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The effect of a combination of gabapentin and donepezil in an experimental pain model in healthy volunteers: Results of a randomized controlled trial

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ABSTRACT

This double-blind, placebo-controlled, 3-period cross-over, 4-treatment option, incomplete block study (ClinicalTrials.gov number NCT01485185), with an adaptive design for sample size re-estimation, was designed to evaluate gabapentin plus donepezil in an established experimental model of electrical hyperalgesia. Thirty healthy male subjects aged 18–55 years were randomized to receive gabapentin 900 mg or gabapentin 900 mg + donepezil 5 mg for 2 of the 3 treatment periods, with 50% of subjects randomized to receive placebo (negative control) and 50% to gabapentin 1800 mg (positive control) for the remaining period. Each treatment period was 14 days. Gabapentin or corresponding placebo was administered on Day 13 and the morning of Day 14. Donepezil or corresponding placebo was administered nocturnally from Day 1–13 and the morning of Day 14. Co-primary endpoints were the area of pinprick hyperalgesia (260 mN von Frey filament) and allodynia (stroking by cotton bud) evoked by electrical hyperalgesia on Day 14. Gabapentin 1800 mg (n = 14) significantly reduced the area of allodynia vs placebo (n = 14; −12.83 cm^2; 95% confidence interval [CI] −23.14 to −2.53; $P = 0.015$) with supportive results for hyperalgesia (−14.04 cm^2; 95% CI −28.49–0.41; $P = 0.057$), validating the electrical hyperalgesia model. Gabapentin + donepezil (n = 30) significantly reduced the area of hyperalgesia vs gabapentin 900 mg (n = 30; −11.73 cm^2; 95% CI −21.04 to −2.42; $P = 0.014$), with supportive results for allodynia (−6.62 cm^2; 95% CI −13.29–0.04; $P = 0.052$). The adverse event profile for gabapentin + donepezil was similar to the same dose of gabapentin. Data are supportive of further clinical investigation of a gabapentin-and-donepezil combination in patients with an inadequate response to gabapentin.

1. Introduction

Gabapentin is an approved first-line treatment for peripheral neuropathic pain, such as diabetic neuropathy and postherpetic neuralgia [2,9]. However, its usage is limited by incomplete efficacy (the number needed to treat = 4) and dose-limiting adverse effects in a significant proportion of patients [13]. Combination therapy of gabapentin and another analgesic with a synergistic or additive mechanism of action is, therefore, a rational approach to potentially achieve efficacy at lower doses, thereby reducing the side effects associated with gabapentin.

The mechanism of action of gabapentin is primarily ascribed to its binding to the α2-δ1 subunit on presynaptic voltage-gated calcium channels located throughout the peripheral and central nervous systems, modulating release of neurotransmitters [20]. Preclinical studies have shown that gabapentin acts supraspinally to increase noradrenaline release, which in turn activates the descending pain inhibitory noradrenergic-cholinergic pathway [14,20,24]. Therefore, combination therapy with gabapentin and a cholinesterase inhibitor would be expected to further increase the inhibition of pain via this pathway [3].

Donepezil is a centrally acting, reversible, and selective acetylcholinesterase inhibitor, and is currently the frontline treatment

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for cognitive deficits observed in Alzheimer's disease [6]. The utility of donepezil as an adjunct to gabapentin for the treatment of pain can be hypothesized from animal studies where synergistic effects up to 10-fold have been demonstrated in several rodent models [11,15]. Controlled clinical trials of this combination therapy are lacking, but a recent open-label uncontrolled study in a small number of patients with posttraumatic neuropathic pain showed that the addition of donepezil to existing gabapentin treatment resulted in clinically relevant reductions of pain and improved mental well-being in patients who did not receive sufficient pain relief from gabapentin alone [3].

The aim of the present exploratory study was to investigate the potential synergy between gabapentin and donepezil, compared to gabapentin alone, in established experimental pain models in healthy volunteers [1,19], before committing to larger-scale efficacy studies of the combination in patients. No single experimental model in humans can address all the potentially relevant mechanisms for pathological pain, but the well-established electrical hyperalgesia model, which invokes hyperalgesia (exacerbated sensitivity), allodynia (touch evoked pain), and ongoing pain by repetitive electrical stimulation of the skin, mimics some facets of pain disorders and is thought to be representative of central sensitization [7,19]. As a secondary model, we used repetitive electrical stimulation of the sural nerve to give an indication of central temporal integration in the nociceptive system [1].

The primary endpoint of our study was to determine acute effects on secondary hyperalgesia (areas of pinprick hyperalgesia and touch-evoked allodynia) in the electrical hyperalgesia model [19]. Secondary endpoints were to determine acute effects on sural nerve pain thresholds, tolerance, and temporal summation following sural nerve stimulation [1], and the intensity and area of flare and the intensity of spontaneous pain evoked by cutaneous electrical stimulation [19].

2. Methods

2.1. Study design and participants

This was a double-blind, placebo-controlled, 3-period crossover, 4-treatment option, incomplete block study with an adaptive design for sample size re-estimation. The study was conducted at the GlaxoSmithKline Clinical Unit Cambridge, United Kingdom between October 2011 and June 2012. The protocol was reviewed and approved by an independent ethics committee, and written informed consent was obtained from each subject. The trial is registered with ClinicalTrials.gov, registration number NCT01485185.

Study visits consisted of screening, baseline, 3 14-day treatment periods with a washout of approximately 21 days between each, and a follow-up. For each treatment period, subjects were dosed at home on Days 1–12 and attended the unit on Days 13 and 14. Pharmacodynamic assessments occurred at baseline and on Day 14 of each treatment period.

Healthy males aged 18–55 years with body weight $\geqslant$50 kg, body mass index 18.5–29.9 kg/m^2, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin $\leqslant$1.5 $\times$ upper limit of normal, and QTcB or QTcF <450 ms were eligible for enrolment. Female subjects were not enrolled because of potential variability in pain thresholds due to hormonal influences. Subjects were familiarised with the pharmacodynamic testing procedures at screening. Subjects who were unable to tolerate the electrical hyperalgesia model or sural nerve stimulation during the screening session, or who did not produce an area of hyperalgesia or allodynia in the electrical hyperalgesia model, were excluded.

2.2. Interventions

All subjects were randomized to receive gabapentin 900 mg and the combination of gabapentin 900 mg + donepezil 5 mg for 2 out of the 3 treatment periods, with 50% of subjects randomized to receive placebo (negative control) and 50% to receive gabapentin 1800 mg (positive control) for the remaining period. The randomization schedule was generated by GlaxoSmithKline prior to the start of the study using validated software. Treatment ratios were balanced across the 3 periods.

Each treatment period was 14 days, with donepezil 5 mg or corresponding placebo capsules administered on all 14 days (nocturnally from Day 1 to 13 and on the morning of Day 14), and gabapentin or corresponding placebo capsules administered during the last 2 days of treatment (300 mg or 600 mg, depending on total daily dose administered 3 times daily at 8-hour intervals on Day 13 and on the morning of Day 14). The dosing schedule was designed so that pharmacodynamic testing on Day 14 was done at or near steady-state conditions and as close as possible to the predicted time of peak plasma concentrations for each drug. Donepezil has a long half-life and steady state is achieved after approximately 14 days, with peak plasma concentration (coinciding with maximal acetylcholinesterase inhibition) occurring approximately 4 hours after dosing [25]. Gabapentin has a much shorter half-life, and steady state is achieved within 24–48 hours, with peak plasma concentration occurring 3–4 hours after dosing [4].

Donepezil-placebo capsules were matched to donepezil capsules in size, weight, and appearance. Gabapentin-placebo capsules were matched to gabapentin capsules in size and weight, but were a different colour. Therefore, to maintain blinding, the gabapentin or corresponding placebo capsules given on Days 13 and 14 were administered while subjects were blindfolded, by staff not involved in collecting pharmacodynamic data.

2.3. Pharmacodynamic assessments

Pharmacodynamic assessments were conducted at intervals over a 1-hour time period at baseline and on Day 14 (from 4 to 5 hours post dose). Assessments were done by 2 trained nurses familiar with the testing protocols, which were well established within the clinical research unit. Wherever possible, the same nurse performed all the assessments for a particular subject.

The electrical hyperalgesia model was conducted as described by Koppert et al. [19]. Two electrodes (modified microelectrode neurography needle; FHC Inc., Bowdoin, ME, USA) were inserted intracutaneously in the subject's forearm approximately 5–7 mm apart. Electrical stimulation (pulse width 0.5 ms, 5 Hz) was delivered via an alternating constant current stimulator (DS7A, Digitimer, Hertfordshire, UK). The intensity was gradually increased from ~10 mA, targeting a pain rating of 6 on a numeric pain rating scale (0 = no pain; 10 = worst pain imaginable), and then kept constant for the rest of the experiment. At 15-minute intervals during electrical stimulation, superficial blood flow was measured by Laser Doppler Imager (LDI, Moor Instruments Ltd., Devon, UK), the area of pinprick hyperalgesia was determined with a 256-mN (26 g) von Frey filament, and the area of touch-evoked allodynia was determined with a cotton bud gently stroked on the skin. The borders of the area of hyperalgesia/allodynia were delineated by stimulating along 4 linear paths from distant starting points toward the stimulation site, until the subject reported increased pain sensations evoked by the von Frey filament (pinprick hyperalgesia) and unpleasant sensations by stroking with the cotton bud (allodynia). Subjects rated pain intensity at approximately 5-minute intervals during electrical stimulation.