Use of TDM of new antiepileptic drugs in children with refractory epilepsy at two National Epilepsy Centers, Denmark and Norway

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Background

The most recently approved antiepileptic drugs (AEDs) have indications first as add-on therapy in adults, adolescents and then children with focal epilepsy. Serum concentration measurements are offered at some specialised laboratories. Data on pharmacokinetic variability in young patients is scarce, since they are most often not included in clinical studies or exposed to drugs early after approval of new drugs (1). Lacosamide and eslicarbazepine have been investigated in a clinical setting at our center in adult patients (2,3). The purpose of this study was to investigate the use of therapeutic drug monitoring (TDM) of new AEDs in children with refractory epilepsy at two national epilepsy centers and to study factors contributing to pharmacokinetic variability. 1) Johannessen Landmark et al 2016. 2,3) Svendsen et al 2016, 2017

Method

Retrospective anonymous data regarding children/adolescents (<18 years) from the TDM-databases at the National Center for Epilepsy (SSE), Oslo University Hospital Oslo, Norway, and The Danish Epilepsy Center, Filadelfia, Denmark, and clinical data from medical records during 2012-18 were collected for the new AEDs eslicarbazepine, lacosamide, rufinamide and stiripentol. The study was approved by the regional ethics committee.

Results

- Laboratory data from a total of 385 samples from children/adolescents were included, Tab 1.
- For eslicarbazepine the median age was 13 years, Tab 1.
- For lacosamide the median age was 15 years, and serum concentration measurements are shown in relation to dose in Fig 1.
- The concentration/dose-ratios varied several-fold for both drugs and were not significantly different between age groups.
- Most patients used these drugs as add-on therapy in refractory epilepsy

Tab. 1 Included drugs and clinical data

Antiepileptic drugs	Clinical data and patient characteristics
Lacosamide (n=69)	37 girls/32 boys Median age 15 (range 2-17) Median dose 300 mg/day (range 50-600) and serum concentration 20 (range 6.2-138) µmol/L. Median concentration/dose (C/D)-ratio was 0.07(0.03-0.23). Details are shown in Fig 1. 20% used monotherapy, 43% used 1, 30% used 2 and 6% used 3 other AEDs in combination Indications: Monotherapy and add-on in focal or generalised seizures
Eslicarbazepine (n=50)	21 girls/88 boys Median age 13 (range 3-16) Median dose 800 mg/day (range 400-1600) and serum concentration 58 (range 10-100) µmol/L (n=17). Indications: Focal or generalised seizures, most as add-on therapy
Rufinamide (n=70)	Concomitant use of 1-3 other AEDs Indications: Dravet or Lennox-Gastaut syndrome
Stiripentol (n=121)	Concomitant use of 1-3 other AEDs Indications: Dravet or Lennox-Gastaut syndrome

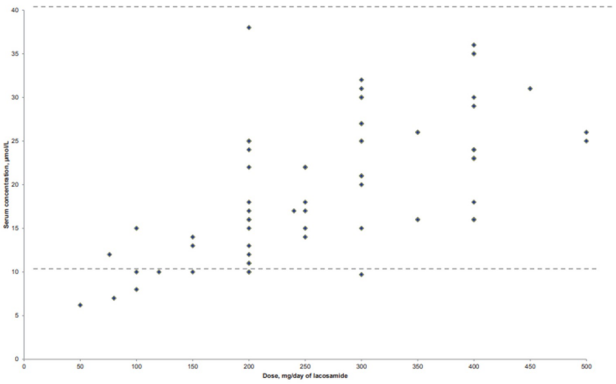

Figure 1. Doses and serum concentrations of lacosamide in children and adolecents (n=69). One patient received 600 mg with a serum concentration of 140 µmol/L. The reference range is 10-40 µmol/L (dotted lines).

Conclusions

- Implementation of TDM of new AEDs in children and adolescents in a clinical setting highlights extensive pharmacokinetic variability.
- Polypharmacy with other AEDs was common.
- This vulnerable patient group needs individualised monitoring for an optimal treatment outcome and a balance between efficacy and tolerability.