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Determination of the Effective Dose of Pregabalin on Human Experimental Pain Using the Sequential Up-Down Method

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Abstract: The intradermal capsaicin pain model has been used to evaluate analgesic effects of a variety of drugs. Using the sequential up-down method, we examined the analgesic effects of pregabalin on intradermal capsaicin pain. Using a double-blind, placebo-controlled, crossover study, healthy adult men were randomized to oral pregabalin or placebo on the first visit and returned for the opposite treatment after a washout period. Dosing was set by the Dixon sequential up-down method; that is, a greater or less than 30% reduction in capsaicin pain decreased or increased the dose, respectively, by a fixed interval for the next subject. The median effective dose (ED50) was derived once 7 changes in dose direction occurred. Secondary outcome measures included secondary hyperalgesia and tactile and thermal allodynia, and their respective areas (cm^2). Thirteen subjects were required to derive the pregabalin ED50: 252 mg (95% confidence interval 194, 310 mg). Most common side effects were drowsiness (46%), euphoria (31%), and dizziness (7%). Those with ≥30% pain reduction as compared to placebo also had similar reductions in secondary outcome measures. The intradermal capsaicin pain model can be used to efficiently derive the pregabalin ED50, but well-powered dose-response curve studies are needed for comparison and validation.

***Perspective:** Using the Dixon sequential up-down method, the ED50 of pregabalin on intradermal capsaicin induced pain was successfully calculated (252 mg) using only 13 subjects.*

***Key words:** Pregabalin, median effective dose, up-down method, experimental, pain.*

There are evident challenges in studying pain drug efficacy. Human experimental models have been developed to permit a well-controlled, reproducible, ethical study of the response to experimental pain stimuli.[19] Although there is no evidence that these models predict clinical success, there is an interest in using them as a screening method to detect analgesic signals. One particular model is the intradermal injection of capsaicin, which elicits both acute and neuropathic-like pain elements. It produces a severe burning sensation that resolves within minutes, accompanied by prolonged hypersensitivity around the area of injection. All effects of the capsaicin injection are temporary. It does not cause any major or long-term side effects, making it a safe means of studying human pain. Moreover, the experimenter can reliably induce pain by administering a controlled amount of capsaicin.[14]

The use of human experimental pain models may be useful in evaluating analgesic efficacy. One method that can be incorporated into the human experimental pain models is the sequential up-down method to determine the median effective dose (ED50). The sequential up-down method, created by Dixon, utilizes a staircase experimental design that increases or decreases a dose for the next subject depending on the all-or-none response of the previous subject. It is repeated until these dose changes eventually oscillate around the true population ED50. This stepwise approach can be used to efficiently derive the ED50 of analgesics with significantly fewer subjects than conventional dose-response curve studies.[5,13] As few as 6 subjects are required to complete the analysis. This may not only increase cost-effectiveness but also decrease subject exposure to painful stimuli and drug side effects. This method has been used previously to derive the ED50 for volatile and spinal anesthetics[2,12] but has not been well studied for oral pain medications.

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To date, only gabapentin has been tested under this model for preemptive analgesia in spine surgery.[17] Because the small sample size of the sequential up-down method is heavily affected by random variation, oral pain drug choice must be done judiciously when using this model, that is, minimize as much variation caused by drug absorption, distribution, metabolism, and elimination. One oral pain drug that is ideal for the intradermal capsaicin up-down method is the anticonvulsant pregabalin, which has known analgesic effects on neuropathic pain, a high therapeutic index, predictable serum levels, relatively high potency, opiate-sparing advantages, and benign side effect profile.[1,7,15,17] It has been well investigated under randomized, placebo-controlled trials and shown to have a more titratable dose response compared to gabapentin, which similarly binds to the alpha-2-delta subunit of neuron calcium channels.[6,15,18] Pregabalin's high bioavailability and linear pharmacokinetics can confer a dose response to neuropathic pain that is titratable.

For this double-blind, randomized, placebo-controlled crossover study, our primary goal was to assess the feasibility of applying the sequential up-down method for rapidly deriving the ED50 of pregabalin for intradermal capsaicin pain.

Methods

Subjects

After receiving approval from the University of California San Diego institutional review board, 13 healthy male volunteers from San Diego County who gave written consent were enrolled into the study. Inclusion criteria were males age 18 and above that were free from any pain. Subjects were then screened for capsaicin sensitivity. Eligible subjects must report a visual analog scale (VAS) pain score[3] of at least 50 out of 100, 5 minutes after injection of intradermal capsaicin (250 μg in a volume of 25 μL 20% cyclodextrin solution) on the volar aspect of the forearm. Exclusion criteria were significant medical problems of cardiac, neurologic, and/or renal etiology; psychological disease and depression; consumption of any analgesic or adjuvant analgesic within 24 hours; and known allergy to the study drug. Females were excluded from the study to minimize the confounding effect of gender on our data analysis (unpublished pilot data with alfentanil on capsaicin pain demonstrated that females reported significantly higher average pain scores than their male counterparts). It was also important to have a homogenous sample population because our statistical method assumes normality and homogeneity. Thus, only healthy male subjects free of pain were recruited. Subjects were given a small monetary compensation for participating in the study.

Experimental Design

For this double-blind, randomized, placebo-controlled crossover study, each subject participated in 2 sessions separated by a washout period of greater than 4 days. A simple randomization table was used, consisting of a binary response (eg, A or B). This table was balanced and blinded to subjects and investigators. Subjects were randomized to either pregabalin or placebo on the first visit and given the opposite treatment for the crossover.

Each visit consisted of the following:

- Baseline vital signs were noted.
- Baseline hot pain threshold (in degrees Celsius) and von Frey filament pain threshold (in grams) were determined.
- Subjects were given the oral drug and waited 75 minutes to allow for peak pregabalin serum levels.
- Intradermal capsaicin injection: 25 μL of capsaicin solution (10 μg/μL) was injected intradermally on the volar aspect of the right forearm.
- Pain assessment: VAS pain scores were measured at the time of injection and every 5 minutes for 20 minutes. At this point, the hyperalgesic area surrounding the injection site was mapped by von Frey hair and allodynic areas with foam brush strokes.
- Pain assessment continued every 10 minutes for the next 40 minutes. Area-under-the-curve VAS pain scores were calculated over the total 60-minute testing.
- Postdrug hot pain threshold was measured and areas of hyperalgesia, allodynia, and flare size recorded.

The primary outcome measure was defined as a 30% or greater reduction in spontaneous capsaicin pain for drug vs placebo. Secondary outcome measures included 1) area of hyperalgesia/allodynia (measured post capsaicin injection) around the injection site and 2) hot pain thresholds and evoked pain scores measured next to the injection site. Blood pressure, heart rate, blood oxygen saturation, temperature, and respiratory rate were monitored throughout the study to assess the subject's well-being.

Pain Scores

All neurosensory testing was performed on the volar aspect of the forearm over the area injected with capsaicin. Pain scores were measured on a visual analog pain scale from 0 (no pain) to 100 (worst imaginable pain) on a 100-mm line. Four pain scores were obtained: 1) spontaneous pain, 2) mechanical hyperalgesia with a 5.18 von Frey hair, 3) mechanical allodynia with a 1-inch foam brush, and 4) heat allodynia with a 40°C probe.

The elicited neurosensory tests were performed within a 4 cm radius surrounding the capsaicin injection site. Hot pain measurements were elicited with a thermal sensory analyzer probe that was placed over the injection site. Hot pain thresholds were obtained by increasing the temperature to a maximum of 50.0°C from 32.0°C. The subject was asked to click a mouse button upon perceiving hot pain, causing the probe to rapidly cool and return to 32.0°C. The threshold was derived from the mean of 3 trials. Heat allodynia was elicited with a 40°C stimulus for 5 seconds at each of the measured time points.