Drug-induced seizures in children and adolescents presenting for emergency care: Current and emerging trends

Y. FINKELSTEIN, J. R. HUTSON, S. B. FREEDMAN, P. WAX, and J. BRENT; on behalf of the Toxicology Investigators Consortium (ToxIC) Case Registry

1Division of Emergency Medicine, Hospital for Sick Children, Toronto, ON, Canada
2Department of Pediatrics, Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, ON, Canada
3Faculty of Medicine, University of Toronto, Toronto, ON, Canada
4Division of Emergency Medicine, Clinical Pharmacology Research Program, Children’s Hospital Boston, Harvard Medical School, Boston, MA, USA
5Sections of Pediatric Emergency Medicine and Gastroenterology, Alberta Children’s Hospital and Alberta Children’s Hospital Research Institute, University of Calgary, Calgary, AB, Canada
6Department of Surgery (Emergency Medicine) UT Southwestern School of Medicine, Dallas, TX, USA
7Departments of Medicine and Pediatrics, University of Colorado, School of Medicine, Aurora, CO, USA

Context. Seizures may be the presenting manifestation of acute poisoning in children. Knowledge of the etiologic agent, or likely drug-class exposure, is crucial to minimize morbidity and optimize care. Objectives. To describe the agents most commonly responsible for pediatric drug-induced seizures, whose evaluation included a medical toxicology consultation in the United States. Methods. Using the 37 participating sites of the Toxicology Investigators Consortium (ToxIC) Case Registry, a cross-country surveillance tool, we conducted an observational study of a prospectively collected cohort. We identified all pediatric (younger than 18 years) reports originating from an Emergency Department (ED) which included a chemical or drug-induced seizure, and required a medical toxicology consultation between April 1, 2010 and March 31, 2012. Results. We identified 142 pediatric drug-induced seizure cases (56% male), which represent nearly 5% of pediatric cases requiring bedside consultation by medical toxicologists. One-hundred and seven cases (75%) occurred in children aged 13–18 years, and 86 (61%) resulted from intentional ingestions. Antidepressants were the most commonly identified agents ingested (n = 61; 42%), of which bupropion was the leading drug (n = 30; 50% of antidepressants), followed by anticholinergics/antihistamines (n = 31; 22%). All antidepressant-induced seizures in teenagers were intentional and represented self-harm behavior. Sympathomimetic agents, including street drugs, represent the most common agents in children younger than 2 years (n = 4/19). Conclusion. Antidepressants, and specifically bupropion, are presently the most common medications responsible for pediatric drug-induced seizures requiring medical toxicology consultation in the United States. In teenagers presenting with new-onset seizures of unknown etiology, the possibility of deliberate self-poisoning should be explored, since most drug-induced seizures in this age group resulted from intentional ingestion.

Keywords Poisoning; Pediatrics; Convulsions; Emergency medicine; Registry

Abbreviations ACMT, American College of Medical Toxicology; ED, Emergency Department; ToxIC, Toxicology Investigators Consortium

Introduction

Seizures are a worrisome, yet relatively common event. About 3–4% of children in the general population experience at least one convolution, frequently associated with fever,1,2 often resulting in the need for Emergency Department (ED) management and potentially hospital admission. While most are idiopathic, seizures may reflect exposure to drugs. The latter are associated with exposure to a wide range of medications, recreational drugs, and natural health products. In fact, 6% of new-onset generalized tonic–clonic seizures in individuals older than 16 years presenting for ED care are attributed to drug exposures.3 This proportion has been reported as high as 9% among adults treated for status epilepticus at an urban hospital.4

Many drugs have the potential to provoke seizures. Unfortunately, there is paucity of data describing which drugs are most commonly responsible for drug-induced seizures, particularly in children. Since exposure histories may not be readily available at time of presentation, knowledge of the
most likely etiologic agents would be valuable to clinicians and could potentially guide the therapeutic approach, which may include antidote administration. This issue is of increasing importance as the number of young children presenting to ED care due to accidental pharmaceutical ingestions has increased over the last decade. Recent exposure trends are also important because prescribing patterns and the use and abuse of prescription and non-prescription medications and recreational drugs continue to change rapidly over time. In this study, we sought to identify the ingestions most commonly responsible for pediatric drug-induced seizures treated in the United States, whose evaluation included a medical toxicology service consultation.

Methods

Study sites

In 2010, The American College of Medical Toxicology (ACMT) established a prospective, nationwide toxico-surveillance system, the Toxicology Investigators Consortium (ToxIC) Case Registry. The ToxIC Registry exclusively and prospectively compiles all cases managed at the bedside by the medical toxicologists in its 37 participating sites from 21 states across the United States. Most contributing sites are university-affiliated academic institutions across the United States, including 19 of the 30 medical Toxicology Fellowship training programs (63%). Case entries are performed online, at each participating site, into a password-protected database which is maintained centrally by the ACMT. The Registry database allows for identification, and subsequent extraction and pooling of information on toxicological exposures across centers. It also provides the most likely etiology of patients’ symptoms. A detailed description of the Registry has been previously published. The Registry has been cleared to function without restriction by the Western Institutional Review board, as long as there are no patient interventions as a result of being in the Registry and all patient data are de-identified. Sites contribute cases into the registry with the consent or waiver of their individual Institutional Review Board. As part of participation in the registry, all contributors agree to enter all eligible consulted cases which may be employed for research purposes.

Patients

We identified all reports, entered prospectively into the ToxIC Case Registry database between April 1, 2010 and March 31, 2012. Eligible individuals were identified employing the following search criteria: those < 18 years who received a bedside consultation by a medical toxicologist after presenting with a seizure attributed to a well-defined toxic exposure. Exposures and seizure etiologies were determined by the responsible physician and were confirmed by the performance of a detailed, bedside history, and physical examination by a board-certified medical toxicologist. When appropriate, additional diagnostic tests (e.g., urine toxic screen, serum drug level, and negative brain imaging) were recommended. Data output from the registry was sorted by patient age, and information entered into the database for each case was reviewed by the authors (Janine R Hutson, Yaron Finkelstein) to ensure eligibility.

Data collection

We analyzed all potentially eligible cases to explore the substances each patient was exposed to and to determine the identity of the most likely etiologic agent(s). No chemicals, medications, or substances were excluded. Detailed demographic and clinical data were collected on each patient including age group, source of referral, circumstances and reasons for exposure and clinical signs. We recorded all substances to which each patient was exposed, as captured by the medical toxicologist. The most likely etiologic agent(s) were primarily assigned and graded by the medical toxicology team managing the patient and reviewed for plausibility by the authors. Demographic information and clinical data were tabulated. Proportions were compared using the Chi-square test using Prism 4 for Macintosh (La Jolla, CA, 2004).

Results

A total of 11,977 poisonings were reported to ToxIC registry during the study period, of which 3,005 (25.1%) involved patients younger than 18 years (Fig. 1). There were similar proportions of adults compared to pediatric patients presenting with drug-induced seizures, 4.5% (406/8972) versus 4.7% (142/3005), respectively (p = 0.65). Of the 142 pediatric seizure cases, 80 (56%) occurred in males. Nineteen of the 142 pediatric patients (13.4%) were younger than 2 years, 16 (11.2%) were aged 2–12 years, and 107 (75.4%) were between 13 and 18 years. The source of referral to the medical toxicology service was captured in 97% of cases.
(137/142). Of these, 52 patients (38%) were consulted while in the ED, 39 (27.5%) while admitted, 33 (24%) involved hospital transfer of patients to one of the ToxIC sites, 11 (7.7%) were referred by a poison control center, and 2 (1.4%) referrals were from a primary care provider. Multiple (>2) agent exposures were recorded in 38% of cases (54/142). The median number of drugs involved in multiple exposure cases was 2 (range: 2–7; IQR: 2, 3).

Reasons for drug exposure

Eighty-six patients (60.6%) experienced drug-induced seizures following intentional overdose, followed by unintentional pharmaceutical overdose (31; 21.8%), illicit and recreational drug use (13; 9.2%), prescription drug abuse (6; 4.2%), unintentional non-pharmaceutical toxin (4; 2.8%), medication error (1; 0.7%), and opioid plus benzodiazepine withdrawal (1; 0.7%).

Of the 86 intentional exposures, 84 (97.7%) were among individuals aged 13–18 years, one in a child of the 7–12 years age group, and one in a newborn. The latter case involved intentional (self-harm) ingestion of a rodent poison containing brodifacoum, a long acting anticoagulant, by a pregnant woman. She underwent emergency cesarean section and the newborn suffered from severe coagulopathy and seizures, likely due to the resulting intraventricular hemorrhage, and required prolonged antidote (vitamin K) therapy. The reasons for drug exposure and substances involved in patients less than 2 years of age are provided in Table 1.

Drug exposures

Antidepressants were the most common agent class involved in drug-induced seizures (Fig. 2), accounting for 61 (42.4%) of 142 seizure cases, and 52 (60.5%) of the 86 intentional ingestions (Fig. 3). Within the 61 antidepressant-induced seizure cases, bupropion was the etiologic agent in 30 (49.2%) of which 27 were intentional ingestions. Anticholinergics/antihistamines were the second most common cause of seizures (31/142; 21.8%) accounting for 26.7% (23/86) of intentional ingestions leading to seizures. While most of these exposures were to diphenhydramine (21/31, 67.7%), others included chlorpheniramine (n = 4), doxylamine (n = 3), orphenadrine (n = 1), dimenhydrinate (n = 1), and cyproheptadine (n = 1). Other drug classes leading to seizures are shown in Figs. 2 (total) and 3 (intentional). Stratifying ingestions by age groups, the most common agents in the <2 years group were sympathomimetics (4/19), followed by muscle relaxants (2/19) and antidepressants (2/19). In the 3–12 year and 13–18 year group the leading agents resulting in seizures were antidepressants (44% and 49%, respectively) and anticholinergics/antihistamines (25% and 24%, respectively). In the 88 single-agent cases, antidepressants were the leading drug class (33/88; 37.5%) followed by anticholinergics/antihistamines (11/88; 12.5%), anticonvulsants (6/88; 6.8%), psychoactive drugs (6/88; 6.8%), and anti-tuberculosis medications (e.g., isoniazid; 5/88; 5.7%). Acetaminophen co-ingestion was recorded in 15 cases (10.6%) and 10 of them received N-acetylcysteine therapy.

Table 1. Types of encounters and exposure agents recorded in children younger than 2 years of age with drug-induced seizures reported to the ToxIC Case Registry.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Reason for drug exposure</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Phencyclidine</td>
</tr>
<tr>
<td>Female</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Glipizide</td>
</tr>
<tr>
<td>Male</td>
<td>Non-pharmaceutical exposure – unintentional</td>
<td>Aethusa cynapium</td>
</tr>
<tr>
<td>Male</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Cyclobenzoprine</td>
</tr>
<tr>
<td>Male</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Male</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Female</td>
<td>Unintentional pharmaceutical overdose – unintentional</td>
<td>Bupropion, venlafaxine</td>
</tr>
<tr>
<td>Female</td>
<td>Non-pharmaceutical exposure</td>
<td>Methamphetamine</td>
</tr>
<tr>
<td>Female</td>
<td>Non-pharmaceutical exposure – unintentional</td>
<td>Isopropanol</td>
</tr>
<tr>
<td>Male</td>
<td>Medication error resulting in harm</td>
<td>Lidoceaine</td>
</tr>
<tr>
<td>Female</td>
<td>Withdrawal</td>
<td>Morphine, midaazolam, Nicotine</td>
</tr>
<tr>
<td>Male</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Flecainide</td>
</tr>
<tr>
<td>Female</td>
<td>Intentional overdose (by caregiver)</td>
<td>Brodifacoum (“superwarfarin”)</td>
</tr>
<tr>
<td>Female</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Male</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Female</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Female</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Baclofen</td>
</tr>
<tr>
<td>Female</td>
<td>Unintentional pharmaceutical overdose</td>
<td>Methadone</td>
</tr>
</tbody>
</table>

ED, Emergency Department

Discussion

In our United States-based study, nearly 5% of pediatric patients requiring bedside consultation by a medical toxicologist presented with drug-induced seizures. The majority were teenagers between 13 and 18 years in whom the seizure event results from intentional ingestion. Overall, antidepressants were the most common drug class resulting in pediatric drug-induced seizures reported to ToxIC. In addition, they were also the most common drug class implicated in intentional ingestions leading to seizures in children, with bupropion being the most commonly identified drug. The second most common drug class leading to pediatric seizures was over-the-counter anticholinergics/antihistamines.

Our study highlights the fact that the common agents responsible for drug-induced seizures are rapidly changing.
Between 1988 and 2003, the leading causes of drug-related seizures in all age groups transitioned from cocaine, benzodiazepine withdrawal, and tricyclic antidepressants to atypical antidepressants in California.\(^8,9\) Our findings show that the pattern observed in a large general population is mirrored in our cohort of pediatric patients, with cocaine inducing seizures in only one child in our cohort. Since patterns of toxicological exposures are a fast-moving target, the ToxIC Registry, a prospective, real-time toxico-surveillance tool, enhances our ability to detect emerging trends in accidental and intentional exposures and remain abreast of newly introduced compounds and designer drugs.\(^7\)

A second important point is that 61% of our cases involved intentional overdoses. Nearly all of these occurred in teenagers, and were intentional. Thus, in teens presenting with new-onset seizures, the possibility of an antidepressant drug overdose should be considered as a potential diagnosis. Importantly, urinary drug screens available in most EDs in the United States are incapable of detecting some of the agents that led to seizures in our cohort, including bupropion and citalopram.\(^10\) Thus, a falsely negative drug screen can be misleading in such situations and may result in misdiagnoses and inappropriate management. In addition, false-positive bupropion samples were identified with urine immunoassay screening after exposure to amphetamines.\(^10\) This issue is critical in intentional ingestions when a reliable history may not be available, and where some agents may require specific therapy. We also documented acetaminophen co-ingestion in 15 cases (10.6%). While not seizure-inducing, acetaminophen toxicity is important to capture early, and our findings suggest that its screening is relevant in various clinical scenarios.

Sixty-seven percent (58/86 cases) of intentional exposures involved a psychotropic drug. The largest drug class in all exposures was antidepressants (42%). Remarkably, over half resulted from bupropion, for which 90% (27/30) were intentional exposures. Unintentional ingestion of bupropion in children usually has limited toxicity\(^11-14\); however, large or intentional exposures are often associated with seizures.\(^14-16\) Bupropion-induced seizures may occur over a large range of doses\(^3\) and may be delayed up to 24 h after overdose with extended release formulations.\(^17\) Shortly after its introduction into the market in 1985, bupropion was removed because seizures were identified as a common adverse effect.
However, in 1989 it was re-introduced after it was determined that the frequency of seizures was greatly reduced when a daily adult dose of 450 mg or less was employed.\(^{17}\) Currently, bupropion is prescribed to approximately 14% of patients receiving monotherapy for depression,\(^{18}\) and as a third-line therapy for resistant attention-deficit disorder. Its popularity partially stems from the fact that it provokes less headaches, nausea, and vomiting when compared with selective serotonin reuptake inhibitors.\(^{18}\)

The mainstay of acute management of bupropion-induced seizures is similar to that of seizures of unidentified etiology, namely, the administration of intravenous (IV) benzodiazepines. It should be noted that drug-induced seizures, such as those caused by bupropion, are toxic–metabolic in nature and are usually generalized. Since they lack a focal brain lesion they are thought to be less responsive to phenytoin or fosphenytoin,\(^{19,20}\) and may require the addition of IV barbiturates or propofol. Certain other seizure-inducing ingestions may be resistant to standard anticonvulsant therapy requiring specific therapies and antidotes [e.g., pyridoxine for isoniazid (INH)-induced seizures].\(^{21}\)

In contrast, among infants and toddlers, sympathomimetics including illicit drugs were the leading agents involved in drug-induced seizures (Table 1). This is consistent with our previous study, evaluating the most common agents reported in all poisonings under the age of 2 years.\(^{7}\) Exposure of young children to illicit drugs should raise the concern of neglect, unsafe environment, and child maltreatment. This is especially relevant in the first year of life, when coordinated and purposeful reaching of objects is unlikely.\(^{7}\)

Six cases (4%) involved exposure to newer synthetic cannabinoids (Fig. 2). This represents an emerging trend in recreational drug use.\(^{22}\) Three of them involved a single-agent exposure, whereas the other three involved a second exposure to methamphetamine, the designer drugs sold as “bath salts”, or dextromethorphan. Synthetic cannabinoids have gained popularity since 2008, and are easily accessible on the street and over the internet. They are sold under a wide variety of names, such as Spice, K2, K3, and Mr. Nice Guy.\(^{22}\) In 2010, the American Poison Control Centers responded to about 3,200 calls related to synthetic marijuana and bath salts; this number increased to over 13,000 calls in 2011 with 60% of patients being \(\leq \) 25 years of age.\(^{22}\) Serious central nervous system effects include confusion, agitation, loss of consciousness, and seizures.\(^{22,24-28}\) The mechanism leading to seizures in synthetic cannabinoid exposures is presently unknown.\(^{22,26,27}\)

This study has several limitations. The ToxIC registry primarily captures cases from academic tertiary care centers, and may not be representative of the experience and practice in primary health-care facilities.\(^{7}\) Our data likely represent the more serious and consequential poisonings\(^{29}\) and may represent poisonings resulting from agents that clinicians may not be comfortable in recognizing and managing. At present, there is no universal, standardized work-up for patients presenting with suspected drug-induced seizures and investigations are made case-by-case as per clinical judgment. In addition, due to patient privacy, we do not have access to individual laboratory data. However, all ToxIC cases were consulted by a medical toxicologist at the bedside, and have been confirmed by either history, physical exam, or laboratory testing. In addition, the registry relies on individual sites to report all of their cases. This requirement is embodied in an agreement between ToxIC and each participating site. An internal quality assurance survey conducted by ToxIC found that missing cases are infrequent. Last, in the context of the present study, it is unlikely that there would have been any differential non-reporting of cases, if any occur.

In summary, drug-induced seizures are a relatively common reason for pediatric medical toxicology consultation. Most teenagers presenting with drug-induced seizures in our study represent intentional overdose. Over two-thirds of such cases involve psychotropic agents including bupropion and other antidepressants. Clinicians managing teenagers presenting with seizures should have a high index of suspicion for intentional ingestion of antidepressants.

**Declaration of interest**

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

Janine R Hutson is supported by the Pediatric Research and Clinical Summer (PeRCS) program at the Hospital for Sick Children, mentored by Yaron Finkelstein.

**References**

14. Shenoi AN, Gertz SJ, Mikkilineni S, Kalyanaraman M. Refractory hypotension from massive bupropion overdose successfully treated...