Rational dosing of gabapentin and pregabalin in chronic kidney disease

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Introduction

Renal dose adjustments for gabapentin and pregabalin are ubiquitously evident in the medical literature. All manufacturers for these branded and generic dosage forms list dosing recommendations relative to creatinine clearance (CrCl) for both medications (Table 1).^{1,2} However, the basis of these recommendations has not been well articulated.

Pharmacology

Gabapentin and pregabalin are commonly used first-line agents for diabetic peripheral neuropathy and other common neuropathies. Pharmacologically, both agents inhibit alpha-2-delta ($\alpha 2\delta$) subunit of N-type voltage-gated calcium channels, a key receptor involved in regulating the excitability of neurons.³ Peripheral nerve injury results in the upregulation of $\alpha 2\delta$ -1 receptors in the dorsal root ganglion neurons and subsequent increase in the trafficking of $\alpha 2\delta$ -1 to nerve terminals within the spinal cord.³⁻⁵ Inhibition of $\alpha 2\delta$ -1 receptors decreases calcium-mediated release of excitatory neurotransmitters into the dorsal horn and subsequently reduces pain signaling.⁴⁻⁶ Despite sharing the same mechanism of action, there are key pharmacologic differences between both agents. Pregabalin has six times higher binding affinity for the $\alpha 2\delta$ -1 receptor compared to gabapentin.⁷ Gabapentin follows zero-order saturable absorption, where its bioavailability decreases as the dose increases.^{1,7} Following oral administration, gabapentin's bioavailability is 60%, 47%, 34%, and 33%, with 900, 1200, 2400, and 3600 mg/day in three divided doses, respectively.¹ Notwithstanding, the two extended-release branded products, Horizant (gabapentin enacarbil) and Gralise (a prodrug), are pharmaceutically designed to enhance absorption.^{8,9} Pregabalin exhibits linear absorption with bioavailability equal to or greater than 90% irrespective of the dose, which gives it a more predictable pharmacokinetic profile.^{2,7}

Pharmacokinetics and renal handling

Challenges to achieving therapeutic concentrations necessary to achieve efficacy require consideration of the pharmacokinetic properties of both gabapentin and pregabalin. Both medications do not undergo hepatic metabolism and are primarily excreted unchanged in the urine.⁷ A pharmacokinetic advantage is the absence of hepatic cytochrome P450-related drug–drug and drug–food interactions. In pharmacokinetic

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Table I Recommended dose adjustments based on varying degrees of renal impairment

CrCl cutoff	Maximum recommended dosing	
	Gabapentin ¹	Pregabalin ²
30–59 mL/min	700 mg BID	150 mg BID 100 mg TID
15–29 mL/min	700 mg once a day	75 mg BID 50 mg TID
<15 mL/min	300 mg once a day	75 mg once a day
Supplemental doses in hemodialysis	100–300 mg post dialysis	75–150 mg post dialysis

Abbreviation: CrCl, creatinine clearance.

studies, clearance of both medications was linearly correlated with CrCl. Gabapentin's apparent total clearance is 100 mL/min in adults with normal renal function, which is essentially equivalent to CrCl and does not suggest the involvement of tubular reabsorption.¹ Some evidence suggest that active tubular secretion mediated by organic cation transporter-1 (OCT-1) may play a role in gabapentin's renal clearance. Individuals with genetic variation in OCT-1 may have altered renal clearance; however, the clinical significance has yet to be elucidated and may be negligible as gabapentin is primarily excreted unchanged via filtration.¹⁰

Pregabalin's apparent total clearance is 67–81 mL/min in young healthy subjects and is therefore thought to undergo tubular reabsorption to some extent.² Hemodialysis (HD) removes approximately 35% of gabapentin and 50%–60% of pregabalin, where supplemental doses are generally recommended post-HD.^{1,2}

Therapeutic dosing targets

Therapeutic dosing targets of both medications have been established in clinical trials for neuropathic pain (gabapentin 1800–3600 mg/day; pregabalin 150–600 mg/day). However, patients with renal impairment were often excluded from these studies.^{11–17} The aforementioned renal dose adjustments were mainly based on pharmacokinetic studies, some of which were conducted in healthy individuals. To date, no study has evaluated the impact of recommended dosing strategies on clinical efficacy in the management of neuropathic pain for patients with renal dysfunction.

Dosing considerations in chronic kidney disease (CKD)

CKD alters renal drug elimination by affecting glomerular blood flow, filtration rate, tubular secretion and reabsorption, and renal bioactivation and metabolism.¹⁸ Additionally, pharmacokinetic handling of medications (absorption,

distribution, metabolism, and elimination) may be affected.¹⁹ Reducing the dose is recommended for medications with narrow therapeutic index.²⁰ Extending the interval is recommended for medications with prolonged half-life in renal impairment; however, this may be subtherapeutic and may cause end-of-dose failure. Understanding the pharmacokinetic and pharmacodynamic profiles of medications is important when making these adjustments. Nevertheless, while dosing gabapentinoids, we must also consider reports by the patient that include side effect profile and tolerability as measured against efficacy, irrespective of the theoretical calculations.

A theoretical approach: the Rowland and Tozer equation

A widely accepted approach to individualize drug dosing in CKD patients based on CrCl is the Rowland–Tozer method.²¹

Figure 1 correlates with the manufacturer's recommendation for pregabalin to follow a 50% dose reduction in patients with CrCl below 60 mL/min and greater than 30 mL/min. For medications with concentration-dependent efficacy, extending the interval while maintaining the same dose is appropriate. For medications with area under the curve (AUC)-dependent efficacy, extending the interval or reducing the dose is appropriate while maintaining the same AUC. The efficacy of pregabalin and gabapentin for neuropathic pain with respect to blood concentration or AUC remains unclear. Notwithstanding, most reports of toxicities were associated with concentrations higher than 15 mg/L for gabapentin and concentrations higher than 13 mg/L for pregabalin, whereas individuals with

$Q = 1 - [Fe (1 - KF)]$

Q: drug dose adjustment factor (kinetic parameter)
Fe: fraction of drug excreted unchanged in the urine
KF: ratio of patient's CrCl to normal (normal CrCl = 120 mL/min)

Example
Calculate a pregabalin dose in a patient with CrCl of 60 mL/min

1. Approximately 98% of the administered dose is found unchanged in the urine.
 - Fe = 0.98 or ~1 for simplicity.
2. Patient's renal function is 60 mL/min.
 - KF = (60/120).
3. Insert patient values into the equation to find Q.
 - $Q = 1 - [1 (1 - (60/120))] = 0.5$

Answer
Q of 0.5 means administering 50% dose at the normal dosing interval or the normal dose at twice the dosing interval.

Figure 1 Rowland–Tozer method.

normal renal function on maximum recommended dosing yielded concentrations of ~5–8 mg/L for gabapentin and 2.8–8.2 mg/L for pregabalin.^{22–25} The elimination half-lives of gabapentin and pregabalin are prolonged with renal impairment leading up to accumulation with repeated dosing. The half-life of gabapentin immediate-release formulation is 5–7 hours in patients with normal renal function and is prolonged up to 52 hours in patients with CrCl<30 mL/min.²⁶ The half-life of pregabalin is 16.7 hours in patients with CrCl 30–59 mL/min, 25 hours in patients with CrCl 15–29 mL/min, and 48.7 hours in patients with CrCl<15 mL/min.²⁷ Therefore, finding the right pharmacokinetic balance is key to promote safety and efficacy, yet this balance remains unknown.

Conclusion

Gabapentin and pregabalin are commonly used for neuropathic pain in CKD patients but are not fully understood as this population remains excluded from efficacy and safety trials. Renal adjustments for the gabapentinoids are prodigiously recommended in the literature. However, current guidance is based on pharmacokinetic and toxicity studies, but studies confirming efficacy of these dosing strategies are lacking. Considering their widespread use for numerous neuropathic pain conditions, studies evaluating their efficacy at recommended doses in renal impairment should be a priority for future research.

Disclosure

JF reports the following: Daiichi Sankyo (advisory board); DepoMed (advisory board, speakers bureau); Endo (consultant, speakers bureau); Kaléo (speakers bureau, advisory board); Kashiv Pharma (advisory board); KemPharm (consultant); Pernix Therapeutics (speaker); Remitigate, LLC (owner); and Scilex Pharmaceuticals (consultant). The other authors report no conflicts of interest in this work. This editorial represents the opinions of the authors and has not been reviewed or prepared as part of any government agency or companies listed.

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