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A mechanistic study in healthy volunteers

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Original Experimental

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Although tapentadol and oxycodone both increase colonic volume, tapentadol treatment resulted in softer stools and less constipation: a mechanistic study in healthy volunteers

Abstract

Objectives: Opioids are often used in treatment of severe pain, although many patients experience gastrointestinal side-effects like constipation. The aim of the current study was to investigate changes in colonic volume, as the result of both colonic motility and fluid transport, in healthy volunteers during opioid treatment with tapentadol as compared with oxycodone and placebo.

Methods: In a randomized, double-blind, cross-over study, 21 healthy male volunteers were administered equianalgesic dosages of oral tapentadol (50 mg bid), oxycodone (10 mg bid) or corresponding placebo for 14 days. Segmental colonic volumes were quantified using T2-weighted magnetic resonance images, and gastrointestinal side-effects were assessed with questionnaires.

Results: Total colonic volume increase during treatment was higher during tapentadol and oxycodone treatment (median 48 and 58 mL) compared to placebo (median −14 mL, both p≤0.003). Tapentadol (and placebo) treatment resulted in more bowel movements (both p<0.05) and softer stool consistency as compared with oxycodone (both p<0.01). Only oxycodone treatment was associated with increased constipation, straining during defecation, and tiredness (all p≤0.01). The colonic volume increase during treatment was directly associated with softer stools during tapentadol treatment (p=0.019).

Conclusions: Tapentadol treatment increased colonic volume without leading to harder stools, likely as the opioid sparing effects result in less water absorption from the gut lumen. Oxycodone treatment also increased colonic volume, but with a simultaneous increase in stool dryness and gastrointestinal and central nervous system side-effects. The results confirm that tapentadol treatment may be advantageous to oxycodone regarding tolerability to pain treatment.

Keywords: colon; MRI; opioids.

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Introduction

Severe pain is often treated with classical opioids, but treatment is far from optimal. This is mainly due to the many side-effects where constipation and other symptoms related to opioid induced bowel dysfunction present a major challenge [1–3]. There are several approaches to decrease side-effects, although no solution fits all patients. Tapentadol is a newer analgesic that exerts its analgesic properties by combining moderate μ-opioid receptor agonistic affinity with noradrenaline reuptake inhibition. The noradrenergic activity may provide a genuine opioid-sparing effect, maintaining analgesic

efficacy despite reduced μ-opioid receptor affinity and at the same time reducing the opioid induced bowel dysfunction [4]. The analgesic effect of tapentadol has been investigated in previous studies [5, 6], however, its mechanic effect on colon function and how this interacts with gastrointestinal (GI) symptoms lacks evidence. It has previously been shown that magnetic resonance imaging (MRI) of segmental colorectal volumes provides an advantageous insight into colonic function, and how it can be affected due to diets or opioid treatment in healthy subjects [7, 8]. The method has been found to have low inter-reader and day-to-day variability, high spatial resolution, and includes no contrast-enhancing agents or irradiation [9]. Colonic volume is the result of GI motility and net water transport (secretion and absorption) and thereby a proxy measure for evaluating e.g. side-effects during opioid treatment. In patients with comorbidities and concomitant drug use, it is difficult to investigate GI side-effects following opioid treatment as the many confounders interfere with the findings. Instead, healthy volunteers can be included in an experimental model to exclude such bias, which may provide a more useful approach to investigate mechanistic effects of opioid treatment.

It was hypothesized that tapentadol compared to oxycodone treatment would induce a lower increase in colonic volume and fewer GI side-effects. The present study aimed at investigating GI side-effects to treatment with tapentadol as compared with oxycodone and placebo in healthy volunteers, including: (1) quantitative assessment using MRI-evaluated segmental colonic volumes and (2) questionnaires.

Methods

Study overview

This study was a randomized, double-blind, placebo-controlled, cross-over study, where 21 healthy male volunteers were administered tapentadol (Palexia®, 50 mg extended release), oxycodone (OxyContin®, 10 mg extended release) or placebo in three study periods of 14 days. Tablets were administered once orally on days 1 and 14 (morning) and twice orally on days 2–13 (morning and evening). Tablets were identical in appearance and were manufactured at the Hospital Pharmacy, Aarhus University Hospital, Aarhus, Denmark. The tablets were encapsulated in DPcaps® (red color, size AA, 13.07–14.44×9.39 mm, Capsugel®) that are shell capsules of hard gelatin that hides the appearance of the original tablets. The drug release properties of the tablets were not affected as previous shown *in vitro* and *in vivo* [10, 11]. The wash-out period between treatments was at least 7 days, where the effect of tapentadol and oxycodone has worn off in line with the halftime of the active components [12, 13]. The dosages of tapentadol 50 mg and oxycodone 10 mg were believed to be equianalgesic as previous shown in a

phase II trial by Stegmann et al. and a phase III trial by Hartrick et al. [5, 14]. Included subjects were randomized to the order of treatment into one block with six possible sequences (randomization.com), see detailed overview in Figure 1. Mirror randomization was performed in case of participant drop out. The research was carried out at the research facilities of Mech-Sense, Aalborg University Hospital, Departments of Gastroenterology & Radiology, Aalborg, Denmark. Included subjects did not have current GI symptoms or history of GI diseases. They underwent an MRI examination of the abdomen at study day 1 (pre-treatment) and at study day 14 (post-treatment). Subjects were asked to fast 6 h before MRI, and no instructions on toilet visits were given. The clinical trial was approved by The North Denmark Region Committee on Health Research Ethics and the Danish Health and Medicines Authority (reference numbers: N-20170009 and 2017041794). The clinical trial was registered at www.clinicaltrialsregister.eu (EudraCT number: 2017-000141-52).

The data presented in the current study were secondary endpoints obtained as part of a larger study protocol. The primary endpoint is not included in this manuscript and has been submitted for publication elsewhere.

Magnetic resonance imaging

Abdominal MRI scans were carried out using a 1.5 T GE Discovery MR450 System (GE Healthcare, Milwaukee, WI). One coronal T2-weighted single-shot fast spin-echo scan was performed with the following settings: Repetition time (TR)=715 msec, echo time (TE)=93 msec, flip angle=90°, field of view=480×480 mm, matrix size=512×512 pixels, acceleration factor=2, in-plane resolution=0.9375×0.9375 mm, 30–40 slices, and a slice thickness of 4 mm. The images were obtained in two breath-holds lasting approximately 20 s each.

Data analysis

Image segmentation was performed using a semi-automatic segmentation platform (Matlab version R2016a, MathWorks, Natick, MA, USA) [15]. The final segmented volume included the outer surface of the colon (and hence the total colon volume including bowel wall, faeces and gas). The segmentation was divided in the four colonic segments: ascending colon/cecum, transverse colon, descending colon, and sigmoid colon/rectum, see Figure 2. The analysis procedure was that the observer outlines a coarse region of interest encapsulating the colon on each coronal image where the colon was visible. The software allows the observer to scroll through images and add or delete regions of interest after which the software automatically uses a clustering algorithm (k-means initiated with three random cluster centres) to discard non-colon voxels based on their relative MRI signal intensities. The observer can afterwards correct failed classifications of areas. The classified colonic volume was then quantified (voxel width×height×slice thickness). A single observer (KKJ, trained radiographer) did all segmentations. Segmentations were approved by another observer (EBM). The observers were blinded to study treatment during analysis.

Questionnaires

Study subjects were asked to fill in three questionnaires for evaluation of side-effects during treatments. (1) A modified version of the Gastrointestinal Symptom Rating Scale (GSRS) were filled in at first
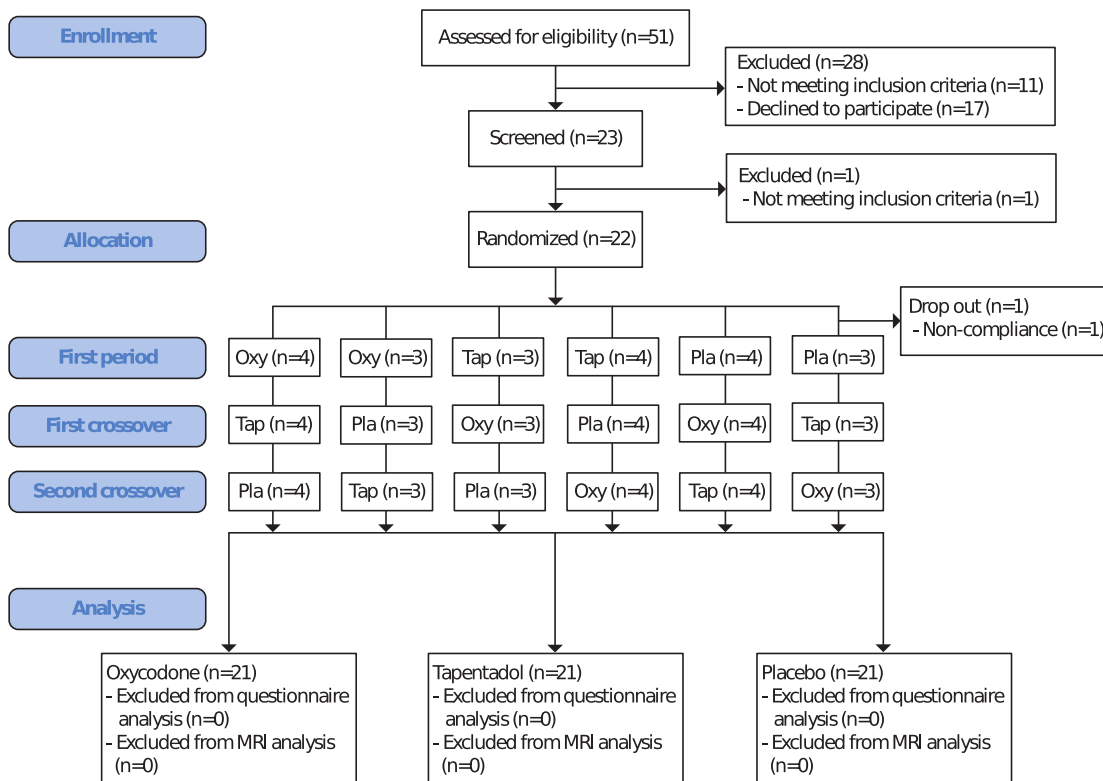
Figure 1: An overview of the study flow. One drop-out participant was replaced using mirror-randomization.
Data were analyzed according to intention-to-treat. Oxy, oxycodone; Tap, tapentadol; Pla, placebo; MRI, Magnetic resonance imaging.
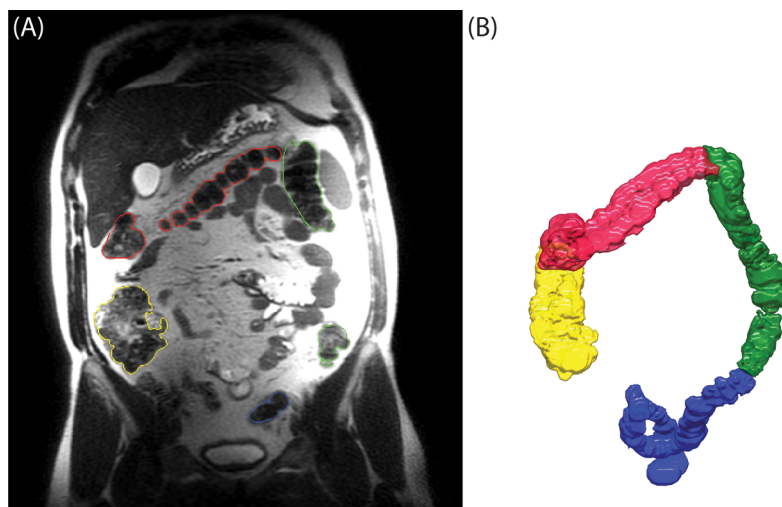

Figure 2: Coronal T2-weighted magnetic resonance image of the abdomen.
(A) Segmented colonic segments are super-imposed on the image; yellow, ascending colon and cecum; red, transverse colon; green, descending colon; blue, sigmoid colon and rectum. (B) Three-dimensional model of the segmented colon.

(pre-treatment) and last study day, where 11 side-effects were rated on a 7-points Likert scale. (2) The Bristol stool scale for evaluation of spontaneous bowel movement, including frequency and stool consistency rated on a scale from 1 to 7, where 1=very hard stool, 3–4=normal, and 7=diarrhoea [16], (Bristol stool scale data has been submitted for publication elsewhere). (3) Treatment side-effects were rated at first (pre-treatment), fourth, and last study day, on a 4-points Likert scale, where 0=no, 1=mild, 2=moderate, 3=severe and 4=unbearable.

For simplification of analysis, data from the side-effect questionnaires were divided into three sub-categories (see Table 1) including (1) GI-related questions, (2) central nervous system (CNS)-related questions, and (3) other questions. Redundant questions were left out from analysis.

Subjects were also asked to fill out the Subjective Opiate Withdrawal Scale questionnaire three days after each treatment period [17]. A total score of 1–10 means mild withdrawal, a score of 11–20 means moderate withdrawal, and a score of 21–30 means severe withdrawal.

Table 1: Side-effects affecting more than two subjects.

Adverse event	Day	Tapentadol (50 mg twice daily)	Oxycodone (10 mg twice daily)	Placebo	p-Value	Adjusted p-Value
Gastrointestinal tract						
Abdominal pain[a]	1	1	1	1	1	1
	14	1	3	4	0.378	1
Acid reflux[b]	1	4	4	3	0.891	1
	14	2	3	1	0.620	1
Constipation[a]	1	1	0	2	0.356	1
	14	6	15	6	**0.0002**	**0.007**
Difficulty swallowing[b]	1	1	0	1	0.601	1
	14	0	2	0	0.137	1
Dry mouth[a]	1	4	3	2	0.736	1
	14	6	8	3	0.218	1
Heartburn[b]	1	1	3	1	0.434	1
	14	0	3	1	0.147	1
Hunger pains[b]	1	7	3	4	0.382	1
	14	4	5	4	0.835	1
Reduced appetite[b]	1	2	3	2	0.885	1
	14	3	11	2	**0.002**	0.068
Straining during defecation[b]	1	5	5	6	0.922	1
	14	8	17	11	**0.0001**	**0.003**
Central nervous system						
Discomfort[b]	1	4	3	2	0.675	1
	14	4	10	3	**0.013**	0.442
Dizzy[a]	1	4	2	1	0.331	1
	14	5	12	4	**0.005**	0.170
Headache[a]	1	1	4	2	0.341	1
	14	5	9	4	0.125	1
Nausea[a]	1	1	0	0	0.368	1
	14	2	9	1	**0.002**	0.054
Tired/drowsy[a]	1	8	11	9	0.613	1
	14	9	18	9	**0.0003**	**0.010**
Other						
Difficulty during urination[b]	1	2	0	0	0.131	1
	14	1	4	2	0.298	1
Hyperhidrosis[a]	1	2	2	3	0.871	1
	14	1	5	1	0.075	1
Skin irritation[a]	1	1	2	4	0.370	1
	14	3	6	3	0.394	1

Values are number of subjects experiencing the side-effect. Severity of side-effects can be seen in Supplementary data. Differences are tested with the Kruskal-Wallis test on reported severity of side-effects. p-values are adjusted using Bonferroni correction and significant differences are shown in bold font. [a]Data from adverse event questionnaire. [b]Data from gastrointestinal symptom rating scale questionnaire (data obtained at day four is shown in Supplementary data).

Pain tolerance threshold

The efficacy of the administered dosages of tapentadol, oxycodone and placebo were tested in an experimental pain tolerance test using a handheld pressure algometer (Type 2, Somedic production AB, Sweden) with a probe of 1 cm². The pain tolerance threshold was found during a continuous and increasing pressure (30 kPa/s) on the thigh 15 cm proximal to the patella. The test was performed at day 1, day 4 and day 14.

Statistical analysis

All data are presented as means ± standard deviation or medians with interquartile range (IQR) according to data distribution. The effect of treatments was analysed on baseline-corrected colonic volume, i.e. the result on day 14 minus the result on day 1, in order to minimize physiological fluctuations. Analysis was performed using repeated measures mixed models with the two factors treatment and colonic segment and adjusted for multiple comparisons with Bonferroni post

hoc tests. Differences between study periods were investigated for evaluation of potential carry-over effects using the same type of repeated measures mixed models. Questionnaire scores were tested for each question with Kruskal-Wallis one-way analysis of variance and adjusted for multiplicity using Bonferroni correction. Correlations between questionnaires (global score for each questionnaire) and total colonic volume change were tested for each treatment with Spearman correlation analyses. The pain tolerance threshold was tested using a repeated measures one-way ANOVA. p-values less than 0.05 were considered statistically significant. Statistical analysis was performed with STATA, version 15 (StataCorp LP, College Station, Texas, USA).

Results

Study subjects

The 21 enrolled healthy male subjects had a mean (± standard deviation) age of 28.0 ± 9.0 years, mean height of 182.2 ± 5.7 cm, and a mean BMI of 23.9 ± 2.7 kg/m². All the 21 subjects successfully completed the imaging protocol; thus 126 imaging sets were included in analysis.

Colonic volume

Difference between total colonic volumes obtained on study days 1 and 14 are shown in Figure 3. Oxycodone treatment increased total colonic volume change compared to placebo (p=0.002). Tapentadol treatment likewise increased total colonic volume change compared to placebo (p=0.003), while no difference was observed between oxycodone and

tapentadol (p=0.9). The post hoc analysis revealed no segmental differences, see Figure 3. There were no differences between colonic volumes obtained in the three study periods (when data was in chronological order of study visits before stratification into treatments).

Treatment side-effects

Table 1 summarizes the number of subjects that reported side-effects with the GSRS and side-effects questionnaires. The severity of reported side-effects can be seen in Supplementary data. At day 14 of oxycodone treatment, subjects reported increased GI-related side-effects including constipation and straining during defecation as compared to both tapentadol and placebo (both p≤0.007). Moderate or severe constipation symptoms (2 or 3 on the Likert scale) were reported of 11 subjects (52%) during oxycodone treatment, 1 subject (5%) during tapentadol treatment and 0 during placebo. Subjects likewise reported increased tired/drowsy (p≤0.010) at the last study day during oxycodone treatment compared to both tapentadol and placebo. Moderate or severe nausea were reported by 7 subjects (33%) on the last study day (all 7 during oxycodone), and 2 subjects (10%) experienced vomiting (1 during oxycodone and 1 during placebo). No differences were observed on the baseline data or between tapentadol treatment and placebo.

No subjects scored more than 10 on the Subjective Opiate Withdrawal Scale questionnaire, meaning that no
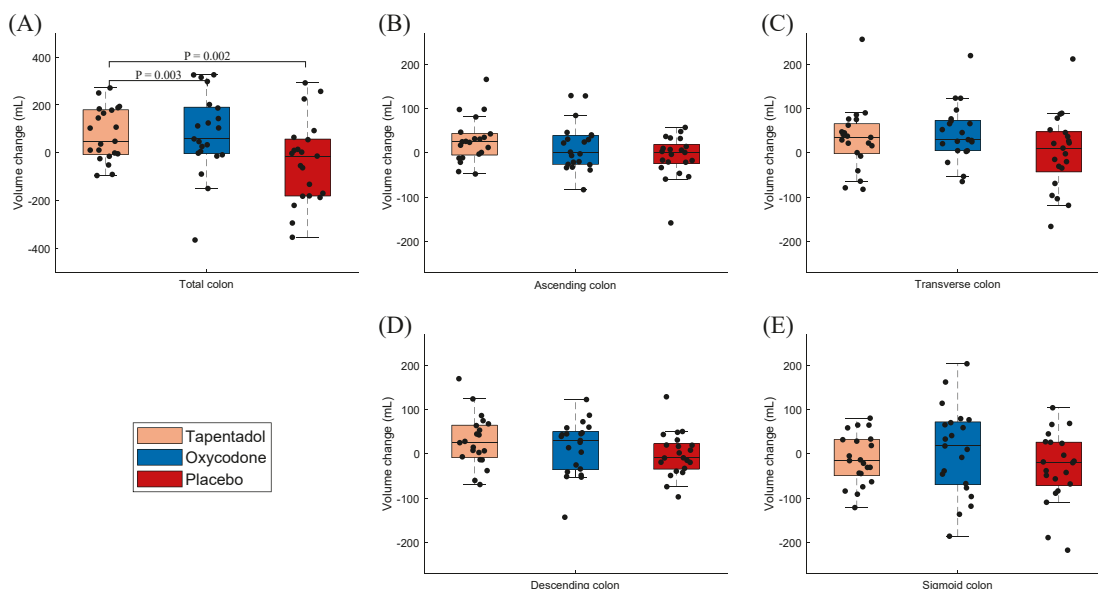

Figure 3: Boxplots of change in colonic volume from day 1 to day 14 during treatment with oxycodone, tapentadol or placebo. (A) Total colon, (B) ascending colon and cecum, (C) transverse colon, (D) descending colon, (E) sigmoid colon and rectum.

Table 2: Number of spontaneous bowel movements and stool consistency assessed on the Bristol stool scale.

	Tapentadol (50 mg twice daily)	Oxycodone (10 mg twice daily)	Placebo
Spontaneous bowel movements			
Week 1	**8.8 ± 4.2[a]**	6.7 ± 2.7	**9.6 ± 3.8[c]**
Week 2	8.6 ± 4.1	7.3 ± 2.9	8.1 ± 4.0
Bristol stool scale			
Week 1	**3.9 ± 0.5[c]**	3.2 ± 0.7	**4.2 ± 0.9[c]**
Week 2	**3.9 ± 0.7[c]**	3.2 ± 0.9	**3.8 ± 0.9[b]**

Values are mean ± standard deviation. *Difference from oxycodone is shown in bold font and tested with a repeated measures mixed model, [a]p<0.05, [b]p< 0.01, [c]p≤0.001.

subjects experienced more than mild withdrawal symptoms after the opioid treatments.

Bristol stool scale

The mean weekly number of spontaneous bowel movements and mean Bristol stool scale are summarized in Table 2. Compared to placebo, oxycodone treatment decreased the number of bowel movements the first week (p<0.001) and decreased mean stool consistency both in the first week (p<0.001) and in the second week (p=0.005). Compared to placebo, tapentadol treatment did not change the number of bowel movements or stool consistency (all p>0.6). Compared to tapentadol, oxycodone treatment decreased the number of bowel movements in the first week (p=0.02) and decreased mean stool consistency in the first week (p<0.001) and the second week (p=0.001). The bowel movement frequency for each individual subject is

illustrated in Figure 4 and the frequency and distribution of the different stool patterns are visualised in Figure 5. The frequency of spontaneous bowel movements and the Bristol stool scale were not affected by which order treatments were administered.

Pain tolerance threshold

An overview of the pain tolerance thresholds during the three treatments can be seen in Table 3. There were no differences in the pain tolerance thresholds during any of the treatments (p=0.35).

Associations between colonic volume change and side-effects

An association between change in total colonic volume and mean stool Bristol stool scale was observed during tapentadol treatment (Spearman's Rho=0.51, p=0.019), meaning that a colonic volume increase was related to more watery stool. No other associations were found (all Spearman's Rho< ± 0.26; all p>0.255).

Discussion

The main findings of this study were that treatment with oxycodone and tapentadol in equianalgesic dosages increased total colonic volume compared to placebo, but softer stools during tapentadol treatment may suggest softer faecal content. Furthermore, tapentadol treatment increased the number of spontaneous bowel movements,
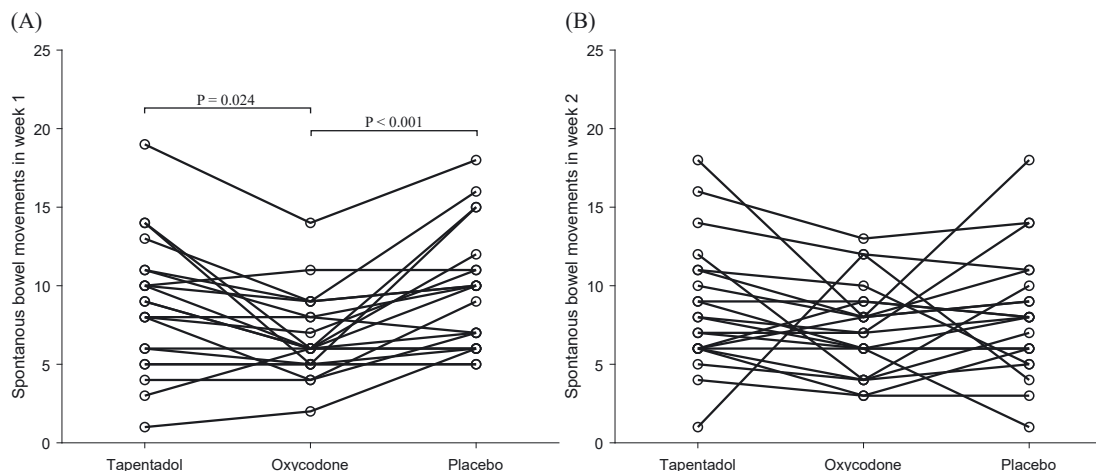

Figure 4: Line plots of the number of spontaneous bowel movements during treatment with tapentadol, oxycodone and placebo. (A) Spontaneous bowel movements during week 1. (B) Spontaneous bowel movements during week 2.
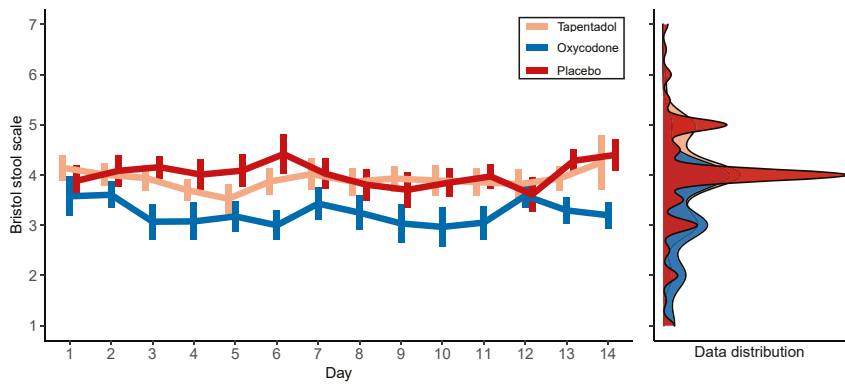
Figure 5: Bristol stool scale for 14 days of treatment with tapentadol, oxycodone and placebo.
Data is presented in mean ± standard error of the mean (SEM). The data distribution is shown in the panel to the right.

Table 3: Pain threshold test performed on the thigh.

Timepoint	Tapentadol (50 mg twice daily)		Oxycodone (10 mg twice daily)		Placebo	
	Mean	SD	Mean	SD	Mean	SD
Baseline, kPa	1105.2	475.6	1202.0	462.5	1179.1	449.5
Day 4, kPa	1264.1	458.1	1392.0	486.5	1308.0	517.4
Day 14, kPa	1118.0	402.8	1256.0	505.8	1292.9	505.7

No differences between pain threshold tests were observed.
SD, standard deviation.

as compared to oxycodone treatment, meaning that colonic dysmotility may not be as severe. Oxycodone but not tapentadol treatment affected how subjects reported straining during defecation, indicating that the anal sphincter tone was not negatively affected from tapentadol. At last, less reported CNS-related side-effects (tiredness) indicates that the opioid-sparing effect was present during tapentadol compared to oxycodone treatment.

All the planned 126 T2-weighted MRI scans were successfully completed, which contrasts to our previous research studies, where 6–17% of scans were failed due to non-optimal study protocols including non-compliance of research equipment and failed scans [18, 19].

Activation of peripheral opioid receptors during treatment with opioid agonists leads to unwanted GI side-effects [20]. Tapentadol depends less on activation of the opioid receptors due to its dual mode of action, why we expected less influence on colonic volume along with less severe side-effects during the treatment. However, the colon volume increased both during treatment with oxycodone and with tapentadol, although side-effects were less pronounced during tapentadol.

Previous mechanistic studies of opioid side-effects used shorter treatment periods of 2–6 days [18, 19, 21]. In the current study we used a longer treatment period of 14 days to provide a more clinically realistic insight into

side-effects of tapentadol, as it has been shown that the optimal clinical effect is presented after two weeks of treatment [22]. We expected the increase in colonic volume during oxycodone treatment to be higher as we have shown in previous studies of 5–6 days treatment periods [18, 19, 23]. This was consistent with the decreased number of spontaneous bowel movements and more dry faeces reported in the Bristol stool scale during the first week during oxycodone treatment. In a previous study applying the same methodology as in the current study, we succeeded in reducing GI side-effects during oxycodone treatment by co-administration of naloxegol, a peripheral acting μ-opioid receptor antagonist [19]. Naloxegol did, however, not affect the colonic volume compared to oxycodone alone, why it was hypothesized that the colonic luminal content was more liquid, consistent with the findings reported on the Bristol stool scale [24]. Having this knowledge, the increase in total colonic volume during oxycodone treatment in the current study may also be caused by less water content.

GI-related side-effects were most severe during oxycodone treatment. A previous clinical study of the acute GI side-effects of tapentadol, reported more severe scores than found in our study [21]. However, a higher dose of tapentadol (75 mg bid) than in our study (50 mg bid) was used. The observed side-effects following oxycodone treatment were comparable to our previous observations using oxycodone [18, 19, 23].

More severe GI-related side-effects did not associate to an increase in total colonic volume, although an increase in colonic volume was associated with softer stools in the tapentadol arm. The fact, that this was not observed in the other treatment arms, suggests that tapentadol may increase the water content compared to oxycodone. The water in colonic luminal content can be assessed using detailed analysis of MR images, which we previously have shown using both T2-weighted and DIXON-type water images [8]. However, our current data were sub-optimal for

this analysis and image acquisition should be optimized in future studies so that information on the water in the colonic content can be further investigated. Another and more thoroughly validated method for investigation of water content in the colon depends on T1/T2 relaxometry, where a calculated relaxation time of a region of interest inside the colon correlates well with the amount of faecal water (measured by freeze-drying faeces) [25].

In our previous studies using this MRI method, no associations were seen between total and segmental colon volume and GI side-effects for any treatment arms [18, 19, 23]. Colonic volumes may be too simplistic for direct explanation of GI-related side-effects, why it is important to look into both patient-reported outcomes and objective outcomes. Objective measurements of GI function seldom correlate to clinical parameters and symptoms, especially in studies where sub-optimal techniques are used [26]. Less reported GI symptoms during tapentadol treatment (compared to oxycodone) may partially be explained by less activation of central opioidergic mechanisms and may not necessarily be explained by a distended colon. The gut-brain axis plays an important role in this matter and inclusion of more central oriented measurements needs to be used before further conclusions can be drawn.

The pain tolerance threshold test did not show any differences between the active treatments and placebo. We expected to show that the active treatments equally increased the pain tolerance threshold, although the test might not be sensitive enough. A phase III study by Daniels et al. concluded that oxycodone 15 mg has the same analgesic effect as tapentadol 100 mg, meaning that the dose of tapentadol in the current study might have been too low compared to the dose of oxycodone [6]. Another phase III study and a phase II study of the efficacy of tapentadol 50 mg and oxycodone 10 mg in pain patients did, however, show comparable analgesic effects with the same doses as used in the current study [5, 14].

Study limitations

The data presented in this manuscript were secondary end-points obtained as part of a larger study protocol in the randomized trial. The study may be underpowered for evaluation of colonic volume, although the included sample size is similar or higher compared to other studies of colonic volume [7, 18, 23].

Baseline-corrected measurements were used in analysis to account for a large variation in the baseline measurements. The high physiological variation in colonic volume between study periods implies that the colonic volume is dependent on several factors including e.g. diet or toilet visit prior to assessment [7, 9]. The randomized study design minimizes the effect of this bias. In future studies, control of diet and even toilet visits (if possible) may minimize physiological variation in data and make interpretation of any intervention effect easier. Lastly, the findings in the healthy volunteers may not translate directly into patients having comorbidities, taking different medications or having higher tolerance of opioid usage due to longer treatment periods.

Conclusion

In conclusion, we found that tapentadol and oxycodone treatments both increased the total colonic volume after 14 days in healthy subjects. Despite this finding, tapentadol treatment did not induce more gastrointestinal and CNS-related side-effects than placebo, while oxycodone induced classical opioid-related side-effects. Furthermore, the increase in colonic volume was associated with stool consistency for the tapentadol arm indicating that the increased colonic volume likely represents more soft stools that are easier to defecate. The findings may pave the road for a more mechanistic treatment against gastrointestinal side effects during opioid therapy.

Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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