Gabapentin withdrawal causing adrenergic toxidrome

A case report and literature review

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Vikas K. Singh MD[1], Obiomachukwu Chukwurah MD[1], Alycia Petraglia DO[1], Khaled Fernainy MD[2]
1 University of Pittsburgh Medical Center Mckeesport, **2** University of Pittsburgh School of Medicine
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Abstract

Gabapentin is an anticonvulsant most often prescribed for off-label indications, such as neuropathic pain. Rarely, an adrenergic toxidrome may occur after discontinuation of gabapentin. We describe a case of gabapentin withdrawal precipitating an autonomic hyperactive state which resolved with administration of gabapentin. Gabapentin withdrawal should be considered in patients presenting with unexplained autonomic hyperactivity after abrupt discontinuation of chronic gabapentin, especially at higher doses.

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Introduction

Gabapentin was approved by United States Food and Drug Administration (FDA) in 1993 as an adjunctive therapy for partial seizure, and is also indicated for treatment of postherpetic neuralgia.[1] Since its introduction, “off-label” use of gabapentin (marketed as Neurontin®, Gralise®, Horizant®, and Fanatrex®) has eclipsed its approved uses. Of gabapentin’s brand-name $2.3 billion in sales in 2002, $2.1 billion were asserted to have been for off-label use; up to 95% of gabapentin doses are prescribed for unapproved uses such as neuropathic pain.[1,2,3,4]

Gabapentin was designed as a lipophilic GABA agonist, but it does not act directly on GABA receptors in in vitro experimental models and its exact mechanism of action is not clear.[5] Gabapentin is not protein bound and is excreted unchanged, mainly in urine.[3]

Since the first case report of gabapentin withdrawal in 2001 with autonomic hyperactivity, 13 case reports describing gabapentin withdrawal have been reported.[6] We present a case of gabapentin withdrawal with an adrenergic toxidrome presentation, and review previous published cases. We used a PubMed search with the MeSH terms “gabapentin” and “gabapentin withdrawal”.

Case Presentation

Our case, a 57 year old female with a history of rheumatoid factor positive rheumatoid arthritis on tocilizumab, sicca syndrome, HTN, lower back pain and neuropathic pain in lower extremities, allergy to naproxen presented with anaphylactic reaction to Aleve (naproxen). She was not aware that Aleve is naproxen and took it for headache. She presented with angioedmea and anaphylaxis manifesting as worsening generalized itching, difficulty in swallowing, tongue swelling and wheezing. She received IM epinephrine, IV methylprednisolone and IV diphenhydramine and ultimately needed intubation to maintain airway. She was maintained on propofol infusion and prn fentanyl and lorazepam during mechanical ventilation. After 36 hours of intubation her angioedema had subsided and she was extubated without issues.

Within 2 hours, her post-extubation period was complicated by hyperactive delirium with autonomic hyperactivity (tachycardia, hypertension, diaphoresis and tachypnea). She failed to respond to repeated IV lorazepam and IV haloperidol. Discussion with close family confirmed that she does not drink alcohol on any regular basis – she had been abstinent due to her use of Methotrexate for rheumatoid arthritis. Review of home medication raised the possibility of gabapentin withdrawal. She was on gabapentin 800mg qid. Her other home medication were HCTZ, amitriptyline, tramadol, MDI albuterol and cevimeline. Her routine labs and imaging studies were unremarkable.

Gabapentin resumption was complicated as it is not available in IV, IM or per-rectal preparation and patient because of delirium and agitation was not cooperative enough to take oral medication. We were finally able to administer a single dose of 300 mg of gabapentin. Within hours of the first dose delirium started improving, and symptoms resolved completely within 6 hours. She was discharged home next day in calm, coherent and stable condition.

Discussion and Clinical Pearls

In review of published cases most of the cases were on high doses of gabapentin (1200mg or higher) and had a wide variability in duration of therapy, range 1 month to 60 month (Table-1). Most of the cases (~75%) had abrupt discontinuation of gabapentin and early onset of withdrawal symptoms. Early onset of withdrawal symptom could be explained by the short half-life (5-7 hours) of drug. Gabapentin withdrawal symptoms are similar to alcohol and benzodiazepine withdrawal but gabapentin withdrawal does not respond to benzodiazepines. In most of the cases initiation of gabapentin was delayed and could be due to lack of awareness of gabapentin withdrawal. Patients will benefit from early recognition of gabapentin withdrawal as prompt resolution (within hours) of withdrawal symptoms happens with gabapentin initiation. A patient on chronic gabapentin should have doses administered enterally, perhaps in lower doses, to decrease the risk of an abrupt discontinuation.

Table 1. Literature review of case reports of gabapentin withdrawal. *(Click image or link to view full-size.)*

Table 1: Gabapentin withdrawal: A case report and literature review

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