Evaluation of Safety in Exceeding Maximum Adult Doses of Commonly Used Second-Generation Antiepileptic Drugs in Pediatric Patients

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OBJECTIVE Pediatric patients often require larger doses of antiepileptic drug (AED) than adults in order to attain therapeutic serum concentrations and/or achieve seizure control. Safety and efficacy data are often extrapolated from adult literature; hence, optimal dosage may only be determined anecdotally or based on expert opinion. With limited pediatric dosing guidelines, milligrams per day that are based on weight may exceed the maximum adult dose. The primary objective of this study is to evaluate the safety of exceeding maximum doses as specified by the US Food and Drug Administration or manufacturers of commonly used AEDs in pediatric patients.

METHODS This study is a single-center, retrospective analysis of all pediatric patients seen in the outpatient clinic between October 2010 and October 2014 who were prescribed a dose that exceeds the maximum approved dose of oxcarbazepine, zonisamide, topiramate, levetiracetam, lamotrigine, or clobazam. Baseline demographics (ie, sex, age, race/ethnicity, weight, height, diagnosis), serum drug concentrations, and appropriate laboratory tests were collected. Side effects were reviewed.

RESULTS During the 4-year study period, 41,137 prescriptions were included. A total of 2% of prescriptions exceeded the maximum dose of 1 of the included AEDs. The most common AED prescribed above the maximum dose was levetiracetam (53%), whereas lamotrigine was the least common (6%). The largest doses prescribed exceeded the maximum by 3-fold (ie., levetiracetam dose of 9000 mg/day).

CONCLUSION It appears safe to use doses exceeding the maximum approved dose of the evaluated AEDs in pediatric patients, with appropriate counseling and monitoring for adverse effects.

ABBREVIATIONS AED, antiepileptic drug; CLB, clobazam; CNS, central nervous system; FDA, US Food and Drug Administration; LEV, levetiracetam; TPM, topiramate; ZNS, zonisamide

KEYWORDS antiepileptics; epilepsy; maximum dosage; pediatrics; safety

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Introduction

Antiepileptic drugs (AEDs) are considered first-line methods for the treatment of epilepsy. Although most patients will have seizure freedom with their initial AED,

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the likelihood of successfully responding to a new AED declines with every sequential drug tried.¹ Therefore, it is imperative to use appropriate medications, use adequate doses, and achieve therapeutic drug concentrations before considering a drug ineffective.

Because the pharmacokinetics of pediatric patients differs from adults, children often need relatively larger doses than adults to attain therapeutic drug concentrations and thus achieve seizure control.² In pediatrics, AED use is frequently off-label because of limited randomized controlled trials in this population. Safety

and efficacy data are often extrapolated from adult trials, and thus optimal dosage may only be determined anecdotally or based on expert opinion. Additionally, many AEDs were approved as adjunctive therapies but are commonly used as monotherapy, although tolerable and efficacious doses for this purpose have not been determined.³ Because approximately one-third of patients will continue to have seizures despite appropriate and even aggressive monotherapy, multiple AEDs may be needed for most patients, particularly those who become pharmacoresistant—that is, those who have failed 2 appropriately chosen and dosed medications.^{4,5} Currently there is no standardized way to assess adverse effects from AEDs, although there have been recent efforts to create a systematic way to review medication side effects in pediatric epilepsy patients.⁶ The primary objective of this study is to evaluate the safety of exceeding maximum adult doses as specified by the US Food and Drug Administration

(FDA) or manufacturer of commonly used AEDs in pediatric patients.

Materials and Methods

This study is a single-center, retrospective analysis of all pediatric patients seen in the outpatient neurology clinic at Texas Children's Hospital between October 2010 and October 2014, who were prescribed a dose that exceeded the maximum daily doses based on manufacturer or FDA recommendations of at least 1 of the following AEDs: levetiracetam (LEV; 3000 mg), lamotrigine (700 mg [based on dose given with inducer]), clobazam (CLB; 40 mg), oxcarbazepine (2400 mg), topiramate (TPM; 400 mg), or zonisamide (ZNS; 600 mg). Medications were chosen based on greatest use in the clinic. Data were obtained via the electronic medical record. Information obtained at each clinic visit varies and is dependent on physician and case-by-case patient (i.e., assessment of adherence, ordering serum drug concentrations, and pertinent laboratory monitoring). Patients were excluded if age exceeded 18 years at the time the AED was prescribed.

Baseline demographics (i.e., sex, age, race/ethnicity, weight, height, and diagnosis), serum drug concentration, and appropriate laboratory tests were collected. Side effects and changes to the medication were reviewed by the primary author (MMM) through chart review. Descriptive statistics were performed.

Results

During the 4-year study period, 53,302 prescriptions were reviewed. Of these, 41,137 prescriptions, in 11,458 unique patients, contained sufficient dosage information to enable inclusion. A total of 761 of these prescriptions (1.84%) exceeded the maximum adult dosage. A total of 166 patients (1.4%) had an AED prescription that exceeded the maximum dose. Slightly more than half of these patients were male, with a median age of 14.4 years and median weight of 55.7 kg. Most of the patients had a symptomatic localization-related epilepsy and received polytherapy AED therapy for management of their disease. Complete demographics are listed in Table 1.

The most common AED prescribed above the maximum dose was LEV (53% of included), whereas lamotrigine was the least common (6%). The largest doses prescribed exceeded the maximum upwards of 2- to 3-fold, both in mg/day and mg/kg/day. Serum concentrations were drawn in half of all patients, with the exception of CLB concentrations, which are not routinely drawn at our institution. Complete information regarding dosage and serum concentrations can be found in Table 2.

A total of 20% of all patients who received an AED that exceeded the maximum daily doses experienced an adverse effect, and 11% of patients had a laboratory abnormality (Table 3). These led to discontinuation of

Table 1. Baseline Demographics (N = 166)

Demographics	Results
Patient characteristics	
Male, n (%)	94 (56.6)
Age, yr, median (range)	14.4 (1.8–17.9)
Weight, kg, median (range)	55.7 (14.1–148.1)
Race, n (%)	
White	112 (67.5)
African American	30 (18.1)
Asian	3 (1.8)
American Indian and Alaska Native	1 (0.6)
Native Hawaiian and other Pacific Islander	0 (0)
Unknown	20 (12)
Ethnicity, n (%)	
Hispanic	66 (39.8)
Non-Hispanic	87 (52.4)
Unknown	13 (7.8)
Diagnosis, n, (%)	
Cryptogenic localization-related epilepsy	31 (18.7)
Symptomatic localization-related epilepsy	63 (38)
Idiopathic localization-related epilepsy	3 (1.8)
Cryptogenic generalized epilepsy	17 (10.2)
Symptomatic generalized epilepsy	8 (4.8)
Idiopathic generalized epilepsy	18 (10.8)
Unspecified	25 (15.1)
Non-epilepsy	1 (0.6)
Antiepileptic use, n (%)	
Monotherapy	57 (34.3)
Polytherapy	109 (65.7)

the AED in 3.6% of patients. The dose was decreased in an additional 7.8% of patients because of an adverse effect or a laboratory abnormality. Most of the adverse effects involved the central nervous system (CNS) and included dizziness and drowsiness. Changes in mood and appetite were also prominent. More than half of all patients on TPM (72%) and ZNS (60%) experienced a laboratory abnormality, the most common being metabolic acidosis (72%).

Time from beginning the large dose to reporting of the adverse effect was evaluated, but no correlation was seen. Adverse effects were reported an average of 170 days following initial prescription and up to 2 years after beginning the large-dose AED.

Table 2. Dosage and Serum Concentrations

AED	Dosage			Serum Drug Concentration, mg/L	
	Maximum Adult Dose, mg/day*	Study Population, mg/day, Median (Range)	Study Population, mg/kg/day, Median (Range)	Reference Range [†]	Study Population, Median (Range)
LEV (n = 88)	3000	4000 (3191–7500)	78 (37–327)	12–46	36.5 (< 2 to 118)
OXC (n = 19)	2400	3000 (2700–3600)	39.3 (20.3–55.6)	3–35	33.9 (6.9–87.6)
TPM (n = 19)	400	600 (450–1000)	11.5 (5.7–26.2)	5–20	12.8 (3.7–33)
CLB (n = 17)	40	50 (45–60)	1.6 (0.5–4.2)	—	—
ZNS (n = 13)	600	800 (700–1000)	14.8 (7.4–23.5)	10–40	21 (2.1–43.2)
LTG (n = 10)	700	800 (750–1500)	11.4 (6.4–16.3)	2.5–15	9 (6.2–23.9)

AED, antiepileptic drug; CLB, clobazam; LEV, levetiracetam, LTG, lamotrigine; OXC, oxcarbazepine; TPM, topiramate; ZNS, zonisamide

* US Food and Drug Administration or manufacturer approved

[†] Not all serum drug concentrations are clinically useful or recommended (i.e., LEV, CLB). Nonetheless, there are established reference ranges or proposed ranges (i.e., ZNS) for some AEDs

Discussion

Literature is sparse regarding the safety and efficacy in exceeding maximum FDA-approved adult dosages in commonly used antiepileptic drugs. A total of 20% of all patients in our study experienced an adverse effect, which may be similar or less than what is experienced at doses recommended for pediatric patients. The medications examined in this study were all second-generation AEDs, because these are the most commonly prescribed AEDs at our institution. Despite a small percentage of patients requiring a dose exceeding approved adult doses, it is nonetheless important to evaluate the safety of these medications in our 166 patients. The adverse effects reported were the common and expected (per individual medication), and not the rare and/or serious adverse effects.

A retrospective study by Obeid and Pong⁷ evaluated safety and efficacy for LEV in dosages larger than the recommended mg/kg/day in pediatrics (i.e., looking at dosages above 60 mg/kg/day). They found that 32 patients used a median dosage of 146 mg/kg/day (range, 70–275 mg/kg/day). Of these, 14 patients (44%) experienced a 50% reduction in seizures and 5 (16%) achieved seizure freedom, thus showing that most patients benefited from a larger dose. The prevalence of adverse effects reported for LEV in this study was similar to that in our population (13.6%). Of our 32 patients, 4 patients (12.5%) exhibited behavioral effects. This is slightly higher than the 10% of patients who developed behavior changes (i.e., aggression) in the LEV group reported by Obeid and Pong.⁷ In their study, the drug was discontinued in half of patients or was ameliorated by adding pyridoxine. Pyridoxine (vitamin B₆) has been reported in case reports and retrospective studies to help mitigate behavioral side effects of LEV in as high as 41% of patients.^{8,9} Assessing for these behavioral changes, particularly after exceeding the maximum dose, is recommended, with potential drug discontinua-

tion or dose modifications should these changes occur.

Oxcarbazepine has been associated with a high prevalence (91%) of adverse effects in pediatric patients receiving dosages up to 51 mg/kg/day.¹⁰ This was higher than the prevalence in our population, which was 37%. Dizziness was one of the most commonly noted adverse effects in both studies. In a retrospective chart review, Klehm et al¹¹ studied 300 pediatric patients (median age 9 years) who received CLB in dosages between 0.26 and 0.8 mg/kg/day. A total of 60% discontinued use because of adverse effects, the most common being tiredness. Although doses of CLB in our cohort were larger, adverse effects were similar to our population, where 60% experienced drowsiness.

A study in adults examined whether large dosages of ZNS (defined as >500 mg/day) were safe and effective in pharmacoresistant epilepsy.¹² A total of 9 patients received a mean dosage of 633 mg/day, and this was found to be efficacious (>50% reduction rate of seizures) in 55% of those patients. Adverse events were seen in 3 (37%) and included anorexia, weight loss, and somnolence. A study in a pediatric population was published examining the rate of seizure freedom during 6 months between using ZNS at small dosages (3–4 mg/kg/day) versus large dosages (6–8 mg/kg/day), in addition to assessing the adverse effect of change in cognition and behavior. Close to two-thirds of patients in each arm achieved seizure freedom, and those in the larger-dose arm had worsened scores on vocabulary subtests ($p = 0.02$). The limitation with this study was that it did not define the mg/day dosage, only the mg/kg/day, making it more difficult to make conclusive recommendations regarding the significance of exceeding maximum approved adult dosages.

Although metabolic acidosis was commonly seen in the TPM and ZNS groups (73% and 60%, respectively), this did not manifest clinically, lead to drug discontinuation, or require any therapeutic intervention or hospitalization. However, 1 patient on ZNS did require

Table 3. Patient Tolerability*

	AED					
	LEV (n = 88)	OXC (n = 19)	TPM (n = 19)	CLB (n = 17)	ZNS (n = 13)	LTG (n = 10)
Adverse effects, n (%)						
No	76 (86.4)	12 (63.2)	16 (84.2)	12 (70.6)	11 (84.6)	6 (60)
Yes	12 (13.6)	7 (36.8)	3 (15.8)	5 (29.4)	2 (15.4)	4 (40)
Drowsiness	3 (25)	1 (14.3)	1 (33.3)	3 (60)	—	—
Dizziness	—	5 (71.4)	—	1 (20)	—	4 (100)
Blurred vision	—	—	—	—	—	1 (25)
Language changes	—	—	1 (33.3)	—	—	—
Mood changes	8 (66.6)	—	1 (33.3)	—	—	—
Cognitive slowing	1 (8.3)	—	—	—	—	—
Decreased appetite	—	—	—	—	2 (100)	—
Increased appetite	—	1 (14.3)	—	—	—	—
Drooling	—	—	—	1 (20)	—	—
Laboratory abnormalities, n (%)						
No	88 (100)	18 (94.7)	8 (42.1)	16 (94.1)	8 (61.5)	10 (100)
Yes	0 (0)	1 (5.3)	11 (57.9)	1 (5.8)	5 (38.5)	0 (0)
Hyponatremia	—	1 (100)	—	—	—	—
Hyperchloremia	—	—	2 (18.2)	—	2 (40)	—
Metabolic acidosis	—	—	8 (72.7)	—	3 (60)	—
Elevated CO ₂	—	—	1 (9.1)	—	—	—
Elevated LFTs	—	—	—	1 (100)	—	—
Dose changes due to adverse effects or laboratory abnormalities, n (%)						
No change	74 (81)	17 (89.5)	16 (84.2)	16 (94.1)	13 (100)	7 (70)
Discontinuation	4 (4.5)	1 (5.3)	1 (5.3)	0 (0)	0 (0)	0 (0)
Lowered dose	7 (8)	1 (5.3)	2 (10.5)	1 (5.9)	0 (0)	2 (20)
Change [†]	3 (3.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)

AED, antiepileptic drug; CLB, clobazam; LEV, levetiracetam; LFT, liver function test; LTG, lamotrigine; OXC, oxcarbazepine; TPM, topiramate; ZNS, zonisamide

* Numbers for the adverse effects are not mutually exclusive because 1 patient can have more than 1 side effect

[†] Change: Added pyridoxine for levetiracetam, changed to extended-release formulation for peak related adverse effects for lamotrigine

use of sodium citrate–citric acid 1 year after metabolic acidosis was initially detected. These adverse effects are expected because these medications are carbonic anhydrase inhibitors. Studies have shown an estimated prevalence of metabolic acidosis occurring in 31% to 37% of patients on TPM or ZNS, which was similar in adults and children. Baseline and periodic monitoring of serum bicarbonate is recommended.^{13, 14}

Limitations of this study include its single-center and retrospective design. Some patients who met eligibility criteria may not have been captured if their prescription was written as 2 separate orders (i.e., 1 prescription for the morning dose, 1 prescription for the evening dose). Efficacy data were not reviewed because there are a number of existing confounders. It is safe to assume that

the reason for the medication increase was to continue to improve seizure control; however, the retrospective nature of the study did not always allow the authors to determine what effect the increase in dosage had on the patient's seizure frequency. A prospective study with more robust documentation would allow the authors to evaluate efficacy in the future.

Conclusions

Prescribing doses exceeding the maximum adult dose are infrequent in children, but they may be indicated when seizure control is incomplete at lower doses. Adverse effects were only seen in 20% of patients, with CNS-related adverse effects being the most common. No serious adverse effects occurred. Counseling pa-

tients on CNS-related adverse effects and other common adverse effects per AED, in addition to routinely assessing tolerability, is therefore recommended when using larger-than-recommended doses. In conclusion, in our institutional experience in a pediatric population primarily impacted by localization-related epilepsy it appears safe to use doses exceeding the maximum approved dose of the evaluated AEDs, with appropriate counseling and monitoring for adverse effects.

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