International Journal of Neuropsychopharmacology (2008), **11**, 879–881. Copyright © 2008 CINP
doi:10.1017/S146114570800878X

LETTER TO THE EDITOR

CINP

Potential role of pregabalin in the treatment of lithium-induced tremor: a case report

Received 16 February 2008; Reviewed 23 February 2008; Revised 25 February 2008; Accepted 9 March 2008; First published online 7 April 2008

Pregabalin is a structural analogue of gamma-aminobutyric acid (GABA), one of the key inhibitory neurotransmitters in the brain. It is approved by the United States Food and Drug Administration (FDA) for the treatment of pain related to diabetic peripheral neuropathy, post-herpetic neuralgia, adjuctive therapy for partial onset seizures, and fibromyalgia (US FDA, 2007). Pregabalin has also shown efficacy in other conditions for which it is used off-label, including anxiety (Feltner et al., 2008). The current report describes the first documentation of the usefulness of pregabalin in treating lithium-induced tremor. In the case described, pregabalin was prescribed as an anxiolytic to an in-patient with treatment-refractory major depressive disorder and generalized anxiety disorder; the beneficial effect on tremor was coincidental and unexpected. However, a pilot randomized, double-blind, placebo-controlled clinical trial demonstrated the efficacy of pregabalin in the treatment of benign essential tremor (Zesiewicz et al., 2007) and a large multicentre trial (clinicaltrials.gov NCT00584376) is currently in process to evaluate its efficacy and safety for this indication. It is plausible that pregabalin may therefore have a unique role in the treatment of patients with lithium-induced tremor, particularly considering the frequent comorbidities of anxiety in patients treated with lithium (bipolar and major depressive patients). To our knowledge, there have been no published case reports of the use of pregabalin for lithium-induced tremor.

Case report

Mr A was a 65-yr-old man with a history of major depressive disorder and generalized anxiety disorder who was voluntarily admitted to an in-patient psychiatric facility for a 3-wk exacerbation of anxiety symptoms and to a lesser extent depressive symptoms. More specifically, he developed severe worsening of his multiple excessive worries, restlessness mixed with fatigue, initial insomnia, and poor concentration. He also endorsed depressed mood and hopelessness, but did not exhibit anhedonia or suicidality. Manic or psychotic symptoms were absent. He was alcohol- and drug-free, and had been compliant with his outpatient regimen of 50 mg paroxetine at bedtime, 300 mg lithium carbonate in the morning and 600 mg at bedtime, 10 mg zolpidem at bedtime, and 0.5 mg lorazepam twice a day. According to history, he had been taking lithium at this dose (level 0.78–0.90 mmol/l) for 2 yr which had demonstrated good efficacy as an augmenting agent for his depression; however, it produced a persistent side-effect of fine motor tremor of the hands and arms at rest and with intention. This tremor was clearly noticeable to observers and led to social anxiety and impaired confidence, although it did not affect his ability to eat, drink, or conduct other activities of daily living. The tremor was observed on admission to the hospital, and Mr A had an otherwise normal neurological examination. Upon admission, Mr A was started on 50 mg pregabalin three times a day which was titrated to 100 mg three times a day after 4 d. Lorazepam 0.5 mg twice a day was also discontinued on admission in favour of 15 mg clorazepate twice a day (equipotent to 1 mg lorazepam twice a day). The change in benzodiazepine was intended to provide greater anxiolytic efficacy and to utilize a new agent for him since he was biased against benzodiazepines that he previously felt to be ineffective. No other medication changes were made during his hospitalization. Approximately 3 d after admission, Mr A was observed to have marked subjective and objective improvement in the amplitude and frequency of his tremor, although his anxiety and depressive symptoms had not significantly changed. This improvement in tremor persisted during the remainder of his 5-d hospital stay. Ultimately, his anxiety and subsequent depression improved mildly to the point where he was discharged with intensive outpatient treatment scheduled.

Discussion

The incidence of tremor associated with lithium treatment has been reported to be 10–65% (Vestergaard et al., 1980). Lithium-induced tremor does not improve with dopamine agonists or anticholinergics (Carroll et al., 1987), although beta blockers such as

Address for correspondence: D. M. Marks, M.D., Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, 2218 Elder Srt., Suite 201, Durham, NC 27705, USA.
Tel.: 1-919-681-3840 *Fax*: 1-919-919-668-5418
E-mail: d.marks@duke.edu

propanolol, metoprolol, atenolol, pindolol, and nadolol have been shown to be effective in case reports (Dave and Langbart, 1994; Gaby et al., 1983) and crossover studies (Floru et al., 1979; Kirk et al., 1973). Vitamin B6 has been described to be efficacious in a small open-label study (Miodownik et al., 2002). Anticonvulsants have not been reported to be of use in lithium-induced tremor, and to our knowledge this is the first report of pregabalin or other anticonvulsant showing benefit for this condition. In the case reported here, pregabalin was initiated simultaneously with a change in benzodiazepine which increased the total daily benzodiazepine equivalents. It is possible that clorazepate exerted a therapeutic effect on this patient's lithium-induced tremor. However, it should be noted that previous multiple benzodiazepine trials at high doses for anxiety failed to reduce this patient's tremor. Moreover, the reduction in tremor observed can not be attributed to reduced anxiety, since the anxiolysis did not occur until days later. Unfortunately, no tremor rating scales were conducted since this was an unexpected and unanticipated effect. The efficacy of pregabalin in the treatment of lithium-induced tremor warrants more scientific study, but we believe this agent (and potentially other anticonvulsants) has promise for this indication. Pregabalin may be especially useful when comorbid disorders such as anxiety or pain syndrome are present. The potential therapeutic mechanism of pregabalin for treating lithium-induced tremor may relate to its action on voltage-sensitive calcium channels and potentiation of GABA neurotransmission, which are assumed to be relevant to control of tremor (Johannessen Landmark, 2008). In this regard, gabapentin may also hold promise for the treatment of lithium-induced tremor since it has a similar molecular structure to pregabalin and an identical mechanism of action (i.e. increased human brain GABA levels and reduced intracortical excitability); emerging evidence supports the efficacy of gabapentin for various tremor types (Gironell et al., 1999; Rodrigues et al., 2005). In conclusion, this case report suggests the potential effectiveness of pregabalin for the treatment of lithium-induced tremor and postulates that this effect may be shared by similar anticonvulsant drugs. Clinical trials with pregabalin and similar agents are warranted to confirm this hypothesis and elucidate the safety and efficacy of such medications in patients suffering from lithium-induced tremor.

Acknowledgements

None.

Statement of Interest

Dr Marks is a consultant for Bristol–Myers Squibb, is on the speakers' bureau of Eli Lilly and Company, and has received research support from DOV, Endo, Janssen, GlaxoSmithKline, Pfizer, Bristol–Myers Squibb, Johnson & Johnson, Eli Lilly and Company, Saegis Pharmaceuticals, Sepracor, and Somaxon. Dr Pae has received research grants from GlaxoSmithKline Korea, GlaxoSmithKline, AstraZeneca Korea, Janssen Pharmaceuticals Korea, Eli Lilly and Company Korea, Korean Research Foundation, Otsuka Korea, Wyeth Korea, and the Korean Institute of Science and Technology Evaluation and Planning; has received honoraria and is on the speakers' bureaux of GlaxoSmithKline Korea, Lundbeck Korea, AstraZeneca Korea, Jansssen Pharmaceuticals Korea, Eli Lilly and Company Korea, and Otsuka Korea. Dr Patkar is a consultant for Bristol–Myers Squibb, GlaxoSmithKline, and Reckitt Benckiser; is on the speakers' bureaux of Bristol–Myers Squibb, GlaxoSmithKline, and Reckitt Benckiser; has received research support from National Institutes of Health, AstraZeneca, Bristol–Myers Squibb, Forest, GlaxoSmithKline, Janssen, McNeil Consumer and Specialty Inc., Organon, Jazz Pharmaceuticals, and Pfizer.

References

Carroll JA, Jefferson JW, Greist JH (1987). Treating tremor induced by lithium. *Hospital & Community Psychiatry 38*, 1280–1288.

Dave M, Langbart MM (1994). Nadolol for lithium tremor in the presence of liver damage. *Annals of Clinical Psychiatry 6*, 51–52.

Feltner D, Wittchen HU, Kavoussi R, Brock J, Baldinetti F, Pande AC (2008). Long-term efficacy of pregabalin in generalized anxiety disorder. *Journal of Clinical Psychopharmacology 23*, 18–28.

Floru L, Tegeler J, Wolmsen H (1979). Treatment of lithium tremor with the beta receptor blocker, pindolol. *International Pharmacopsychiatry 14*, 149–157.

Gaby NS, Lefkowitz DS, Israel JR (1983). Treatment of lithium tremor with metoprolol. *American Journal of Psychiatry 140*, 593–595.

Gironell A, Kulisevsky J, Barbanoj M, López-Villegas D, Hernández G, Pascual-Sedano B (1999). A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. *Archives of Neurology 56*, 475–480.

Johannessen Landmark C (2008). Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs 22*, 27–47.

Kirk L, Baastrup PC, Schou M (1973). Propranolol treatment of lithium-induced tremor. *Lancet 2*, 1086–1087.

Miodownik C, Witztum E, Lerner V (2002). Lithium-induced tremor treated with vitamin B6: a preliminary case series. *International Journal of Psychiatry in Medicine 32*, 103–108.

Rodrigues JP, Edwards DJ, Walters SE, Byrnes ML, Thickbroom G, Stell R, Mastaglia FL (2005). Gabapentin can improve postural stability and quality of life in primary orthostatic tremor. *Movement Disorders 20*, 865–870.

U.S. Food and Drug Administration (2007). Pregabalin prescribing information (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails). Accessed 16 February 2008.

Vestergaard P, Amdisen A, Schou M (1980). Clinically significant side effects of lithium treatment: a survey of 237 patients in long-term treatment. *Acta Psychiatrica Scandinavica 62*, 193–200.

Zesiewicz TA, Ward CL, Hauser RA, Salemi JL, Siraj S, Wilson MC, Sullivan KL (2007). A pilot, double-blind, placebo-controlled trial of pregabalin (Lyrica) in the treatment of essential tremor. *Movement Disorders 22*, 1660–1663.

David M. Marks[1], Chi-Un Pae[1,2] and Ashwin A. Patkar[1]
[1] ***Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA***
[2] ***Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, South Korea***