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PAIN

Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers[†]

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Background. Central sensitization is an important mechanism of neuropathic pain; its human models could be useful for early detection of efficacy of novel treatments. The electrical hyperalgesia model invokes central sensitization by repetitive stimulation of the skin. To assess its predictive value, we have investigated pregabalin, a standard neuropathic pain treatment, and aprepitant, an NK₁ antagonist, as an example of a drug class active in animal models but not in neuropathic pain patients. Furthermore, we explored if combinations of either of these drugs with the COX-2 inhibitor parecoxib could improve its efficacy.

Methods. This was a double-blind, two-period, placebo-controlled study using incomplete block design. Thirty-two healthy volunteers received either oral pregabalin (titrated to 300 mg) or aprepitant (titrated to 320 mg), or matching placebo over 6 days before testing. Sensitization was assessed over 3 h; at 2 h, subjects received either parecoxib (40 mg) or saline i.v.

Results. Pregabalin significantly reduced the areas of punctate mechanical hyperalgesia and dynamic touch allodynia vs placebo (both $P < 0.0001$); no significant reduction in the area of hyperalgesia or allodynia vs placebo was observed with aprepitant. In the pregabalin+parecoxib treated group, the area of allodynia was significantly reduced ($P < 0.0001$) and the area of hyperalgesia insignificantly attenuated ($P = 0.09$) vs placebo+parecoxib; no efficacy improvement was observed with aprepitant+parecoxib.

Conclusions. The model can serve to predict analgesic efficacy in early human development and investigate the mechanism of action. The model could also be used to explore efficacy of analgesic combinations to provide a rationale for patient studies.

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Chronic pain affects millions of people and substantially reduces their quality of life; current treatments only provide a partial relief.^{1 2} Development of novel analgesics requires large-scale patient trials. However, the record of pre-clinical efficacy translating into humans is poor, one much-discussed example being tachykinin NK₁ receptor

antagonists.³ Thus, the current approach to analgesic development is prone to high attrition rates. One potential solution to this problem is the use of human pain models

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in early development before committing to large-scale patient trials. However, such models need to mimic key mechanisms of pain pathophysiology and be predictive for patients.

Central sensitization is a key mechanism in the development and maintenance of chronic pain, particularly neuropathic pain.^{4–7} A model of electrically evoked pain and hyperalgesia has been developed; it evokes central sensitization by noxious peripheral stimulation in human volunteers.⁸ This model can be of utility in Phase 1 of development of new treatments for neuropathic pain as it offers a good control over test duration, stability, a demonstrated central mechanism of sensitization, and sensitivity to a number of i.v. analgesics.^{8–12} However, to assess the predictive value of a model, it is crucially important to demonstrate the efficacy of standard treatments, with dosing regimens used in patients; this has not been done with this model. Furthermore, the negative predictive value, that is, the ability to detect lack of efficacy of drugs known not to relieve pain in patients, has never been explored in this and, to our knowledge, any other human model of central sensitization. Therefore, we conducted a controlled study of chronic oral pregabalin, a gabapentin analogue used for the treatment of neuropathic pain, with the dosing regimen utilized in patients. We also investigated amitriptyline, a centrally acting NK₁ antagonist marketed for the treatment of nausea and vomiting. Along with other compounds of this class, this drug was efficacious in a wide range of animal pain models, but failed to alleviate pain in patients (see Hill³ for review). Demonstrating lack of efficacy of amitriptyline would thus provide some evidence of the model's value as an efficacy filter in humans.

Our secondary objective was to investigate the effect of COX inhibition in combination with pregabalin or amitriptyline. This was based on the hypothesis of greater redundancy in pain pathways in humans compared with animals, resulting in lower efficacy of single mechanisms, and explaining the lack of analgesia with NK₁ antagonists (see Hill³ and comments thereon). This redundancy would imply that combining an NK₁ antagonist with a known analgesic drug acting at a single mechanism might lead to improved efficacy. Prostaglandins are important mediators of pain and COX inhibitors are widely used as analgesics in humans. Recently, parecoxib, a COX-2 inhibitor pro-drug, was shown to attenuate electrically evoked central sensitization.¹² Thus, demonstrating benefits of such combinations could give useful hints for chronic pain therapy. The results of this study have been published in abstract form.¹³

Methods

Subjects and study design

The study was conducted at the University Hospital of Erlangen. Thirty-two healthy volunteers (16 females, 16

males, age range 19–45 yr, median 25 yr) were recruited for this study (see Statistical analysis for sample size calculations). All subjects were familiar with the described stimulation procedures. Each subject gave written informed consent before taking part in the study. The study was performed in accordance with Good Clinical Practice guidelines and the 1996 version of the Declaration of Helsinki, the experimental protocol was approved by the Ethics Committee of the University of Erlangen-Nuremberg. In each session, subjects were screened for drugs of abuse (urine) and alcohol breath test was performed before all other assessments.

We utilized a double-blind, placebo-controlled, two-period, cross-over, incomplete block design. After initial screening that involved medical history, physical examination, and laboratory screening tests, a short baseline session was performed (Table 1) in order to establish individual current intensities for using in the rest of the study (see Study procedures). The subjects were randomized using randomization software (Matlab, Version 6.5, 2002; MathWorks, Natick, MA, USA) into two treatment groups (16 subjects each): one group received oral pregabalin or placebo (in a randomized order) for 1 week before the testing session; the other group received oral amitriptyline or placebo, respectively. Thus, each subject underwent two testing sessions, receiving one of the two drugs (either pregabalin or amitriptyline) or matching placebo once daily over 6 days before each session (see Figure 1). Both groups were further subdivided into two equal subgroups of eight subjects: those receiving an active treatment in Session 1 received an i.v. infusion of parecoxib approximately after 2 h of the 3 h testing session; those on placebo had an i.v. infusion of isotonic saline (Figure 1, Table 1). Session 2 always involved an i.v. infusion of parecoxib around the 2 h time point. Thus, the numbers of subjects treated with each of the three combinations (parecoxib+placebo, parecoxib+pregabalin, and parecoxib+amitriptyline) were equal ($n=16$). To maintain the blind, subjects were not instructed how many infusions of parecoxib *vs* saline they would receive over the course of the study. One week was allowed between the baseline session and Session 1, and 2 weeks were allowed between Sessions 1 and 2.

Treatments and dose rationale

Pregabalin (Lyrica[®], Pfizer) was administered twice daily at increasing doses up to 300 mg day⁻¹ p.o. for 6 days, including the day of testing (75 mg–150 mg–225 mg–300 mg–300 mg–300 mg). This dose has been shown to significantly reduce pain in postherpetic neuralgia and painful diabetic neuropathy patients.^{14,15} The 300 mg dose appears to be safe and well tolerated in patients. Amitriptyline (Emend[®], Merck Sharp & Dohme) was administered twice daily at increasing doses up to 320 mg day⁻¹ p.o. for 6 days (80 mg–160 mg–240 mg–320 mg–320 mg–320 mg). A dose of 300 mg has failed to alter pain intensity

Table 1 Experimental protocol. This table shows time and events in Sessions 1 and 2. The baseline session was 65 min long but otherwise identical to the first 65 min as shown

	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180			
Time relative to start of stimulation																																								
Electrical stimulation					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pain score																																								
Punctate hyperalgesia					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tactile allodynia																																								
I.v. injection																																								

in postherpetic neuralgia patients after 2 weeks of treatment.¹⁶ On the other hand, similar or lower single doses of aprepitant have demonstrated efficacy in trials in patients with chemotherapy-induced nausea and vomiting (CINV).¹⁷ Moreover, the 300 mg dose has been demonstrated to produce a >90% occupancy of NK₁ receptors in the striatum using positron emission tomography.¹⁸ On the day of testing, one of the oral treatments was given 3 h before the start of electrical stimulation. Parecoxib (40 mg, Dynastat[®], Pharmacia) or saline was administered as an i.v. bolus approximately after 2 h of the testing session (Table 1). This dose is similar to those used in the clinic for the treatment of postoperative pain and has shown a significant inhibitory effect on central sensitization in the electrical hyperalgesia model.¹²

Study procedures

Two intradermal electrodes (Dermal Dialysis, Erlangen, Germany) were inserted into central volar forearm as described earlier.⁸ Pulses of electrical current (pulse width 0.5 ms, 2 Hz) were delivered via an alternating constant current stimulator (DS7A mod, Digitimer, Hertfordshire, UK). In the baseline session, the current intensity was gradually increased over 15 min from zero, targeting a pain rating of six on the 11-point numeric rating scale (NRS, 0=no pain, 10=maximum pain imaginable), and then kept constant for the rest of the session. This was done in order to take into account individual sensitivity to electrically evoked pain as it varies substantially across subjects. As previously described, these current intensities were always sufficient to activate high-threshold nociceptors and central sensitization as evidenced by flare and secondary hyperalgesia, respectively.^{8,9} To ensure that no experimental bias was introduced that way, the step increments and final current intensity were recorded for each subject and used in the two subsequent sessions; thus, each subject served as his or her own control.

The area of punctate mechanical hyperalgesia was measured at 20 min intervals (Table 1) using a hand-held von Frey filament of 256 mN. In this and previous studies where filaments of this force were used, subjects described the sensation evoked by this filament using terms such as 'sharp', and 'pricking', and 'pin-like'. This is consistent with other published reports in healthy volunteers (e.g. Rolke and colleagues¹⁹ reported mean mechanical pain threshold on the hand as 129 mN). The borders of the hyperalgesia were delineated by stimulating along four linear paths radiating from the stimulation site (proximal vs distal vs left vs right), starting in skin with normal sensation moving towards the stimulation centre in a 0.5 cm stepwise manner at a rate of approximately 1 cm s⁻¹. Subjects were asked to report when the sensation changes to an increased pain sensation evoked by the filament (punctate mechanical hyperalgesia). Similarly, the area of touch-evoked allodynia was determined at intervals (Table 1) by gently

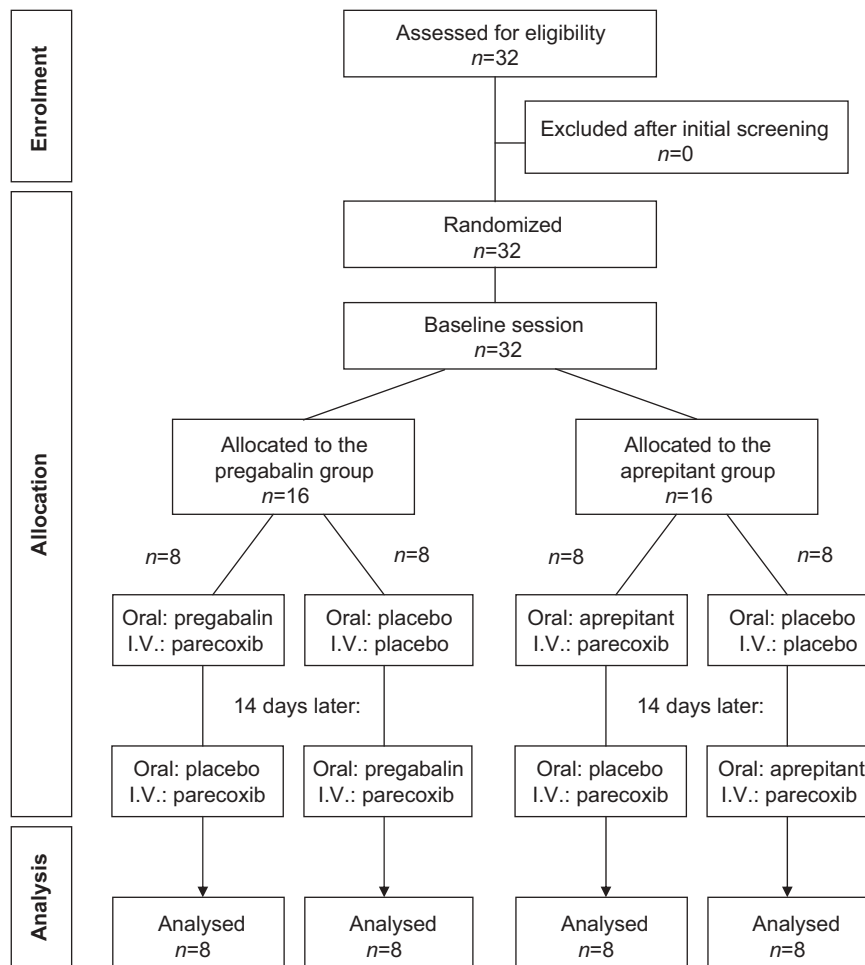


Fig 1 Enrolment, treatment allocation, and analysis groups.

stroking a hand-held cotton wool bud on the skin at a rate of approximately 1 cm s^{-1} . The borders of the allodynia were delineated similarly to the determination of hyperalgesia described earlier. Subjects were asked to report when the sensation changed to a painful/unpleasant sensation by stroking the skin with the cotton wool bud (allodynia). Areas of punctate mechanical hyperalgesia and dynamic allodynia were calculated from the recorded distances as follows: $\text{Area (cm}^2\text{)} = \pi * (L + R) * (P + D) / 4$, where L , R , P , and D are distances in centimetres from the stimulation site to the left, right, proximal, and distal borders of the sensitization area, respectively.

Throughout the electrical hyperalgesia, testing subjects were asked to rate the intensity of ongoing pain at 5 min intervals using the 11-point NRS (where 0=no pain and 10=maximum pain imaginable). Blood pressure, heart rate, and blood oxygen saturation were monitored throughout the session.

Statistical analysis

Before the study, we performed sample size calculations based on the within-subject standard deviation (σ_w)

observed in our previous study using the electrical hyperalgesia model.¹⁰ Thus, our estimate of the within-subject variance for area of hyperalgesia and allodynia (σ_w^2) was 41 cm^2 . From this, the estimated within-subject SD of the difference was calculated as: $\sigma_w^* \sqrt{2} = 9.05 \text{ cm}^2$. The estimate of the magnitude of pregabalin effect was based on our previous study of gabapentin in the capsaicin model of central sensitization, where the drug–placebo difference for the area of allodynia was 7.72 cm^2 (see Gottrup and colleagues²⁰). On the basis of these the sample size needed to achieve 80% power using a crossover design was calculated to be 13 subjects, or 17 subjects to achieve 90% power. Thus, with the planned 16 subjects per arm we estimated to have at least 80% power to detect the expected difference between pregabalin and placebo.

The hyperalgesia and allodynia data were analysed by a mixed effect repeated-measures analysis of variance (ANOVA), fitting fixed effect terms for period, assessment time, and treatment. Assessment time was fitted as a repeated variable. Subject was fitted as a random effect. The full model was used to investigate interactions. Treatment effect was based on the additive model. Weighted mean pain ratings data were investigated by

means of ANOVA. With both types of analysis, measurements taken before the start of dosing were summarized per subject; this baseline was added to the model as covariate to account for potential individual differences. The analyses were performed on absolute values, separately for the time-points 20–100 min (to assess the effects of the oral treatments) and 120–180 min (to assess the effects of the combinations with i.v. parecoxib). A probability value of ≤ 0.05 was considered to indicate statistical significance. The data were analysed using SAS software system V8.2 (SAS Institute Inc., Cary, NC, USA).

Results

The mean current that was used in the baseline session to achieve a pain rating of six was 32.3 (4.3) mA; the same current was used in the subsequent sessions. The currents used in this study and baseline values of pain intensity, hyperalgesia, and allodynia were similar to those reported in previous studies utilizing this model [mean values over 20–60 min (SD): pain intensity 5.3 (1.0) u, area of hyperalgesia 44.69 (26.09) cm², and area of allodynia 38.44 (24.37) cm²].

Effects of oral pregabalin and amitriptyline on hyperalgesia, allodynia, and pain

Subjects who received oral placebo for 1 week before the testing session developed areas of hyperalgesia and allodynia in response to electrical stimulation; the time-course and size of these areas (Figure 2) were similar to previously published results of this model.^{8 10 21} Pregabalin highly significantly reduced the areas of punctate mechanical hyperalgesia and dynamic touch allodynia compared with placebo (Figure 2 and Table 2). For hyperalgesia, the least square mean (LSM, calculated over the 20–100 min interval, with 95% confidence interval, CI) of the difference between the pregabalin and placebo sessions was -9.09 cm² (95% CI: -12.03 to -6.15 cm², $P < 0.0001$). For allodynia, the respective values were -10.75 cm² (95% CI: -14.76 to -6.74 cm², $P < 0.0001$).

In contrast to the pregabalin-treated group, no significant reduction in the size of area of hyperalgesia or allodynia vs placebo was observed in the group treated with amitriptyline (Figure 2 and Table 2). Thus, the LSM difference for the area of hyperalgesia was -0.89 cm² (95% CI: -3.93 to 2.14 cm², $P = 0.56$). For the area of allodynia, the difference was -2.95 cm² (95% CI: -7.22 to 1.33 cm², $P = 0.18$).

Neither pregabalin nor amitriptyline had any significant effect on the intensity of electrically evoked pain compared with placebo (Table 2). For pregabalin, the LSM difference from placebo was -0.36 u (95% CI: -0.89 to 0.18 , $P = 0.18$); for amitriptyline, the respective values were -0.45 u (95% CI: -0.99 to 0.09 , $P = 0.10$).

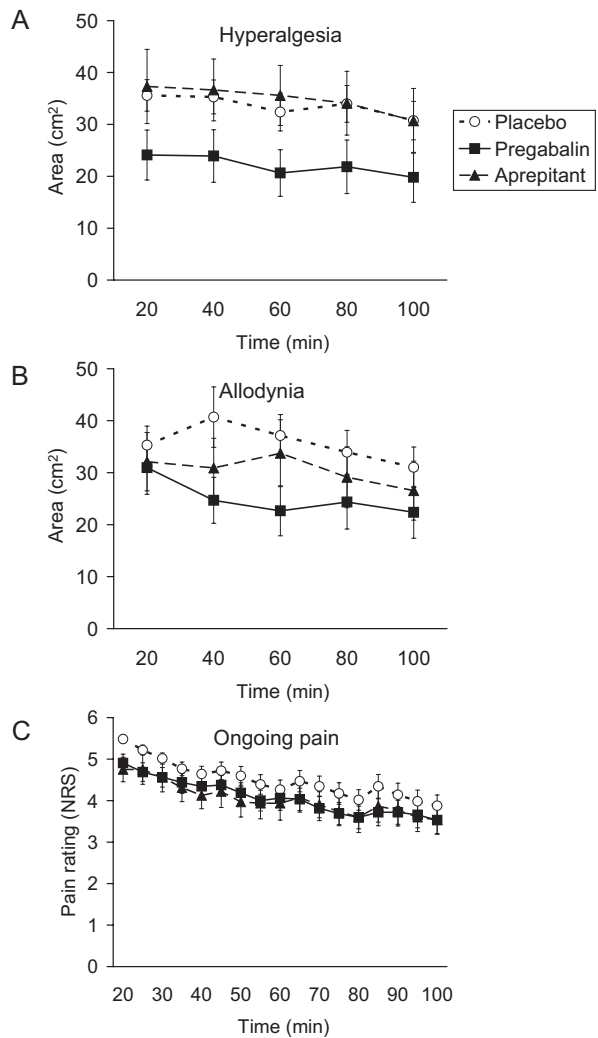


Fig 2 The effects of oral pregabalin, amitriptyline, and placebo on hyperalgesia, allodynia, and pain evoked by electrical stimulation of the skin. The time-course of the area of punctate mechanical hyperalgesia (A), dynamic touch allodynia (B) and ongoing pain intensity (C) for the three treatment groups is plotted as mean (SE) over 20–100 min from the onset of stimulation.

Effects of i.v. parecoxib in combination with oral pregabalin and amitriptyline

As the efficacy of parecoxib in this model was demonstrated earlier,¹² the purpose of this part of the study was to establish if combining this COX-2 inhibitor with either

Table 2 Effects of orally administered pregabalin, amitriptyline, and placebo on punctate mechanical hyperalgesia, dynamic touch allodynia, and ongoing pain evoked by electrical stimulation of the skin. LSM (SD) data for the areas of hyperalgesia and allodynia, and for pain intensity ratings, were calculated over 20–100 min from the stimulation onset. *Significant differences from the respective placebo group, $P < 0.0001$

Treatment	Hyperalgesia (cm ²)	Allodynia (cm ²)	Pain (NRS units)
Placebo (n=32)	33.48 (13.42)	35.50 (14.52)	4.55 (1.02)
Pregabalin (n=16)	24.40 (10.34)*	24.75 (11.66)*	4.14 (0.71)
Amitriptyline (n=16)	32.59 (10.45)	32.56 (12.05)	4.04 (0.74)

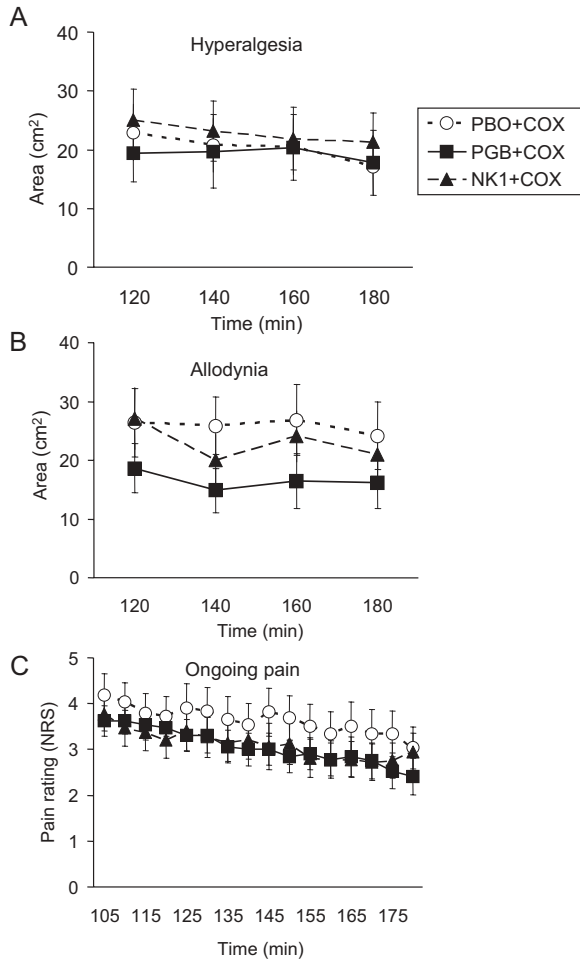


Fig 3 The effects of orally administered pregabalin (PGB), aprepitant (NK1), and placebo (PBO) in combinations with i.v. parecoxib (COX) on punctate mechanical hyperalgesia, dynamic touch allodynia, and ongoing pain evoked by electrical stimulation of the skin. The time-course of the area of punctate mechanical hyperalgesia (A), dynamic touch allodynia (B), and ongoing pain intensity (C) for the three treatment groups is plotted as mean (SE) over 120–180 min (A, B) or 105–180 min (C) from the onset of stimulation. Parecoxib was administered between 105 and 115 min.

aprepitant or pregabalin could lead to enhanced overall efficacy. Comparison of the group that received parecoxib in combination with pregabalin vs parecoxib with placebo indicates that this may be the case (Figure 3 and Table 3). Thus, after the administration of parecoxib, the area of allodynia was significantly smaller in the pregabalin-treated group compared with placebo (LSM difference: -8.43 cm^2 ,

95% CI: -12.14 to -4.72 , $P < 0.0001$). With the area of hyperalgesia, a trend towards a greater effect of parecoxib in the presence of pregabalin vs parecoxib+placebo was noticed, although the magnitude of this difference was small and did not reach the level of significance (LSM difference: -2.74 cm^2 , 95% CI -5.92 to 0.44 , $P = 0.09$).

In the aprepitant and parecoxib treated group, there was no evidence for improved efficacy of the combination (Fig. 3 and Table 3). In fact, the area of hyperalgesia was somewhat enlarged after aprepitant + parecoxib vs placebo + parecoxib treatment (LSM difference: 5.54 cm^2 , 95% CI 1.74 – 9.35 , $P = 0.005$). The area of allodynia with the aprepitant–parecoxib combination was not different from that after placebo+parecoxib (LSM difference: -1.65 cm^2 , 95% CI -6.12 to 2.82 , $P = 0.46$).

Consistent with the findings on the lack of efficacy of the two oral treatments alone on ongoing pain, no significant differences from placebo+parecoxib were observed either with pregabalin- or aprepitant-combination (LSM differences: 0.09 u, 95% CI -0.15 to 0.32 , $P = 0.39$; 0.55 u, 95% CI -0.45 to 1.55 , $P = 0.24$, respectively; see also Fig. 3).

Adverse events of the study

The study treatments and procedures were generally well tolerated and no subject has withdrawn from the study. During the assessments, all of the subjects reported being fully alert and free from side-effects and were able to co-operate with the operator normally. A summary of study adverse events experienced over the treatment period is provided in Table 4. There were no differences between any of the treatment groups in blood pressure, heart rate, and blood oxygen saturation (data not shown).

Discussion

The electrical hyperalgesia model mimics the positive symptoms of neuropathic pain, that is, ongoing pain, hyperalgesia, and allodynia, the latter two being viewed as measures of central sensitization.⁸ Experiments with local anaesthetic blocks have demonstrated the central origin of sensitization in the model.⁹ Thus, in terms of mechanisms, the models bear similarity with neuropathic pain states where central sensitization is triggered and maintained by peripheral afferent barrage.^{5,6} It also provides good control over the magnitude and duration of peripheral input and

Table 3 Effects of orally administered pregabalin (PGB), aprepitant (NK1), and placebo (PBO) in combinations with i.v. parecoxib (COX) on punctate mechanical hyperalgesia, dynamic touch allodynia and ongoing pain evoked by electrical stimulation of the skin. LSM (SD) data for the areas of hyperalgesia and allodynia, and for the pain score, were calculated over 120–180 min (parecoxib was administered between 105 and 115 min). Significant differences from parecoxib+placebo, $**P < 0.005$, $*P < 0.0001$

Treatment	Hyperalgesia (cm ²)	Allodynia (cm ²)	Pain (NRS units)
COX+PBO (n=16)	28.21 (12.92)	26.08 (16.45)	3.43 (1.49)
COX+PGB (n=16)	23.79 (11.60)	16.64 (14.95)*	3.17 (1.31)
COX+NK1 (n=16)	33.76 (13.41)**	24.81 (15.12)	3.02 (1.48)

Table 4 Summary of adverse events (AEs) reported over the course of the study

	Placebo	Pregabalin	Aprepitant
Number of subjects dosed	32	16	16
Number of subjects with AEs	6	11	8
Fatigue	3	4	4
Dizziness	0	9	1
Abnormal dreams	0	0	1
Dry mouth	0	4	0
Taste change	1	0	1
Anxiety	0	0	1
Diarrhoea	2	0	4
Drowsiness	1	6	2
Muscle weakness	0	1	0
Feeling energetic	0	2	0
Headache	1	0	0
'Heavy tongue'	0	1	0

hence stability of the endpoints.⁸ Thus, it could potentially serve as an early indicator of central analgesic and antihyperalgesic efficacy in humans and provide confidence necessary for initiating large-scale patient studies. By way of model validation, efficacy of some i.v. drugs known to relieve pain in patients has been demonstrated in this model. Fast-acting opioids, the NMDA antagonist ketamine, the sodium channel blocker lidocaine, and adenosine reduced central sensitization in this model after acute i.v. administration.^{8 10 21} These data provide confidence that the model is sensitive to a range of antihyperalgesic mechanisms; however, the model validation would have been incomplete without data on the efficacy of standard treatments and essential negative controls.

One important finding of the present study is that the electrical hyperalgesia model can detect efficacy of repeated oral doses of pregabalin. This drug is a selective ligand of the $\alpha_2\delta$ subunit of calcium channels and close analogue of gabapentin, a standard treatment for a range of neuropathic pain conditions (see Backonja and Glanzman²² for review). Pregabalin appears similarly efficacious to gabapentin in several neuropathic pain states, with the claimed advantage of a fast onset of action not requiring dose titration.^{14 15} The reduction by repeated doses of oral pregabalin in hyperalgesia and allodynia areas in the electrical hyperalgesia model strongly suggests that this drug can inhibit central sensitization in humans and, because of the similarity of the dosing regimen with that used in the clinic, implies that this mechanism may be responsible for the attenuation of neuropathic pain in patients. This result is consistent with recent findings with oral gabapentin in two models of capsaicin-evoked sensitization in healthy volunteers.^{20 23} The reduction of sensitization in the electrical hyperalgesia model, where allodynia and hyperalgesia are independent from peripheral nociceptor sensitization,^{8 9} indicates a central mode of action of pregabalin.

Thus, together with previous data, our finding provides further confidence that the model has a positive predictive

value for analgesics developed for neuropathic pain. Moreover, for the first time ever, we have demonstrated that an NK₁ antagonist is inactive in a human model of central sensitization. The NK₁ antagonist class is one much-discussed example of an analgesic mechanism that failed to show analgesic activity in the clinic (see Hill³ and comments therein). Several highly selective, potent compounds have been developed and demonstrated efficacy in a range of animal models of chronic pain (reviewed by Hill³ and Boyce and Hill²⁴). However, all compounds of this class that reached clinical trials failed to show analgesic efficacy, raising general concerns about the predictivity of animal models.^{3 16 24–26} Aprepitant, the selective NK₁ antagonist, has recently become available for the treatment of CINV.²⁷ This drug has a good CNS permeability, and doses similar to or lower than the one used in our study have demonstrated high levels of brain NK₁ receptor occupancy^{18 28 29} and efficacy in CINV trials in patients.¹⁷ On the other hand, aprepitant failed to alter pain intensity in postherpetic neuralgia patients after 2 weeks of treatment,¹⁶ despite good efficacy in a range of animal pain models.²⁴ The fact that in our study aprepitant failed to significantly attenuate any measures of sensitization suggests that the electrical hyperalgesia model has some negative predictive value and could serve as an efficacy filter. It cannot be excluded that the lack of effect of aprepitant is related to the study size. However, the study was formally powered to detect an approximately 30% reduction in measures of allodynia and hyperalgesia, as previously observed with gabapentin in another human model of sensitization.²⁰ This effect was observed with the chronic dose of gabapentin known to produce a clinically meaningful attenuation of pain intensity in patients with neuropathy. Thus, by inference, this magnitude of reduction of experimental sensitization endpoints could be considered meaningful. Indeed, pregabalin in the present study caused similar attenuation of allodynia and hyperalgesia, again at a clinically efficacious dose. Despite the nearly 90% power that this study had to detect efficacy of this magnitude, aprepitant showed no significant effect and no clear trend for attenuation of sensitization. It is therefore unlikely that a larger study could have demonstrated efficacy of this drug. Hence, this result most likely reflects the difference between the roles of the NK₁/tachykinin mechanism in animal and human pain pathways and emphasizes the importance of early exploration of efficacy of novel analgesics in humans.

In discussing the predictive value of the electrical hyperalgesia model for chronic pain indications, several points need to be considered. First, although important, central sensitization is only one of the mechanisms of neuropathic pain, and this model does not address several other potentially relevant mechanisms, for example, ectopic afferent discharge. Second, the duration of sensitization in this model is limited and unlikely to fully mimic the long-term sensory plasticity expected to develop in chronic pain

patients. Thus, the model's ability to detect analgesic efficacy may be limited to those mechanisms that interfere with such relatively short-term plasticity. Third, although central sensitization is a common mechanism of many chronic pain types, central sensitization in different pain states may well be different and extrapolation of data from the electrical model onto pain states other than neuropathic pain requires great caution and further studies. It is also noteworthy that none of the treatments tested in this study including pregabalin had any significant effect on pain intensity ratings. Although this is at variance with neuropathic pain trials in which attenuation of pain with gabapentin or pregabalin has been demonstrated,^{14 15 22} it is consistent with previous studies of this drug in experimental pain models.²⁰ It is important to emphasize that the main aspect of this and similar human models is sensitization (measured by assessing hyperalgesia and allodynia) rather than pain; the latter is likely to reflect direct activation of nociceptive fibres and hence be sensitive to acute analgesic mechanisms such as opioids.⁸

It has been hypothesized that analgesic efficacy in humans of drugs with a single mechanism may be limited because of high redundancy of neurotransmitters in nociceptive pathways. This could be one reason for the failure of the NK₁ antagonist class as an analgesic treatment, whereby the role of tachykinins in humans may be less important compared with animals (see Hill³ and comments therein). This could also underlie the limited efficacy of many available chronic pain treatments, such as pregabalin and gabapentin. Thus, combinations of analgesic mechanisms could lead to improved efficacy; this would be beneficial even in case of a sub-additive interaction.^{30 31} The prostanoid pathway is an important pronociceptive mechanism inhibited by NSAIDs and selective COX-2 inhibitors, which are widely used for the treatment of various pain conditions in humans. Importantly, the COX-2 inhibitor parecoxib was shown to attenuate sensitization in the electrical hyperalgesia model,¹² suggesting a role of central COX-2. In the present study, a combined administration of pregabalin and parecoxib was more efficacious in attenuating measures of central sensitization than parecoxib with placebo. It must be noted that this part of the study had a low power because of the parallel group design, and it is not possible to conclude whether the interaction was sub- or supra-additive. Nevertheless, this result suggests that a combination of gabapentin-like drugs and COX-2 inhibitors may provide an efficacy benefit in chronic pain states where central sensitization is a key mechanism, for example, neuropathic pain; this should be explored further in appropriately designed studies in pain patients. Recently, a study of a combination of gabapentin and rofecoxib in postoperative pain demonstrated a similar benefit in the treatment of pain after hysterectomy.³²

Contrary to the pregabalin–parecoxib combination, aprepitant did not appear to improve the efficacy of

parecoxib. Interestingly, the area of hyperalgesia was somewhat enlarged in the aprepitant-treated group, whereas the areas of allodynia were similar. Again, the parallel design of this part of this study limits its power and we cannot be certain that the significant effect on hyperalgesia is not due to type I statistical error. At any rate, these data do not lend any support to the hypothesis that analgesic efficacy of NK₁ antagonists in humans could be enhanced by inhibition of another pathway, such as COX-2 mediated prostaglandin synthesis.

In conclusion, this study has demonstrated that a clinically efficacious dose of chronic oral pregabalin inhibits measures of central sensitization in the electrical hyperalgesia model in human volunteers, whereas a centrally active dose, the NK₁ antagonist aprepitant is inactive. Together with previous findings, these results highlight the value of this model as a predictor of efficacy in pain states driven by central sensitization, such as neuropathic pain, and its potential utility in early human phases of development of new analgesics (although several important limitations need to be borne in mind). Because of the role of central mechanisms in this model, it can also provide hints on the mechanism of action; thus, our result is consistent with a central mechanism of pregabalin in humans. Finally, the model may be used to explore efficacy of analgesic combinations in order to provide a rationale for testing these combinations in pain patients, as exemplified by the combination of pregabalin and parecoxib.

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