

Review

Gabapentin in the treatment of neuropathic pain

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Abstract: This paper reviews the pharmacology and clinical effectiveness of gabapentin in the treatment of neuropathic pain. Gabapentin has antihyperalgesic and antiallodynic properties but does not have significant actions as an anti-nociceptive agent. Its mechanisms of action appear to be a complex synergy between increased GABA synthesis, non-NMDA receptor antagonism and binding to the $\alpha_2\delta$ subunit of voltage dependent calcium channels. The latter action inhibits the release of excitatory neurotransmitters. Clinically, several large randomized controlled trials have demonstrated its effectiveness in the treatment of a variety of neuropathic pain syndromes. Patients with neuropathic pain can expect a mean reduction in pain score of 2.05 points on an 11 point numerical rating scale compared with a reduction of 0.94 points if they had taken the placebo. Around 30% of patients can expect to achieve more than 50% pain relief and a similar number will also experience minor adverse events; the most common of which are somnolence and dizziness. In patients with neuropathic pain due to cancer, higher response rates might be observed with gabapentin when administered with opioids because of a synergistic interaction. *Palliative Medicine* 2004; **18**: 5–11

Key words: Gabapentin; neuropathic pain

Introduction

Drug development

Gabapentin, 1-(aminomethyl) cyclohexane acetic acid, was licensed for use as an antiepileptic agent in the UK in 1993 and in the USA in 1994. It was originally synthesized as a cyclic analogue of gamma aminobutyric acid (GABA) to be used to reduce seizure frequency when added to conventional antiepileptic drugs. GABA is a principal neurotransmitter found in inhibitory interneurons in the dorsal horn. Like GABA, gabapentin is lipophilic and therefore able to pass through the blood–brain barrier easily. Gabapentin gained a UK licence for the treatment of neuropathic pain in 2000. It is available as tablets or capsules. The marketing authorization allows a maximum of 1.8 g per day in three divided doses for this indication. However, it is sometimes used clinically in higher doses.

Rationale for antiepileptics in neuropathic pain

Conventional antiepileptic drugs, such as phenytoin and carbamazepine, have been used to treat neuropathic pain

since the 1940s.¹ This practice was based on observations that the paroxysmal pain of trigeminal neuralgia, or tic douloureux, resembled epilepsy and led to the term 'epileptiform neuralgia'.² Current evidence suggests that the pathophysiology of paroxysmal pain may be related to bursts of ectopic discharges from damaged nerves. The mechanism responsible for spontaneous ectopic firing is membrane remodelling. This results in an excess of voltage sensitive sodium channels in the area of nerve damage at either end-bulbs^{3,4} or demyelinated areas.⁵ Phenytoin and carbamazepine may block use-dependent sodium channels in preference to inactive channels^{6,7} and phenytoin has been shown to reduce ectopic discharges *in vitro*.⁸

Other important approaches to the control of chronic neuropathic pain have involved GABA mechanisms. Activation of GABA-mediated inhibition can result in analgesia and a number of agents have been examined in this context. Sodium valproate enhances GABA function by an unknown mechanism, but it is thought to be either through binding to the GABA_A complex or enhancing GABA synthesis or release.⁹ Anecdotal evidence exists for sodium valproate's analgesic effect in the treatment of trigeminal and post herpetic neuralgia.^{10,11} Benzodiazepines, such as clonazepam (that bind to GABA_A/

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benzodiazepine receptor complexes to enhance GABA-mediated inhibition) have little evidence to support their role in neuropathic pain.¹² Baclofen is a GABA_B agonist that results in a presynaptic reduction of excitatory neurotransmitter release and postsynaptic inhibition of neuronal response.¹³ There is good evidence that baclofen is effective in trigeminal neuralgia.¹⁴ Vigabatrin, a newer antiepileptic drug, competitively inhibits GABA aminotransferase, and thus enhances synaptic concentrations of GABA. This drug may have a future role in the treatment of neuropathic pain, but no data are available to support this at present.

Antiepileptics and analgesia

There have been two systematic reviews of randomized, controlled trials of antiepileptic drugs used to treat all pain types.^{15,16} These demonstrated little evidence for their use in acute pain, but significant benefit over placebo was seen for chronic neuropathic pain conditions, such as diabetic neuropathy and trigeminal neuralgia.

Against this background, gabapentin, that was thought to be active on GABA mechanisms, was used in the treatment of neuropathic pain from the late 1990s.

Pharmacology

Pharmacokinetics

Following oral administration, gabapentin is absorbed from the small intestine rapidly and reliably. This occurs via a specific, though unidentified, transport mechanism that becomes saturated at higher doses.¹⁷ This has the effect of reducing bioavailability at higher doses. The bioavailability of a 300 mg dose is approximately 60%, for 600 mg it is 40% and only 35% with 1.6 g given three times daily.^{18,19} Gabapentin has no significant protein binding and maximum plasma concentrations (C_{\max}) are reached after around 3.2 hours following oral ingestion.¹⁸ In healthy subjects, age has no effect on C_{\max} or time to C_{\max} but a 25% increase in C_{\max} was observed in females compared to males owing to gender differences in body size.²⁰ Gabapentin has a half life of 6–8 hours, hence the need for three daily doses.

In common with other newer antiepileptics, gabapentin is excreted unchanged through the kidneys. It does not induce or inhibit hepatic enzymes. It does not significantly interact with other antiepileptics.¹⁷ The predominant influence on gabapentin pharmacokinetics is renal function. An inverse linear correlation exists between creatinine clearance and C_{\max} , time to C_{\max} and half life.²¹ That is, impaired renal function results in higher gabapentin concentrations and a longer elimination half life. Renal function rather than age accounts for clinically different effects seen in the elderly.

Site of action of gabapentin

The mechanism of action of gabapentin remains unknown. Evidence suggests that it is most likely to be the result of a complex synergy between increased GABA synthesis, non-NMDA receptor antagonism and binding to the $\alpha_2\delta$ subunit of voltage dependent calcium channels. The latter action inhibits the release of excitatory neurotransmitters.

Although it was expected to act as a GABA agonist, gabapentin does not act directly on GABA receptors,^{22,23} nor does it influence the reuptake of GABA.²⁴ It does increase the synthesis of GABA from glutamate and enhances its release from astrocytes.^{25,26}

Initially, gabapentin was also thought to behave as an antagonist at NMDA receptors, but the situation appears more complex. Kaneko *et al.*²⁷ found that gabapentin did not behave like an NMDA antagonist in rat models of neuropathic pain, and they concluded that it was unlikely to act directly on NMDA receptors. Furthermore, Chen *et al.*²⁸ have demonstrated a synergistic action between a non-NMDA receptor antagonist and gabapentin when both drugs were administered intrathecally. This supports the view that gabapentin can modify the spinal transmission of noxious mechanical input to spinal neurones via non-NMDA receptor antagonism.

The most important action of gabapentin appears to be binding to the $\alpha_2\delta$ subunit of voltage dependent calcium channels.²⁹ These binding sites are located in the spinal cord, with particularly high density in the superficial laminae of the dorsal horn. The action of gabapentin at these sites may inhibit the release of excitatory neurotransmitters and reduce glutamate availability at NMDA and non-NMDA receptors.^{30,31}

Pharmacodynamics

To better understand the effects of potential agents on neuropathic pain, it is useful to clarify some definitions. 'Antinociceptive' refers to the ability of an agent to reduce the reception of noxious stimuli at the level of the sensory organ, e.g., the action of aspirin in reducing inflammatory activation of cutaneous nociceptors at nerve endings. 'Antalgesic or analgesic' refers to the action of an agent in modulating the neural pathways that transmit pain. If pain is the result of increased sensitivity to a painful stimulus, and treatment restores the sensitivity to normal, the effect is termed 'antihyperalgesic'. If a normally non-painful stimulus evokes pain because of increased sensitivity (e.g., lightly brushing the skin), and treatment restores the sensitivity to normal, the term 'antiallodynic' is used.

Animal studies of the action of gabapentin suggest that it has antihyperalgesic and antiallodynic effects rather than antinociceptive effects.^{32,33} Furthermore, a dose-response relationship has been demonstrated for these effects.

Formalin injected into rat paws results in an initial painful inflammatory response (lasting around 10 minutes) followed by a later second phase of hyperalgesia (lasting around 45–60 minutes). When gabapentin has been studied in this context, Kaneko *et al.*²⁷ have demonstrated that it has no effect on the initial phase, but significantly reduces hyperalgesia in the late phase. They also showed that gabapentin was about three times as potent as an antihyperalgesic agent if it was given before formalin injection, rather than if it was given 7–8 minutes after injection. This suggests that gabapentin is effective at preventing the initial development of hyperalgesia and allodynia.

Abdi *et al.*³⁴ examined the effects of systemic gabapentin, amitriptyline and lidocaine on ectopic discharges from injured sensory fibres in rats. Their study showed significant reductions in discharges after amitriptyline and more dramatically after lidocaine, but gabapentin was without effect. In contrast, Pan *et al.*³⁵ found a dose–response effect after intravenous gabapentin on ectopic discharge activity from injured nerves in rats. The mechanism of this peripheral effect remains unclear. Although an action on voltage sensitive sodium channels would fit with the known actions of other antiepileptic drugs, there is only weak evidence to support this. Rock *et al.*³⁶ failed to show any effect of gabapentin on sodium channels, but Wamil and McLean³⁷ did demonstrate an inhibitory effect *in vitro*.

Welty *et al.*³⁸ found that after gabapentin administration, the antihyperalgesic effects occur much more rapidly than the antiepileptic effects. The antiepileptic effect of gabapentin may rely on active cellular entry of gabapentin into astrocytes, but it appears that the antihyperalgesic effects do not rely on this process. This indicates that there may be separate underlying mechanisms for the action of gabapentin in epilepsy and in neuropathic pain.

Gabapentin has been shown to have a superior anti-allodynic profile than morphine or amitriptyline in work by Field *et al.*³⁹ These authors induced static and dynamic allodynia in rats through streptozocin injection into the hind paw. Amitriptyline and morphine dose dependently blocked static allodynia, but not dynamic allodynia. Gabapentin blocked both types of allodynia in a dose dependent manner between 10 and 100 mg/kg.

These studies suggest that gabapentin has significant antihyperalgesic and antiallodynic effects. It suggests that these are mediated predominantly at a spinal or supraspinal level through stabilization of dorsal horn neurones, and to a lesser extent at a peripheral level.

Interaction with opioids

Although there is no evidence to support a direct effect of gabapentin on opioid pathways, animal studies have pointed to an indirect effect. Rocha *et al.*⁴⁰ found raised

levels of extracellular opioid peptide in rat brains following a single dose of gabapentin. Shimoyama *et al.*⁴¹ demonstrated a synergistic effect between morphine and gabapentin that was significantly greater than the effects of either drug alone, in a rat tail flick latency test to radiant heat.

Clinical studies

Numerous case studies have been published describing the effects of gabapentin in a variety of neuropathic pain conditions. Examples include complex regional pain syndromes (CRPS), deafferentation neuropathies, central post stroke pain and pain associated with multiple sclerosis.^{42–45} In general, treatment with gabapentin was successful in reducing pain and the doses used were between 900 and 1200 mg in three divided doses. Following the apparent success of gabapentin described in case reports, randomized placebo controlled trials were undertaken in various defined neuropathic pain conditions.

Post herpetic neuralgia

Two large randomized controlled trials have been conducted on the use of gabapentin in the treatment of post herpetic neuralgia. The first study recruited 229 patients from North American pain services in whom doses were titrated up to 3600 mg of gabapentin or placebo over a four week period.⁴⁶ Treatment was maintained at maximum dose for a further four weeks; concomitant antidepressants, used as coanalgesics, were continued if therapy was stabilized and remained constant. Around 80% of patients in each arm completed the study; median age was 73 and 74 years in the gabapentin and placebo groups, respectively. There were no significant differences in other medication taken during the study; 72% took no other medication, 12% took tricyclic antidepressants and 19–27% took opioids.

In those that received gabapentin, the average daily pain score was significantly reduced from 6.3 to 4.2 points on an 11-point numerical rating scale. In this group, at least 83% received 2400 mg and 65% received at least 3600 mg of gabapentin. This compares with a reduction from 6.5 to 6.0 in those that received placebo ($P < 0.001$). Other outcome measurements including quality of life, sleep interference and mood also showed significant improvement with gabapentin. The numbers of withdrawals in each group were similar, but patients taking gabapentin reported more somnolence, dizziness and ataxia than those taking placebo. The authors concluded that gabapentin was safe and efficacious at these doses in a predominantly elderly population.

The second and more recent study recruited 334 patients from UK pain clinics using similar methodol-

ogy.⁴⁷ Patients were randomized to receive 1800 mg gabapentin, or 2400 mg gabapentin or placebo. The rationale for the study was to examine whether lower doses would be as efficacious as higher doses, but would have a lower incidence of side effects. This trial excluded patients who had previously failed to respond to gabapentin. Patients taking active treatment were titrated up to 1800 mg gabapentin over two weeks and then up to 2400 mg by week 3 for those randomized to receive the higher dose. All doses remained stable between weeks 3–7. Median age of patients recruited was around 75 years in all three groups. Average daily pain score showed significant improvements after both 1800 and 2400 mg gabapentin; 6.5 to 4.3 and 6.5 to 4.2, respectively, on an 11 point numerical rating scale ($P < 0.001$). In comparison, the reduction for the placebo group was 6.4 to 5.3 points. This translates to an 18.8% reduction in daily pain score using gabapentin instead of placebo. These differences were apparent from the end of the first week of treatment. Between 32 and 34% of patients taking gabapentin achieved more than 50% pain relief compared to only 14% taking placebo. Predominant side effects in the treatment arms were dizziness (31–33%) and somnolence (17.4–20.4%). Between 13 and 17% of patients taking gabapentin withdrew because of side effects.

Diabetic neuropathy

Another large randomized, placebo controlled study of gabapentin was conducted in patients with diabetic neuropathy⁴⁸ attending pain clinics in the USA. Of the 165 patients recruited, 84 were randomized to receive gabapentin and 81 to receive placebo. The methodology and dosing schedule was similar to that used in the trial by Rowbotham *et al.*⁴⁶ Two thirds of the patients taking gabapentin were titrated to 3600 mg daily.

This study also showed a significant reduction in average daily pain score for the gabapentin group from 6.4 to 3.9 points on a numerical rating scale. This compares with a reduction from 6.5 to 5.1 in the placebo group. Quality of life measures, sleep and mood all improved significantly in those taking gabapentin, and 47% of the gabapentin group achieved a 'much or moderately improved' rank on a global change score compared with 25% of those receiving placebo. Although the median age in this study was 53 years (20 years younger than the post herpetic neuralgia trials), the frequency of side effects was similar. Significant differences between gabapentin and placebo were observed for dizziness (23.8 versus 4.9%) and somnolence (22.6 versus 6.2%).

Mixed neuropathic pain

Despite the apparent efficacy of gabapentin in post herpetic neuralgia and diabetic neuropathy, clinical practice is characterized by patients with a variety of

neuropathic pains. These patients are often defined by their pain symptoms and signs rather than discrete diseases. To address this issue, a further clinical trial of gabapentin was undertaken that recruited 307 patients with various neuropathic pain syndromes (excluding cancer) from pain clinics in the UK and Ireland.⁴⁹ Eligible patients were those with mean daily pain scores of at least 4, on an 11 point numerical rating scale, prior to entry. Patients were also required to have at least 2 of the following symptoms and signs; allodynia, burning pain, shooting pain, hyperalgesia. The median age of recruited patients was around 57 years in both groups.

In this study, patients were randomized to receive placebo or to be titrated up to receive 2400 mg of gabapentin over five weeks to be followed by a three week period where doses were stable. By week 5 in the gabapentin arm, 101 patients received 2400 mg, 19 received 1800 mg and 27 received 900 mg daily. The mean weekly pain scores at week 8 showed significant differences for gabapentin. In this group, pain scores were reduced from 7.1 to 5.6 points on an 11 point numerical rating scale compared with a reduction from 7.3 to 6.3 in the placebo group ($P < 0.001$). This difference was significant at the end of week 1 and remained similar for most of the weeks throughout the study period. No significant difference was seen in the number of patients who achieved more than 50% pain relief between the two groups (21% for gabapentin and 14% for placebo). Interestingly, significant improvements in burning pain and hyperalgesia were seen, but this was not observed for allodynia or shooting pain, when gabapentin was compared with placebo. Significant improvements were also seen after gabapentin in various quality of life measures particularly social and emotional functioning. The most frequent side effects with gabapentin compared with placebo were dizziness (24.2 versus 7.9%) and somnolence (14.4 versus 5.3%).

Cancer neuropathic pain

To date there have been no randomized trials of gabapentin in patients with neuropathic pain due to cancer. One open-label trial has been reported in which 22 patients with cancer, whose neuropathic pain was not controlled by opioids, were given gabapentin as 'add-on' treatment.⁵⁰ The dose of gabapentin was titrated over three to seven days up to a mean daily dose of around 1004 mg (range 600–1800 mg). Opioid doses were unchanged throughout the study period. Compared to baseline scores, mean global pain scores on a numerical rating scale were reduced from 6.4 to 3.2 points at the final assessment that took place 7–14 days later. Symptoms of burning pain, shooting pain and allodynia were all also significantly reduced compared to baseline. Overall, no additional side effects were attributed to

gabapentin treatment, apart from one case of sedation and one case of dizziness.

This study was commented upon in a letter by Chandler and Williams,⁵¹ who argued that gabapentin has a much lower incidence of efficacy in this context based on their experience. They reported on a retrospective review of 20 patients with neuropathic pain due to cancer who were treated with gabapentin in addition to their usual analgesia. Only nine patients reported significant improvement and six others discontinued gabapentin because of side effects. In the remaining five patients, efficacy could not be established. Further analysis of the data in the Caraceni *et al.* study⁵⁰ shows that 13 of 22 (59%) patients achieved more than 50% pain relief compared to 45% (assuming 'significant relief' is equivalent) in Chandler and Williams's series. Both of these series compare favourably to larger randomized controlled trials,^{47,49} which were performed in presumably fitter patients, where between 21 and 34% achieved this degree of pain relief.

Comparative studies with other drugs

A small number of studies exist that directly compare the effectiveness of gabapentin against other analgesics in the treatment of neuropathic pain. Dallochio *et al.*⁵² randomized 25 patients with diabetic neuropathy to receive amitriptyline (mean dose 53 mg daily) or gabapentin (mean dose 1785 mg daily) in an open label trial. Doses were titrated over four weeks and maintained for eight weeks. Pain scores were measured on a five point scale (0 = none, 4 = excruciating). Baseline pain scores in the gabapentin group were reduced by a mean of 1.9 (2.9–1.0) and those in the amitriptyline group were reduced by a mean of 1.3 (2.75–1.5), $P < 0.026$. Significant differences in the reduction in paraesthesia scores also favoured gabapentin. Adverse events were more frequent in the amitriptyline group and these limited dose escalation according to the authors.

However, an earlier double blind, randomized crossover trial had not found any difference in efficacy between the two drugs in patients with painful diabetic neuropathy.⁵³ In this study, 21 of the 25 patients enrolled completed the six week trial of each drug with a one week washout period in between drug dosing (mean doses were 59 mg amitriptyline and 1565 mg gabapentin). Pain score diaries showed no statistical differences for patients taking either treatment; 11 (52%) taking amitriptyline experienced moderate or greater pain relief compared to 14 (67%) of those taking gabapentin.

Eckhardt *et al.*⁵⁴ have compared morphine, gabapentin and combined treatment with both drugs in a double blind, placebo controlled four way crossover study. This was conducted in 12 volunteers whose pain tolerance and pain threshold were measured during forearm immersion in cold water under experimental conditions. Although

this was not a study of clinical neuropathic pain, the results are interesting. Neither gabapentin nor morphine had any significant effect on pain threshold, but morphine had a significant effect on pain tolerance. Importantly, the combination of the two drugs significantly raised pain threshold and tolerance (above that of morphine alone). This synergistic effect had been previously demonstrated in rats.⁴¹ It also supports the findings of Caraceni *et al.*,⁵⁰ suggesting that gabapentin augments the action of morphine via an unexplained mechanism.

Meta-analyses

Information from meta-analyses and systematic reviews allows comparisons of effectiveness of drugs in various neuropathic pain conditions. These are expressed as NNT (number needed to treat) and NNH (number needed to harm).^{16,55,56} In post herpetic neuralgia, the NNT for gabapentin was 3.2 (C.I. 2.4–5.0) which compares with 2.3 (C.I. 1.7–3.3) for tricyclic antidepressants and 2.5 (C.I. 1.6–5.1) for oxycodone. In diabetic neuropathy, the NNTs are; gabapentin 3.8 (2.4–8.7), tricyclic antidepressants 3.0 (2.3–4.3) and carbamazepine 2.3 (1.6–3.8). Using the calculation for NNT suggested by Cook and Sackett,⁵⁷ and the data for mixed neuropathic pain syndromes,⁴⁹ the NNT for gabapentin in this context is 14.

In diabetic neuropathy studies, the NNH for minor events is 2.5 (2.0–3.2) for gabapentin, 3.7 (2.4–7.8) for carbamazepine and 2.8 (2.0–4.7) for tricyclic antidepressants. The NNH for major events (drug related withdrawal from study) is 20–40; this is broadly similar for tricyclic antidepressants and anticonvulsants (excluding gabapentin). In relation to gabapentin, three of the four major trials in neuropathic pain demonstrate no differences between study withdrawals in those taking placebo compared with those taking active treatment.^{46,48,49} In the fourth study,⁴⁷ 6.3% subjects withdrew whilst taking placebo compared to 13 and 17.6% of those taking gabapentin 1800 and 2400 mg, respectively; these results were not assessed statistically. It has been argued that earlier studies of treatments in neuropathic pain (that have contributed to meta-analyses) may have been less able to detect and report adverse events. This would lead to an overestimation of NNH for older anticonvulsants and tricyclic antidepressants (i.e. they appear better tolerated than is the case in clinical practice), when compared with more recent studies of gabapentin.

Summary

Gabapentin appears to be an effective treatment for neuropathic pain, acting centrally to reduce hyperalgesia and allodynia, but it does not have significant actions as

an anti-nociceptive agent. Based on large clinical trials, it has similar (though not superior) efficacy to tricyclic antidepressants and carbamazepine, but it may be better tolerated, particularly in relation to major harms. Evidence suggests that when receiving treatment for diabetic neuropathy and post herpetic neuralgia with gabapentin, around 30% of patients can expect to achieve more than 50% pain relief. The mean reduction in pain score for those taking gabapentin is 2.05 points on an 11 point numerical rating scale, compared with a reduction of 0.94 points for those taking placebo, when the results of four major trials are combined.^{46–49} Around 30% of patients treated with gabapentin will experience minor adverse events, the most common of which are somnolence and dizziness. In neuropathic pain due to cancer, evidence suggests that higher response rates might be observed with gabapentin when administered with opioids. However, the incidence of adverse effects in this patient population has not been assessed and would need to be balanced against any advantage of this combination.

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