Safety of Supratherapeutic Doses of Newer Antiepileptic Drugs in Children: What Have We Really Learned?

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ABBREVIATIONS FDA, Food and Drug Administration

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Trials of new antiepileptic drugs are initially performed as adjunctive therapy in adults with refractory focal onset epilepsy. US Food and Drug Administration

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(FDA) approval is granted before adequate pediatric studies are performed. The pediatric neurologist is then in the awkward position of using the new medication prior to the availability of complete pharmacokinetic data. Pediatric neurologists have typically increased average and maximum adult daily doses by 40%–50% in pre-adolescent children, to approximate the adult dosage range (based on mg/kg/day).

As Messinger et al¹ point out, this often leads to proportionately larger doses being used in children. This has implications for adverse events (both serious and routine). The authors retrospectively reviewed their safety experience at Texas Children's Hospital over a 4-year period, during which 41,137 prescriptions were written. Their primary objective was to determine the safety of exceeding FDA-suggested maximum adult doses for topiramate, lamotrigine, levetiracetam, oxcarbazepine, zonisamide, and clobazam. They found 166 patients (1.4% of the total) who were taking doses that exceeded the FDA recommended maximum adult dose for commonly used newer antiepileptic drugs. Importantly, the study did not have an increased incidence of adverse events. Levetiracetam was the drug most commonly prescribed at doses above those recommended for adults, and lamotrigine was the least commonly prescribed above the therapeutic dose. This is consistent with reports made to poison control centers, where levetiracetam was the lowest in rank for need for interventions, and lamotrigine was the highest.² The authors concluded that it is safe to use doses of these specific antiepileptic drugs that exceeded the maximum FDA-approved dose.

What lessons have we learned from this large, real-world review of the use of newer antiepileptic drugs in children? This trial validated several important concepts

that are critical to keep in mind when treating children with epilepsy. Awareness of these concepts by the pediatric neurologists and pharmacists will improve their care of children with epilepsy.

Lesson 1

Children with refractory and new onset epilepsy may not be fully adherent with their medication schedule, even though the parents are anxious about persistent seizures.^{3,4} Nonadherence is not an uncommon reason for refractory seizures. The typical response to continuing seizures is to increase the daily dose of the medication. In the setting of partial adherence, this may result in supratherapeutic doses without elevated serum concentrations or signs of medication side effects. This is verified in the study by Messinger et al¹ as none of the patients taking supratherapeutic doses of lamotrigine, zonisamide, topiramate, oxcarbazepine, or levetiracetam (see Messinger et al¹ Table 2) had median serum drug concentrations that exceeded the therapeutic range (and for the first 3 medications no patient had a single value exceeding the therapeutic range). Additionally, even with supratherapeutic doses for lamotrigine, zonisamide, and topiramate, median serum concentrations were only mid-range or lower. This can be explained only by the possibility that these children were either partially adherent to medication or all these children were also taking enzyme-inducing antiepileptic drugs that were hepatically metabolized. I suspect partial adherence was the likely cause.

In the modern era, their adherence could be verified by a prospective study that investigated medication refill rates; for example, how often is a 30-day prescription of medication being refilled at the pharmacy? Is it every 25 to 35 days on average? For those patients with extreme serum concentrations resulting from taking levetiracetam and oxcarbazepine (i.e., 118 mg/L and 87.6 mg/L, respectively), I suspect side effects were present. Unfortunately, in a retrospective study, it is hard to correlate side effects with therapeutic concentration.

Levetiracetam may be the exception to this as there is not a clear correlation between daily drug dose and adverse events.⁵

Lesson 2

Despite the lack of FDA labeling that requires or recommends monitoring serum concentrations of the newer antiepileptic drugs, monitoring can be helpful in answering the clinical question: why is my patient still having seizures? Is it partial adherence, alterations in pharmacokinetics profile, drug-drug interactions, or refractory epilepsy? A position paper by the International League Against Epilepsy Commission on Therapeutic Strategies provides guidance on situations in which antiepileptic measurements are most likely to be of benefit.⁶

Lesson 3

Most pediatric patients who receive a new antiepileptic drug respond to average doses. Very few patients with drug-resistant seizures will benefit from supratherapeutic doses; hence, in the modern era, the strategy for treatment has been modified. No longer do we recommend increasing the dose of the drug until clinical toxicity occurs before considering this medication a failure. The dose is titrated up to an average dose, and the patient's response is assessed. If the patient responds as the dose is increased, it is reasonable to further increase the dose to maximize the response.⁷ If the patient shows no improvement, then the medication should be slowly withdrawn and other options considered (eg, typically another medication; but if multiple medications fail, then the patient should be evaluated for epilepsy surgery, a device, or dietary therapy).

Lesson 4

Finally, this review points out the need for pediatric pharmacokinetic and safety studies to be performed (ideally) before a new drug is released or, at the very least, soon after the medication is available. All medications reviewed by Messinger et al⁸ (except for clobazam) were initially approved for use in adults with refractory focal onset seizures. Years later, randomized controlled trials were performed in children. This approach made it difficult and possibly unethical to recruit children for these trials, as the antiepileptic drug could be prescribed for an off-label use. It was realized for quite some time that every antiepileptic agent that has been shown efficacious in adults with focal seizures was ultimately shown to be efficacious in children and adolescents and that the only potential differences were the drug pharmacokinetics and adverse event profiles.⁹

Dr. Jack Pellock et al⁹ and others¹⁰ led efforts to change the FDA approval process for new antiepileptic drugs in children, using an extrapolation method. This change occurred in 2016 and allows for extrapolation

studies, speeding the path to market for pediatric antiepileptic drugs and providing this critical information in a more timely manner. This is based on the concept that, if a therapeutic serum concentration range is established based on an effective dose in adults, then targeting this same concentration range would result in an efficacious dose in children. An awareness of these principles and application of these lessons will help improve care for children with epilepsy, while minimizing adverse events.

ARTICLE INFORMATION

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