INVESTIGATION

Clinical Outcomes in Newer Anticonvulsant Overdose: A Poison Center Observational Study

Brandon Wills · Penny Reynolds · Eileen Chu · Christine Murphy · Kirk Cumpston · Paul Stromberg · Rutherfoord Rose

Abstract Clinicians have limited experience with assessment and treatment of overdose from newer anticonvulsant medications. The aim of this investigation was to evaluate clinical effects of newer anticonvulsant overdose, determine if a relationship exists between dose and clinical effect, and if a particular agent appears more toxic in overdose. This was a retrospective study using electronic poison center data, evaluating clinical outcomes from newer anticonvulsant overdose. The Toxicall™ database from January 1, 2002 to December 31, 2011 was queried using key words: "gabapentin," "lamotrigine," "levetiracetam," "tiagabine," "topiramate," "zonisamide," "pregabalin," and "oxcarbazine." Polypharmacy overdose and children less than 15 years of age were excluded. Charts were reviewed by two abstractors for pharmaceutical, self-reported dose, clinical effect score, and clinical signs, symptoms, and vital signs recorded in the chart. Ordinal logistic regression was used to evaluate the relationship between drug type, dose, age, and sex to clinical effect score. Out of 501 cases identified, 347 met the final inclusion criteria. There were 116 gabapentin, 67 lamotrigine,
15 levetiracetam, 15 tiagabine, 56 topiramate, 23 pregabalin, and 55 oxcarbazepine cases. Overdose of newer anticonvulsants frequently results in altered mental status. Seizures may be more common with tiagabine, lamotrigine, and oxcarbazepine. There was one death reported from intentional overdose of topiramate. An information index was created to rank drug toxicity based on reported signs and symptoms for each overdose. There was no significant effect of dose on severity of outcome ($\beta=0.12$, $p=0.23$). However, the risk of a more severe outcome score was significantly increased with tiagabine relative to other drugs ($\beta=2.8$, $p=0.001$). Lamotrigine ranked highest in terms of toxicity (HT=1.66) and number of interventions performed (HI=1.17), and levetiracetam the lowest (HT=0.98; HI=0.88). We could not identify a dose-effect in these data which likely reflects the limitations of self-reported doses. Despite limitations of these data, the risk of more severe outcome scores appear to be higher with tiagabine overdose while lamotrigine overdose appears to result in more reported signs, symptoms, and interventions.

Keywords Anticonvulsant · Overdose · Toxicity · Seizure

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Introduction

Clinicians have limited experience with assessment and treatment of overdose from newer anticonvulsant medications. Unlike the traditional anticonvulsants (phenytoin, carbamazepine, valproic acid, and phenobarbital), serum drug levels are not readily available for newer agents. In 2011, there were over 31,000 cases of "other" anticonvulsant drug exposures reported to regional poison centers with 6,481 evaluated in healthcare facilities. Unfortunately these data do not specifically delineate all newer anticonvulsants [10]. While case reports provide some correlation with clinical effects in

overdose, publication bias may favor severe clinical outcomes and skew perceptions of toxicity. Such a bias has the potential to overestimate the anticipated effects following overdose.

Despite the potential for bias, to date, case reports provide us the most information about clinical effects in overdose of the newer antiepileptics. Lamotrigine has been reported to cause seizures and electrocardiographic conduction delay [7, 9, 11, 13, 15, 24, 26–28]. Levetiracetam has been reported to cause respiratory depression with decreased muscle tone and diminished deep tendon reflexes in an adult overdose [4]. There are reports of levetiracetam causing pruritus and decreased muscle tone in pediatric overdoses [3]. Gabapentin toxicity has been reported in hemodialysis patients. In these cases, gabapentin was noted to cause tremors, altered mental status, and respiratory depression requiring intubation [17, 29]. Tiagabine has been noted to cause convulsive and non-convulsive status epilepticus in patients with and without a prior seizure history [4, 16, 24, 25]. Topiramate has been reported to cause ataxia and hallucinations in pediatric overdose [20], as well as altered mental status, somnolence, vertigo, agitation, coma, metabolic acidosis, and seizures in adults with no prior seizure history [2, 8, 12, 32]. There are several reviews of poison center data of newer anticonvulsant overdose, specifically topiramate, lamotrigine, and tiagabine, that reveal a wide variety of potentially serious, life-threatening effects such as coma, seizures, and respiratory depression [21, 22]. One poison center review of gabapentin adverse effects described drowsiness, dizziness, tachycardia, ataxia, and hypotension; however, all cases were managed in an outpatient setting [18]. These studies provide some understanding of individual anticonvulsants in overdose yet no direct comparison of newer anticonvulsants has been made.

The aim of this investigation was to evaluate the clinical effects of newer anticonvulsant overdose, determine if there is a relationship between dose and clinical effect, and determine if there is a particular agent(s) which appears more toxic in overdose.

Methods

Study Design

This was a retrospective cross-sectional chart review using electronic poison center data, evaluating clinical outcomes from newer anticonvulsant overdose. Institutional Review Board approval was obtained.

Setting and Population

The Virginia Poison Center provides toxicology consultation in the central Virginia region with an annual call volume of approximately 27,000. The poison center electronic database

Toxicall™ was queried from January 1, 2002 to December 31, 2011 for hospitalized patients using the key words: "gabapentin," "lamotrigine," "levetiracetam," "tiagabine," "topiramate," "zonisamide," "pregabalin," and "oxcarbazepine." Chart acquisition was performed by specialists in poison information who are unaware of the study design. Poison center charts were abstracted onto a database with no patient identifiers.

Study Protocol

Charts were reviewed and abstracted onto a spreadsheet by two trained abstractors who were blinded to the purpose of the study. Inclusion criteria included all cases of anticonvulsant overdose referred to a healthcare facility. Patients were excluded if they were not treated in a healthcare facility. Cases involving children less than 15 years old were excluded to mitigate inaccuracies converting dose to multiples of maximum daily dose. Poly-substance ingestions were excluded after chart abstraction due to concerns about confounding the clinical outcomes. Clinical data were abstracted to a Microsoft Excel® database (Microsoft Corporation, Redmond, WA) and included the following: age, gender, estimated dose, time of ingestion, time to presentation, and past medical history. Ingested dose, when available, was converted to multiples of maximum daily dose by dividing estimated dose by the maximum daily dose to facilitate comparison between pharmaceuticals. Maximum daily doses used included: gabapentin 3,600 mg, lamotrigine 400 mg, levetiracetam 3,000 mg, tiagabine 56 mg, topiramate 400 mg, and zonisamide 600 mg. The effect severity score mirrors the categories used by the American Association of Poison Control Centers to document outcomes. Briefly, the effect score increases with severity of the outcome (0=no effect, 1=minor effect, 2=moderate effect, 3=major effect, 4=death). Examples of the severity score are available online (http://www.aapcc.org/data-system/). All clinical effects, laboratory abnormalities, and medical interventions available were recorded. The abstractors received training on identification of relevant data to include in the analysis. This included a key, which listed descriptions of elements to be imported in each cell, example cases, and standard units of measurement, and abbreviations to be used. A 5 % sample of charts was randomly assigned for both abstractors for the purpose of determining inter-rater reliability.

Measures

The primary endpoint was the determination of the poison center composite severity score. Clinical outcomes were originally scored by raters in three categories: *neurological* effects (1=seizures, 2=altered mental status (AMS), 3=coma, 4= delirium/hallucinations/agitation); *cardiovascular effects* (1=

hypotension, 2=hypertension); and *miscellaneous* (1=hyperthermia, 2=rhabdomyolysis, 3=other, listed specifically in a separate column). To incorporate information in the latter category, to eliminate as many coding discrepancies between raters as possible, and for ease of analysis, patient data were re-coded as presence/absence (1/0) in the following categories: seizures; CNS effects (including headache, AMS, confusion, agitation, delirium, lethargy, or coma); neurological/pupillary response (mydriasis, nystagmus); neuromuscular (tremors, fasciculations, ataxia, asterixis, dystonia, myoclonus); GI (emesis, diarrhea, nausea, vomiting); dermatological; cardiac dysrhythmia (tachycardia, bradycardia); blood pressure effects (hypotension, hypertension); metabolic effects (hyperthermia, rhabdomyolysis, electrolyte imbalances, acidosis).

Data Analysis

Descriptive statistics (means, standard deviations, median, interquartile range (IQR), proportions) were used to summarize demographic data, clinical outcomes, and clinical effect scores. To evaluate the association between outcome severity and categorical predictor variables (drug type, age, sex), data were modeled by cumulative logit ordinal regression on a 4-level ordinal scale response (0=no effect, 1=minor effect, 2=moderate effect, 3=severe effect). As only one death was recorded, this category was eliminated from analysis. The ordinal logistic regression models the relationship between the cumulative logits of Y and the predictor variables X_j as logit $Y_{ij} = \alpha_i + b_j X_j$, where α_i is the intercept for $i=1, 2, 3$, and quantifies the "shift" of the regression of each outcome severity category compared to the "baseline" response of no effect, and the coefficient b_j quantifies the strength of the relationship between the outcome severity response and each predictor variable. The odds ratio was computed as $\exp(b_j)$. To determine an approximate dose–response relationship for each drug, cumulative logit ordinal regression was performed on log-transformed estimated doses. Data were analyzed in SAS v. 9.3 [1].

Ranking of drug toxicity was based on the presence of clinical signs and symptoms, and quantified by the Shannon information index H' calculated for each drug. Clinical outcome signs and symptoms in nine categories (seizures, altered mental status/CNS changes, pupillary response, neuromuscular, GI, dermatological, cardiac, hypotension, metabolic) were scored for presence or absence as 1 or 0, respectively. The composite outcome score was calculated as the proportional occurrence of signs and symptoms P_i summed across each clinical category occurring for each ith patient, and was estimated as $P_i = n_i/N$, where n_i is the total count of signs and symptoms present for each patient across all categories and N is the total number of individuals. The information index was then calculated as $H' = -\Sigma P_i \cdot \ln(P_i)$. The standard deviation of

H' is calculated as the square root of the variance, where Var $(H') \approx [\Sigma n_i \cdot \ln(n_i)^2 - [\Sigma n_i \cdot \ln(n_i)]^2/N]/N^2 + (S-1)/2N^2$ [23]. Drug rankings were assessed for equality of variances by Levene's test, then compared by ANOVA on the summary statistics [19]; differences between rankings were assessed with Dunn method. These analyses were performed in JMP Pro 9.0.2 (SAS Inc., Cary, NC).

We determined inter-rater reliability on the original clinical scoring categories by randomly selecting 5 % of charts ($n=40$) for re-abstraction by both abstractors. The kappa statistic κ was used to calculate inter-rater reliability for the paired rater data for gender, presence/absence of clinical signs and symptoms, and common interventions. Analyses were performed in SAS ver. 9.3, PROC FREQ (SAS Inc., Cary, NC).

Results

Out of 501 hospital-based cases identified, 104 pediatric and 50 co-ingestion cases were excluded, leaving 347 cases which met the final inclusion criteria. Patient summary data are presented in Table 1. There were 116 gabapentin, 67 lamotrigine, 15 levetiracetam, 15 tiagabine, 56 topiramate, 23 pregabalin, and 55 oxcarbazepine cases. There was one death reported from intentional overdose of topiramate. Patients were predominantly young (median age 30 years; IQR 20, 44) and female (69.5 %). Estimated dose in milligrams and standardized units (dose/maximum daily dose) is listed in Table 2.

Outcome Severity

The majority of patients (73 %) had no or minimal clinical outcome severity effects (Table 1). There was no statistically significant effect of drug type (OR 1.065; 95 % Wald CI 0.987, 1.150; $p=0.104$), age (OR 1.012, 95 % Wald CI 0.998, 1.026; $p=0.084$), or sex (OR 0.851; 95 % Wald CI 0.557, 1.298; $p=0.453$) on outcome severity score.

Dose Response

With the lowest outcome severity, only lamotrigine had a statistically significant relationship between dose and outcome severity (Table 3).

Toxicity Rankings

There were statistically significant differences in toxicity rankings between drugs (Levene's test $F=3.635$, $p=0.0016$; Welch ANOVA $F=96.076$, $p<0.0001$). Lamotrigine, followed by topiramate, ranked highest, and levetiracetam ranked lowest. However, the low ranking of levetiracetam could be partially attributed to the small sample size ($n=12$) and resulting lack of

Table 1 Summary demographic and outcome data for 347 patients admitted following anticonvulsant overdose

Drug	Gabapentin	Levetiracetam	Lamotrigine	Pregabalin	Tiagabine	Topiramate	Oxcarbazepine
n	116	15	67	23	15	56	55
Variable							
Age (year) mean	38.4	25.9	32.2	38.3	43.5	27.3	26.2
SD	13.2	11.4	15.2	18.7	14.2	10.3	12.3
Min	16	16	15	16	15	15	15
Max	69	49	84	85	62	52	65
Sex *n* (%) M	41 (35)	6(40)	15 (22)	7 (30)	6 (40)	10 (18)	21 (38)
F	75 (65)	9 (60)	52 (78)	16 (70)	9 (60)	46 (82)	34 (62)
Outcome severity score *n* (%)							
0 (No effect)	39 (34)	6 (40)	17 (25)	8 (35)	0 (0)	24 (43)	10 (18)
1 (Minor effect)	57 (49)	8 (53)	26 (39)	5 (22)	4 (27)	19 (34)	31 (56)
2 (Moderate effect)	17 (15)	1 (7)	20 (30)	10 (44)	8 (53)	11 (20)	14 (25)
3 (Severe effects, death)	3 (3)	0 (0)	4 (6)	0 (0)	3 (20)	2 (4)	0 (0)
Clinical signs/symptoms *n* (%)							
Neuromuscular	12 (10)	0(0)	10 (15)	4 (17)	2 (13)	4 (7)	3 (5)
Seizures	2 (2)	0 (0)	3 (5)	0 (0)	3 (20)	0 (0)	2 (4)
CNS	47 (41)	9 (60)	30 (45)	8 (35)	10 (67)	14 (25)	29 (53)
GI	7 (6)	1 (7)	24 (36)	3 (13)	1 (7)	2 (4)	13 (24)
Cardiac	13 (11)	0 (0)	11 (16)	5 (22)	2 (13)	6 (11)	17 (31)
Blood pressure	19 (16)	1 (7)	6 (9)	1 (4)	3 (20)	4 (7)	3 (5)
Metabolic	6 (5)	0 (0)	3 (5)	1 (4)	0 (0)	6 (11)	1 (2)
Dermatological	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	1 (2)
Interventions *n* (%)							
Sedation	4 (3)	0 (0)	10 (15)	3 (13)	5 (33)	4 (7)	3 (5)
IV fluids	10 (9)	0 (0)	5 (8)	3 (13)	0 (0)	4 (7)	3 (5)
Mechanical ventilation	3 (3)	0 (0)	5 (8)	0 (0)	1 (7)	2 (4)	1 (2)
Vasopressors	0 (0)	0 (0)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)

Table 2 Estimated dose for anticonvulsant drugs included in a chart review of 347 patients

Drug	Estimated dose (mg)						
	Units	*N*	Median	Min	IQ 25 %	IQ 75 %	Max
Gabapentin		94	6,000	300	2,700	12,000	96,000
Levetiracetam		11	15,000	1,000	2,500	29,250	50,000
Lamotrigine		53	1,000	200	400	2,000	50,000
Pregabalin		18	2,375	100	1,000	6,000	9,000
Tiagabine		10	28	12	16	48	144
Topiramate		43	750	100	400	2,000	30,000
Oxcarbazepine		45	3,150	60	1,800	6,600	36,000
Drug	Standardized dose (dose/max daily dose)						
	N	Median	Min	IQ 25 %	IQ75%	Max	
Gabapentin	94	1.7	0.1	0.8	3.3	26.7	
Levetiracetam	11	5.0	0.3	0.8	9.8	16.7	
Lamotrigine	53	2.5	0.5	1.0	5.0	125.0	
Pregabalin	18	4.0	0.2	1.7	10.0	15.0	
Tiagabine	10	0.5	0.2	0.3	0.9	2.6	
Topiramate	43	1.9	0.3	1.0	5.0	75.0	
Oxcarbazepine	45	1.3	0.3	0.8	2.8	15.0	

Table 3 Dose-effect relationships based on cumulative logit ordinal regression between clinical outcome severity score and ln-transformed estimated doses for anticonvulsant drugs

Drug	Odds ratio	95 % Wald CI		p
		LCI	UCI	
Gabapentin	0.869	0.626	1.206	0.400
Levetiracetam	0.187	0.026	1.366	0.099
Lamotrigine	1.869	1.132	3.086	0.015
Pregabalin	1.739	0.817	3.703	0.152
Tiagabine	5.427	0.634	46.522	0.123
Topiramate	0.887	0.564	1.396	0.605
Oxcarbazepine	1.543	0.935	2.544	0.089

Table 5 Reliability of clinical effects and intervention judgements

Variable	Reliability	Ratings N/Y	
	κ (95 % CI)	Rater 1	Rater 2
Gender M/F	0.9 (0.71, 1.0)	6/22	7/21
Intentional	1.0	16/11	16/11
Clinical effects			
Neurological[a]	0.19 (−0.07, 0.45)	22/1/5/0	12/1/14/1
Hypotension	1.0	25/3	25/3
Nausea/vomiting[b]	0.46 (0.04, 0.89)	25/1/1/1	25/2/1/0
Photophobia	1.0	26/2	26/2
Ataxia	0	28/0	24/4
Dizziness	0	26/2	28/0
Lethargy	0	18/10	28/0
Tachycardia	1.0	25/3	25/3
Tremors	1.0	26/2	26/2
Headache	0.65 (0.02, 1.0)	27/1	26/2
Interventions			
IV fluids	0	23/5	28/0
Sedatives	1	25/3	25/3
Charcoal, other drugs	0.79 (0.57, 1.0)	15/12	16/11

[a] None/seizures/AMS/coma

[b] None/nausea only/vomiting only/both

information about signs and symptoms in most clinical categories evaluated (Table 4). For all drugs evaluated, CNS signs and symptoms were most prevalent (40 % of all cases). Dermatological signs and symptoms were least commonly recorded (1 %).

Inter-Rater Reliability

The reliability coefficients κ with corresponding 95 % CIs and ratings distributions for both observers are shown in Table 5. The κ values for clinical outcome judgments ranged from 0 to 1. Although differences between raters were minor for categories with relatively "hard" clinical outcomes (such as cardiac, blood pressure, and tremors), the neurological categories in particular were subject to the greatest scoring discrepancies. Capture of lethargy, ataxia, dizziness, and altered mental status were most likely to differ between raters, and showed the poorest agreement (Table 5).

Discussion

The newer antiepileptic agents in overdose are generally well tolerated with only one fatality reported to this poison center database. Levetiracetam appears to have the lowest toxicity

Table 4 Toxicity rankings of anticonvulsant drugs based on Shannon information indices H′

Drug name	H′	SD
Gabapentin	1.645	0.082
Levetiracetam	0.566	0.248
Lamotrigine	1.809	0.078
Pregabalin	1.540	0.121
Tiagabine	1.502	0.166
Topiramate	1.800	0.108
Oxcarbazepine	1.689	0.095

and number of interventions performed. The predominant finding of AMS (60 %) is consistent with other series of levetiracetam overdoses [6].

This study revealed tiagabine, a selective GABA reuptake inhibitor, to have the highest severity outcome score. This result could be related to seizures found in 20 % and altered mental status in 67 % of overdose patients, the highest proportion of any of the AEDs evaluated in this study (Table 2). In previous reports, tiagabine has been found to induce nonconvulsive status epilepticus [5, 30].

Lamotrigine, a glutamate inhibitor, sodium channel blocker, and serotonin reuptake inhibitor, was the most toxic and required the greatest number of interventions performed during overdose. Reported clinical effects include ataxia, nystagmus, decreased level of consciousness, seizures, and intraventricular conduction delay in overdose [30]. One review of Poison Center data of 493 patients with single substance lamotrigine exposures reported about half of patients experiencing toxic side effects, the most prominent being lethargy (20.9 %), vomiting (11 %), nausea (5.1 %), ataxia (4.9 %), and dizziness/vertigo (4.5 %), and tachycardia (4.3 %). Medical outcome was reported as minor in 150 (30.4 %), moderate in 73 (14.8 %), and major in 13 (2.6 %) cases [14, 21]. Similar to our study, altered mental status was the most common finding (45 %), and nearly a third of patients experienced gastrointestinal symptoms [21].

Limitations

This was a retrospective poison center chart review that has inherent limitations in the quality of data. Information contained in poison center charts is generated passively through voluntary discussions with healthcare providers by poison center specialists, sometimes by providers peripherally involved in patient care. This process undoubtedly results in omission of complete vital signs, physical exam findings, signs, symptoms, and laboratory data. Exposure or self-reported overdose does not necessarily represent an actual overdose and can bias the data suggesting less severe outcomes. Dosing information was self-reported and subject to significant inaccuracies, and rarely confirmed with plasma concentrations. For example, large variations in dosages for each severity category in this study precluded finding statistically significant dose-effect relationships for drugs other than lamotrigine. Imputing incomplete data into the information index used in our study can result in significantly limited information and should only be hypothesis generating. Repeating the information index with prospectively collected data by a bedside toxicology service, such as the Toxicology Investigator Consortium [31], and confirmatory drug concentrations, would provide more clinically robust data.

The information index H' is sensitive to the quality of the presence/absence data for clinical signs and symptoms. To be reliable, the signs and symptoms lists must be comprehensive, and all clinical categories must be surveyed and checked off for each patient. However, patient surveys may be inadequate because all signs and symptoms are not equally "detectable." For example, infrequently observed signs and symptoms are easily missed by less-experienced providers, or may be overlooked if they have a lower priority for patient treatment. H' is strongly affected by sample size, and the effects of sampling variability on the calculation of H' are not completely known [23].

Since our inter-rater reliability score was lowest for neurological findings, the organ system most commonly affected by antiepileptic medications in overdose, a future study using standardized bedside toxicologist assessment [31] would be helpful.

Conclusion

Overdose of newer anticonvulsants frequently results in altered mental status. Seizures may be more common with tiagabine, lamotrigine, and oxcarbazepine. We could not identify a dose-effect in these data which likely reflects the limitations of self-reported doses. Risk of more severe outcome was higher with tiagabine overdose while lamotrigine overdose appears to result in more reported signs, symptoms, and interventions.

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