

CME

Using gabapentin to treat neuropathic pain

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ABSTRACT

OBJECTIVE To review use of gabapentin as an adjuvant agent to treat neuropathic pain.

QUALITY OF EVIDENCE MEDLINE was searched from 1995 to October 1998 for reports. There were approximately 20 citations. Additional articles from *Pain* and other medical journals were reviewed. No double-blind studies have examined gabapentin and its use as an analgesic adjuvant agent.

MAIN MESSAGE Gabapentin is an anticonvulsant medication used recently as an effective adjuvant agent for treating neuropathic pain. It is a structural analogue of γ -aminobutyric acid (GABA), but its receptor and biochemical function remain unknown. Gabapentin has desirable pharmacokinetic properties and acceptable side effects, which simplify its use. There are very few interactions between gabapentin and other medications, and gabapentin is well tolerated.

CONCLUSION Gabapentin could be an effective adjuvant agent for many neuropathic pain states.

RESUME

OBJECTIF Examiner le recours au gabapentin comme agent adjuvant dans le traitement des douleurs neuropathiques.

QUALITÉ DES DONNÉES Une recension de rapports a été effectuée dans MEDLINE, de 1995 à octobre 1998, et environ 20 citations ont été relevées. Des articles additionnels tirés de *Pain* et d'autres revues médicales ont également été examinés. Aucune étude à double insu n'a porté sur le gabapentin et son utilisation comme agent analgésique adjuvant.

PRINCIPAL MESSAGE Le gabapentin est un médicament anticonvulsif utilisé récemment comme agent adjuvant efficace dans le traitement des douleurs neuropathiques. C'est un analogue structurel de l'acide γ -aminobutyrique (GABA), mais son action biochimique et de récepteur demeure inconnue. Le gabapentin a des propriétés pharmacocinétiques souhaitables et ses effets secondaires sont acceptables, ce qui simplifie son utilisation. Il existe très peu d'interactions entre le gabapentin et d'autres médicaments et il est bien toléré.

CONCLUSION Le gabapentin pourrait se révéler un agent adjuvant efficace pour de nombreux cas de douleurs neuropathiques.

EX62

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Cet article a fait l'objet d'une évaluation externe.
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Injury to nerves within the peripheral nervous system or the central nervous system can lead to intractable neuropathic pain, manifested by several forms of dysesthesias.¹ These unpleasant sensations are frequently described as burning, squeezing, or numbing and can be constant or lancinating.

Neuropathic pain often resists treatment because several generators of pain can require multimodal treatment.² Therapy is really by trial and error, as there is no way to predict which medications will be most effective; there have been a few clinical trials of medication, but often treatment is based on anecdotal reports rather than empirical proof.³ Antidepressant medications, such as the tricyclics, and anticonvulsants, such as phenytoin, have been used traditionally to treat some neuropathic pain conditions, but their use is often limited because of side effects.⁴ Opioid medications are less effective for treating neuropathic pain,⁵ and unfortunately, many patients continue to suffer pain despite optimal use of available agents.⁶

Gabapentin is an anticonvulsant medication used in recent years as an adjuvant agent for treating neuropathic pain. Its first reported use for treating neuropathic pain was in a letter describing sustained pain control and reversal of some disease symptoms in a group of nine patients with reflex sympathetic dystrophy.⁷ Gabapentin is a structural analogue of γ -aminobutyric acid (GABA), but its receptor and biochemical function remain undiscovered.⁸

The rationale for using an anticonvulsant medication for treating neuropathic pain is its ability to repress discharges in pathologically altered neurons.⁹ Gabapentin has attractive pharmacokinetic properties. It does not bind to plasma proteins and is not metabolized by the liver; it is eliminated unchanged by renal excretion. Consequently, there are very few interactions between gabapentin and other medications.⁷

Quality of evidence

We searched MEDLINE from 1995 to October 1998 for reports. Approximately 20 citations used search words relating to pain control: gabapentin, neuropathic pain, chronic pain, reflex sympathetic dystrophy, and diabetic neuropathy. Anecdotal reports provided evidence for the effectiveness of

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gabapentin for treating various pain states. There were no reports of randomized controlled studies, however, to support the use and efficacy of gabapentin as an analgesic adjuvant.

In our practice, which focuses on treating chronic pain, gabapentin has become the most commonly ordered analgesic adjuvant because of its efficacy and acceptable side-effect profile. We report on three patients who received benefit from gabapentin.

Case 1

A 40-year-old man with a history of severe degenerative arthritis secondary to juvenile rheumatoid arthritis had multiple joint replacements and required further surgery for revision of right total hip arthroplasty. The patient suffered severe postoperative pain described in terms of lancinating dysesthesias in the right hip and leg despite resumption of his regular analgesics, which included methadone (120 mg every 4 hours). Subsequently, gabapentin (300 mg at bedtime) was ordered, to be titrated to 900 mg/d in divided doses.

The dysesthesias were substantially reduced after the initial dose of gabapentin, and the patient slept comfortably for the first time since his surgery. No adverse side effects were reported. Now, several months later, he continues gabapentin at this dose and reports satisfaction with pain control, rating his pain on a numerical rating scale (NRS) at 4 or 5 out of 10, with 0 as "no pain" and 10 as "excruciating pain." He also continues to take the same doses of methadone.

Case 2

A 47-year-old woman had a 4-year history of multiple sclerosis with associated muscle spasms, severe dysesthesias, and allodynia from her waist to her feet. On occasion, pain "like an electric current" would become so severe it would cause her to cry for half an hour, and she was so sensitive to touch, she could not bear the pressure of water on her skin. Transdermal fentanyl (125 μ g/h) was ordered to treat the nociceptive pain, rated by the patient as 9 out of 10 on an NRS. Although this pain was reduced to 4 to 6 out of 10, the dysesthesias continued to be troublesome.

Gabapentin (100 mg at bedtime, titrated to 300 mg/d), was initiated and was gradually increased to 2400 mg/d in divided doses. The patient was very pleased with the resultant improvement in dysesthetic pain, as well as improvement in sleep. No side effects were reported. Fourteen

months later, she continued to function independently and had been able to discontinue the transdermal fentanyl patches and maintain good pain control with an NRS of 2 out of 10.

Case 3

A 63-year-old gentleman was diagnosed with malignant mesothelioma of the left lung and was referred for treatment of a burning type of pain ("like a bruise") over the left thorax. In addition to oral hydromorphone (144 mg/d), gabapentin (300 mg at bedtime, titrated to 900 mg/d in divided doses) was ordered. The dose was subsequently increased to 1800 mg/d with moderate to good benefit. Pain scores were reduced from 6 out of 10 to 2 or 3 out of 10. There were reports of upper body fluid retention unresponsive to a diuretic; this could have been a side effect of gabapentin or possibly related to tumour progression. The patient continued using opioids and gabapentin until his death approximately 6 months later.

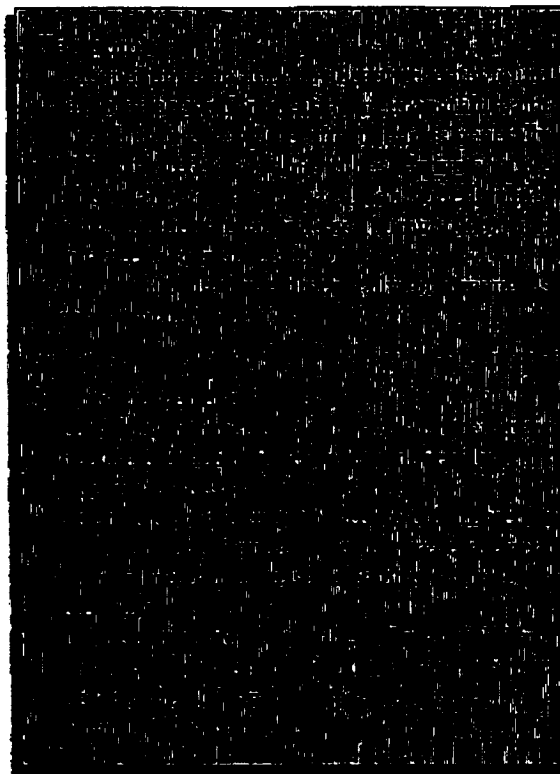
Discussion

We have used gabapentin to treat neuropathic pain related to cancer and non-cancer pain syndromes, and we suggest initiating this agent in a 300-mg dose at bedtime on the first day, 300 mg twice daily on the second day, and 300 mg three times daily on the third day and thereafter. Some patients report immediate benefit; others require titration to effect. Doses may be increased on a weekly basis by 300 to 400 mg/d; we suggest the dosing interval be every 6 to 8 hours. Some patients require doses up to 3200 mg/d to provide relief from the dysesthesias, but elderly people and people who are hypersensitive to medications benefit from only 300 mg/d, in divided doses.

We have one elderly patient who takes 100 mg of gabapentin at bedtime, and this is sufficient to improve sleep and pain. She was unable to tolerate a higher dose due to somnolence and ataxia.

Houtchens and colleagues suggest cautious escalation in dose of gabapentin for patients with multiple sclerosis.¹⁰ If benefit is not apparent 3 to 4 weeks after titration to these higher doses, gabapentin may be tapered down over a 4- to 6-day period and discontinued. Its effect needs to be considered in view of cost. A month's supply, using 900 mg/d, costs approximately \$110.

Gabapentin is usually well tolerated.^{11,12} The most commonly reported side effects have been gastrointestinal symptoms, drowsiness, dizziness, ataxia, and fluid retention.^{13,14} Risk of drowsiness can increase,



especially in elderly patients, when gabapentin is used in conjunction with opioids. These symptoms usually dissipate after 3 to 5 days. Patients with a history of headaches, however, might be unable to tolerate gabapentin. Worsening headaches could be related to fluid retention.

Gould has recently reported development of a painful polyneuropathy in a patient treated with gabapentin,¹⁵ and Childers and Holland describe two cases suggesting that gabapentin causes agitation in cognitively impaired patients.¹⁶

Because there are no known drug interactions with gabapentin, there is no need to monitor serum levels, as one must with other anticonvulsant medications.¹⁷ It is not bound to plasma proteins nor metabolized by the liver; gabapentin is eliminated by renal excretion in its original form.¹³ There is evidence that opioids, in conjunction with appropriate adjuvant agents that target new areas in pain transmission, are most helpful in treating chronic pain.⁴ The door is opening for other membrane stabilizers, such as lamotrigine and topiramate, for use as analgesic adjuvants, and it will be important to study the safety and effectiveness of these medications.

Conclusion

Gabapentin is an important adjuvant medication for treating neuropathic pain. Randomized controlled trials are needed to set a criterion standard to assess the effectiveness of gabapentin as an analgesic adjuvant. Its desirable pharmacokinetic properties and low side-effect profile make it appealing to both practitioners and patients in the struggle to ease chronic pain. ♦

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