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Randomised clinical trial: pregabalin attenuates the development of acid-induced oesophageal hypersensitivity in healthy volunteers – a placebo-controlled study

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SUMMARY

Background
Acid infusion in humans induces primary and secondary oesophageal hypersensitivity. The effects of pregabalin, a centrally-acting modulator of voltage-sensitive calcium channels, on development of acid-induced oesophageal hypersensitivity remain unknown.

Aim
To study the effects of pregabalin on development of secondary oesophageal hypersensitivity in healthy humans.

Methods
Placebo-controlled, double-blind, randomised, cross-over study of 15 healthy volunteers (six women, age 21–56 years). After oesophageal manometry, baseline pain thresholds (PTs) to proximal oesophageal electrical stimulation were determined using bipolar ring electrodes. A 30-min infusion of HCl was performed in the distal oesophagus followed by PT measurements at 30 and 90 min. This protocol was repeated after administration of pregabalin (dosing schedule: 75 mg twice daily for 3 days then 150 mg twice daily for 1 day and then 150 mg on the morning of study) or placebo.

Results
T0 PTs were similar in patients after receiving placebo or pregabalin [mean (s.d.) 32.9 mA (20.5) vs. 34.1 (15.7), $P = 0.42$]. Pregabalin reduced development of acid-induced hypersensitivity in the proximal oesophagus at 30 min [mean change in PT (C.I.) placebo −6.2 mA (−11.3 to +1.3) vs. pregabalin +0.20 mA (−2.7 to +3.3)] and 90 min [placebo −3.7 mA (−10.0 to +2.0) vs. pregabalin +0.7 mA (−4.7 to 7.3)] overall $P = 0.001$. Pregabalin reduced median visual analogue scale score for acid-induced pain (1/10 vs. placebo 3/10, $P = 0.027$).

Conclusions
Pregabalin attenuates development of secondary hypersensitivity in the proximal oesophagus after distal oesophageal acidification; it may thus have a role in treatment of patients with proven oesophageal pain hypersensitivity.

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a very common disorder with 20–44% of Western populations experiencing GERD symptoms at least once a month, and 20% weekly.[1, 2] GERD can be divided on the basis of endoscopic findings into erosive oesophagitis and non-erosive reflux disease (NERD).[3] Other patients are defined as having functional heartburn (FH) when symptoms occur in the absence of abnormal acid exposure. Studies of acid exposure across the spectrum of GERD have revealed an increasing prevalence of abnormal oesophageal acid exposure times, as defined by 24-h pH monitoring, as one progresses from FH and NERD through to erosive oesophagitis.[4, 5] This suggests that a factor other than acid reflux must be responsible for symptom generation in patients with NERD and FH.[6] It is proposed that oesophageal pain hypersensitivity (hyperalgesia) is more common in patients with NERD and FH in comparison to erosive oesophagitis, and may cause symptoms in response to either physiological amounts of acid reflux or other luminal stimuli.[7] The mechanism of hypersensitivity remains unclear, but involves (amongst other potential mechanisms) dilatation of epithelial intercellular spaces[8] and exposure of sub-epithelial nerves to acid.[9, 10] This leads to sensitisation of peripheral afferent nerves (peripheral sensitisation), but more critically, sensitisation of spinal dorsal horn neurons[11] (central sensitisation). Once central sensitisation is established, it can continue to potentiate pain after the initiating peripheral stimulus is discontinued. Patients with established hypersensitivity may be those who fail acid suppressing therapy,[12] with some progressing to more invasive interventions such as surgery.[13]

A model in which infusion of acid in the distal oesophagus induces sensitisation at the site of acid infusion (primary hyperalgesia) as well as in the proximal oesophagus (secondary hyperalgesia) due to peripheral sensitisation and central sensitisation, respectively, has been described previously.[14] This model has been used to study the effects of various drugs on oesophageal hypersensitivity.[15–18] For instance, Ketamine, an *N*-methyl D-Aspartate (NMDA) receptor antagonist was effective in both preventing and reducing the secondary hyperalgesia induced by experimental acid infusion.[18] However, Ketamine has considerable central side effects and requires intra-muscular or intravenous administration, making it impractical for routine clinical use.

Pregabalin is a specific ligand of alpha-2-delta type 1 and 2 subunits of voltage-gated calcium channels;[19] it can be given orally and is centrally acting. Pregabalin, although structurally related to GABA, does not interact with GABA[20] or NMDA receptors,[21] but reduces the pain modulators including substance P[22] and glutamate in the brain.[21] It is a gabapentinoid like gabapentin, but has more predictable pharmacological effects and achieves therapeutic effects at lower doses, thereby reducing dose-related side effects.[23] It is effective in non-inflammatory somatic pain including neuropathic pain,[24] pain associated with diabetic neuropathy[25, 26] and fibromyalgia.[27–29] A similar potential effect in visceral conditions is suggested by a very recent study of healthy volunteers, which demonstrated that pregabalin reduces gas and pain sensation to colonic distension[30] and a study of patients with irritable bowel syndrome (IBS) in which pregabalin increased pain thresholds to rectal distension.[31] The effect of pregabalin on upper GI pain has not been investigated.

The aim of this study was to determine the effect of pregabalin in healthy volunteers on reducing the development of acid-induced oesophageal secondary hyperalgesia compared with placebo (primary outcome). Secondary outcomes were to determine: (i) the proportion of subjects in whom pregabalin prevented sensitisation; and (ii) whether pregabalin affected subjective pain and unpleasantness to acid infusion.

PATIENTS AND METHODS

Study design

A prospective, double-blinded, placebo-controlled, cross-over study was conducted over three visits (CONSORT[32] diagram: Figure 1). Visit 1 (screening) determined eligibility and baseline sensitisation data, selecting only those volunteers who sensitised to acid (defined on the basis of previous studies[33] as a fall in proximal oesophageal PT ≥ 6 mA). Eligible volunteers were then randomised according to a cross-over sequence (performed by the Barts and the London NHS Trust pharmacy using computer generated randomisation schedule) and given medications with written instructions. At visits 2 and 3, (T0) electrical threshold data were obtained prior to acid infusion for subsequent comparison with those data obtained at 30 (T30) and 90 (T90) minutes post infusion. The researchers and participants were blinded throughout the study. All experiments were conducted in human physiological laboratory, Wingate Institute, Barts and the London School of Medicine and Dentistry, with patients seated on a couch, having fasted for a minimum of 6 h, usually from the night before. A short medical interview was performed during all visits. At visits 2 and 3, a short

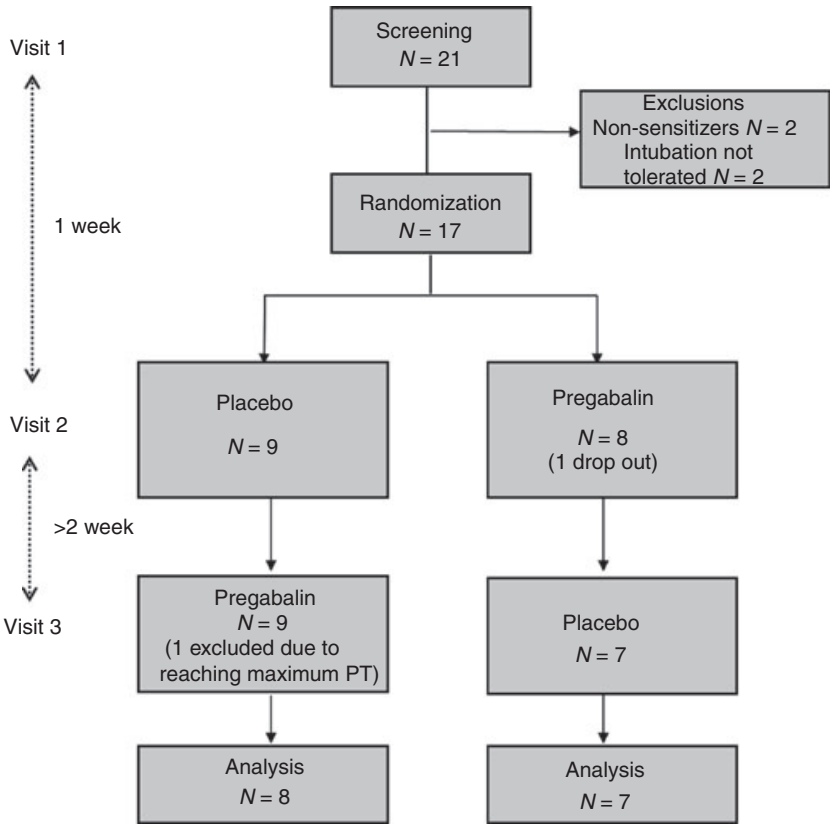

Figure 1 | Consort diagram.[32]

interview on side effects and compliance was also performed.

Subjects

Adult healthy volunteers, aged 18–60, were recruited by advertisement. All had normal medical assessments including detailed medical interview, and none was taking any regular medication. Urine tests were performed at all visits to exclude pregnancy (First Step FS208 Euromed Limited, London, UK) and drugs of abuse (Triage 8 TM, Biosite, San Diego, CA, USA). Oesophageal manometry was carried out at the screening visit on each subject to exclude motility disorders and to locate the lower oesophageal sphincter. Written consent was obtained, and the protocol was approved by the local ethics committee (Research ethics committee reference: 07/MRE08/39 and MHRA (Medicine and Healthcare products Regulatory Agency). The study was also published in ISRCTN website (ISRCTN40924266).

Interventions

As in previous studies,[34, 35] pregabalin (Pfizer, Kent, UK) was self administered, 75 mg twice daily for 3 days, 150 mg twice daily on the fourth day and 150 mg in the morning of return visit on the fifth day (12 × 75 mg capsules total provided in single bottle). Capsules and bottles of exact appearance were provided for placebo. Medications and instructions were given at the end of visits 1 and 2. The interval between visit 1 and visit 2 was at least 1 week apart, as retrospective analysis of departmental data has shown that sensitisation is reproducible within 1 week.[36] However, the interval between visits 2 and 3 was at least 2 weeks to allow time for complete washout of pregabalin.[37] Volunteers were asked to return the medication bottle on subsequent visits.

Methods

Oesophageal acid infusion. The catheter and pH probe assembly was passed transnasally into the oesophagus without local anaesthetic. Hydrochloric acid (HCl; 0.15 mol/L) was infused through a port in the electrical stimulation catheter (Gaeltec, Isle of Skye, UK), sited 3 cm above the lower oesophageal sphincter (LES) at a constant rate of 8 mL/min for 30 min via an infusion pump (Graseby Medical, Hertfordshire, UK). Previous studies have indicated that this acid concentration induces oesophageal hypersensitivity in the majority of healthy subjects.[14] A twin-channel pH catheter (Synectics Medical, Enfield, UK) measured pH in both the proximal oesophagus (at the site of electrical stimulation) and in

the distal oesophagus (at the site of acid infusion) for the duration of each study.

Electrical stimulation. Oesophageal electrical stimulation was delivered at T0, T30 and T90 using a pair of 1 cm spaced silver–silver chloride bipolar ring electrodes (Gaeltec) as described in detail previously.[16, 17, 38] To act as a somatic control, pain thresholds to electrical stimulation were determined on the dorsum of the right foot using silver-silver chloride electrodes with 2 cm spacing: frequency 0.3 Hz, square wave pulses of 500 μs duration; intensity 0–100 mA (Model DS7, Digitimer Ltd, Welwyn Garden City, UK).

Outcomes. Primary outcome: pain threshold to electrical stimulation was recorded in the proximal oesophagus (19 cm above the lower oesophageal sphincter) as the lowest intensity in mA at which each patient reported pain to 2 mA stepwise stimulus increments (based on the average of three readings at each time point).

Secondary outcomes:

(i) Proportion of subjects re-sensitising to acid after pregabalin or placebo (compared with 100% of eligible patients at screening);

(ii) Subjective visual analogue scale (VAS) ratings of pain and unpleasantness intensity during acid infusion: 0 being completely without pain or unpleasantness, 3 = mild, 5 = moderate, 7 = severe but tolerable and 10 = maximum possible pain/unpleasantness.

Data analysis

Retrospective analysis of data from 57 subjects (aged 20–58 years) confirmed that patients who were successfully recruited into previous studies (sensitised) had average change in PT (proximal oesophagus) of −7.4 mA (−8.4 to −6.3) at 30 min post acid infusion. This was maintained up to 120 min.[36] On the basis of intent to treat, and using a more conservative estimate of −6 mA, 16 patients were required to detect this difference with 90% power at the 5% significance level. Changes in stimulation thresholds were analysed using a linear mixed effects regression model with maximum restricted likelihood (fixed effects: time, intervention i.e. drug/no drug; random effect = subject) with T0 thresholds accounted for in the model as zero to yield a regression coefficient for drug effect (with C.I). Results have been presented as mean (with s.d.) or proportions dependent on data type. Analyses were performed using proprietary software (Stata V10.0, Stata Corp., College Station, TX, USA). $P < 0.05$ was taken to indicate statistical significance.

RESULTS

Subjects and recruitment

A total of 21 patients were assessed for eligibility. Two patients could not tolerate prolonged nasal intubation (even though intubations were successful), and a further two showed no evidence of oesophageal sensitisation following acid infusion during the screening visit and were excluded as per protocol. One patient decided not to continue with the study post-randomisation, leaving 16 patients who completed all three visits. All were naïve patients who were never previously subjected to this model of acid perfusion. Of the 16 patients who completed the study, one patient was excluded from analysis. This volunteer reached maximum pain threshold (100 mA) for all stimuli at both 2nd and 3rd visits, a magnitude of threshold not observed in any previous study, suggesting a methodological error such as loss of contact. Results from a total of 15 patients are presented: age 21–56 (median 31) years, six women.

Drug administration and adverse events

All 15 patients complied fully with medication instruction. Compliance was acceptable based on the number of capsules in returned bottles and self reporting [median number of capsules remaining per visit was 0 for both placebo and drug with maximum 1 capsule]. As expected, mild drowsiness was the most common side-effect reported.[39] Euphoria was reported in one patient. Dizziness was also reported in two patient, once after the placebo visit and once after the pregabalin visit. Seven patients were completely symptom free at all visits.

Oesophageal acid infusion

During acid infusion, pH fell to <2.0 in the distal oesophagus of all patients, but remained >6.0 in the upper (unexposed) oesophagus. The most common symptom reported with acid infusion was nausea. Other sensations included a cold sensation in the chest region, feeling of hunger and/or heartburn.

Primary endpoint

Absolute threshold data at baseline assessment and with drug or placebo, before (T0) and after acid infusions (T30 and T90) are shown in Table 1 and Figure 2. There were no differences in absolute values of pain thresholds (PT) at T0 in patients after receiving placebo or pregabalin [mean (s.d.) 32.9 mA (20.5) vs. 34.1 (15.7), $P = 0.42$]. Pregabalin almost abolished the development of acid-induced hypersensitivity in the proximal oesophagus

Table 1 | Absolute values for proximal oesophageal pain thresholds before (T0) and after (t30 and T90) acid infusion at baseline assessment and with placebo or drug (n = 15)

	T0	T30	T90
a. Pain threshold in study subjects before intervention (baseline)			
Pain threshold (mean, s.d.) mA	37.5 (19.2)	24.4 (13.0)	27.4 (15.7)
Change in pain threshold (mean, s.d.) mA	-	−13.1 (9.3)	−10.1 (7.3)
b. Pain threshold in study subjects after receiving placebo			
Pain threshold (mean, s.d.) mA	32.9 (20.5)	26.7 (19.8)	29.2 (20.5)
Change in pain threshold (mean, s.d.) mA	-	−6.2 (7.2)	−3.7 (6.8)
c. Pain threshold in study subjects after receiving drug			
Pain threshold (mean, s.d.) mA	34.1 (15.7)	34.2 (14.1)	34.7 (13.4)
Change in pain threshold (mean, s.d.) mA	-	+0.2 (6.2)	+0.7 (8.1)

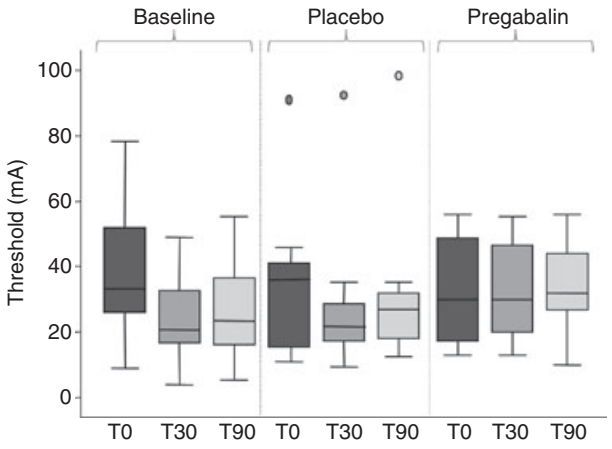

Figure 2 | Box graph showing absolute stimulation thresholds in mA at all three visits (baseline, placebo and pregabalin). For each, data are shown before acid infusion (T0), 30 min (T30) and 90 (T90) min after end of infusion. Data are shown as medians, interquartile and total ranges with outlying data points. It can be seen graphically that pregabalin attenuates the decrease in thresholds observed at baseline and with placebo.

(Figure 3). At 30 min, mean change in PT (C.I.) was −6.2 mA (−11.3 to +1.3) after placebo, compared with an increase of +0.20 mA (−2.7 to +3.3) after pregabalin. This pattern was also observed at 90 min: change in PT −3.7 mA (−10.0 to +2.0) after placebo and +0.7 mA (−4.7 to 7.3) after pregabalin [mixed effects regression: coeff. 3.6 (CI 1.5–5.6), P = 0.001].

Somatic control area. Pregabalin had no significant effect on T0 pain thresholds on the foot compared with placebo [placebo 38 mA (24–46) vs. pregabalin 36.7 mA (31–73), P = 0.77]. These thresholds were unchanged by acid infusion with no differences between placebo and pregabalin [30 min: placebo: median change in PT = 0 mA (CI 0–3.3) vs. pregabalin: median change = 0 mA (CI −2 to 2.7), P = 0.36; 90 mins: placebo: median change in PT = 0 mA (CI −7 to 4) vs. pregabalin: −1.3 mA (CI −4 to 6), P = 0.90].

Secondary endpoints

(i) At the screening visit, all patients demonstrated proximal oesophageal sensitisation following distal acidification (as per inclusion criteria). After placebo, the proportion of sensitisers was significantly reduced to 53% at 30 min and 47% at 90 min; after pregabalin, these proportions were reduced to 20% at both time points (P = 0.01, chi-squared).

(ii) Median VAS was 1 of 10 for pain to oesophageal acid infusion after treatment with pregabalin compared with 3 of 10 after treatment with placebo (P = 0.027, Wilcoxon). The median VAS score for unpleasantness during acid infusion was unchanged at 5 of 10 after both pregabalin and placebo (P = 0.76).

DISCUSSION

This randomised crossover study of healthy volunteers selected on the basis of previous sensitisation to oesophageal acid has shown that in comparison to placebo, pregabalin attenuated development of hypersensitivity to electrical stimulation in the non-exposed proximal oesophagus after distal oesophageal acidification. This was mirrored by reduced subjective pain sensation during acid infusion. The study thus provides some proof of concept that pregabalin, in addition to established efficacy in somatic pain conditions, might also be effective in treating oesophageal conditions characterised by pain. It is accepted that the study has some limitations, notably the small sample size (n = 15) and observation of significant placebo responses. Thus, although all subjects sensitised in the screening visit after distal acid infusion as per our inclusion criteria, the proportion of sensitisers

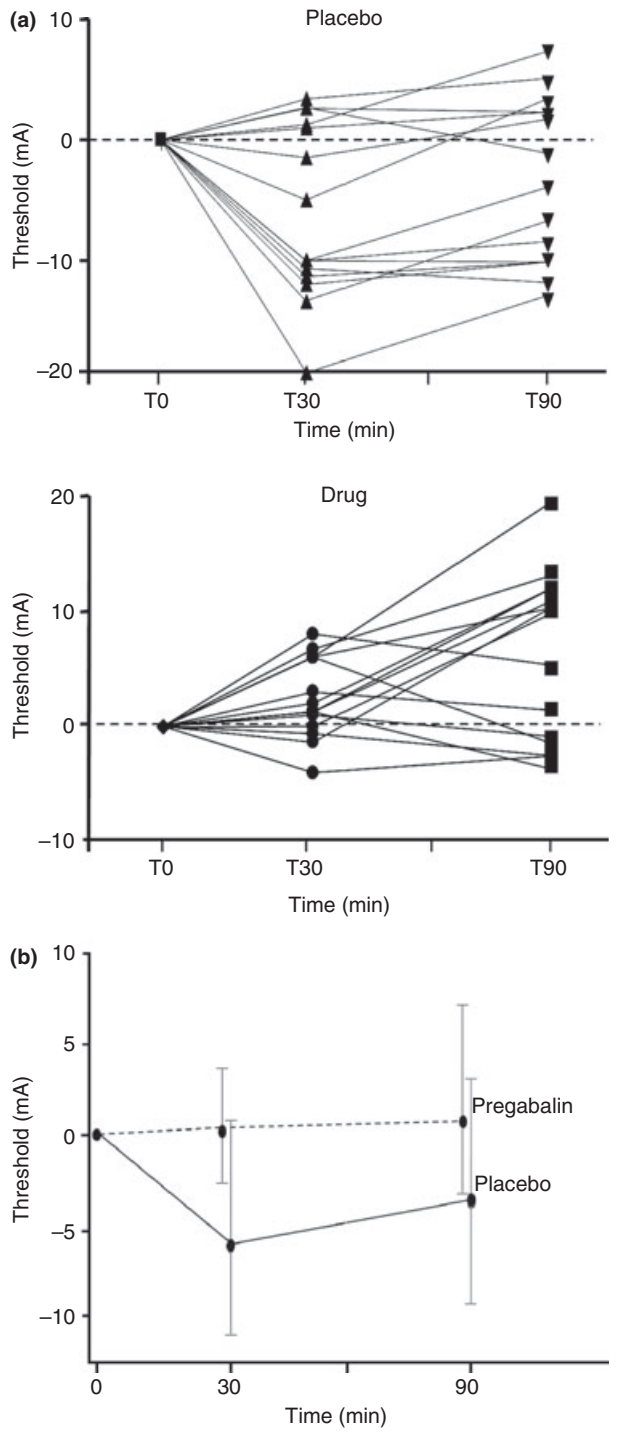

Figure 3 | Graphs showing changes in electrical stimulation pain thresholds at T0 (before acid infusion) and at 30 and 90 min post infusion: (a) individual connected data for placebo and pregabalin; (b) summative data shown as means + 95% CI. Volunteers receiving pregabalin showed a significant attenuation of the reductions in PTs observed at both time points with placebo [mixed effects regression: coeff. 3.6 (CI 1.5–5.6), $P = 0.001$].

postplacebo was approximately 50% at both time points. Such placebo responses are common to nearly all studies of visceral pain, and it should be noted that despite such effects, the proportion of sensitisers was further halved by pregabalin (20%).

The demonstration of antihyperalgesic effects of pregabalin in our model of acid-induced oesophageal hypersensitivity suggests a central mechanism of action i.e. a reduction in central sensitisation as suggested by decreased hypersensitivity in the proximal non-exposed oesophagus.[14] This is in keeping with data from rodents which suggest that the primary site of action of pregabalin (and the related molecule gabapentin) is central.[40] Both drugs are considered to modulate processing of nociceptive signals at the dorsal horn[41] with evidence that both can also modulate descending inhibition of pain processing by higher brain centres.[40] Furthermore, no direct analgesic effects of pregabalin were observed as evidenced first by the absence of any electrical threshold changes at T0 in the oesophagus after pregabalin or placebo, and secondly by the absence of somatic threshold changes (on the foot) at all time points.

The efficacy of pregabalin in reducing hypersensitivity has been extensively demonstrated in somatic chronic pain conditions.[24, 42] Similarly, evidence is emerging of the antihyperalgesic effects of pregabalin in animal[43] and human models[30] of visceral pain. For example, in rodents, pregabalin has been shown to reduce hypersensitivity to rectal distension following injection with bacterial lipopolysaccharide.[44] In a recent preliminary study of patients with IBS, pregabalin reduced rectal hypersensitivity to distension.[31] The distinction between analgesic and antihyperalgesic effects of pregabalin may be dose-related. In rodent studies using injections of either trinitrobenzene sulphonic acid or lipopolysaccharide in the colon, antihyperalgesic effects of intra-peritoneal pregabalin were obvious at lower doses,[43, 44] but at higher doses, analgesic effects were also observed.[44] In studies of patients with chronic neuropathic pain e.g. postherpetic neuralgia and diabetic peripheral neuropathy, doses up to 600 mg per day either in fixed doses or escalating regime of up to 12 weeks[42] were associated with significant improvements in pain. It is thus possible that had higher doses of pregabalin been administered in the current study or been continued for longer, an analgesic effect may have been observed in addition to the antihyperalgesic effects.

It has been estimated that up to 40% of patients with GERD fail to respond symptomatically, either partially or completely, to standard doses of proton pump

inhibitors (PPI); PPI-resistant symptoms have thus become the most common presentation of GERD in specialist practice with many patients having been prescribed or self-escalated PPI doses that are many times above those with any added efficacy. Most GERD patients who are not responsive to PPIs originate from the NERD phenotype, primarily due to their relative large numbers in the GERD patient population (up to 70%) and low response rate to PPI once daily (response pooled rate 36%).[45] Patients with FH exhibit the lowest symptom response rate to PPI. Given numerous studies that demonstrate oesophageal hypersensitivity in patients with NERD and FH,[4, 5] it is likely that part of the refractoriness of these patients to PPI therapy is due to persistent hypersensitivity. The effects of pregabalin in reducing proximal oesophageal hypersensitivity (in this study) may be particularly relevant to PPI refractory patients, who by definition are symptomatic after at least 8 weeks of double dose PPI treatment i.e. the lower oesophagus is no longer exposed to acid. In such patients, the impact of previous acid exposure is hypothesised to lead to a persistently sensitised oesophageal mucosa that reacts when it is in contact with other components of the refluxate that are still present in the patient on PPI. It is also known that refractory GERD patients on PPI perceive symptoms when reflux reaches a high proximal extent and the refluxate contains gas.[46] Therefore, reducing proximal oesophageal hypersensitivity to non-acidic gastric components or air distension with pregabalin might contribute to treatment of GERD patients with persistent symptoms in spite of adequate acid suppression. In this study, a relatively low dose of pregabalin and short duration of treatment was effective in reducing development of proximal oesophageal hypersensitivity. Future large scale clinical studies will be required to prove effectiveness in conditions such as PPI-resistant NERD and FH. Use of lower doses is likely to minimise potential side effects, but use of larger doses and different regimes could also be explored in particularly refractory patients. It is envisaged that this study of healthy volunteers, like that recently performed in the colon,[30] will provide translational confidence for the development of such clinical trials.

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