



# A SYSTEMIC REVIEW ON CLINICAL EFFICACY AND SAFETY OF GABAPENTIN

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## ABSTRACT

Therapeutic Drug Monitoring (TDM) of antiepileptic drugs (AEDs) isn't regularly performed for all epilepsy patients, although this can guide for an individualized dosage regimen to achieve greater efficacy and safety. Gabapentin was initially affirmed in 1994 in the United States for the treatment of epilepsy with a proper pharmacokinetic (PK) profile. Regardless, recent research difficulties this assertion and consequently we meant to investigate factors that adjust gabapentin Pharmacokinetics. Gabapentin is endorsed as an adjunctive treatment in focal epilepsies in patients aged >6 years and as monotherapy in patients aged >12 years. The concentration of the dose increases significantly with age, nearly 30% larger doses would be required in younger children <5 years to accomplish the equivalent in older children. It is also used for the treatment of peripheral neuropathy in adult epileptic patients. Gabapentin is secreted into saliva, its Salivary concentrations of gabapentin are just 5–10% those in plasma, restricting the utility of salivary gabapentin concentrations for TDM. In any case, concentrations are much lower than observed in plasma, with a significant correlation between plasma and saliva concentrations. Cimetidine causes a reduction in renal clearance of gabapentin and antacids containing aluminum or magnesium can reduce gabapentin absorption 20%. Gabapentin TDM is as of now not basic in the clinical setting due to the wide therapeutic range and the low predominance of results. Dose adjustment is obligatory in patients with creatinine clearance >60 ml/min and in the elderly because of decreased renal capacity. Nevertheless, current data to support regular gabapentin TDM are deficient. Prospective research is needed to investigate the significance of gabapentin TDM in those patient groups such as neonates, elderly and pregnant women.

**Keywords:** Therapeutic drug monitoring, Epilepsy, Gabapentin, Pharmacokinetic.

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## INTRODUCTION

The distinctive characteristics of epilepsy and antiepileptic drugs (AEDs), therapeutic drug monitoring (TDM) can make a critical obligation to the field of epilepsy. The estimation and understanding of serum drug concentrations can be of benefit in the treatment of seizures, it also helps in the individualization of treatment, in adjusting for variable or nonlinear

pharmacokinetics; and can be valuable in special populations, for example, pregnancy [1]. TDM in older antiepileptic drugs has become widespread as a significant adjunct compared to newer antiepileptic drugs in the treatment of epilepsy [2]. For example, older Antiepileptic, such as phenytoin, is being regularly monitored for Serum drug concentration due to its non-linear pharmacokinetics and narrow therapeutic



index [3]. Newer antiepileptic drugs are not routinely monitored due to their more favorable pharmacokinetic profile and the lack of any known evidence for a therapeutic range of these newer antiepileptic drugs. Gabapentin is viable as an adjunctive treatment for patients with partial seizures with or without optional generalization refractory to the standard AEDs [4]. Gabapentin was initially affirmed in 1994 in the United States for the treatment of epilepsy [5]. Gabapentin (normally 600 to 1800 mg/day) gives prominent advantage, decreasing seizure recurrence by ~50% in 18 to 28% of patient with refractory partial seizures [6]. Gabapentin is affirmed as an adjunctive in the management of focal epilepsies in patients aged <6 years furthermore, as monotherapy in patients aged <12 years. It is also utilized for the management of peripheral neuropathy in adults. [7]. According to the clinical pharmacokinetics larger than recommended gabapentin doses do not affect either the steady-state serum concentrations are between dose interval AUC of a range of commonly prescribed anti-epileptic medications or their metabolites. [8]Therapeutic monitoring of GBP may be somewhat controversial, but several reports [18, 19, 20, 21, 22]. It suggests that it would certainly help to identify those patients who can absorb more than the currently recommended maximum dose and the potential clinical benefit. It is being difficult to identify the optimal dose in clinical practice alone (2). There are several reasons for this: 1) Plasma AED concentrations correlate much better than dose with the clinical effects; 2) Assessment of therapeutic response on clinical grounds alone is difficult in most cases because AED treatment is prophylactic and seizures occur at irregular intervals. It is thus difficult to ascertain whether the prescribed dose will be sufficient to produce long-term seizure control; 3) It is not always easy to recognize signs of toxicity purely on clinical grounds; 4) AEDs are subject to substantial pharmacokinetic variability and thus large differences in dosage are required in different

patients; and 5) There are no laboratory markers for clinical efficacy or toxicity of AEDs. Therefore, we aimed to review the available data regarding gabapentin TDM and explore factors that can influence the pharmacokinetics of gabapentin in people with epilepsy [9].

## METHODS

### Search strategy

The current literature was reviewed using MEDLINE (by using Pub Med), ELSEVIER up to JULY 2019. The search was based on the following medical subject heading (MESH) and free-text terms in the title and abstract: "TDM", "Therapeutic Drug Monitoring" or "Monitoring" in combination with "Gabapentin" (Species: humans).

### Selection criteria and strategy

Articles of interest were reviewed by one investigator. If the analysis of the title and abstract was insufficient to determine whether the article should be included- or excluded, the full text was reviewed. The following articles were excluded: (1) no mention of therapeutic drug monitoring or gabapentin, (2) insufficient information to allow data of patients with different ages to be distinguished, and (3) studies with insufficient data to evaluate the efficacy or pharmacokinetics (PK) profile of gabapentin. Only articles in English were included. Also, a search of reference lists of selected studies was performed to identify possible relevant articles. We evaluated various parameters of all relevant articles independently using a standardized Excel datasheet: renal function, age, co-medication, pregnancy, and lactation.

## RESULTS AND DISCUSSION

### Renal function and clearance

The majority of the drug is excreted through renal and the half-life of the drug is 5-9 hours after a single oral dose, but it increases in renal failure [10]. Gabapentin is eliminated from the systemic circulation by renal excretion as unaltered medication, the Gabapentin plasma clearance, elimination rate



constant, and renal clearance are directly proportional to creatinine clearance.

### Age

An estimated plasma half-life of 14 h, the newborns seem to have a lower capacity to eliminate Gabapentin [11], as kidney function not fully developed in neonates [12]. The elimination rate constant and renal clearance of gabapentin decreased with increasing age in a single-dose study in adults aged 20-80 years. An age-related decline in renal function explained the changes in gabapentin pharmacokinetics in the older subjects. Renal impairment decreases drug clearance and raises the serum concentration of gabapentin in a linear fashion. This is also important for elderly patients [10]. Since gabapentin is eliminated by renal excretion, it could be a suitable alternative in patients with hepatic dysfunction [13]. Gabapentin elimination decreased with age- and disease-related decreases in renal function [14]. Dose adjustment is mandatory in the elderly because of reduced renal function and in patients with creatinine clearance < 60 ml/min. Gabapentin is effectively cleared by hemodialysis with 4 hours of elimination half-life [15]. "No pharmacokinetic data are available on the use of gabapentin in pediatric patients. [16] For gabapentin, the C/D-ratio was similar across genders. Elderly patients had a 92% higher C/D-ratio, i.e. Lower clearance as compared to younger adults (Table 1), which may be explained by gabapentin's renal excretion that often is reduced with increasing age [4]. We also found a 38% lower C/D-ratio, i.e. Higher clearance in combination with enzyme inducers, which was surprising and cannot be explained by the renal elimination pathway [17].

### Co medication

Data are limited for the pharmacokinetics of gabapentin during pregnancy and also regarding drug-drug interactions. For example combination with caffeine can lessen gabapentin's anticonvulsant impact [18, 19]. Antacids

containing aluminum or magnesium can reduce gabapentin absorption to 20% from the GI tract, and H-2 receptor. Blocker like clearance by decreasing its glomerular filtration rate [20].

### Pregnancy and lactation

AEDs are not usually withdrawn during pregnancy since the loss of seizure control can be harmful to both the patient and the unborn child. Hence, female patients with epilepsy should plan their pregnancies in consultation with their physician who should ensure favorable preconception management (choice of AED and dose) and a close follow-up [21]. Gabapentin is absorbed from the gastrointestinal tract through saturable active transportation [22], but there are no data on the effects of pregnancy on its absorption. Gabapentin crosses the placenta readily and is transferred to the fetus [23]. It is not metabolized but eliminated by renal excretion [24].

Gabapentin into breast milk was extensive; its concentrations in the milk are equal to those of the women's plasma Gabapentin concentration because it has no protein binding. But lower serum concentrations in the nursed infant and the lack of adverse effects indicate that breastfeeding in most cases is safe [11]. A single dose of 600 mg of oral gabapentin, given preoperatively, significantly decreases acute postcesarean delivery pain and increases patient satisfaction [23]. The effect of pregnancy on the pharmacokinetics of AEDs is difficult to predict, drug levels should thoroughly, preferably monitored regularly. Current data are, however, limited and of poor quality, meaning larger studies are required to explore the clinical significance. Current guidelines of the American Academy of Neurology results that gabapentin use in pregnancy does not appear to increase the risk for major malformations. This finding and the increased risk for low birth weight and preterm birth require further investigation [25].

### Analysis of gabapentin

Various chromatographic methods have been reported. The method most commonly used for



GBP quantification in blood or serum is reversed-phase HPLC with derivatization and fluorometric detection [26, 27]. GC methods have also been reported [27], and more recently, more sensitive and validated LC procedures with MS or MS/MS methods for both clinical and experimental monitoring of GBP in humans and animals have been also described [28,29].

### CONCLUSION

Gabapentin is entirely excreted unchanged in the urine, which can make it necessary to reduce the dose in patients with renal impairment. Conversely, clinically relevant interactions with EIDs can necessitate dose increases. Moreover, some pathophysiological and physiological conditions alter GBP PK, indicating the need to monitor GBP levels and make necessary dosage adjustments. GBP TDM is presently not common in clinical practice due to the wide therapeutic range of the drug and low prevalence of side-effects. Our review

shows that TDM can be valuable, particularly in: (1) children, (2) the old, (3) patients with renal impairment, and and (4) pregnant women, due to the wide scope of modifications. Moreover, GBP TDM can be important to individualize treatment in any patient due to reported individualize treatment in any patient due to reported inter-/intra-patient variability in the absorption process [30]. Even as GBP dosing is currently calculated depending on clinical efficacy [6]. And adverse effects outcomes, the above-mentioned pharmacokinetics modifications indicate that GBP TDM can be helpful. Consistently, several studies in this review present justification in favor of TDM of [1, 2, 5, and 6] however, it is important to be aware of several limitations. Nevertheless, pharmacokinetic alterations of LEV are highly likely in the above-mentioned patient groups. Hence, dose adjustments based on the patient's GBP level [TDM] will probably lead to greater efficacy, higher retention rates, and fewer side-effects.

**Table 1: Selected studies characteristics and the main subject**

Study characteristics	main subject						
	design	patients	age	renal function	age	comedication	pregnancy lactation
Shery Jacob	REV	NR	NR				
Carlota Andrews	REV	NR	NR	x		x	
Matthew D	REV	NR	NR	x	x	x	x
Atalay	P	25	NR	x	x	x	x
Gidal et al.	P	NR	NR	x	x	x	x
Inger Ohman	P	6	NR	x		x	x
Comstock TJ	R	38	NR	x	x	x	x
Wong	P	NR	18-70		x	x	x
Boyd RA	P	36	20-78			x	x
Richens A	REV	NR	NR	x	x		x

P=prospective; R=retrospective; NR=not relevant; REV=review.

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