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Short communication

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

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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.

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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, $p < 0.01$.

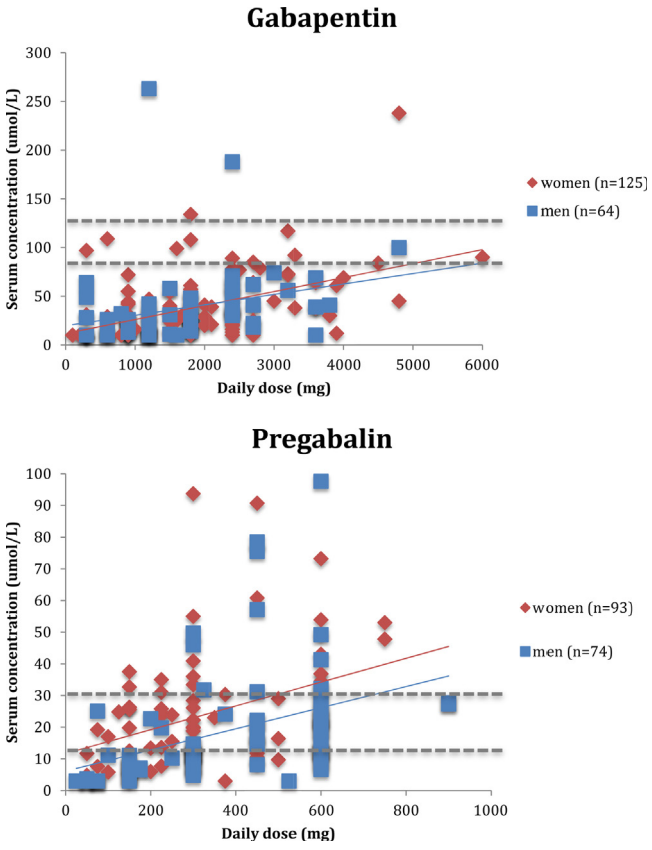

Fig. 1. (a) Dose and concentration relationship of (a) gabapentin (n = 189), ref. range (70–120 μmol/L) and (b) pregabalin (n = 167), ref. range (10–30 μmol/L).

3.2. Gabapentin

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 [7] (Table 1). In a study of 41 children/young adults no effect of concomitant enzyme inducers was reported [8]. Of the five patients with concentrations above 120 μmol/L, there were two women and three men.

A large number of patients (87%) had serum concentrations below the lower limit of the proposed reference range (70 μmol/L), which could result in unsatisfactory seizure control or pain relief. Clinical data of effect and tolerability were, however, not accessible from our database. This indicates a need to reevaluate the reference range. There is a limited capacity of absorption of gabapentin and large inter-/intra-patient variability in the absorption process. A mean bioavailability of 49% was reported by Gidal et al. [9]. The present results show many low concentrations and more frequent use of TDM indicated by therapy failure in users of gabapentin than in pregabalin, which may illustrate that many patients are not optimally controlled. A dose of gabapentin does not correlate to effect if it is not absorbed. Another explanation could be poor adherence or non-continuous use.

Some laboratories use a lower limit of 10–20 μmol/L, whereas our laboratory uses 70 μmol/L, based on early observations of patients in clinical practice. In the present study, 35% of the patients had concentrations below 20 μmol/L (Fig. 1a). A lower limit may not be necessary, and may be misleading for the clinicians, as the patient may have a clinical effect even below the reference range [3].

3.3. Pregabalin

For pregabalin the *C*/*D*-ratio in women was 42% higher than in men ($p < 0.05$), although the mean doses were similar (Table 1). The higher number of elderly women could partly explain this finding due to lower elimination (80%). Another explanation could be that higher doses than prescribed may have been taken. There was also a similar decrease in *C*/*D*-ratio of 35% in combination with enzyme inducers, similar to gabapentin (Table 1). A previous study also demonstrated extensive variability with pregabalin in 167 adult patients with epilepsy, a decreased elimination in older patients and a similar effect with enzyme inducers as we found [10].

The variability in serum concentrations was also extensive for pregabalin, as 21% of the patients had serum concentrations below the lower limit of 10 μmol/L and 18% had concentrations above the upper limit of 30 μmol/L (Fig. 1b). Some patients tolerate concentrations above the proposed range and even need it for optimal clinical efficacy. On the other hand, this also calls for attention to the possibility of misuse, tolerance and dependence of pregabalin, reported in international databases [11]. Of the 34 patients with concentrations above 30 μmol/L, there were 22 women. This finding calls for attention regarding a possibility of use of higher doses than prescribed.

Reasons for the extensive variability in pharmacokinetics presented include increased age and possible reduced renal function, gender, and concomitant treatment with enzyme-inducing AEDs.

3.4. Indications

Indications for TDM were stated in 155 cases (44%) and were similar for gabapentin and pregabalin, except for more therapy failure indications with gabapentin (Table 1).

A clinical indication was stated in only 26% of the cases (epilepsy/pain/minor indications) (Table 1). Since serum concentrations of other AEDs were measured in about 50% of patients we assume an epilepsy indication in many of these patients. The results were similar between gender and AEDs. This means that many of the few patients that use gabapentin or pregabalin for epilepsy in Norway have implemented TDM, but few of the patients treated for neuropathic pain.

The data from the NorPD demonstrated an increase in the patient populations of gabapentin and pregabalin of 52% and 15%, respectively (2009–2013). In Norway, gabapentin is the preferred drug of the two for reimbursement of neuropathic pain treatment, which may explain this finding.

3.5. Clinical implications

Patients treated for neuropathic pain often use other CNS-active drugs (benzodiazepines/opioids), and thus pharmacodynamic interactions are of importance. Pharmacokinetic interactions are not a major concern due to renal excretion of both drugs, but still we observed a more than 30% decrease in *C*/*D*-ratios of both drugs with enzyme inducers. This may be of clinical significance in some patients. Gabapentin has variable absorption, which is possibly revealed by low concentrations in many of the cases. Many of the patients are elderly, and dosage reductions may be necessary due to declining kidney function. Gabapentin has level A evidence for use in the elderly with focal epilepsies [12], although it does not seem to be frequently chosen in clinical practice. High serum concentrations of pregabalin in

women are most predominant, and this calls for concern regarding possible use of higher doses than prescribed.

In conclusion, the pharmacokinetic variability is extensive, elucidating a need for individualisation of therapy and TDM. Age, gender and enzyme inducers are contributing factors. The low concentrations seen with gabapentin form the basis for reevaluation of its reference range. Gabapentin and pregabalin are more used in women than in men, with the most common practice of applying TDM in patients with epilepsy. Regardless of indication, TDM can be useful in acute and routine situations.

Conflict of interest statement

The authors have no conflicts of interest or any financial disclosures regarding this manuscript.

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