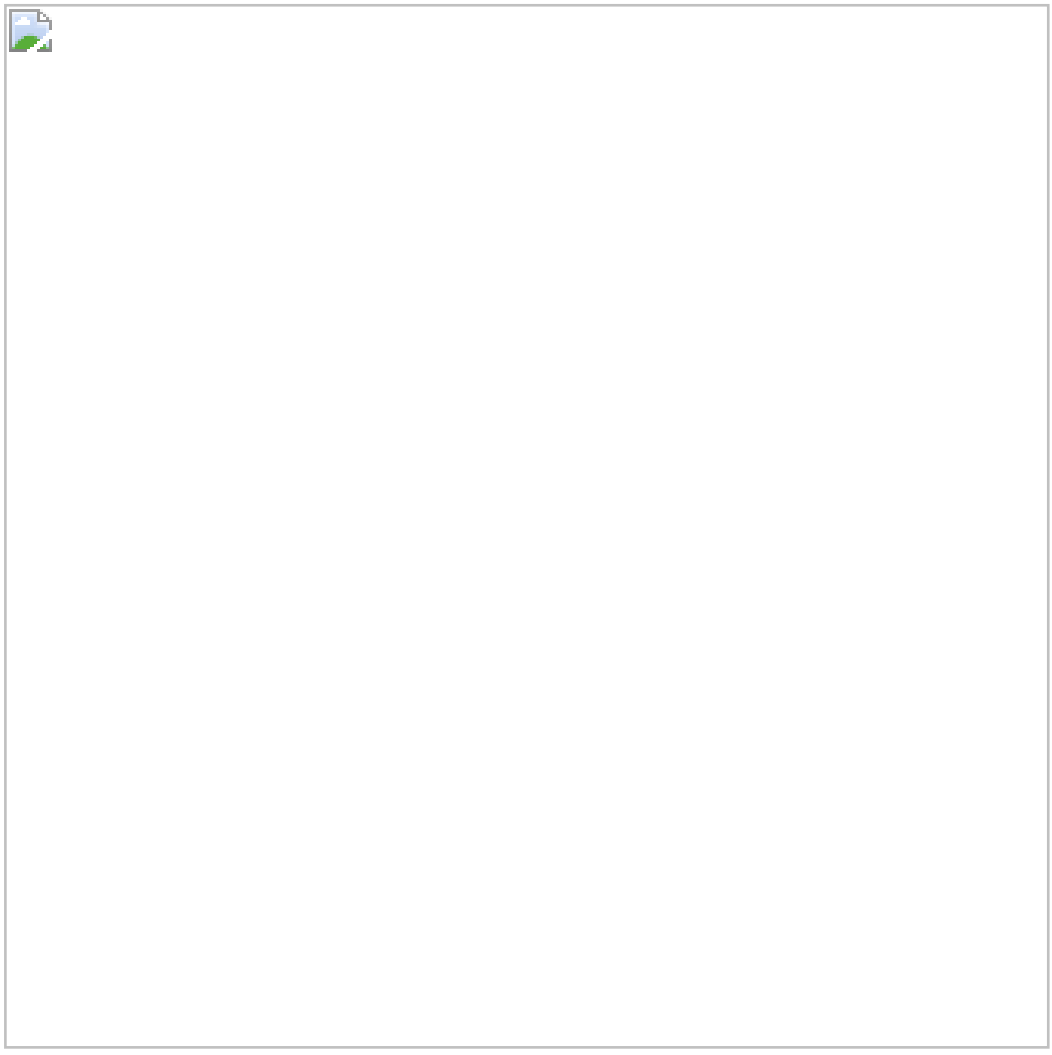

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Case Series

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Sage

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Abstract

Case series summary This case report describes the history and presentation of two cats with presumed gabapentin-induced myoclonus. Although this phenomenon is well documented in people, there are no previous reports in cats. Both cats in the current report had International Renal Interest Society (IRIS) stage 2 chronic kidney disease, a history of seizures (one generalized, one focal), and received gabapentin before veterinary hospital visits to alleviate anxiety (doses in the range of 11.8–16.4 mg/kg). While in the hospital, both cats were noted to have intermittent short jerks of the head that were different from the seizure activity previously noted by their owners at home. These cases appear to be the first published reports of this potential adverse effect of gabapentin in cats and risk factors in the present cases mirror those described in people.

Relevance and novel information Clinicians should be aware of the potential for this phenomenon in cats receiving recommended doses of gabapentin, and future studies should focus on the role of chronic kidney disease and other neurologic conditions as risk factors for development of this condition.

Keywords: Gabapentin; myoclonus; gabapentin-induced myoclonus; gabapentin adverse effects

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Introduction

Gabapentin is frequently prescribed to cats for treatment of chronic pain and stress reduction in the veterinary clinical setting.[1,2] Although it is structurally similar to gamma-aminobutyric acid (GABA), gabapentin itself does not interact with GABA receptors; instead, it binds to a subunit of voltage-sensitive calcium channels to inhibit release of excitatory neurotransmitters.[3–5] Gabapentin is generally regarded as safe, with a wide therapeutic index and minimal adverse effects. The recommended dosing range is 10–50 mg/kg;[6–8] anecdotally, dosing in healthy cats starts at 10 mg/kg and is titrated upwards for response. Although uncommon, reported adverse effects include sedation and ataxia.[9]

In people, myoclonus secondary to gabapentin administration is well documented.[10–12] Myoclonus is a movement disorder characterized by sudden and unexpected muscle jerks. Compared with other movement disorders (such as tics, dystonia or spasms), myoclonus is uncontrolled, brief and has an abrupt onset and termination.[13] Although initial safety studies of gabapentin in people estimated that myoclonus occurred in 0.1% of cases, recent studies report a prevalence as high as 12.5–21%.[10,11] Gabapentin-induced myoclonus is more common in people with diffuse brain damage, epilepsy or renal disease,[14] and dose reduction is recommended with these conditions.[12]

Here, we present two cases of presumed gabapentin-induced myoclonus in cats. In both cases, myoclonic jerks developed shortly after gabapentin was administered, and disappeared when gabapentin was discontinued or given at a reduced dose. To the authors'

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knowledge, this is the first published report of gabapentin-induced myoclonus in cats.

Case series description

Case 1

A 17-year-old female spayed domestic shorthair cat was presented to The Ohio State University (OSU) Neurology Service for evaluation of two seizures occurring 6 months apart. A year prior, the cat had a generalized seizure after receiving sedation. The seizure was attributed to hypotension (Doppler blood pressure was measured at 65 mmHg after the seizure event); however, 6 months later, a second isolated seizure occurred at home. This event was reported by the owner to last a few minutes and was characterized by paddling, hypersalivation, decreased consciousness and acting disoriented for 5 mins after the event. On arrival at the hospital, systolic blood pressure was measured at 100 mmHg. There were no neurologic abnormalities on examination. Blood work revealed mild hyperlactatemia of 3.1 mmol/l (reference interval [RI] <2.0) and azotemia (BUN 39 mg/dl [RI 22–22) and creatinine 1.96 mg/dl [RI 0.7–1.9]). The cat's past medical history also included a right nephrectomy for renal carcinoma at the age of 14 years; it was diagnosed with International Renal Interest Society (IRIS) stage 2 chronic kidney disease (CKD) at that time, and multiple subsequent chemistry panels measured its creatinine level at >2.1 mg/dl. In addition, it had a previously diagnosed ductal plate anomaly and grade II/VI systolic heart murmur.

Since the second event, the owners had not observed any seizures or twitching. The owner was instructed to administer 50 mg of gabapentin (11.8 mg/kg) 2 h before the appointment to prevent anxiety. Neurologic examination on presentation revealed a mildly sedated cat with no neurologic abnormalities. During examination, the cat exhibited at least 10 events of apparent myoclonic jerks, each lasting 0.5–1 s. The events were characterized by rapid jerking motions of the head to the side or up and down and appeared to be associated with blinking, moving its whiskers or leaning its head backwards or forwards (see Video 1 in the supplementary material). Initially, focal seizures were considered as a differential for the events, although the owners reported that they had never observed these at home. Since a generalized seizure had not occurred for several months, the owners were advised to monitor for additional episodes.

Before a follow-up veterinary visit 1 week later, the cat was again administered the same dose of gabapentin. At this appointment, it was noted to have the same brief intermittent jerking movements of the head. The owners reported that they had not seen any events at home between the two visits, and a tentative diagnosis of gabapentin-induced myoclonus was made. The owner independently decreased the gabapentin dosage to 25 mg (5.9 mg/kg) 2 h before subsequent veterinary visits and no further episodes were noted.

Case 2

A 12-year-old female spayed domestic shorthair cat was presented to the OSU Primary Care service for a routine dental cleaning. Five years prior, the cat had been diagnosed with presumed primary epilepsy. Its seizures at that time were characterized by a brief pre-ictal period where it would stare off into space before its face would twitch for a few seconds. The cat's neurologic examination at the time was normal. Phenobarbital therapy was initiated, which decreased the seizure frequency. This medication was eventually discontinued because of adverse effects and the cat continued to have short focal events daily. The cat also had a 4-year history of IRIS stage 2 CKD (creatinine >1.6 mg/dl [RI 0.7–1.9] on multiple blood work assessments) for which it was not receiving any specific therapy.

In preparation for the dental visit, the cat was given gabapentin (16.4 mg/kg) for anxiety prevention. While in the car, the owner noted several episodes of head bobbing, eye twitching and head twitching at least once every 2 mins. On arrival at the clinic, the cat was administered 3 mg (0.5 mg/kg) midazolam intramuscularly owing to concern for continuous focal seizure activity. This reduced the frequency of the episodes, and the cat did not have any episodes noted during anesthesia for the dental procedure; however, upon recovery, the episodes resumed and eventually stopped later that evening.

Three days after the dental procedure, the cat was presented to the emergency room for evaluation of hematuria. It was normotensive on examination (systolic blood pressure measured 110 mmHg). The cat was prescribed antibiotics and gabapentin (8.1 mg/kg) and was discharged. When gabapentin was administered at home, the cat developed the same episodes of head jerking that had been noted at its dental visit. The owner noted that these new episodes that occurred after gabapentin administration occurred markedly more frequently than the previous daily focal seizure events. These movements happened intermittently for approximately 1 h. The owner then brought the cat back to the hospital where they administered midazolam and the movements slowly subsided over an hour. After this, gabapentin was discontinued and no further clustered twitching episodes were observed.

Discussion

Myoclonus can originate from either the central or peripheral nervous system and can be secondary to degenerative disorders or caused by exogenous factors, including various medications.[15] This phenomenon can be caused by neurochemical imbalances secondary to metabolic encephalopathies, dysfunctional neural circuits in the context of myoclonic epilepsy or brainstem mediated myoclonus, or lesions of the peripheral nerve or nerve root (peripheral myoclonus).[16] Alterations in serotonin levels have also been demonstrated to play an

important role in the development of myoclonus in certain conditions.[17,18] Myoclonus can be further classified as positive or negative: positive myoclonus is caused by abrupt spontaneous muscle contractions, while negative myoclonus is caused by abrupt cessation of sustained muscle contraction.[16] Although both types have been reported in people after gabapentin administration, the cats in the current report appeared to exhibit events that could be classified as positive myoclonus.

In people, development of transient or persistent myoclonus has been reported in association with many medications, most commonly full agonist opiates, beta-lactam and quinolone antibiotics, and gabapentin.[19] Although the pathophysiology of the condition in context of gabapentin administration is poorly understood, the link is temporally well established and the myoclonus typically resolves fully with discontinuation of the medication,[12] or with hemodialysis in cases of severe renal impairment.[20] Although the relationship between gabapentin administration and the development of myoclonus is presumptive in both feline cases described in this report, neither cat had been noted to have myoclonic episodes previously, and the myoclonic events did not recur once gabapentin was reduced (cat 1) or fully discontinued (cat 2).

Both cats had a diagnosis of IRIS stage 2 CKD, a common condition in the feline population where the prevalence is in the range of 1–50%.[21,22] Gabapentin is solely excreted by the kidneys,[23] and cats with CKD have significantly higher serum gabapentin concentrations than healthy cats administered the same dose.[24] Although it has been noted that cats with CKD have slower excretion of gabapentin, there is limited information on the role of CKD as a risk factor for increased side effects of this medication.[24] Although gabapentin-induced myoclonus can occur in the face of normal renal function,[25] people with reduced glomerular filtration rates have higher than expected serum gabapentin concentrations, and subsequently have an increased frequency of gabapentin toxicity effects such as ataxia, altered levels of consciousness and myoclonus.[26]

In people, gabapentin-induced myoclonus can be dose-dependent.[11] In cats, higher dosages appear to be correlated with an increased risk of adverse effects, most notably increased sedation.[7] Cat 1 had no further episodes of myoclonus when gabapentin was administered at a reduced dose. This might indicate some dose-dependence of gabapentin-induced myoclonus in cats as well. Although further studies are needed to determine dosing risk for myoclonus in cats, dose reduction might be warranted in cats with documented CKD.

Both cats in this report also had a history of epilepsy, and neither cat had advanced imaging of the brain performed; as such, structural causes of epilepsy were not excluded in either case. In people, both primary epilepsy and diffuse structural brain disease (such as cerebral palsy or encephalitis) are risk factors for the development of gabapentin-induced myoclonus.[10,12] Cat 2 continued to have isolated focal seizures after gabapentin administration was discontinued; however, these were consistent with previous seizure semiology and the cat had no further 'cluster events' after stopping gabapentin. It is possible another primary brain condition might have contributed to the risk of gabapentin-induced myoclonus in the cats in the present report.

Differential diagnoses for neurologic episodes such as those described in the present case series include focal seizures, dyskinesias or tremor syndromes.[27] Myoclonus has a distinct clinical appearance, although it may be confused for other types of neurologic events in those not familiar with the condition, particularly if drug-associated myoclonus is not on the clinician's radar. In fact, both cats were initially suspected of having focal seizures on presentation, and only after repeated association with gabapentin dosing were other differentials considered.

Conclusions

This case series describes myoclonus as a potential adverse effect of gabapentin administration not previously reported in cats. Future research aimed at understanding the pharmacokinetic properties of gabapentin in cats with various degrees of renal function might help predict which patients are at higher risk of developing this adverse effect. With the above information, and in keeping with recommendations in people with similar conditions, it appears warranted to adjust gabapentin dosing for cats with documented CKD and potentially in patients with intracranial disease. It is also important for clinicians to recognize the difference between gabapentin-induced myoclonus and other neurologic conditions to prevent the misguided recommendation of expensive diagnostic procedures or inappropriate therapies. Gabapentin is an important tool for preventing hospital anxiety in feline patients, and care should be taken when prescribing it to patients with the aforementioned comorbidities.

Supplementary material The following file is available as supplementary material:
Video 1: Cat 1 exhibiting myoclonus.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognized high standards

('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers, tissues and samples) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

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