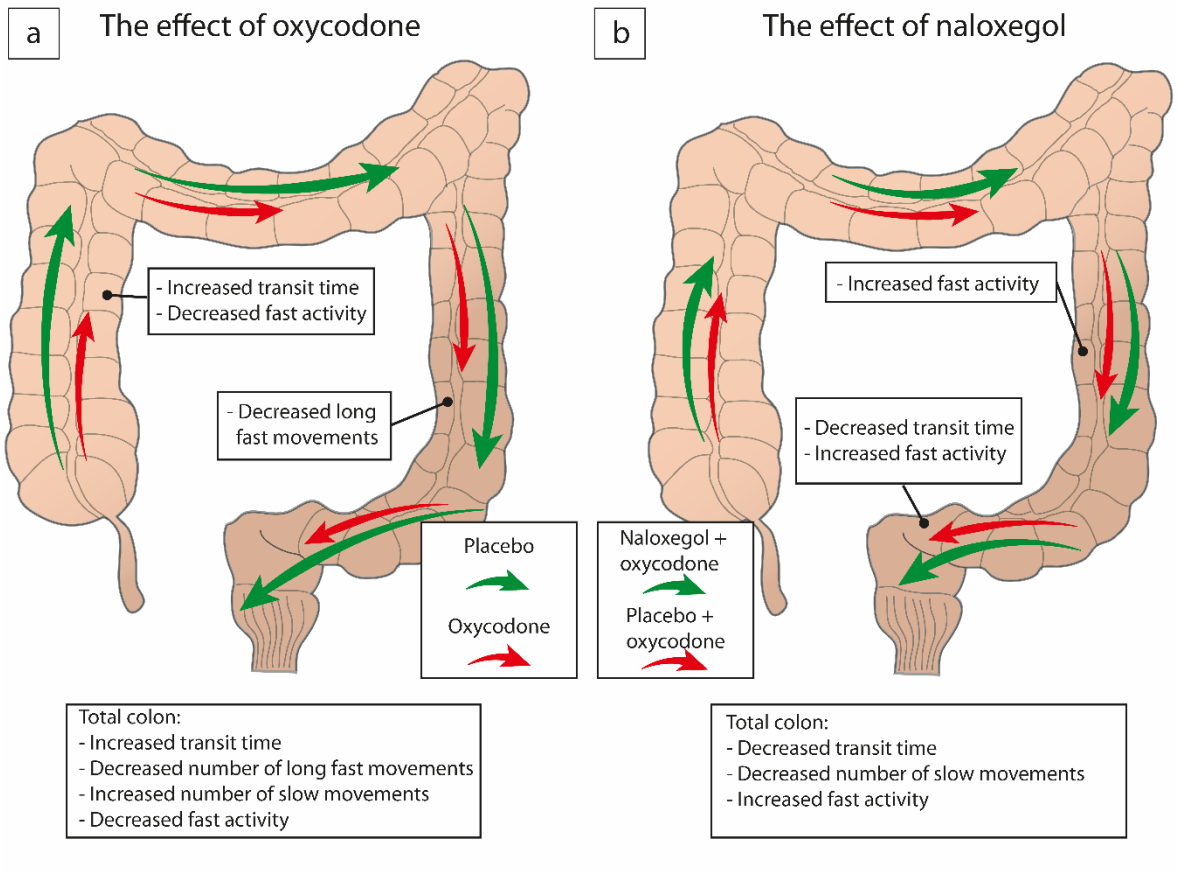

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