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Original experimental

The effects of gabapentin in human experimental pain models☆

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ABSTRACT

Background: The antidepressant drugs imipramine and venlafaxine relieve clinical neuropathic pain and have been shown to increase pain thresholds in healthy volunteers during repetitive electrical sural nerve stimulation causing temporal pain summation, whereas pain during the cold pressor test is unaltered by these drugs. If this pattern of effect in experimental pain models reflects potential efficacy in clinical neuropathic pain, the pain summation model may potentially be used to identify new drugs for such pain conditions. Gabapentinoids are evidence-based treatments of clinical neuropathic pain and could contribute with additional knowledge of the usefulness of the pain summation model.
The aim of this study: To test the analgesic effect of the gabapentinoid gabapentin in a sural nerve stimulation pain model including temporal pain summation and the cold pressor test.
Method: 18 healthy volunteers completed a randomized, double-blind, cross-over trial with medication of 600 mg gabapentin orally dosed 3 times over 24 h against placebo. Pain tests were performed before and 24 h after medication including pain detection and tolerance to single sural nerve stimulation and pain summation threshold to repetitive stimulation (3 Hz). Peak pain intensity and discomfort were rated during a cold pressor test.
Results: Compared to placebo, gabapentin had a highly significant effect on the threshold of pain summation to repetitive electrical sural nerve stimulation ($P = 0.009$). Gabapentin significantly increased the pain tolerance threshold to single electrical sural nerve stimulation ($P = 0.04$), whereas the pain detection threshold to single electrical sural nerve stimulation tended to be increased ($P = 0.06$). No significant differences were found on pain ratings during the cold pressor test.
Conclusion: Gabapentin had a selective hypoalgesic effect in a human experimental pain model of temporal pain summation and the results lend further support to the usefulness of the pain summation model to identify drugs for neuropathic pain.

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1. Introduction

Experimental pain models, when designed with careful consideration of the pharmacological mechanisms and pharmacokinetics of analgesics, may help to evaluate the mechanisms of analgesics and target the clinical indications for their use [1]. The antidepressant drugs imipramine and venlafaxine relieve clinical neuropathic pain [2] and have been shown to increase pain thresholds in humans using single and repetitive transcutaneous electrical sural nerve stimulation, whereas pain during the cold pressor test (CPT) is unaltered by these drugs [3,4]. Especially, repetitive nerve stimulation is believed to be of major interest, since it reflects temporal pain summation. The experimental temporal pain summation model is based on a methodical study in which the optimal frequency for facilitating the psychophysical threshold for temporal pain summation was found to be 3 Hz [5]. Temporal pain summation is believed to contribute to central sensitization of pain which represents an important pathopsychological mechanism in the characteristics of chronic pain [6]. Abnormal temporal summation is often a part of the clinical picture in neuropathic pain conditions such as postmastectomy pain and pain in multiple sclerosis [7,8]. The cold pressor test (CPT) is considered a model reflecting opioid analgesia and drugs with non-opioid analgesic mechanisms such as the sodium channel blocking anticonvulsants phenytoin and lamotrigine have only minor effect on pain induced by CPT [9,10], and imipramine is without pain-relieving effect [3]. A pattern with effect in the pain summation model and no effect in the cold pressor model might reflect specific efficacy in clinical neuropathic pain and as such, it is possible that the pain model could be used to identify new drugs for such pain conditions.

The anticonvulsant gabapentin is effective in several clinical neuropathic pain conditions [11]. In experimental human pain models, gabapentin has been proven to relieve induced cutaneous hyperalgesia, but not noxious pain induced by heat or cold [12–14].

The aim of this study was primarily to test whether the analgesic effect of gabapentin can be detected in a sural nerve stimulation pain model with single and repetitive electrical stimulation. Assessment of temporal pain summation was included in order to determine the potential of this experimental model as a screening tool to identify substances to be tested in clinical trials in neuropathic pain. Gabapentin has not previously been tested in this pain model using transcutaneous electric nerve stimulation. The temporal summation threshold was the main endpoint in this study. The cold pressor test was added as a supplemental pain model. A previous study has shown that a single dose of 600 mg gabapentin by itself did not reduce pain induced by the cold pressor test in healthy volunteers, but increased the analgesic effect of 60 mg morphine [13]. Since the clinical analgesic effect of gabapentin on chronic neuropathic pain is observed at repetitive doses at 1800 mg daily or higher, an analgesic response at this dose of gabapentin could not be excluded. Gabapentin shows a saturable absorption kinetic, which limits the benefit of a high single dose [15]. Thus, we found it relevant to test the impact of gabapentin using a repetitive dosing design.

2. Methods

2.1. Subjects

The study included 20 healthy volunteers (14 men and 6 women) aged 23–31 years (median 24.5 years). The volunteers were not allowed to consume alcohol or any drugs except for the study medication on study days, and were instructed to consume their usual daily quantity of coffee and tea, if any. Written informed consent was obtained from the volunteers before the study procedure, and the study was approved by Scientific Ethical Committee of the Vejle and Funen counties (J.No. VF 20030233) and the Danish Medicines Agency (J.No. 2612-2429).

2.2. Design

The study design was randomised, double-blind, balanced and cross-over, including 2 study periods of 2 days' duration with a total oral dose of gabapentin 1800 mg, divided into 3 doses of 600 mg, (2 capsules of 300 mg; manufacturer: Pfizer, Denmark) against identical placebo. Each volunteer was instructed to take the medication with intervals of 8 h, so the last dose of the study medication was taken 2 h before the beginning of the test round of day 2. The study periods were separated by at least one week for washout.

2.3. Nociceptive tests

At the time of inclusion in the study, the volunteers were familiarised with the test procedures. On each study day, the measurements of the nociceptive tests were performed in the same way. On the first study day in each round, the volunteers initially were subjected to a test round in which all pain stimulation tests were performed during which no measurements were obtained. This was done in order to minimize adaptation phenomena. As described below, the effect variables were determined before and 24 h after the start of medication.

2.4. Electrical sural nerve stimulation

Percutaneous electrical stimulation of the sural nerve was performed along its retromalleolar path by applying a constant-current rectangular pulse consisting of 5 pulses (each of 1 ms duration) delivered at 200 Hz (single stimulation) or this stimulation mode repeated 5 times with a frequency of 3 Hz (repetitive stimulation). Psychophysical pain detection and tolerance thresholds were determined to single stimulation. For the repetitive stimulation, pain summation threshold was defined as the stimulation strength at which the pain distinctly increased through the 5 stimulations and reached a painful level at the 4th or 5th stimulation. All thresholds were determined twice and the mean value was used in the data analysis.

2.5. Cold pressor test

The left hand was immersed into iced water (1.0 Celsius (±0.3 Celsius)) that was continuously stirred by a pump. The subject removed his/her hand from the water after 2 min of immersion, or sooner if the pain was considered intolerable. In the event that the subject had to remove his/her hand from the iced water, pain was automatically determined to be 100 mm on the VAS. Pain intensity was continuously rated during the test by use of an electronic visual analogue scale coupled to a computer. From the data obtained, peak pain intensity was determined [9]. Immediately after the test, the subjects rated the discomfort experienced during the procedure on a visual analogue scale (0–100 mm). The subject was asked to rate the worst discomfort during the cold pressor test by marking a point on the 0–100 mm scale using a pen.

2.6. Reaction time and side effects

Reaction time to auditory stimuli was determined by use of a computer program to control for a possible sedating effect of the study drug. A sound was generated at random intervals and reaction time was determined as the time elapsed from appearance of the sound and to the subject responded by pressing a button. A total of 3 tests were carried out for each subject at each pain measurement