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Review on the relevance of therapeutic drug monitoring of levetiracetam

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ABSTRACT

Therapeutic Drug Monitoring (TDM) of anti-epileptic drugs (AEDs) is not routinely performed, although this can guide the dosage regimen to achieve greater efficacy and safety. Levetiracetam (LEV) has been introduced as an AED with an almost perfect pharmacokinetic (PK) profile. Nonetheless, recent research challenges this statement and therefore we aimed to explore factors that modify LEV PK.

Age and enzyme-inducing drugs (EIDs) appear to be major factors influencing the PK profile of LEV. Therefore, 30–50% lower dosages should be used in the elderly (> 65 years of age) and the dosing regimen should be guided by monitoring SDC (TDM). In contrast, higher LEV dosages are necessary in children aged between 2 months and 12 years (compared to adults) due to a 30–70% increase of LEV clearance (CL). Higher dosages are also required if a patient receives EIDs, again due to a higher CL of LEV (range 24–60%). This could also be true for pregnant women.

LEV TDM is currently not common in the clinical setting due to the wide therapeutic range and the low prevalence of side-effects. However, LEV dose should on the one hand be increased in certain physiological situations (pregnancy, neonates) and patients on EIDs (especially carbamazepine). On the other hand, dose reductions are necessary when the LEV CL is impaired (elderly). Nevertheless, current data to support regular LEV TDM are lacking. Prospective research is needed to explore the importance of LEV TDM in elected patient groups; i.e. neonates, elderly, patients on EIDs and pregnant women.

1. Introduction

In clinical practice, most dosing schemes for pharmacological treatment of epilepsy are based on efficacy (i.e. seizure reduction) and tolerability (i.e. side-effects). However, one can anticipate clinical effects (efficacy and tolerability) by measuring anti-epileptic drug (AED) serum drug concentrations (SDCs). This constellation is true for some older AEDs, such as phenytoin, since they imply regular monitoring of SDCs due to their non-linear pharmacokinetics and/or small therapeutic range [1]. For most new AEDs however, therapeutic drug monitoring (TDM) is not routinely used in clinical practice due to their more favorable pharmacokinetic profile and the lack of any known reference for the therapeutic range of these AEDs. Nevertheless, TDM could contribute to managing patients on polypharmacy and to individualizing therapy (due to reported interpatient variability) [2].

Levetiracetam (LEV) is one of the newer and most frequently used AEDs [3]. It has proven effective in treating multiple seizure types, in both adults and children older than one month. In addition, it can be valuable for acute seizure management [4] and LEV is the therapy of first choice in critically ill patients due to its rapid onset of action and minimal side-effect profile [5]. It was introduced in 1999 as an anti-epileptic drug with a clean pharmacokinetic profile with almost

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complete absorption from the small intestine, non-significant plasma protein-binding, negligible cytochrome P450 (CYP) metabolism, nearly total excretion by the kidneys and a good correlation between creatinine clearance and LEV clearance [6]. TDM is not routinely recommended for LEV [7]. Dosing of LEV might be more complicated in the presence of polypharmacy (especially with concomitant use of enzyme-inducing drugs [EIDs]) when CYP enzyme metabolism of LEV may be greater. Also, decreased kidney function in the elderly or chronic illness can lead to LEV accumulation and less straightforward dosing [5,8]. Conversely, in pregnant women there is an increased clearance of LEV [9]. TDM might have an important role in optimizing the individual drug regimen in these specific cases [10]. Therefore, we aimed to review the available data regarding LEV TDM and explore factors that can influence pharmacokinetics of LEV in people with epilepsy. In these specific patient groups, dose adjustments based on TDM could reduce side-effects and increase LEV efficacy and retention rates.

2. Methods

2.1. Search strategy

The current literature was reviewed using Cochrane, EMBASE, PROSPERO register and MEDLINE (by using PubMed) up to March 2018. 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 “levetiracetam” (*Species: humans*).

2.2. Selection criteria and strategy

Articles of interest were reviewed by one investigator (JS). If analysis of title and abstract was insufficient to determine whether the article should be in- or excluded, the full text was reviewed.

The following articles were excluded: (1) no mention of therapeutic drug monitoring or LEV SDC, (2) insufficient information to allow data of patients with different ages to be distinguished, and (3) studies without sufficient data to evaluate the efficacy or pharmacokinetic (PK) profile of LEV. Only articles in English or Dutch 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, comedication, pregnancy and lactation. The major findings are summarized in the tables (*see results section*).

3. Results and discussion

The literature search identified 76 abstracts, from which 54 articles were excluded as the data were insufficient for evaluation of the different parameters (*see methods* Section 2.2). To the remaining 22 relevant articles, 12 more were included after screening the references. Only 8 were prospective studies (8/34, i.e. 24%). All other study characteristics and their main subject(s) are summarized in Table 1. The similarities and contradictions between the manufacturer’s product guidance of LEV [11] and the experience in the clinical setting (based on our review) are provided as supplementary information.

3.1. Renal function and LEV clearance

The majority of the administered LEV dose is excreted unchanged by the kidneys (66% of the parent drug [6]). Renal impairment will decrease the clearance of LEV (LEV CL) and, therefore, increase the half-life ($t_{1/2}$) from 6 to 8 h to 10–11 h. This increase has also been documented in the older population due to an age-related decline in renal function. Even very mild renal dysfunction (creatinine clearance (CL_{CR}) of ≤ 70 mL/min/1.73 m^2) can lead to a 35% decrease of LEV CL [6].

One should be aware of significant changes in LEV CL in cases of renal impairment, since it will directly affect LEV SDC and thus the clinical efficacy and tolerability. Moreover, comedication and specific clinical situations (e.g. pregnancy) can affect the LEV CL (Table 2), as discussed in this review.

3.2. Age

Fifteen out of 34 studies (44%) examined the effect of age on LEV CL. At birth, the kidneys do not yet function optimally, which causes a relatively longer half-life of LEV in very young neonates (6–28 h) [30]. Nevertheless, LEV CL almost doubles one week after birth, and during the first year of life, LEV CL values may even be 60–70% higher than in adults. Overall, compared to adults, an average increase of LEV CL by 30–70% has been reported in children and the PK variability was more pronounced when receiving EIDs (7–13% higher LEV CL if also treated with CBZ) [16].

Thus, on a mg/kg basis, children (between 2 months and 12 years of age) should receive 30% higher LEV dosages than adults in order to achieve comparable SDC [16,20,24,27,30].

In the elderly, the significantly longer half-life (10–11 h) was believed to be due to the age-related decline in renal function, resulting in less LEV CL [6]. Consistently, Contin and colleagues suggested that the elderly population should receive lower LEV dosages: 30% and 50% for those aged 65–80y and > 80y, respectively, to achieve SDC comparable to that reported in adults [8]. A recent study also suggested a slower titration rate to prevent LEV-related adverse events in the elderly [35].

These age-related PK changes underline the need for careful monitoring of the clinical response to optimize LEV therapy, especially at the extremes of age. Although age appears to be a major influencing factor on LEV PK, other factors (e.g. comedication) should also be taken into account [30].

3.3. Comedication

The main metabolic pathway of LEV is non-CYP-dependent hydrolysis in the blood by a cytosolic amidase, considered to be non-inducible [2,13]. This results in the carboxylic acid metabolite, referred to as ucbLO57 (± 24% of the administered LEV dose) [1,15].

in vitro research predicted the low propensity of LEV to exhibit drug interactions since LEV and its major metabolite, UCBLO57, did not show any inhibitory effect on CYP enzymes (CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4 and 2A6), UDP-glucuronyltransferases and epoxide hydrolase [15]. Initial clinical research confirmed the absence of clinically relevant interactions with drugs that are metabolized by the above-mentioned enzymes, e.g. carbamazepine and valproic acid (VPA), which makes LEV a suitable add-on AED [1,13]. EIDs (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, ethosuximide or primidone) have, however, been shown to affect the PK of LEV: (1) lower AUC_{0-12}; (2) higher weight-normalized CL; (3) shorter half-life. In contrast, patients on VPA appeared to have higher LEV levels compared to those receiving other drugs, not considered to affect drug-metabolizing enzymes (gabapentin, lamotrigine, vigibatrin) [13,16].

More recent studies confirmed an increased CL of LEV (by 20–30%) in the presence of concomitant EID therapy. Twenty-one studies (54%) mentioned the possible effect of comedication on LEV CL, although only 17 of them actually investigated this. Twelve of these 17 (71%) demonstrated a clinically relevant effect on LEV CL by EIDs (Table 3). It is, therefore, possible that an EID induces the enzymatic hydrolysis of LEV, an effect that has already been described for other drugs metabolized by hydrolases [24]. The only recent study that did not demonstrate any effect of EIDs on the LEV CL was by Ito and colleagues; the high interindividual variability may have resulted in insufficient sensitivity to detect a possible effect [3].

In conclusion, LEV’s metabolism can be altered in patients who also

Table 1
Selected studies: characteristics and main subject.

	STUDY CHARACTERISTICS			MAIN SUBJECT			
	DESIGN	PATIENTS (n)	AGE (range)	Renal function	Age	Co-medication	Pregnancy and lactation
Patsalos [6]	P	16**	6-88 y	x	x	x	
May [12]	R	297	2-76 y	x		x	
Perucca [13]	R*	590	14-70 y	x		x	
Patsalos [1]	REV	NR	NR	x	x	x	
Contin [14]	P	100	16-50 y	x		x	
Touw [10]#	REV	NR	NR				
Patsalos [15]	R	40	19-73 y				
Fountain [16]	P	21	4-12 y	x	x	x	
Hirsch [17]	R§	308	16-88 y	x	x	x	
Otoul [18]	R	187	4-16 y	x	x	x	
Tomson [19]	P	15	21-37 y	x			x
Toublanc [20]	R	228	3 m-18 y	x	x	x	
Patsalos [7]	REV	NR	NR	x			
Westin [21]	R	20	21-38 y	x			x
Sabers and Tomson [22]	REV	NR	NR	x			x
Lopez-Fraile [23]	P	5	29-40 y	x			x
Dahlin [24]	R	103	0-18 y	x	x	x	
Thurman [25]	IECR	NR	NR	x			x
Freitas-Lima [26]	P	30	18–65 y	x		x	
Contin [8]	P	272	30-80 y	x	x	x	
Johannessen Landmark [27]	R	289	2-93 y	x	x	x	
Hoeritzauer [28]	C***	NR	NR	x			x
Mathew [29]	R	69	0-18 y	x		x	
Italiano and Perucca [30]	REV	NR	NR	x	x		x
Wright [4]	REV	NR	NR	x			x
Reisinger [9]	R§	27	15-43 y	x			x
Krasowski and McMillin [2]	REV	NR	NR	x	x	x	x
Stepanova [31]	P	42	19-69 y			x	
Naik [32]	R	330	1-64 y	x	x	x	
Cappellari [33]	R	1	36 y	x			x
Gupta [34]	R§	29	18-35 y	x		x	
[3]	R	225	1-89 y	x	x	x	
Theitler [35]	R	115	60-90 y		x		
Aldaz [36]	R	205	16-90 y		x	x	

P = prospective; R = retrospective; #general review of TDM; *pooled analysis 4 phase III double-blind trials; ** healthy volunteers; ***C = comment letter to the editor; §timing of blood draw (LEV serum drug concentrations) was not standardized; NR = not relevant; REV = review; IECR = ILAE epidemiology commission report; PK = pharmacokinetics.

Table 2
Influence of age and renal function on LEV CL.

AGE GROUP/CONDITION	TIME POINT	LEV CL (compared to adults 18–65 y)
Neonates	0-1 w	≤50% increase
Infants	0-1 y	60-70% increase
Child	1-18 y	30-60% increase
Elderly	> 65 y	20-60 % decrease
Renal impairment	All ages	> 35% decrease
Pregnancy	3rd trimester	> 50% increase
Postpartum	0-2 w	decrease to normal pre-pregnant levels

LEV CL = levetiracetam clearance; w = week(s); y = year(s); adjusted from Refs. [6,22,30,9].

receive EIDs. Increased LEV CL has been reported. Hence, when an EID is added, one might consider monitoring the serum LEV levels to avoid sub-therapeutic LEV levels that can lead to a reduction in its clinical efficacy [31].

3.4. Pregnancy and lactation

Eleven out of 34 studies (32%) investigated the effect of pregnancy and lactation on LEV CL. AEDs are not usually withdrawn during pregnancy since the loss of seizure control can be harmful for both the patient and the unborn child. Hence, female patients with epilepsy should plan their pregnancies in consultation with their physician who should ensure a favorable preconception management (choice of AED and dose) and a close follow-up [16]. LEV is increasingly used in women of child-bearing age due to its relatively better safety profile compared to older AEDs [38]. Hence, clinicians should be aware of the LEV PK alterations during pregnancy and postpartum.

In pregnant women, LEV CL can be elevated which could warrant TDM, especially during the last trimester. These changes in LEV CL can rise to 40% and higher during pregnancy, emphasizing the need to increase the dose to maintain therapeutic LEV levels [9,19,21,28].

In line with increasing LEV CL, LEV levels decreased by more than 35% compared to preconception levels which led to a dose increase (up to 37%) in 87% of the patients on LEV monotherapy [9]. Furthermore, Thurman and colleagues reported a LEV dose increase in 49% of the patients during pregnancy [25].

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 (AAN) state that TDM of LEV during pregnancy may be considered [9].

In addition, the effects of pregnancy on LEV levels differ significantly between the distinct cases (interpatient variability). Moreover, relevant fluctuating LEV levels across two pregnancies have been reported in the same person [33]. Finally, other pregnancy-related influences, like gastro-intestinal disorders (hyperemesis gravidarum), should be considered [4].

After pregnancy, a rapid increase of LEV levels appears during the first two weeks postpartum which necessitates rapid dosage reductions [21,23].

Table 3
Influence of comedication.

REFERENCE AUTHOR	STUDY DESIGN	EFFECT	EIDs	LEV CL		VPA CL EIDs	VPA	LEV CL	VPA CL
Patsalos [6]	P	strong	EIDs*	43% higher		ND	ND	ND	ND
Perucca [13]	R**	modest (NS)	PHT-CBZ-OXC-PB-PRM	higher		ND	modest (NS)	lower	ND
May [12]	R	strong	PHT-CBZ-OXC	60% higher		ND	NS	NS	ND
Contin [14]	P	strong	PHT-CBZ-PB	30% higher		ND	NS	NS	NS
Fountain [16]	P	modest (NCR)	CBZ*	10% higher		NS	NS	NS	NS
Hirsch [17]	R	strong	PHT-CBZ-PB-PRM	24% higher		ND	ND	ND	ND
Otoul [18]	R	NS	EIDs	NS		NS	ND	ND	ND
Toublanc [20]	R	modest	EIDs	higher		ND	ND	ND	ND
Dahlin [24]	R	strong	PHT-CBZ-OXCPB-ETS	30% higher		ND	NS	NS	NS
Freitas-Lima [26]	P	strong	PHT-CBZ-PB	25% higher		ND	ND	ND	ND
Contin [8]	P	strong	PHT-CBZ-OXC-PB	36% higher***		ND	ND	ND	ND
Johannessen Landmark [27]	R	strong	EIDs	25% higher		ND	ND	ND	ND
Stepanova and Beran [31]	P	strong	CBZ	higher		NS	NS	NS	lower
Mathew [29]	R	strong	EIDs	higher	ND		NS	NS	NS
Naik [32]	R	strong	EIDs	higher	ND		NS	NS	NS
[34]	R	strong	EIDs	57% higher	ND		modest (NS)	lower	ND
Ito [3]	R	NS	PHT-CBZ-PB	NS	ND		ND	ND	ND
Aldaz [36]	R	strong	CBZ-OXC-PB	44% higher		ND	ND	ND	ND

P = prospective; R = retrospective; EIDs = enzyme inducing drugs (not defined); LEV = levetiracetam; LEV CL = levetiracetam clearance; ND = not determined; NS = no significant effect; NCR = no clinical relevance; VPA = valproic acid; PB = phenobarbital; PHT = phenytoin; CBZ = carbamazepine; OXC = oxcarbazepine; PRM = primidone; ETS = ethosuximide; *compared to the VPA-treated group; **pooled analysis (4 phase III double-blind trials); ***in the non-elderly group.

Relevant levels of LEV can be found in breast milk, in concentrations similar to maternal SDCs. Nonetheless, infant SDCs during prolonged breastfeeding remained very low (i.e. < 15% of the maternal SDC) [27,30]. This finding indicates an efficient elimination in newborn infants [22].

In conclusion, evidence of LEV TDM during and after pregnancy is scarce, but it has been clearly demonstrated that LEV levels can alter significantly leading to a possible increased seizure risk [28].

4. Conclusions

LEV is predominantly excreted by the kidneys, which can make it necessary to reduce the dose in patients with renal dysfunction. Conversely, clinically relevant interactions with EIDs can necessitate dose increases. Moreover, some physiological and pathophysiological situations alter LEV PK, indicating the need to monitor LEV levels and make proper dosage adjustments.

LEV TDM is currently not common in clinical practice due to the wide therapeutic range of the drug and low occurrence of side-effects [7]. Our review shows that TDM can be useful, especially in: (1) neonates, (2) the elderly, (3) patients on EIDs and (4) pregnant women, due to the wide range of alterations in LEV CL (range 20–70%). Moreover, LEV TDM can be valuable to evaluate compliance [2,32] but also to individualize treatment in any patient due to reported interpatient variability [3,7,27,32]. Even as LEV dosing is currently guided by clinical efficacy and adverse effects outcomes, the above-mentioned pharmacokinetic alterations indicate that LEV TDM can be useful. Consistently, several studies in this review clearly present justifications in favor of TDM of LEV [8,9,17,23,29,32], however, it is important to be aware of several limitations. First, we identified only a few prospective studies (8/34, 24%). Second, prospective studies investigating whether TDM of LEV leads to greater efficacy or better tolerability in clinical practice are lacking. Third, the outcome measure differed between studies, making a direct comparison difficult. Fourth, three of the included studies [9,17,34] did not report the timing of the blood draw. LEV SDC should be the trough concentration (immediately before the next dose) since large fluctuations in LEV SDCs are possible due to its short half-life (6–8 h) [1]. Future research should therefore standardize the sampling time in relation to the dose [37]. Finally, there is no clear correlation between LEV SDC and efficacy/tolerability that is consistent to the broad therapeutic range of LEV (12–46 micrograms/mL), established by the International League Against Epilepsy (ILAE) [7].

Nevertheless, pharmacokinetic alterations of LEV are highly likely in the abovementioned patient groups. Hence, dose adjustments based on the patient's individual LEV level (TDM) will probably lead to greater efficacy, higher retention rates and fewer side-effects.

Our review clearly shows the potential role of LEV TDM at the extremes of age, in patients on EIDS and in pregnant women. Whether the clinical value is significant, however, has yet to be confirmed by further prospective research.

Conflicts of interest

The authors have no conflict interest directly relevant to the content of this research.

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