# Therapeutic Drug Monitoring of Pregabalin in a critically ill patient with Acute Kidney Injury undergoing Continuous, Prolonged Intermittent, and Intermittent Kidney Replacement Therapy modalities

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**Abstract**

Pregabalin is an anti-epileptic drug which also represents one of the most frequently prescribed medications for neuropathic pain management worldwide. Moreover, in recent years its use has widely increased also in critically ill patients in the setting of multimodal analgesia. Commonly available as capsules and oral solution, it is characterized by a predominant kidney elimination. Consequently, in patients with kidney failure posology adjustments are needed. According to the pharmacokinetic parameters (low molecular weight and volume of distribution, negligible protein binding), pregabalin is expected to undergo a significant extracorporeal clearance, which should be taken into account when one of the different Kidney Replacement Therapy (KRT) modalities is required for Acute Kidney Injury (AKI). The case of a critically ill patient with AKI undergoing Therapeutic Drug Monitoring of Pregabalin in course of Continuous, Prolonged Intermittent KRT (CKRT and PIKRT, respectively), and conventional intermittent hemodialysis (IHD) is presented here for the first time.

## Introduction

Pregabalin is an anti-epileptic drug representing one of the most frequently prescribed medications for neuropathic pain management worldwide, whereas its use as an anti-convulsant is currently limited [1]. Despite being an analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), like gabapentin, pregabalin shows no binding activity to GABA receptors. Instead, it binds with high affinity to the alpha-2-delta subunit of voltage-gated calcium channels, located at neuronal presynaptic endings at different levels in the nervous system, decreasing the depolarization-induced influx of calcium into neurons and ultimately reducing the synaptic release of excitatory neurotransmitters [2]. The reduction of abnormal neuronal excitability within the brain may account for its anticonvulsant and anxiolytic effects, while a decrease in synaptic release of several neuromediators at the spinal cord level, such as glutamate, Calcitonin gene-related peptide (CGRP), and substance P, is likely to be responsible for its analgesic effects [2]. Pregabalin is available in US and Europe as capsules (25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg) and as an oral solution (20 mg/ml), with recommended doses between 150 mg and 600 mg a day, split into 2 or 3 separate doses. Extended-release tablets for single daily administration are also available (82.5 mg, 165 mg, 330 mg) [2]. It has rapid absorption following oral administration, with peak plasma concentrations

occurring between 0.7 and 1.3 hours, and shows 90% bioavailability, independently of dose and administration frequency. Half-life is approximately 6 hours, with steady state achievement within 1 to 2 days [3, 4]. It mainly undergoes renal elimination (98% as unchanged drug), and posology adjustments are needed in patients with kidney failure (**Table 1** ) [5]. Side effects are less severe respect to other anti-epileptic drugs, being the most frequently reported somnolence, dizziness, dry mouth, angioedema, blurred vision, and weight gain [1]. Pregabalin is currently approved in US and Europe for the treatment of neuropathic pain deriving from diabetic neuropathy, post-herpetic neuralgia, and spinal cord injury, besides being recognized as an adjunctive therapy of partial-onset seizures in adults. Therapeutic indications have been expanded to generalized and social anxiety disorders, whereas only in the US it is FDA-approved for the treatment of fibromyalgia syndrome [6]. Off-label pregabalin uses include bipolar disorder, insomnia, restless legs syndrome, and chronic pain conditions other than those above listed, such as cancer pain and post-surgical pain [6]. Patients with Chronic Kidney Disease (CKD) often take pregabalin with heterogeneous therapeutical indications, such as neuropathic pain, pruritus, and restless legs syndrome [7]. Not least, pregabalin is gaining an emerging role for pre-emptive preoperative multimodal analgesia, with different randomized clinical trials showing its efficacy in reducing post-operatory pain and opioid consumption after different types of surgical interventions [8, 9]. Mostly in this context, given the pharmacokinetic profile of pregabalin, the start of Kidney Replacement Therapy (KRT) for Acute Kidney Injury (AKI) usually adds further complexity related to the additional extracorporeal clearance. Despite the limited available data, the implementation of the use of Therapeutic Drug Monitoring (TDM) of pregabalin may represent a useful tool to accurately tailor the pharmacological prescription [10-12].

We report here a case of a critically ill patient undergoing different KRT modalities for severe AKI in whom pregabalin levels in the course of different modalities were monitored by TDM.

**Case Report**

A 78 yr-old obese man (usual body weight 110 Kg, BMI 35 $kg/m^2$) was admitted to the Renal Intensive Care Unit (ICU) for oliguric AKI on stage 3b CKD (usual serum creatinine [Scr] concentration, 2 mg/dL, CKD-EPI eGFR 32.6 mL/min/1.73 $m^2$) associated with septic shock due to newly diagnosed infective endocarditis. His drug treatment included pregabalin, 50 mg twice daily, for severe neuropathic pain secondary to diabetic neuropathy. On admission, he complained of severe dyspnea and fatigue. Physical examination revealed a pyretic 118-Kg oliguric patient with severe peripheral edema and diffuse basal pulmonary rales. Blood pressure was 105/70 mmHg while on norepinephrine 16 mcg/min, with pulse rate 100 beats/min. Breaths were 28/min, with peripheral oxygen saturation at 97% while on non-invasive mechanical ventilation (BPAP modality, PSV 12 $cmH_2O$, PEEP 8 $cmH_2O$, $FiO_2$ 50%). APACHE II score was 30. Laboratory findings showed a stage 3 AKI with mild metabolic acidosis. Given the persistent oliguria associated with severe fluid overload unresponsive to the high-dose loop diuretic therapy and hemodynamic instability, KRT was started as Continuous Venovenous Hemodiafiltration (CVVHDF) with regional citrate anticoagulation (RCA), using the Prismax system (Baxter Renal Care, USA) and a polyacrylonitrile AN69 hemofilter (ST 150, 1.5 $m^2$, Baxter Renal Care, USA). A low concentration citrate solution (18 mmol/L; Regiocit, Baxter) was combined with a phosphate-containing solution, used as both dialysis and post-dilution replacement fluid (Biphozyl, Baxter) for a prescribed dialysis dose of 30 ml/Kg/h. Three days after, given the slow but progressive improvement of fluid overload, KRT modality was shifted to Sustained Low-Efficiency Dialysis (SLED) by using the same system and the same dialysis solutions, with a prescribed effluent volume of 100 ml/min. On the fourth ICU day, patient's hemodynamic status definitely improved, and KRT was thereafter continued as every other day conventional Intermittent Hemodialysis (IHD).

Given the reported neuropathic pain and aiming at reducing opioids consumption, chronic therapy with pregabalin was confirmed. Moreover, given the expected extracorporeal clearance, the prescribed pregabalin dose was increased at KRT start to 75 mg every 12 hours.

The evaluation of TDM of pregabalin in course of different KRT modalities was performed by Liquid Chromatography coupled with tandem mass spectrometry (LC-MS/MS system) (Shimadzu Italia, Milano) (**Supplemental Material 1** ) [11]. At the same dose administered (75 mg every 12 hours) a progressive re-

duction of pregabalin serum levels in course of prolonged KRT modalities (CKRT and SLED) was observed, while a rapid decrease was observed during IHD with a negligible post treatment rebound (**Figure 1** ).

**Discussion**

According to our knowledge, this is the first study reporting TDM of pregabalin in course of continuous and prolonged intermittent KRT in a critically ill patient. These modalities of KRT, often used as complementary therapies, are considered the preferred dialysis modalities for critically ill patients with AKI, especially in those with hemodynamic instability [13]. As each treatment session is performed over a long-time span, these KRT modalities allow for slower fluid and solute removal, with better hemodynamic tolerance and lower risk of rapid osmolal shift [14]. In addition, due to their extended duration, prolonged KRTs usually provides an efficient daily solute clearance [15]. As detailed in **Table 1** , pregabalin has small molecular weight, negligible protein binding and low volume of distribution, thus it is characterized by a significant theorical extracorporeal clearance by KRTs. Data regarding the target therapeutic concentration are still limited. Studies on patients with epilepsy with normal kidney function receiving 150-600 mg daily of the drug, reported a serum level ranging from 2 - 8 microg/mL [10-12, 16]. Optimal therapeutic plasma concentrations for neuropathic pain control have not been established yet. However, studies have demonstrated a dose-response relationship for pregabalin in the treatment of painful conditions, like post-herpetic neuralgia. Given the linear absorption of pregabalin, with plasma concentrations increasing proportionately with increasing dose, pregabalin plasma concentration stability likely plays a crucial role in analgesic effect maintenance [17].

Given the increased adoption of pregabalin also in the ICU, not only as a continuation therapy in patients with chronic neuropathic pain, but also in the setting of multimodal analgesia [6-8, 18], a great degree of attention should be required to avoid the risk of inadequate therapeutic concentrations. Indeed, given the prevalent renal metabolism, a dose adjustment is usually recommended in patients with impaired kidney function (**Table 1** ). However, according to the pharmacokinetic profile and in line with the different KRT modalities techniques, our data showed a slow but progressive reduction of pregabalin serum levels in course of the prolonged KRTs (CKRT and SLED,**Figure 1 A-B** ), while a more rapid and significant reduction during conventional IHD was observed (**Figure 1 C** ). In this regard, we found that when a modality of continuous KRT is applied for incident AKI (e.g. CVVHDF), the usual recommended pregabalin dose may become insufficient to maintain the therapeutic concentration range (**Figure 1A** ). Indeed, despite the double daily administration, a slow but progressive decline in serum levels was observed, as reported in a case of gabapentin intoxication treated with CKRT [19]. While in course of the SLED session serum levels remained within the suggested therapeutic range (**Figure 1B** ), a more severe reduction may be supposed with longer duration (e.g. 12-16 hours) and increased dialysis fluid rate (until 300 ml/min). Finally, as already previously reported in chronic hemodialysis patients [4, 5, 20], TDM data obtained during and after the IHD session confirmed a rapid reduction of serum concentration during the treatment session, along with a subsequent normalization after dialysis, also thanks to the double daily administration (**Figure 1C** ).

In conclusion, even though more data are needed to confirm our findings, the TDM of pregabalin may represent a useful therapeutic option in critically ill patients, especially in those requiring continuous or prolonged intermittent KRT. This approach could help to achieve the therapeutic effect while minimizing the risk of side effects.

**Conflict of Interest statement**

The authors declare that they have no conflict of interest.

**Financial Disclosure statement**

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**Legend to Figure**

**Figure 1 A-C.** Time course of serum pregabalin concentration at start, during and after one session of Continuous Kidney Replacement Therapy (CVVHDF modality) [1-A], one 8-hour session of Prolonged Intermit-

tent Kidney Replacement Therapy (SLED-f modality) [1-B] and one conventional Intermittent Hemodialysis (IHD) [1-C]. The Asterisks indicate the time points when pregabalin was administered during KRT. Abbreviations: CVVHDF, Continuous Venovenous Hemodiafiltration; SLED-f, Sustained Low Efficiency Dialysis filtration; KRT, Kidney Replacement Therapy.

**References**

Verma V, Singh N, Singh Jaggi A. Pregabalin in neuropathic pain: evidences and possible mechanisms. Curr Neuropharmacol. 2014 Jan;12(1):44-56.

doi: 10.2174/1570159X1201140117162802.

Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res. 2007 Feb;73(2):137-50.

doi: 10.1016/j.eplepsyres.2006.09.008.

Bockbrader HN, Radulovic LL, Posvar EL, et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol. 2010 Aug;50(8):941-50.

doi: 10.1177/0091270009352087.

Bouchard J, Yates C, Calello DP, et al; EXTRIP Workgroup. Extracorporeal Treatment for Gabapentin and Pregabalin Poisoning: Systematic Review and Recommendations From the EXTRIP Workgroup. Am J Kidney Dis. 2022 Jan;79(1):88-104.

doi: 10.1053/j.ajkd.2021.06.027.

Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol. 2003 Mar;43(3):277-83.

doi: 10.1177/0091270003251119.

Goodman CW, Brett AS. A Clinical Overview of Off-label Use of Gabapentinoid Drugs. JAMA Intern Med. 2019 May 1;179(5):695-701.

doi: 10.1001/jamainternmed.2019.0086.

Ishida JH, McCulloch CE, Steinman MA, Grimes BA, Johansen KL. Gabapentin and Pregabalin Use and Association with Adverse Outcomes among Hemodialysis Patients. J Am Soc Nephrol. 2018 Jul;29(7):1970-1978.

doi: 10.1681/ASN.2018010096.

Zhang Y, Wang Y, Zhang X. Effect of pre-emptive pregabalin on pain management in patients undergoing laparoscopic cholecystectomy: A systematic review and meta-analysis. Int J Surg. 2017 Aug;44:122-127.

doi: 10.1016/j.ijsu.2017.06.047.

Rai AS, Khan JS, Dhaliwal J, et al. Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients undergoing breast cancer surgery: A systematic review and meta-analysis of randomized controlled trials. J Plast Reconstr Aesthet Surg. 2017 Oct;70(10):1317-1328.

doi: 10.1016/j.bjps.2017.05.054.

Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs–best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008 Jul;49(7):1239-76.

doi: 10.1111/j.1528-1167.2008.01561.x.

Krasowski MD. Therapeutic Drug Monitoring of the Newer Anti-Epilepsy Medications. Pharmaceuticals (Basel). 2010 Jun 11;3(6):1909-1935.

doi: 10.3390/ph3061909.

Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018 51(1-02):9-62.

doi: 10.1055/s-0043-116492. Erratum in: Pharmacopsychiatry 2018; 51(1-02):e1.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int 2:1-138.

Griffin BR, Liu KD, Teixeira JP. Critical Care Nephrology: Core Curriculum 2020. Am J Kidney Dis. 2020 Mar;75(3):435-452.

doi: 10.1053/j.ajkd.2019.10.010.

Maynar Moliner J, Honore PM, Sánchez-Izquierdo Riera JA, Herrera Gutiérrez ME, Spapen HD. Handling Continuous Renal Replacement Therapy-Related Adverse Effects in Intensive Care Unit Patients: The Dialytrauma Concept. Blood Purif 2012; 34(2):177–185.

doi: 10.1159/000342064.

Berry D, Millington C. Analysis of pregabalin at therapeutic concentrations in human plasma/serum by reversed-phase HPLC. Ther Drug Monit. 2005 Aug;27(4):451-6.

doi: 10.1097/01.ftd.0000158874.54100.1a.

Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet. 2010 Oct;49(10):661-9. doi: 10.2165/11536200-000000000-00000.

Alles SRA, Cain SM, Snutch TP. Pregabalin as a Pain Therapeutic: Beyond Calcium Channels. Front Cell Neurosci. 2020 Apr 15;14:83.

doi: 10.3389/fncel.2020.00083.

19. Guddati AK, Zafar Z, Cheng JT, Mohan S. Treatment of gabapentin-induced myoclonus with continuous renal replacement therapy. Indian J Nephrol. 2012 Jan;22(1):59-61.

doi: 10.4103/0971-4065.83744

20. Yoo L, Matalon D, Hoffman RS, Goldfarb DS. Treatment of pregabalin toxicity by hemodialysis in a patient with kidney failure. Am J Kidney Dis. 2009 Dec;54(6):1127-30

doi: 10.1053/j.ajkd.2009.04.014.

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`Table_1.docx` available at https://authorea.com/users/505153/articles/584335-therapeutic-drug-monitoring-of-pregabalin-in-a-critically-ill-patient-with-acute-kidney-injury-undergoing-continuous-prolonged-intermittent-and-intermittent-kidney-replacement-therapy-modalities