

## Single Case

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# More Drug Monitoring and Less CT Scans of the Brain: Gabapentin Overdose in Two Peritoneal Dialysis Patients

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## Keywords

Drug dosing · Pharmacokinetics · Iatrogenic complications

## Abstract

In parallel with the decline of renal excretory function, drug dosing of many drugs becomes more challenging. Finding the right dose is even more difficult if kidney replacement therapy is instituted. This is further aggravated by the fact that even for substances with a narrow therapeutic range, drug monitoring is only rarely offered, let alone advocated. This holds also true for gabapentin, an anticonvulsant drug that is increasingly prescribed for indications such as cancer-related pain, restless legs syndrome, migraine, or uremic pruritus. The drug is excreted unchanged in urine, so plasma clearance of gabapentin is directly proportional to creatinine clearance. Hence, renal impairment reduces gabapentin excretion and increases plasma gabapentin concentrations in a linear fashion. Therefore, the elimination half-life of gabapentin is between 5 and 9 h, in patients with normal renal function but increases to 132 h in patients on dialysis. Epidemiological data from the USRDS underline this problem. About 19% of the 140,899 adult USA patients enrolled in Medicare coverage received gabapentin in 2011. Its use was associated with an increased risk of altered mental status, fall, and fracture. We report 2 patients in which overdose of gabapentin occurred. In 1 patient, severe neurological symptoms prompted an extensive diagnostic work up, while the underlying cause of the clinical presentation was a supra-therapeutic drug level of gabapentin. Consequently, symptoms subsided with the discontinuation of the drug. Indication and drug dose of gabapentin in dialysis patients should be tightly controlled, and drug monitoring used to avoid unintended overdose.

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## Introduction

Gabapentin is an amino acid that has the structure of the neurotransmitter  $\gamma$ -aminobutyric acid. It reduces lesion-induced hyperexcitability of posterior horn neurons, which is responsible for central sensitization. Administered orally, gabapentin is absorbed by diffusion as well as by the carrier-mediated, L-amino acid transport system. The latter one is saturable which explains why the bioavailability of gabapentin is inversely dependent on the dose. Gabapentin (molecular weight 171.2 D) has a volume of distribution of 0.6–0.8 L/kg and does not bind to plasma proteins. Unlike  $\gamma$ -aminobutyric acid, gabapentin readily penetrates the blood-brain barrier, yielding concentrations in the cerebrospinal fluid that are about a fifth of the plasma concentrations. In contrast to many antiepileptic drugs, which are metabolized, gabapentin is not metabolized but solely eliminated by renal clearance thus accumulating in parallel to the decline in renal function. While the elimination half-life of gabapentin is between 5 and 9 h in subjects with normal renal function, half-life increases to 132 h in patients on dialysis [1]. Overdose of gabapentin in patients with chronic kidney disease is a frequent problem [2]. The resulting symptoms range from tremor and confusion over ataxia to nausea and vomiting [3]. Epidemiological proof that gabapentin is difficult to handle in the dialysis population stems from a USRDS. In 2011, about 19% of the USA dialysis patients (140,899 adults enrolled in Medicare coverage) received gabapentin [4]. In that study, it was shown that gabapentin was associated with higher hazards of altered mental status (50%), fall (55%), and fracture (38%) when given at a dose of >300 mg per day. Nonetheless, even lower doses were associated with an increased risk of altered mental status (31–41%) and fall (26–30%). This might also be explained by the fact that risk factors of gabapentin toxicity such as advanced age, liver failure, and age-related changes in the nervous system are frequently seen in patients with chronic kidney disease [2]. The therapeutic range of gabapentin is 2–20 mg/L; however, reversible toxicity has been described at gabapentin concentration of 15.1 mg/L. Nonetheless, even in high-risk patients, drug monitoring for gabapentin is usually not recommended.

## Case Report

We report 2 cases of gabapentin overdose. Patient A, an 85-year-old Caucasian male suffered from chronic kidney disease stage 5 D. He had been treated with peritoneal dialysis for over 2 years due to suspected diabetic nephropathy and nephrosclerosis. The patient was admitted to our tertiary care hospital with repeated syncope and faints. For neuropathic pain, he had been treated with gabapentin 300 mg/day. To exclude a neurological cause for the symptoms of patient A, a series of different examinations including cranial computed tomography, computed tomography of the cervical spine, duplex ultrasound of the carotid arteries, and an electroencephalogram had been done. All the examinations remained without any significant pathological findings. The same did hold true for the result of the clinical laboratory evaluation. A 24-h blood pressure measurement showed moderately reduced systolic blood pressure but no severe hypotension. An orthostatic dysregulation as an additional reason for the syncopal episodes could not be detected. Other reasons that could explain the symptoms were excluded. The gabapentin level was, however, markedly elevated (34.1 mg/L), prompting discontinuation of the treatment on hospital day #2. The notion that gabapentin overdose was most likely the cause of his symptoms was underlined by the fact that after discontinuation of the drug, all initial clinical symptoms subsided. Tilidine to reduce neuropathic pain was started in patient A, who did not develop neurological symptoms. On last follow-up, there were no further incidents or symptoms reoccurring that resembled the ones that prompted hospital admission.

Patient B, an 87-year-old Caucasian male patient with chronic kidney disease stage 5, not yet on dialysis, was admitted to the hospital to insert a peritoneal dialysis catheter and to initiate peritoneal dialysis. The underlying diseases were congestive heart failure (NYHA III) and diabetes mellitus type 2. Patient B presented unspecific symptoms such as lethargy. Because of neuropathic pain, the patient was treated with gabapentin 300 mg twice-daily for several years. Gabapentin level was 26.1 mg/L. Because of the elevated level without marked clinical symptoms, gabapentin dose was lowered to 200 mg every other day instead of the previous dosage of 300 mg b.i.d. The pain of the underlying osteochondrosis was additionally treated with a small dose of an opioid.

### Discussion/Conclusion

With a wider spectrum of indications outside of its original use as an anticonvulsive drug [5, 6], gabapentin use is not only increasingly but also less cautiously used [2]. As gabapentin is exclusively eliminated by renal excretion, monitoring of renal function should be a prerequisite in chronic prescriptions of the drug. The real-world experience, however, suggests that this is not the case, best epitomized by gabapentin overdose presented by weakness, ataxia, dizziness, or tremor in patients with chronic kidney disease [7].

As the clearance of gabapentin is dependent on renal function, the pharmacokinetics of gabapentin were investigated in anuric subjects maintained on hemodialysis [7]. The elimination half-life of gabapentin on nonhemodialysis days averaged 132 h. Gabapentin elimination half-life during hemodialysis was approximately 4 h. Thus, patients with chronic kidney disease stage 5 on hemodialysis should receive an initial 300-mg to 400-mg gabapentin loading dose. Plasma gabapentin concentrations can then be maintained by giving 200–300 mg of gabapentin after each hemodialysis [7]. Administration of gabapentin on nonhemodialysis days is not recommended.

While gabapentin is effectively cleared by hemodialysis, the clearance by peritoneal dialysis is poorly understood. In a case of gabapentin toxicity in a patient on cyclo-assisted peritoneal dialysis, it was found that continuous peritoneal dialysis with 2-L exchanges every 2 h provided an apparent elimination half-life of 41.33 h, which is substantially shorter than the reported elimination half-life of 132 h in the absence of kidney function, yet a much longer half-life as compared to in individuals with normal kidney function (5–9 h), requiring dose reduction of gabapentin in patients on peritoneal dialysis [8]. In cases of toxic manifestations due to gabapentin, hemodialysis application can be helpful and is able to resolve neurological symptoms if applied urgently [2]. In conclusion, gabapentin does accumulate in patients with chronic kidney disease causing a variety of toxicity that can range from weakness and dizziness as well as syncope to emotional lability. Although drug monitoring for gabapentin is usually not recommended, it might be useful in patients with chronic kidney disease (on dialysis) (Fig. 1).

### Statement of Ethics

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Written informed consent was obtained from the 2 patients for publication of their medical history and their relevant laboratory parameters. Ethical approval is not required for this case presentation. This is in accordance with the guidelines of the IRB of the Ärztekammer Niedersachsen.

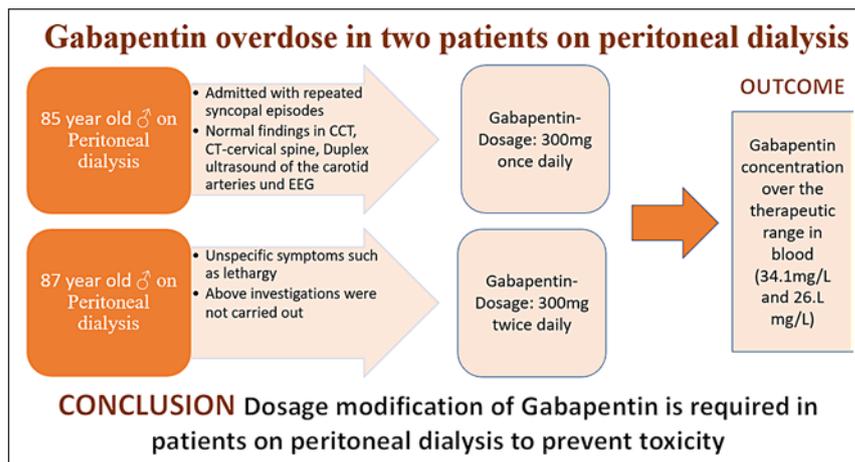


Fig. 1. Visual summary of the case report.

### Conflict of Interest Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Author Contributions

Kijanosh Lehmann, Jan T. Kielstein, and Gabriele Eden treated patient A. Sara Diab and Torsten M. Meyer treated patient B. Kijanosh Lehmann and Jan T. Kielstein wrote the case report.

### Data Availability Statement

All data generated or analyzed during this study are included in this article.

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