INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 4 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact. **The Managing Editor, The Journal of Rheumatology, 365 Bloor Street East, Suite 901, Toronto, ON CANADA M4W 3L4. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

Dose-Dependent Severe Arthralgia Induced by Gabapentin

To the Editor:

Gabapentin is a novel drug used increasingly in the management of complex pain syndromes[1]. Although initially used as an anticonvulsant and more recently as a treatment for neuropathic pain[2,3], rheumatologists may prescribe this drug for conditions such as fibromyalgia or the pain of spinal stenosis. Although the exact mechanism of action remains largely unknown, the analgesic effect of gabapentin is thought to be due to gamma-aminobutyric acid (GABA) mimetic and calcium channel-blocking properties[1]. GABA is one of the major inhibitory neurotransmitters in the brain. We describe a patient with neuropathic pain, successfully treated with gabapentin, who developed such severe arthralgias during treatment with gabapentin that it was necessary to discontinue treatment.

A 36-year-old woman presented with an 8-month history of severe left-hand pain following a fall. Although she was initially thought to have sustained a scaphoid fracture, all subsequent investigations for a structural or traumatic abnormality were negative, and she was finally diagnosed as having complex regional pain syndrome (CRPS) type 1. In addition to severe and constant pain of the hand, she reported frequent episodes of burning pain with radiation to the whole arm. The hand was warm, with swelling in the region of the wrist joint. There was allodynia to light touch over all fingers and reduction in the range of movement of the wrist.

Pain was inadequately controlled with acetaminophen. Treatment was initiated with gabapentin 300 mg at night, and then gradually increased to a daily dose of 900 mg. Within 2 months of initiating gabapentin, she reported definite improved pain control, with almost complete resolution of the episodic burning pain. She had, however, newly developed joint pain, without joint swelling, of the knees, ankles, and hand joints. She complained of stiffness, which was more pronounced in the mornings. Arthralgias were of sufficient severity to interfere with daily activities. There was no evidence of joint swelling or tenderness on examination. All blood tests including a complete blood count, C-reactive protein, erythrocyte sedimentation rate, creatine kinase, rheumatoid factor, antinuclear antibody, extractable nuclear antigens, DNA-binding, and C3 and C4 were within normal limits. Radiographs of knees and ankles were normal. A technetium scintigraphic joint scan was negative. A drug reaction to gabapentin was suspected. Gabapentin was tapered slowly and discontinued over a one-week period, with a report of complete relief of arthralgias within 2 weeks, but worsening neuropathic pain in the hand and recurrence of paroxysmal episodes of pain. In view of the previous excellent pain control achieved with gabapentin, the patient was willing to retry this agent. On a dose of 300 mg a day, she reported inadequate neuropathic pain control, but recurrence of arthralgias, which increased progressively with further small increments of the dose, resulting in unacceptable joint pain and need for discontinuation of gabapentin. Treatment trials for a replacement for gabapentin are continuing.

Although arthralgia has been reported to occur in 0.1–1% of patients in clinical studies, the causal relationship has never been specifically reported. Arthralgia as a severe side effect of treatment with gabapentin has not previously been reported. Although our patient showed no abnormality on physical or laboratory examination, symptoms were sufficiently severe to warrant discontinuation of a medication that had given excellent relief of a disabling pain. It is possible that objective arthritis may have developed with continued use of gabapentin. This agent has an overall favorable safety profile, as well as few known drug interactions. The most common side effects are mostly neurologic, such as somnolence, dizziness, and fatigue[4]. Musculoskeletal complaints, including true arthritis, often associated with immunulogical abnormality, are well recognized to occur with the older anticonvulsants such as phenobarbital and carbamazepine[5,6].

CRPS represents a challenge in understanding the pathophysiology as well as management strategies[7]. An occasional disturbing symptom in CRPS is spontaneous paroxysmal pain, which is often difficult to control, but which responded well to gabapentin in our patient. Regardless of an excellent response, the side effect from the medication was severe enough to preclude continued use. The causal relationship was confirmed by resolution of arthralgia when the drug was discontinued and reappearance of symptoms when the drug was restarted. We also believe that this adverse effect was dose related, as worsening of symptoms with higher doses were observed. As gabapentin is being used more commonly for various painful conditions, arthralgia due to this medication may lead to referral to rheumatologists.

ABDULAZIZ ALMAHREZI, MBChB, McGill Pain Centre, Montreal General Hospital, McGill University; MARY-ANN FITZCHARLES, MBChB, Division of Rheumatology and McGill Pain Centre, Montreal General Hospital, McGill University, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4, Canada. E-mail: mary-ann.fitzcharles@muhc.mcgill.ca

REFERENCES

1. Taylor CP, Gee NS, Su T-Z, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Research 1998;29:233-49.
2. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280:1831-6.
3. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998;280:1837-42.
4. Rose MA, Kam PCA. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002;57:451-62.
5. Holland KD. Efficacy, pharmacology, and adverse effects of antiepileptic drugs. Neurol Clin 2001;19:313-45.
6. Saviola G, Avanzi S, Grioni G. Anticonvulsant-induced rheumatism: does a possible role of carbamazepine exist? A clinical case with a 20-month follow-up. Clin Ter 2001;152:131-4.
7. Raja SN, Grabow TS. Complex regional pain syndrome 1 (reflex sympathetic dystrophy). Anesthesiology 2002;96:1254-60.