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# Gabapentin Toxicity in Renal Failure: The Importance of Dose Adjustment

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**ABSTRACT**

*Objective.* This case report outlines a significant type of morbidity due to continued use of gabapentin during an episode of acute renal failure.

*Setting.* University teaching hospital.

*Discussion.* Gabapentin is widely used in the management of pain. It is entirely excreted through the renal system so this needs to be considered in any patient becoming acutely ill and developing renal failure. We describe a patient who developed significant deterioration in her conscious level due to iatrogenic gabapentin overdose.

*Conclusion.* All doctors need to be aware of the need to review the indications for gabapentin use during periods of acute illness, especially with regard to renal impairment. Off-label use should be discouraged.

*Key Words.* Analgesic; Anticonvulsants; Gabapentin; Older Adults; Sedation

## Introduction

Gabapentin is an effective anticonvulsant and it is also used in the treatment of chronic neuropathic pain [1]. Its sole route of elimination is by the kidney and, therefore, impairment in renal function will result in a higher plasma gabapentin concentration and longer elimination half-life. Signs of toxicity are nonspecific and include sedation, dizziness, and confusion.

We present a probable case of unrecognized gabapentin toxicity in a patient with acute renal impairment.

## Case Report

A 75-year-old female presented to her general practitioner (GP) with a 3-week history of right-sided hip pain. Her medical history included left congenital hip dislocation and hemiarthroplasty, bilateral knee osteoarthritis, open cholecystectomy, and hypertension. Routine check of her renal function, 2 weeks before her presentation, revealed mild renal impairment (urea 60.8 mg/dL, creatinine 1.3 mg/dL, estimated glomerular filtration rate [GFR] 43 mL/min/1.73 $m^2$). There was no history of renal impairment before this time. Her regular prescription medications were diclofenac 75 mg twice daily, tramadol 50 mg four times daily, dihydrocodeine 30 mg four times daily, furosemide 80 mg once daily, amlodipine 5 mg once daily, and irbesartan 300 mg once daily. These medications were long-standing, having been prescribed for her chronic left hip pain and hypertension for many years. In an attempt to preserve her already poor mobility, her GP prescribed an increasing dose of gabapentin as analgesic adjunct, to avoid escalating her other pain medication in light of her impaired renal function. There was no mention of any neuropathic element to her right hip pain.

Two days later, she fell at home and was reassessed by the GP, who found her to be drowsy and vague. She was unable to care for herself, and so she was admitted to the medical unit for assessment and nursing care. At this point, her gabapentin dose was 300 mg three times a day.

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On examination, she was sleepy but easily rousable to a Glasgow Coma Score (GCS) of 15, with an abbreviated mental test score of 7/10. There was no evidence of head trauma. Her temperature was 100.9F, but heart rate, blood pressure, respiratory rate, and oxygen saturations were all within normal limits. Examination of the painful right hip revealed normal range of movement with no deformity but some bruising and tenderness to palpation. A plain X ray of the right hip joint showed changes consistent with osteoarthritis and no evidence of fracture.

Blood tests revealed anemia (hemoglobin [Hb] 9.6 g/dL), renal impairment (urea 89.1 mg/dL, creatinine 1.56 mg/dL, estimated glomerular filtration rate 34 mL/min/1.73 $m^2$), and abnormal liver function tests (alkaline phosphatase 368 u/L, gamma-glutamyl transferase 142 u/L). An abdominal computed tomography scan revealed a dilated common bile duct without obstruction, and bilateral renal cysts.

The provisional diagnosis was of musculoskeletal right hip pain with coexisting biliary infection. In view of her impaired renal function, she was given i.v. hydration and antibiotics, and her diclofenac and irbesartan were discontinued at this time. She continued to receive gabapentin 300 mg three times per day, tramadol 50 mg four times per day, and dihydrocodeine 30 mg four times a day.

Over the next 7 days, her clinical condition deteriorated. She became drowsier and increasingly hypotensive, and her renal function worsened dramatically (creatinine 1.93 mg/dL, estimated GFR 12 mL/min/1.73 $m^2$). She was given i.v. fluids and her tramadol and dihydrocodeine were stopped, but 300 mg gabapentin continued to be administered three times daily.

Ten days after her admission, nursing staff found her unconscious with minimal respiratory effort. She was transferred to the intensive care unit (ICU) for further management of her condition with a provisional diagnosis of severe septic shock complicated by acute renal failure. Her conscious level improved with fluid and norepinephrine therapy. Her urine output was negligible. Antibiotic treatment with meropenem was commenced.

Despite overall improvement in her condition, she remained persistently drowsy, with her GCS fluctuating between 9 and 13/15. Differential diagnoses considered at this time included septic or uremic encephalopathy and possible opioid toxicity. Having excluded hypotension and reduced cerebral blood flow as a cause of her low conscious level, we sought an alternate explanation. There were no lateralizing neurological signs, pupils were small but reactive, respiratory rate was 20 breaths per minute, and there were occasional myoclonic jerks. There was no improvement in her conscious level with a trial dose of 800 μg of naloxone. Review of her prescription chart highlighted the possibility of gabapentin toxicity, and the decision was taken to start continuous veno-venous hemofiltration (CVVH) in an attempt to clear the drug and as renal supportive therapy. Gabapentin administration was discontinued at this point.

After 12 hours of CVVH, she was noticeably more lucid and was able to cooperate with nursing and medical staff. Over the next 24 hours, there were further improvements in her cognitive function, as well as a steady decline in her creatinine level. Her cardiovascular status stabilized and the norepinephrine infusion was stopped. Antibiotic therapy continued for 5 days. No positive microbiological cultures were reported. She required 5 days of renal supportive therapy. She remained fully conscious, and after 7 days in the ICU, she was discharged back to a general ward for rehabilitation. Gabapentin was not restarted.

## Discussion

Gabapentin is known to be effective in the treatment of neuropathic pain [1]. The analgesic mechanism of action of gabapentin has yet to be fully elucidated. Recent work using animal and human models demonstrates one possible mechanism is through the selective inhibition of the alpha 2 delta subunit of voltage-gated calcium channels [2]. Its relatively benign side-effect profile has undoubtedly contributed to its widespread use; several studies have documented only mild clinical effects following significant gabapentin overdose [3,4].

Gabapentin is not significantly metabolized and is excreted solely by the kidney. Thus, plasma levels will rise as renal clearance falls. For this reason, dose adjustment is recommended in patients with renal failure [5].

Failure to account for reduced gabapentin elimination in patients with renal impairment can lead to serious toxicity. Several investigators have reported neurological sequelae following administration of the drug to patients with renal failure [6–8]. These have included subtle changes in mental status, drowsiness, and even coma. Fortunately, gabapentin is removed by renal replace-

ment therapy [9], and if prompt treatment is instituted, the neurological toxicity is completely reversible.

Our case report highlights the need for diligent prescribing. At presentation to hospital, with an estimated GFR of 34 mL/min/1.73 $m^2$, our patient's gabapentin dose of 900 mg daily was initially appropriate. Accumulation of the drug may have contributed to the fall and drowsiness that led to her admission. As her renal function deteriorated, appropriate changes to her drug prescription chart were made to prevent further drug toxicity—but her gabapentin dose was not adjusted. Thus, iatrogenic toxicity continued for several days. The assay for serum gabapentin level is not readily available, but the history, examination findings, and the patient's rapid clinical improvement with CVVH all point toward gabapentin toxicity.

Gabapentin has a nonlinear relationship between therapeutic and toxic levels and exhibits a wide interpatient variability [10], making the analysis of plasma levels of limited use other than to confirm the presence of gabapentin. There are no target plasma levels available for use in titrating gabapentin in the treatment of pain disorders; however, the target range for the treatment of epilepsy is 12–120 μmol/L [11].

It is increasingly recognized that inappropriate use of medication in the elderly—in our patient the off-label prescription of gabapentin for non-neuropathic pain—leads to adverse drug events [12]. Medication errors in some reports account for 2–4% of all hospital admissions; this rises to over 30% in those aged 75 years or more [13]. Education for all doctors about the importance of gabapentin dosage adjustment in renal failure could prevent many similar events from occurring in the future. The rationale for initial prescription of gabapentin for the non-neuropathic hip pain experienced by this patient is questionable and such "off-label" prescribing should be discouraged [14], as the benefit to the patient cannot be weighed accurately against possible harms with any degree of certainty.

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