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Long-term follow-up with therapeutic drug monitoring of antiepileptic drugs in patients with juvenile myoclonic epilepsy

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ABSTRACT

Background and purpose: Patients with juvenile myoclonus epilepsy (JME) may experience uncontrolled seizures and challenges regarding adherence. Implementation of therapeutic drug monitoring (TDM) may contribute to individualization of the therapy with antiepileptic drugs (AEDs). The purpose of this study was to investigate how the treatment of patients with JME is monitored and to demonstrate pharmacokinetic variability within and between patients with a long-term TDM approach.

Method: Retrospective data from patients with JME from the TDM-database at Drammen Hospital and the National Center for Epilepsy in Norway (2007–2018) were included.

Results: Data from 80 of 90 patients with JME using AEDs with TDM measurements was included (88%, 49/31 women/men aged 14–39). One third (27, 33%) was seizure free, 19 (24%) had generalized tonic-clonic seizures, and 53 (66%) myoclonic seizures during the last year. The most common AEDs measured included lamotrigine, valproate, and levetiracetam. Long-term TDM demonstrated variability over time expressed as intra-patient median values and inter-patient ranges of 19% (7–47) for valproate, 43% (10–83) for lamotrigine and 35% (6–111) for levetiracetam. Fifteen pecent (83/563) of serum concentrations were below the reference ranges and clould be due to variable adherence. Comedication with valproate for lamotrigine and pregnancy contributed to variability. The applicability is illustrated in a case of 10 years' follow-up in a young woman.

Conclusion: There was extensive pharmacokinetic variability of AEDs in and between patients with JME. A long-term TDM approach may contribute to closer monitoring of patients with JME and be used as a practical tool during clinical consultations.

1. Introduction

Patients with juvenile myoclonic epilepsy (JME) may experience challenges in the treatment with antiepileptic drugs (AEDs) when it comes to self-initiated withdrawal, adverse effects and impulsive decision making that may affect adherence (Wandschneider et al., 2012, 2013, Zamarian et al., 2013; Syvertsen et al., 2019a, b). JME is a generalized epilepsy and the most common epilepsy type affecting adolescents. It is characterized by myoclonic jerks, predominantly after awakening, aggravated by sleep deprivation and stress (Kasteleijn-Nolst Trenite et al., 2013; Syvertsen et al., 2017). The majority of patients experience occasional generalized tonic-clonic seizures (GTCS), and about one third have absence seizures (Genton et al., 2013). Patients with JME often use AEDs for their whole life (Janz, 1989; Panayiotopoulos et al., 1994). This may imply a long-term burden of AEDs with a range of adverse effects that may affect adherence and quality of life.

AEDs exhibit extensive pharmacokinetic variability, and most of the drugs are susceptible to be involved in pharmacokinetic interactions (Johannessen Landmark et al., 2012; Johannessen Landmark et al., 2016, Johannessen Landmark et al., 2010, Johannessen Landmark and Patsalos, 2010). According to the most recent updates on evidence-based guidelines, valproate, lamotrigine and levetiracetam are the main AEDs used in generalized epilepsies (Nunes et al., 2012; Glauser et al., 2013). The recent restrictions and ban of the use of valproate in women now need careful considerations (EMA, 2018), due to dose-dependent

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teratogenic effects and long-term effects on cognitive development on one hand, and safety risks of uncontrolled generalized seizures and risk of maternal death on the other (Edey et al., 2014; Tomson et al., 2015, 2016, Christensen et al., 2018). Equally effective AEDs as valproate to treat generalized epilepsies may be difficult to find.

Therapeutic drug monitoring (TDM) is a means to adjust for pharmacokinetic variability, to control for variable adherence and to serve as a quality assurance of the treatment (Johannessen Landmark et al., 2012; 2016; WHO, 2003; Samsonsen et al., 2015) and has a long tradition as part of a comprehensive care approach in epilepsy in Norway. We have shown pronounced pharmacokinetic variability among women using valproate and how TDM may be used to elucidate variability (Johannessen Landmark et al., 2017, 2018). A recent study from an extended study population demonstrated that 40% of patients with JME had withdrawn AEDs, the majority against medical advice (Syvertsen et al., 2019b). Close monitoring of the treatment may therefore be of special importance for these patients.

The purpose of the present study was to investigate how the treatment of patients with JME is monitored, to demonstrate pharmacokinetic variability within and between patients by a long-term TDM approach and how this may be used as part of the clinical follow-up.

2. Methods

2.1. Patients, data material and calculations

The patients were recruited from Drammen Hospital during 2016-2018. Drammen Hospital serves all patients with epilepsy in Buskerud County, comprising 9% of Norway's total population. All the included patients had a confirmed JME diagnosis and were aged 14–40 years, as described in detail by Syvertsen et al. (2017, 2019a,b). Routine TDM data were collected retrospectively from the database at the Section for Clinical Pharmacology, National Center for Epilepsy, Oslo University Hospital and from medical records at Drammen Hospital. To study long-term monitoring in patients, data from January 2007 to April 2018 were used. Measurements of AEDs at assumed steady-state conditions were included, based on blood samples that were drawn drug-fasting in the morning as a standard procedure.

Serum concentrations, doses and concentration/dose (C/D) ratios were calculated as means/medians with standard deviation (SD)/minimum-maximum range to demonstrate variability. As an expression of pharmacokinetic variability, the value of C/D-ratio maximum/minimum was used, as previously described (Johannessen Landmark et al., 2017, 2018). To assess to what extent lamotrigine was affected by concomitant use of valproate, the mean C/D ratios were compared at the last visit available of those who used the combination versus those who used lamotrigine in monotherapy or with other AEDs without enzyme inhibiting properties. Measurements at pregnancy or where the use of enzyme inducing oral contraceptives were used were excluded.

Long-term TDM data were used to express intra- and interpatient variability, by use of C/D-ratios for individual patients with multiple measurements (at least three measurements) and between individuals. The coefficient of variation (CV) between patients were calculated based on Conway et al. (2017), as the % of the mean C/D ratio/SD x 100 for the three most commonly used drugs, valproate, lamotrigine and levetiracetam. The median value was an expression for intra-patient variability, whereas the range from minimum to maximum value for one drug shows the inter-patient variability between patients in that group.

2.2. Statistical methods

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 23. Independent Students' t-tests were used for comparison of continuous variables (mean doses and serum concentration relationships), and Chi-Square test were used for comparison of categorical variables, with Yate's Continuity Correction for 2×2 tables. When expected cell count was less than five in any cell, Fisher's Exact Probability test was used. A linear regression model (r^2) was used to evaluate serum concentration and dose relationships and statistical significance evaluated by Anova, where p-values ≤ 0.05 were considered to be statistically significant.

2.3. Ethical considerations

The study was approved by the Regional Committee for Medical Research Ethics, South East Norway (no. 2013/1027) and the data protection officer of Drammen Hospital. Written informed consent was obtained from all participants. Additional consent was given by the patient in the case to elucidate pharmacokinetic variability with long-term TDM.

3. Results

3.1. Patients

Ninety patients were classified with JME. In 80 (88%) TDM measurements had been performed. Mean age was 26 years, and 60% were women. Demographic and clinical characteristics are summarized in Table 1. Only one third was seizure free the last year, and one fourth had GTCS. Two thirds used monotherapy and 24% used two or three AEDs. There were no significant differences between the 80 patients using AEDs who were included and the ten patients where no serum concentrations were measured, regarding gender and age distribution, seizure debut and type and use of AEDs (data not shown).

3.2. Use of therapeutic drug monitoring

Data on use of TDM for nine different AEDs were available. There was a wide variability of the number of serum concentration measurements that had been performed during a period of 10 years, from 1 to 61; 21 (26%) had at least 10 measurements recorded over the years. The distribution between the two laboratories involved was similar. Measurements from 1 to 3 AEDs were performed. The most commonly AEDs requested for TDM analysis included lamotrigine, valproate and levetiracetam, as presented in detail (Table 2).

Pregnancy is an important indication for TDM requests. Data were

Table 1
Patient characteristics for the 80 included patients.

Characteristics	Numbers
Gender, n (%)	
Women	49 (61)
Men	31 (39)
Age, years	
Mean (SD)	26 (± 7)
Median (range)	26 (14-39)
Seizure debut, age, years	
Mean (SD)	15 (± 3)
Median (range)	14 (6-23)
Seizure type last year, n (%)	
Seizure free	27 (33)
Myoclonia	53 (66)
Generalized tonic-clonic seizures (GTCS)	19 (24)
Present AEDs, n (%)	
0	9 (11)
1	53 (67)
2	16 (20)
3	2 (2)

AEDs = antiepileptic drugs.

Table 2
Use of TDM of AEDs in JME.

Details of TDM data (n = 80)	Total number
Initial number of TDM measurements	742
Reasons for exclusion	
Lacking dose	49
Not drug-fasting or not at steady-state	10
Below the limit of detection	9
Total number of included measurements	674
Number of measurements per patient	
Mean (SD)	8.4 (8.4)
Median (min-max)	6.5 (1-61)
Measurements performed at:	
Drammen Hospital (%)	378 (56%)
The National Center for Epilepsy (%)	296 (44%)
Number of measurements per AED (number of patients)	
Lamotrigine	249 (44)
Valproate	216 (43)
Levetiracetam	98 (29)
Topiramate	41 (4)
Zonisamide	35 (4)
Ethosuximide	13 (2)
Oxcarbazepine	8 (8)
Carbamazepine	5 (5)
Clobazam	5 (5)
Brivaracetam	0 (3)*
TDM during pregnancy	
Number of pregnancies/women	13 / 10**
Number of measurements	1-7
Measurements before, all trimesters, after birth	4
Monotherapy/ polytherapy	8 / 2***
Lamotrigine	5
Levetiracetam	4
Valproate	2
Zonisamide	1
Long-term TDM	
Variability over time, CV%, intra-patient median values and inter-patient ranges	
Valproate	19 (7-47) %
Lamotrigine	43 (10-83) %
Levetiracetam	35 (6-111) %

AEDs = antiepileptic drugs, TDM = therapeutic drug monitoring, JME = juvenile myoclonic epilepsy. *3 patients used brivaracetam, but the analyses was not yet established at the time of data collection. **1-3 pregnancies per woman.** 2 patients used 2 AEDs. CV%= Coefficient of variation, mean C/D ratio/SD x 100% as an expression of intrapatient variability.

provided from 13 pregnancies in 10 women, i.e. 20% of the included women. Data from pre-pregnancy throughout all trimesters and post partum were only available in four cases, pointing out incomplete follow-up in the majority of cases. The available data are given in Table 2, and the corresponding C/D-ratios are marked in Fig. 2 (Table 3).

3.3. Pharmacokinetic variability of the most commonly used AEDs

For the three most commonly used AEDs, there was an extensive variability in dose and serum concentration linear relationships both for women and men as illustrated in figure, for valproate (r^2 = 0.195 for women and 0.215 for men), lamotrigine (r^2 = 0.024 for women and 0.084 for men) and levetiracetam (r^2 = 0.465 for women and 0.220 for men). Significant linear relationships between doses and serum concentrations were demonstrated for valproate ($p < 0.0005$) and levetiracetam ($p < 0.0005$), but not for lamotrigine ($p = 0.402$).

For valproate there was a significantly lower daily dosage in women than in men ($p < 0.05$), but the obtained serum concentrations were similar. For the two other drugs there were no such gender differences.

Table 3
Details of dosage and serum concentration relationships of the three most commonly used AEDs, valproate, lamotrigine, and levetiracetam in women and men.

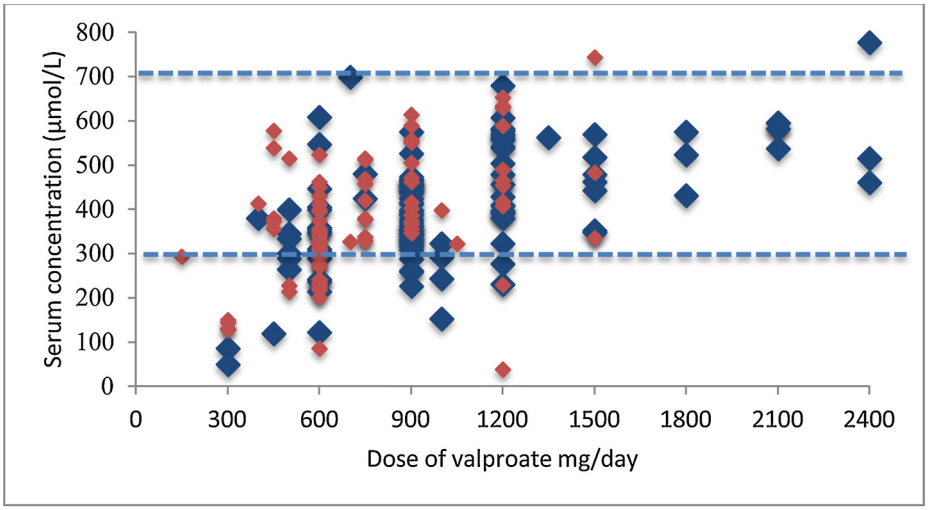
AED	Daily dose, median (min-max)	Serum concentration (μmol/L), median (min-max)	C/D-ratio, median (min-max)
Valproate			
Women* (n = 92)	600 (300-1500)	370 (38-743)	0.50 (0.03-1.95)
Men (n = 124)	900 (300-2400)	390 (49-777)	0.40 (0.15-1.01)
Total (n = 216)	900 (300-2400)	386 (38-777)	0.45 (0.03-1.95)
Lamotrigine			
Women (n = 168)	263 (8-900)	21 (2-70)	0.070 (0.01-0.68)
Men (n = 81)	300 (100-400)	21 (5-76)	0.095 (0.01-0.22)
Total (n = 249)	300 (8-900)	21 (2-76)	0.073 (0.01-0.68)
Levetiracetam			
Women(n = 80)	2000 (500-3000)	69 (13-209)	0.045 (0.008-0.138)
Men (n = 18)	1875 (1000-2000)	66 (21-236)	0.039 (0.014-0.135)
Total (n = 98)	2000 (500-3000)	69 (13-236)	0.45 (0.008-0.138)

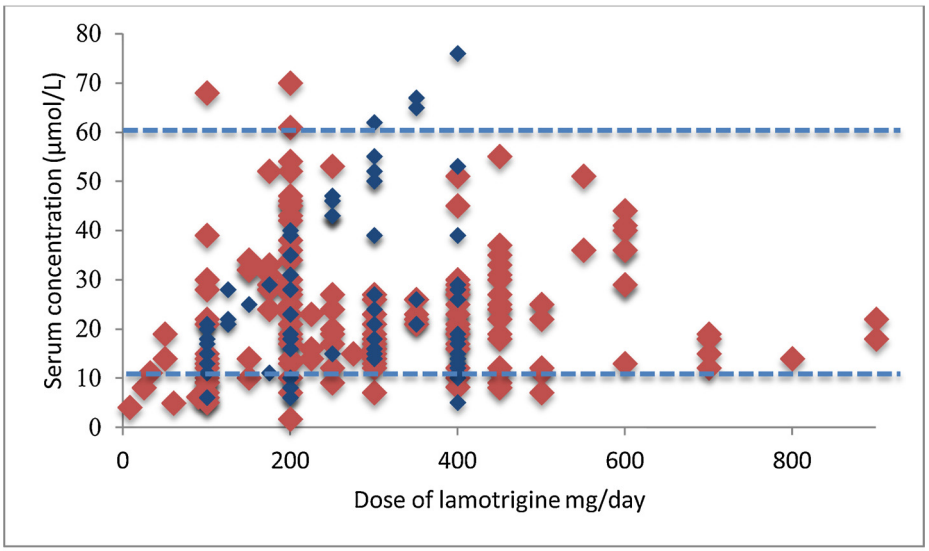
* Women had a significantly lower daily dosage than men ($p < 0.05$) but obtained similar serum concen-trations. No other statistically significant gender differences were found. AED = antiepileptic drug.

The most commonly used dose of valproate was 600 mg/day, with a variability in serum concentrations of 85–608 μmol/L (Fig. 1a). The majority (80%, n = 172) of values were within the reference range (Fig. 1a), while 19% (n = 42) were below the reference range. At the last visit, there were six patients with serum concentrations below the reference range (< 300 μmol/L), where five were seizure free from GTCSs, three used valproate in monotherapy, while two used valproate in combination with lamotrigine and one with levetiracetam. For lamotrigine, the pharmacokinetic variability was by far most extensive. The most commonly used dose was 200 mg/day with serum concentration between 6–70 μmol/L. Lamotrigine was affected by concomitant use of valproate and had a 3.1-fold increase in the C/D-ratio (n = 13, mean 0.19 μmol/L/mg (SD 0.07) as compared to those patients who used lamotrigine in monotherapy or with other non-interacting AEDs (n = 26, mean 0.06 μmol/L/mg (SD 0.02), p = 0.00012). All patients who used doses above 600 mg daily were women during pregnancy. Most values were within the reference range (83%, n = 207), while 10% (n = 25) were below. For levetiracetam, a daily dose of 2000 mg was most common, with serum concentrations between 22–158 μmol/L. Most values were within the reference range (84%, n = 82), while 16% (n = 16) were below. In total, in 15% (83/563) serum concentrations were below the reference ranges.

3.4. Long-term follow-up with therapeutic drug monitoring

Extensive inter- and intraindividual variability in serum concentration and dose relationships is elucidated in Fig. 2 for the three most commonly used drugs in patients with multiple measurements; valproate (a), lamotrigine (b), and levetiracetam (c). Long-term TDM demonstrated variability over time expressed as intra-patient median values and inter-patient ranges of 19% (7–47) for valproate, 43% (10–83) for lamotrigine and 35% (6–111) for levetiracetam (Table 2). The variability between measurements for our patient case described below is shown as #1 in a red box for valproate and lamotrigine. Measurements during pregnancy are marked in Fig. 2a,b and c to highlight pregnancy as a cause of variability.





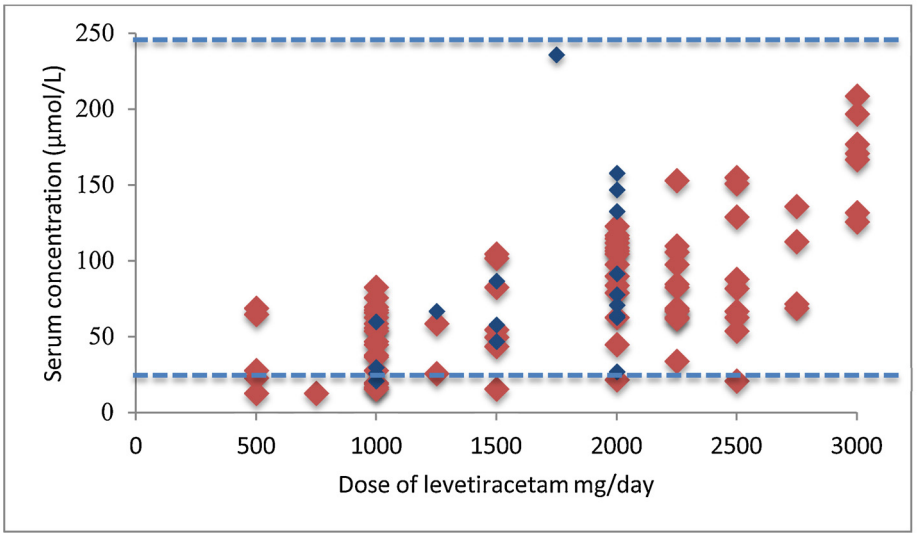
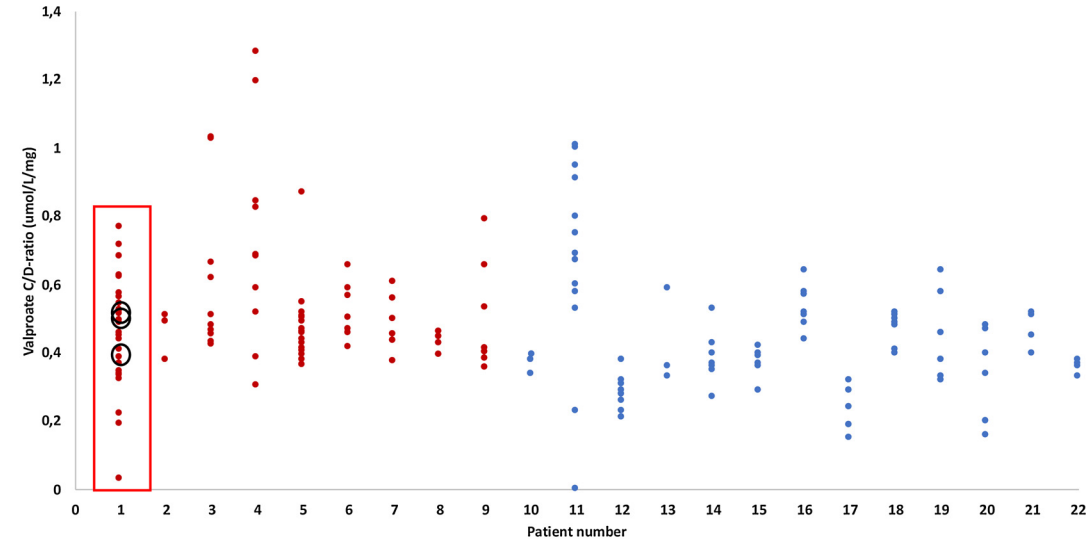
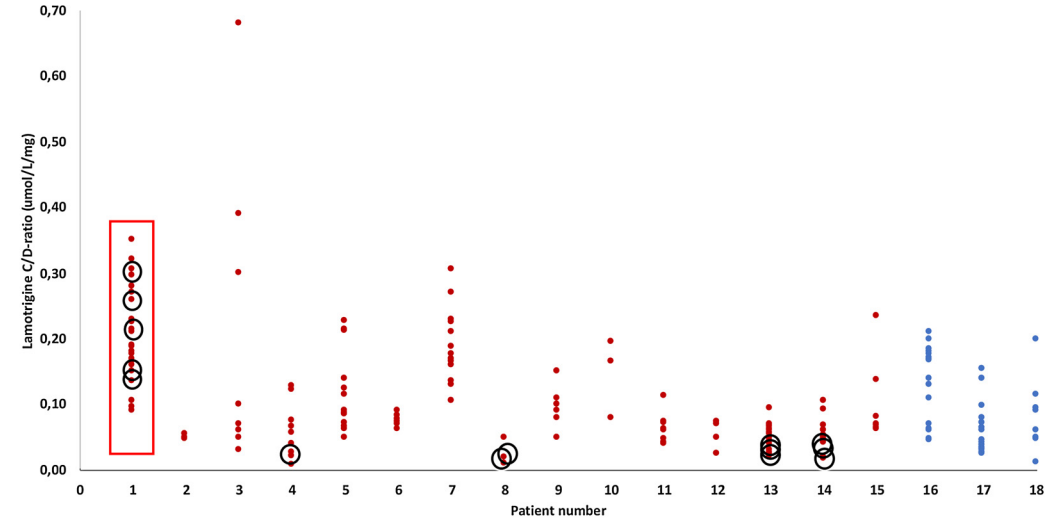


Fig. 1. a,b,c. Pharmacokinetic variability in dose and serum concentrations in female and male patients with JME using the three most commonly used AEDs: a) valproate (n = 22), b) lamotrigine (n = 20), and c) levetiracetam (n = 10) Women = red and men = blue. The reference ranges are marked with dotted lines.





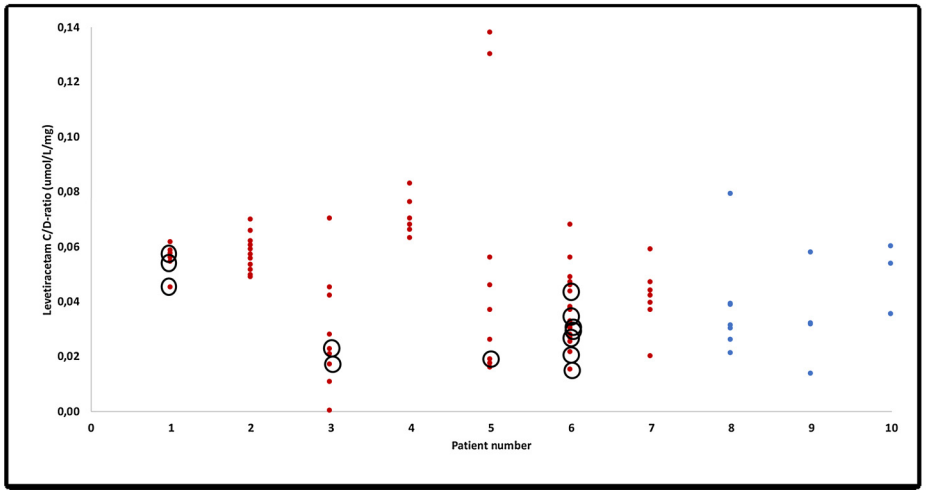


Fig. 2. a,b,c. Intra- and inter-patient pharmacokinetic variability over time with long-term therapeutic drug monitoring (TDM) based on C/D ratios for patients with multiple measurements (three or more values) over time for a) valproate, b) lamotrigine, and c) levetiractam. Women = red and men = blue in a,b,c. The values for our patient in the case description, #1, is marked with a red box for valproate and lamotrigine. Values during pregnancy and post partum are marked with black circles.

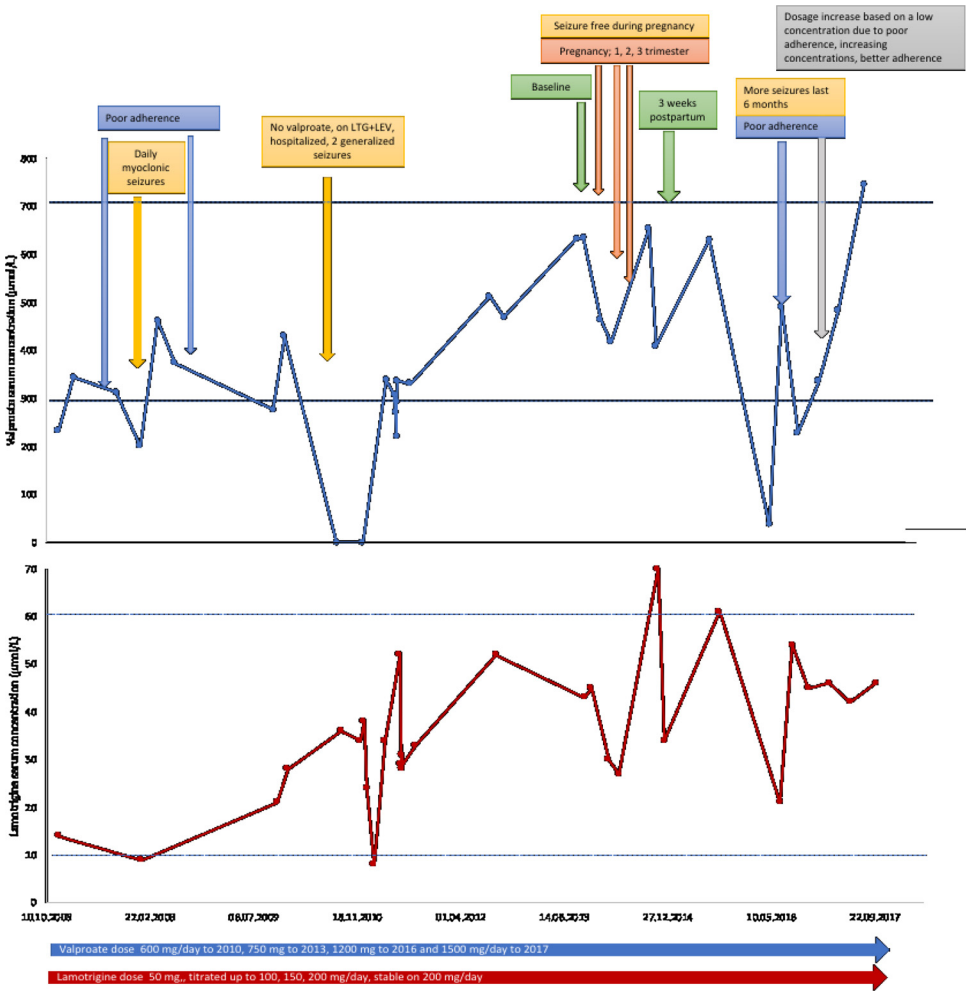


Fig. 3. Intra-patient pharmacokinetic variability by the use of long term TDM. Serum concentrations and doses of concomitantly used antiepileptic drugs, valproate (blue, above) and lamotrigine (red, below), are shown in a young woman with JME over 10 years (2006-17). The variability is related to external factors like seizure situation, dosage adjustments, poor adherence and pregnancy, often affecting both drugs, as shown with arrows where available from the medical record. Blue illustrates poor adherence, yellow seizure situation, green before and after and orange during pregnancy, and grey colour points to an explanation of a decision of a dose increase based on a single low value. The reference ranges are marked with dotted lines.

3.5. Case description of long-term monitoring in a young woman and clinical implications

This young woman had been followed closely for a period of ten years, and TDM was used as part of her follow-up. There were 61 measurements with use of two AEDs all the time, i.e. on average TDM-measurements three times per year for 10 years. The pharmacokinetic variability during the years, in relation to clinical situations or other factors are presented. She had used a combination of valproate and lamotrigine for most of the period as illustrated with all TDM data and complementary clinical data from medical records where available, in Fig. 3. She had once tried levetiracetam instead of valproate but did not tolerate it due to psychiatric adverse effects. There has been a long-term problem of variable adherence with low serum concentrations of AEDs and recurrent GTCSs causing injuries (e.g. at four occasions where the serum concentration was below the reference range, Fig. 3). She underwent one pregnancy in 2014 on valproate and lamotrigine, and this was the only period she was seizure free. Variable adherence, changes in medication, use of an estrogen-containing oral contraceptive and pregnancy all contributed to extensive variability in her dose and serum concentrations, often affecting both drugs (Fig. 3). The misleading use of one serum concentration measurement at a time of low adherence resulted in a dosage increase, followed by a very high serum concentration at the next follow-up. For educational purposes the figure was discussed between the pharmacologists and neurologists, and then with the patient. The discussion contributed to improved understanding of a regular drug intake, and the use of a dosing tool then improved adherence in the following period.

4. Discussion

In the present study, we demonstrate that TDM is used as part of the follow-up in most patients in a large and well-defined cohort of patients with JME. The pharmacokinetic variability in and between patients is extensive, and the most commonly used and measured AEDs including valproate, lamotrigine and levetiracetam, are described in detail. The majority of patients were not seizure free, and low serum concentrations, below the reference range was common, which could indicate poor adherence. Long-term TDM is used to demonstrate this variability over time. This approach is also demonstrated in a clinical case to elucidate reasons for variability in a young woman with JME as an example of its clinical application as part of the clinical follow-up to improve our understanding of the treatment.

4.1. The use of antiepileptic drugs and therapeutic drug monitoring in JME

The present study demonstrates that TDM is used in most patients with JME, where the mean number of measurements was six. However, more than 60 measurements were noted in one single patient (the case description). Valproate, lamotrigine and levetiracetam have a long-standing place in the treatment of JME, which is also reflected in the present findings and is in line with another recent study of 240 patients with JME in Portugal (Cacao et al., 2018). Still, challenges include restrictions in the use of valproate in women of child-bearing potential, possible worsening of myoclonic jerks with lamotrigine, and psychiatric adverse effects seen with levetiracetam. In addition to these drugs, a wide range of different AEDs were used, even if there is a lack of

evidence for their use in JME (Nunes et al., 2012; Glauser et al., 2013). It is a general problem, that the evidence for choice of AEDs in JME is scarce. The majority of patients were not seizure free, which calls for further evaluation of improvement of their follow-up, like implementation of long-term TDM as elucidated in the clinical case.

4.2. Pharmacokinetic variability

Previous studies have pointed to large variability between patients using valproate, lamotrigine and levetiracetam, and the pronounced enzyme inhibiting effect by valproate on lamotrigine levels (May et al., 2003; Reimers, 2009; Johannessen Landmark et al., 2012, 2017). Several reasons, like adherence, comedication (with AEDs or other drugs), and patient-related factors may contribute to this (Johannessen Landmark et al., 2012; Johannessen Landmark et al., 2016). JME is associated with frontal lobe dysfunction and impulsivity, which may impair adherence (Moschetta and Valente, 2013; Wandschneider et al., 2012, 2013, Zamarian et al., 2013). TDM may be a helpful tool in this regard, as it has been considered the most efficient method to control for poor adherence (WHO, 2003), which may be of major importance in this particular patient group.

There were six patients with serum concentrations of valproate below the reference range, and five who were free from GTCSs during the last year, supporting the clinical experience that even low exposure of valproate may protect against generalized seizures. The mean dose of valproate was lower in women than men, but the serum concentrations were similar. Most women used low doses of valproate as recommended below 700 mg/day, when it comes to lowering the risk of malformations (Tomson et al., 2015). We discovered incomplete measurements performed during pregnancy in ten women that did not allow for further calculations on C/D ratios, and unbound valproate was not measured. Women should be more closely followed, and valproate should be monitored to a minimum effective exposure based on the use of TDM, as the pharmacokinetic variability is pronounced, and the dosage is a poor approximation of exposure (Johannessen Landmark et al., 2017, 2018). In addition, TDM could help to decrease the risk of uncontrolled seizures in women by maintenance of an optimal individual serum concentration and controlling for poor adherence. The risk of SUDEP is increased in those with uncontrolled generalized seizures, and the risk of maternal death is 10-fold increased in those with uncontrolled generalized seizures during pregnancy (Edey et al., 2014).

4.3. Clinical implications of long-term therapeutic drug monitoring

The clinical implications of closer follow-up of these patients are important, as only one third of the patients were seizure free and 19% have uncontrolled GTCSs during the last year. In a similar study from Portugal, half of the patients were seizure free the last year and 50% were regarded as being refractory to treatment (Cacao et al., 2018). In patients followed over time, the approach of long-term TDM may improve the evaluation of pharmacokinetic variability as well as patient-related factors over time, within an individual patient and between patients. It is well known that patients are concerned about adherence, adverse effects and seizure control that affect their quality of life (Mevaag et al., 2017; Henning et al., 2019). By collecting all available data for 10 years, we had considerable data to analyze in many of the patients to give a comprehensive long-term overview of the use of TDM and elucidate intra-patient variability and then compare groups among the patients.

As demonstrated by Conway et al. (2017) the use of CVs indicated that more than one serum concentration measurement may be necessary in a patient to determine a true systemic exposure trend over time. Similarly, in patients with JME using various AEDs, the variability of valproate, lamotrigine and levetiracetam was considerable. Lamotrigine is known to be susceptible to drug interactions by enzyme inducers such as carbamazepine and similar drugs (oxcarbazepine, eslicarbazepine), enzyme inhibitors like valproate, and other drugs, such as oral contraceptives (Johannessen Landmark and Patsalos, 2010; Johannessen and Johannessen Landmark, 2010) In the present study, lamotrigine clearly had the most extensive variability within and between patients. Over a period of up to 10 years, often from early adolescent age to adulthood, many changes may happen regarding the therapy and the patients' situation.

Fig. 3 was used as a tool to discuss variability, adherence and seizure control with the patient. The visualization of pharmacokinetic variability and use of TDM over a long time gave rise to an interesting discussion with the patient in our case study, pointing to reasons as variable adherence for subtherapeutic serum concentrations and poor seizure control. The application of the long-term TDM data improved our understanding of variability and seizure situation for the patient, neurologist and pharmacologist.

4.4. Methodological considerations

Retrospective studies have limitations, but they may be the only option for long-term follow-up and for pharmacokinetic purposes (Perucca and Wiebe, 2016). The established practice for TDM in Norway is a standardized blood sampling time, drug fasting before the morning dose at steady-state, but it cannot be assured that this is always correct. We have previously demonstrated that the quality of the information given in the request forms is equally correct to medical records (Svendsen et al., 2017), and this was also checked in the present study. Poor adherence cannot be controlled for in a realistic and retrospective setting, also illustrated in the patient case, where wrong decisions may be taken of dosage adjustments based on one misleading measurement.

4.5. Conclusions

In conclusion, the present study demonstrates extensive inter- and intra-patient pharmacokinetic variability in patients with JME with long-term TDM follow-up. This points to a need for close follow-up in this group of patients. Serum concentrations in many patients below the reference ranges could correspond to poor adherence, resulting in a poor treatment outcome, as the majority of patients were not seizure free. Inter-and intra-patient variability measures may be used in a clinical setting for educational purposes to increase the understanding of the patient towards variability, adherence and risk of seizures. This approach may contribute to closer monitoring of patients with JME and be used as a practical tool during clinical consultations for improved follow-up.

Authors' note

Cecilie Johannessen Landmark, Marte Syvertsen, and Jeanette Koht designed the study. Ida Fløgstad and Arton Baftiu had a major role in the acquisition and analyzing of the data. Cecilie Johannessen Landmark developed the first draft of the manuscript. Marte Syvertsen and Ulla Enger contributed in the patient recruitment and data collection. Arton Baftiu and Svein I. Johannessen contributed in the data analysis and interpretation and discussion of the results. All authors contributed to the final manuscript.

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