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Short communication

Experience from therapeutic drug monitoring and gender aspects of gabapentin and pregabalin in clinical practice

Cecilie Johannessen Landmark [a,b,c,*], Georg Beiske [a], Arton Baftiu [d], Margrete L. Burns [b,c], Svein I. Johannessen [b,c]

[a] Department for Pharmacy and Biomedical Science, Oslo and Akershus University College, Norway
[b] Department of Pharmacology, Oslo University Hospital, Oslo, Norway
[c] National Center for Epilepsy, Oslo University Hospital, Sandvika, Norway
[d] Norwegian Medicines Agency, Oslo, Norway

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ABSTRACT

Purpose: Gabapentin and pregabalin are antiepileptic drugs (AEDs) with epilepsy and neuropathic pain indications. The purpose of this study was to investigate pharmacokinetic variability of gabapentin and pregabalin and indications for therapeutic drug monitoring (TDM) in clinical practice with focus on gender aspects.
Method: Anonymous data from routine TDM-service at the National Center for Epilepsy regarding serum concentration measurements of gabapentin and pregabalin, 2009–2013, were utilised. All included samples were drug-fasting in the morning at steady-state.
Results: In total, 356 patients were included; gabapentin 189 (66% women), average age 53 years and pregabalin 167 (56% women), average age 50 years. For gabapentin, mean serum concentration/dose(C/D)-ratio was similar across genders. Only 13% of the patients had concentrations above the lower limit of the reference range (70–120 μmol/L), which indicates a need for reevaluation of the reference range. For pregabalin, the C/D-ratio in women (0.08 ± 0.06) was 42% higher than in men (0.056 ± 0.05; $p < 0.05$). The pharmacokinetic variability (C/D-ratio) was >100-fold for both gabapentin and pregabalin. An indication of use (epilepsy/pain/other) was stated in only 26% of the cases ($n = 94$). Epilepsy was assumed as indication when other AEDs were also measured (50% of patients). This was similar for both genders and for both AEDs. Indications for TDM were stated in 155 cases (44%) and were similar for gabapentin and pregabalin.
Conclusion: Gabapentin and pregabalin are more used in women than in men, and routine use of TDM is most common in patients with epilepsy. Pharmacokinetic variability is extensive, highlighting a need for individualisation of therapy regardless of indication.

1. Introduction

Gabapentin and pregabalin are antiepileptic drugs (AEDs) with epilepsy and neuropathic pain indications. Pregabalin is also approved for generalised anxiety disorder. Previous population-based studies in Norway have shown that these two AEDs only have minor use in epilepsy and most extensive and still increasing utilisation is in neuropathic pain [1,2]. Thus, many new patients are introduced to these AEDs. Implementation of therapeutic drug monitoring (TDM) reveals pharmacokinetic variability in different patient groups and needs further investigation in clinical practice, regarding possible gender differences and age-related changes [3,4]. The proposed reference ranges for gabapentin vary from 10 to 70 (lower limit) to 120 (upper limit) μmol/L, and for pregabalin it is 10–30 μmol/L. The term "individual reference concentrations" has been proposed for AEDs [3] because TDM is a useful tool to individualise treatment, regardless of established therapeutic range or whether the indication is epilepsy or neuropathic pain.

The purpose of this study was to investigate pharmacokinetic variability of gabapentin and pregabalin and indications for TDM in clinical practice with focus on gender aspects.

* Corresponding author at: Institute of Pharmacy and Biomedical Science, Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences, Pilestredet 50, N-0167 Oslo, Norway. Tel.: +47 67236279.
E-mail address: cecilie.landmark@hioa.no (C. Johannessen Landmark).

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2. Methods

Anonymous data from routine TDM-service at the National Center for Epilepsy regarding serum concentration measurements of gabapentin and pregabalin, 2009–2013, were utilised.

The Norwegian Prescription Database (NorPD) [5] was used to document the total number of patients with prescriptions of gabapentin or pregabalin, gender and age (2009–2013).

2.1. Study material and analyses

The data regarding serum concentration measurements and the use of AEDs were retrieved retrospectively from a TDM database, including samples from the center and elsewhere in Norway (2009–2013). The most recent measurement of AEDs was included for each patient. The analyses were validated using routine liquid chromatographic methods at our department. All included samples were drug-fasting in the morning at assumed steady-state concentrations. All patients were anonymised, and data regarding gender, age, use of AEDs, dose and serum concentration were collected. The study was approved by the Regional Committee for Medical and Health Research Ethics, Norway.

2.2. Calculations and statistics

The concentration/dose (C/D-ratio) relationships were calculated to demonstrate pharmacokinetic variability of the two drugs. Patients ≥65 years were regarded as elderly. C/D-ratio is an inverse proportional expression of clearance. Mean values and standard deviations are presented. Enzyme-inducing comedication was defined as carbamazepine, phenobarbital and phenytoin, and compared to non-inducing comedication/monotherapy [6].

Two-sided Students' t-test with unequal variance was used to calculate significant differences between two groups ($p < 0.05$).

3. Results and discussion

3.1. Patient characteristics

In total, 356 patients were included; gabapentin 189 (66% women), average age 53 years and pregabalin 167 (56% women), average age 50 years. There were 86 patients regarded as elderly (≥65 years), which is 24% of the total population. The mean ages in the TDM database tended to be lower than in the country as a whole (Table 1). Gabapentin was used more than pregabalin in Norway. For both drugs there were 59–60% women users in the population as a whole, which is similar to the results from the TDM database (56–66%, Table 1).

The pharmacokinetic variability (C/D-ratio) was >100-fold for both gabapentin and pregabalin (Fig. 1a and b). Factors contributing to variability, age, gender and comedication are presented for each drug.

Table 1
Characteristics of the patient population and comparison with the Norwegian Prescription Database.

Characteristics	TDM data		Norwegian Prescription Database	
	Gabapentin	Pregabalin	Gabapentin	Pregabalin
Gender (w/m)	Total $N = 189$ 66% w/34% m	Total $N = 167$ 56% w/44% m	Average/year $N = 26.265$ 60% w/40% m 2008: 20 407 patients; 2013: 30 962 patients	Average/year $N = 17.446$ 59% w/41% m 2008: 17 117 patients; 2013: 19 638 patients
Age (years)	Avg 53 years Elderly 30 w (24%), 23 m (36%)	Avg 50 years Elderly 19 w (20%), 14 m (19%)	58.3 w, 56.5 m	58.1 w, 55.6 m
Doses (mg/day)	1744 mg ± 1029 w 1789 mg ± 1106 m	334 mg ± 117 w 387 mg ± 207 m	NA	NA
C/D-ratios				
Gender	0.027 ± 0.03 w, 0.029 ± 0.03 m	0.08 ± 0.06 w 0.056 ± 0.05 m*	NA	NA
Age, elderly vs younger patients	0.044 ± 0.055 vs 0.023 ± 0.0027**	0.11 ± 0.007 vs 0.063 ± 0.006**	NA	NA
Enzyme-inducing comedication vs non-inducing/ monotherapy	$N = 19$, 0.018 ± 0.008 vs $N = 170$, 0.029 ± 0.003**	$N = 21$, 0.049 ± 0.04 vs $N = 146$, 0.075 ± 0.007**	NA	NA
Indications				
For TDM			NA	NA
Routine	44 patients	43 patients		
Adverse effects	13	13		
Dose adjustment	9	9		
Therapy failure	12	5		
Acute intoxication	2	1		
Misuse	2	0		
Driving licence	1	0		
Clinical indication			NA	NA
Neuropathic pain	12 w/5 m	14 w/7 m		
Epilepsy	13 w/9 m	9 w/11 m		
Psychiatry	3 w/0 m	3 w/1 m		
MS	2 w/1 m	0 w/1 m		
Migraine	1 w/1 m	1 w/0 m		
	In total 47 patients Other AEDS 46%	In total 47 patients Other AEDS 56%		

Enzyme-inducing comedication (carbamazepine, phenobarbital, phenytoin). C/D-ratio, concentration/dose ratio; NA, not applicable; w, women; m, men.
* Statistically significant changes, $p < 0.05$.
** Statistically significant changes, $p < 0.01$.