The effect of tapentadol and oxycodone on the human pain system

Study drugs: Tapentadol, oxycodone and placebo

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1 Experimental design

1.1 Study design

This study was a randomized, double-blinded, placebo-controlled, cross-over study in 21 healthy subjects with 3 arms: Tapentadol, oxycodone and placebo.

1.2 Volunteers

21 male subjects with mean age 24.9±2.7 (SD) were included in this study. All subjects participated in a screening visit at the Mech-Sense laboratory in the Department of Gastroenterology. All subjects were informed thoroughly about the specific procedures the study entails, and potential benefits and risks. Every subject gave written, informed consent before participating in the study. Subjects were free to withdraw from the study at any time. After inclusion, the experimental procedures (electrical stimulation on the foot, electrical stimulation of the medial nerve, thermal stimulation on the forearm, immersion of the hand in cold water, and mechanical stimulation of bone and muscle) were performed in order to familiarize these to the subjects. The inclusion and exclusion criteria are seen in Appendix 1.

1.3 Medication

Tapentadol (Palexia® Depot, 50 mg), oxycodone (OxyContin®, 10 mg extended release) and placebo tablets were administered orally on day 1 (after baseline measurements) and day 14 (in the morning) once and on day 2-13 b.i.d. (morning and evening). In total 26 doses were administered per treatment arm. Tapentadol is a combined moderate μ-opioid receptor agonist with noradrenaline reuptake inhibition and oxycodone is a μ-opioid receptor agonist. Tablets were produced at the Hospital Pharmacy Aarhus, Aarhus Hospital, Central Denmark Region, Denmark.

1.4 Objectives

The objectives of this study were 1) to show that tapentadol has effects on limbic and supra-limbic structures like opioids, and activates the brainstem and spinal level like noradrenaline reuptake inhibitors, and 2) to show that tapentadol has less effect on the autonomic and enteric nervous system in comparison with oxycodone in equipotent doses.

1.5 Study overview

During the study period subjects came in for visits at baseline, after four days of treatment, after 11 days of treatment, and after 14 days of treatment in all three arms, see Figure 1. At baseline, after four days of treatment and after 14 days of treatment, different assessment modules were performed. The visit after 11 days of treatment only included a control of whether the magnetic capsule swallowed on day four had passed through the gastrointestinal (GI) system. At baseline the subject started at the Department of Radiology for the “Imaging module” where magnetic resonance imaging (MRI) of the brain was done in about 45 min followed by MRI of the large intestine (5-10 min). The subject went to the Mech-Sense research laboratory for the “Vagal tone module” and the “Neurophysiological module” (4-5 hours). Finally, questionnaires were filled in. The subject was sent home with medication for the next four days and questionnaires to be filled in at home. At day four, the subject returned to the hospital for the “QST module” (approximate 30 minutes) and the “Motility module”, where the subject was instructed in how to swallow and use the 3D-transit system and the

receiver was mounted. The subject was sent home with the 3D-transit capsule and medication for the remaining days. At day 11, the subject returned for a short visit, where it was investigated, if the magnetic capsule swallowed on day four had passed through the GI system. After 14 days, the same modules which were performed at baseline were repeated. The “Motility module” was done 10 days before the last MR module to ensure that the capsule was excreted. On day 14 a blood sample was taken.

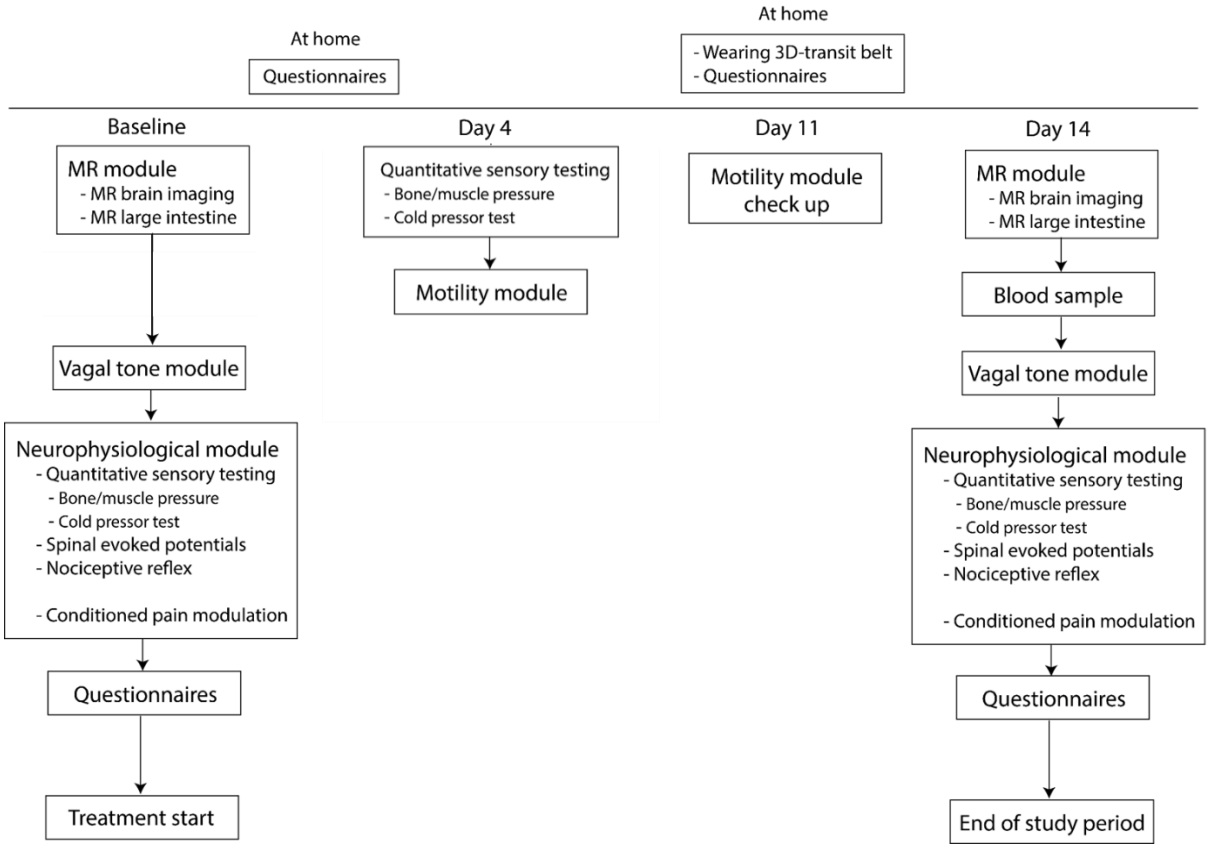

Figure 1: Flowchart showing the different procedures performed at each hospital visit.

2 Experimental procedures

In this preliminary study report, a subset of the experimental procedures is described in short and preliminary results are presented. Demography and characteristics of the included healthy volunteers are provided in Table 1.

Table 1 - Overview of demographical data and subject characteristics.

	Healthy volunteers n=21 (males)
Age (years)	24.9±2.7
BMI (kg/m^2)	25.3±2.6
Height (cm)	181.3±6.3
Weight (kg)	83.2±9.9
Dominant hand (R/L)	18/3

2.1 Quantitative sensory testing (QST)

Bone pressure was applied to the tibia, 10 cm distal to patella with a handheld pressure algometer (Type 2, Somedic production AB, Sweden) to determine pain tolerance threshold (PTT). The probe is a customized probe with a surface area of 1mm2. Pressure was increased at a rate of 30 kPa/sec. until the PTT is reached and subject was instructed to press a button at this point.

Muscle pressure was applied to the thigh, 15 cm proximal to the patella with a handheld pressure algometer (Type 2, Somedic production AB, Sweden) to determine pain tolerance threshold (PTT). The probe has a surface area of 1cm^2. Pressure was increased at a rate of 30 kPa/sec. until the PTT was reached and subject was instructed to press a button at this point.

The cold pressor test was performed by immersing the left hand in chilled water (2.0°C) that is continuously stirred by a pump. The subject was told to hold the hand in the water for up to 120 seconds. The subject was asked to rate the sensation on the pain scale (VAS, where 0 represents no pain and 10 represents the worst pain imaginable) 40 seconds, 80 seconds and 120 seconds after the hand was immersed into the cold water.

Conditioned pain modulation (CPM) is a clinically measureable form of descending pain modulation that can be induced experimentally by a conditioning stimulus (the cold pressor test) and quantified by applying a “test-pain” (pressure stimulation on the forearm) before and after its induction. The difference in pressure stimulus intensity before, during, and after induction of cold pressor pain provides a quantitative index of CPM capacity in the individual patient.

Data are summarized below. Ratios between values after treatment and before treatment (baseline) are stated. A ratio value of 1 indicates no changes after treatment as compared to baseline, a value below 1 indicates a decrease after treatment compared to the baseline measurement and a value above 1 indicates an increase after treatment as compared to the baseline measurements

2.2 Cardiac vagal tone (CVT)

The cardiac derived parameter CVT, which provide information about the parasympathetic activity, was estimated based on five minutes of ECG recordings. The data were manually cleaned for noise,

where heart rate data points deviating from beat to beat with more than 15 beats pr. minute were excluded from the dataset due to unphysiological causative factors.

2.3 EEG during cold pressor test

The cold pressor test was performed by immersing the left hand in chilled water (2.0°C) that is continuously stirred by a pump. The subject was told to hold the hand in the water for up to 120 seconds. 61 channel EEG was recorded while the hand was submerged. The data was filtered offline between 1 and 70 Hz and the frequency bands Delta (1-4 Hz), Theta (4-8 Hz), Alpha1 (8-10 Hz), Alpha2 (10-12 Hz), Beta1 (12-18 Hz), Beta2 (18-24 Hz) and Beta3 (24-32 Hz) were analyzed.

2.4 EEG and nociceptive reflex

The nociceptive withdrawal reflex (NWR) was recorded from the tibialis anterior. The baseline corrected area under the curve was measured for each stimulation and an interval peak Z score was used to determine the latency of the reflex, if any was visible on the EMG trace. Simultaneously EEG was recorded for further analysis.

2.5 Sensory evoked potentials (SEPs)

Sensory evoked potentials were recorded following an electrical stimulation of the right median nerve at motor threshold (1000 stimulations). Peripheral data was recorded at Erb's point on the right side of the body and at the location of C7. Cortical potentials were recorded using a 62 channel EEG cap. Both the peripheral nerve signals, spinal evoked potentials, and cortical SEPs were pre-processed using Neuroscan software (Neuroscan, Version 4.5, Compumedics, Charlotte, NC, USA).

2.6 Magnetic resonance spectroscopy

Magnetic resonance spectroscopy measurements were obtained from three predefined areas: the anterior cingulate cortex (ACC), the right insula (INS) and the prefrontal cortex (PFC). Levels of four metabolites were estimated using LCModel (1) : glutamate/creatine (glu/cre), N-acetylaspartate-/creatine (NAA/cre), myo-inositol/creatine (mI/cre) and glycerophosphocholine/creatine (GPC/cre).

2.7 Magnetic resonance imaging measured colonic volume

Colonic volume measurements were obtained using T2-weighted MR images of the unprepared colon. The volumetric measurements can be used to assess the level of fecal load, when compared over a treatment period. The colon volume is quantified using a semi-automatic segmentation platform (2,3). In the images, colonic tissue shows good contrast to its surrounding tissue (e.g. visceral fat and other organs). This information is used by a clustering algorithm that helps the observer during the image analysis. MRI of the colon are performed at baseline (day 1) and after treatment (day 14).

2.8 Motility module

Gastrointestinal transit times were measured with the 3D-Transit electromagnetic capsule system. At day four in each treatment period, the subjects ingested one capsule that was tracked during its passage through the gut. Using information of capsule rotation and position, it is possible to determine passage from the stomach to duodenum, and passage from ileum to cecum. Thereby, gastrointestinal transit times for the stomach, small bowel, colon and whole gut were determined.

2.9 Side-effects

Side-effects were reported on a scale 0-4, where 0=no, 1=mild, 2=moderate, 3=severe and 4=unbearable. The table below only shows the number of subjects, who experience side-effects and not the intensity of the side-effects. Side-effects are reported at baseline (day 1), after treatment (day 4) and after treatment (day 14).

2.10 PAC-SYM

The PAC-SYM is a sensitive and reliable instrument for monitoring the symptoms of opioid-induced constipation (4). It contains 12 items assigned to 3 subscales: stool symptoms, rectal symptoms, and abdominal symptoms. The means for each subscale and the global score were calculated. (5) PAC-SYM scores are reported at baseline (day 1), after treatment (day 4) and after treatment (day 13, the evening before the final hospital visit).

2.11 Gastrointestinal symptom rating scale

The gastrointestinal symptom rating scale (GSRS) is a disease-specific instrument, developed, based on reviews of gastrointestinal symptoms and clinical experience. The GSRS can be utilized to evaluate common symptoms of gastrointestinal disorders and has been used to evaluate OIBD (6,7). The GSRS contains 11 items. Each item is rated on a seven-point Likert scale from no discomfort to very severe discomfort based on symptoms over the last one week. The items are assigned to five subscales: abdominal pain (abdominal pain, hunger pains and nausea), reflux syndrome (heartburn and acid regurgitation), diarrhoea syndrome (diarrhoea, loose stools and urgent need for defecation), indigestion syndrome (borborygmus, abdominal distension, eructation and increased flatus) and constipation syndrome (constipation, hard stools and feeling of incomplete evacuation). The mean of the items completed within a subscale is calculated and higher scores indicate greater severity of symptoms. (8) GSRS scores are reported at baseline (day 1) and after treatment (day 14).

2.12 Bristol stool form scale

The subjects were asked to fill out the bristol stool form scale every day recording frequency and type of stool. Below is a visual representation of the recorded data for all subjects.