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Clinical predictors of adverse cardiovascular events for acute pediatric drug exposures

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\textbf{ABSTRACT}

\textbf{Context:} Risk factors for adverse cardiovascular events (ACVE) from drug exposures have been well-characterized in adults but not studied in children. The objective of the present study is to describe the incidence, characteristics, and risk factors for in-hospital ACVEs among pediatric emergency department (ED) patients with acute drug exposures.

\textbf{Methods:} This is a prospective cohort design evaluating patients in the Toxicology Investigators Consortium (ToxIC) Registry. Pediatric patients (age \textless 18 years) who were evaluated at the bedside by a medical toxicologist for a suspected acute drug exposure were included. The primary outcome was in-hospital ACVE (myocardial injury, shock, ventricular dysrhythmia, or cardiac arrest). The secondary outcome was in-hospital death. Multiple logistic regression analyses were performed to examine novel clinical risk factors and extrapolate adult risk factors (bicarbonate \textless 20 mEq/L; QTc/C21 500 ms), for the primary/secondary outcomes.

\textbf{Results:} Among the 13,097 patients (58.5% female), there were 278 in-hospital ACVEs (2.1%) and 39 in-hospital deaths (0.3%). Age and drug class of exposure (specifically opioids and cardiovascular drugs) were independently associated with ACVE. Compared with adolescents, children under 2 years old (OR: 0.41, 95% CI: 0.21–0.80), ages 2–6 (OR: 0.37, 95% CI: 0.21–0.80), and ages 7–12 (OR: 0.51, 95% CI: 0.27–0.95) were significantly less likely to experience an ACVE. Serum bicarbonate concentration \textless 20 mEq/L (OR: 2.31, 95% CI: 1.48–3.60) and QTc/C21 500 ms (OR: 2.83, 95% CI: 1.67–4.79) were independently associated with ACVE.

\textbf{Conclusion:} Previously derived clinical predictors of ACVE from an adult drug overdose population were successfully extrapolated to this pediatric population. Novel associations with ACVE and death included adolescent age and opioid drug exposures. In the midst of the opioid crisis, these findings urgently warrant further investigation to combat adolescent opioid overdose morbidity and mortality.

\textbf{INTRODUCTION}

Drug exposures represent a significant public health concern for pediatric populations [1–3], and children are uniquely vulnerable to adverse sequelae of these exposures. The exploratory behaviors of young children lead them to ingest drugs with unpleasant tastes or odors which may be avoided by older children and adults [2,4]. Very young children also have a lower body mass, limited physiologic reserve, and less developed metabolic pathways, making them more susceptible to injury from exposure to even small amounts of drugs [2,4]. In comparison, adolescents have an increased tendency toward intentional drug overdoses which are typically more severe than unintentional drug exposures [1,4]. Although pediatric poisonings account for the minority of poisoning related deaths they require significant healthcare resource utilization: some authors have estimated that more than half of all toxic exposures in children are admitted to an intensive care unit [5].

In adults, adverse cardiovascular events (ACVEs) are a significant cause of morbidity and mortality associated with exposure to drugs [6,7]. ACVEs have been shown to occur in up to one-sixth of adults hospitalized for overdose and risk factors for ACVEs include a history of cardiac disease, a prolonged QTc interval on electrocardiogram, and a low serum bicarbonate concentration [6,7]. A clinical prediction rule has recently been derived using these variables in adults, with a 90.9% positive predictive value for ACVE when two or more risk factors were present [6]. Validation studies for this
Predicadence rule are currently underway in the adult drug overdose population.

Predicting adverse outcomes in pediatric patients with drug exposure can be particularly challenging, and ACVEs have not been well described in this population. Information on pediatric cardiotoxicity and following acute exposures in children is limited to a small number of studies on specific drug classes [8,9]. The objectives of the present study were to (1) describe the incidence rate, characteristics, and potential risk factors for in-hospital ACVEs among pediatric patients following acute drug exposures and (2) replicate a previously derived prediction rule from adults to predict ACVE in this population.

Patients and methods

Study design and data source

We utilized registry data collected from patients evaluated at Toxicology Investigators Consortium (ToxIC) hospital sites. The ToxIC network spans 65 US hospitals in 35 US cities across 23 states (www.toxicregistry.org). All patients were evaluated at the bedside by a medical toxicologist for an acute drug exposure. The ToxIC registry contains de-identified data from all medical toxicology consultations at each site, the majority of which are comprised of academic training institutions. The registry is approved by the Western Institutional Review Board (IRB) [10]. The present study was approved with waiver of consent/assent by the ToxIC Research Core and was deemed exempt of further IRB requirements by the University of Massachusetts Medical School IRB. Data were downloaded directly from the registry by a single investigator (SM).

Study inclusion criteria

Pediatric patients (≤18 years old) presenting to the ED for acute drug exposures that were entered into the ToxIC registry between 2010 and 2016 were screened for inclusion. Patients who were deemed by consulting medical toxicologists as having “no toxicological exposure”, “unlikely toxicology related exposure”, or “chronic drug exposure”, were excluded.

Primary and secondary outcomes

The primary outcome of interest, ACVE, was defined based on the prior literature as the presence of any of the following during the patient’s admission: (1) acute myocardial injury, (2) hypotension/shock necessitating the use of vasopressors, (3) ventricular dysrhythmia, or (4) cardiac arrest [6,7,11–15]. Myocardial injury was defined as a documented serum troponin I > 0.09 ng/ml, consistent with widely accepted cutoffs and prior analyses of ACVEs [7,13]. Cardiac arrest was identified as documented administration of cardiopulmonary resuscitation (CPR). In-hospital death was evaluated as a secondary outcome of interest.

Selection of independent variables

Demographic, historical, and clinical factors were selected as potential predictor variables on the basis of clinical relevance to the primary outcome as well as the availability and completeness of available data. In the second portion of our analyses, when comparing a predictive model for in-hospital ACVE that has previously been derived in adults [6], we utilized a subset of the original cohort with complete data points for all variables of interest – notably age, bicarbonate concentration, and QTc interval. Of note, QRS interval was not evaluated, as it has not been shown to be predictive of ACVE for all comers with heterogeneous drug overdoses [14].

Statistical methods

Descriptive statistics were utilized for sociodemographic variables, encounter characteristics, and exposure characteristics. Differences in continuous variables were tested using ANOVA (normally distributed with equal variance), or Wilcoxon Ranks Sum or Kruskal–Wallis tests (for skewed distributions). Differences in categorical variables were assessed using the Chi-square test. Unadjusted analyses were performed using the Chi-square test to evaluate associations between various drug exposure classes and the primary and secondary study outcomes. Multiple logistic regression analysis was utilized to evaluate the effect of the independent variables on the primary and secondary outcomes. Variables identified as significant at p < .05 in the unadjusted analyses, and those that were deemed to be clinically important by author consensus, were included in the final models. Potential collinearity was assessed by evaluating pairs of variables for high correlation (r > 0.90). Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Post hoc subgroup analyses were performed to evaluate the association of various types of opioids and cardiovascular drug subclasses with the primary and secondary study outcomes given particular interest in these areas.

Finally, we adapted a previously derived prediction model for ACVEs in adults, which includes age, QTc, serum bicarbonate, and history of cardiac disease [6]. Of note, given the low prevalence of cardiac disease in children, this variable was not included in our model. We defined a composite age variable to include age category <2 years or 13–18 years, based on the bimodal distribution of ACVEs and death in our population and author consensus. These categories correlate well to the clinical scenarios of highest risk – exploratory ingestions in young children and adolescent therapeutic misadventure or self-harm attempt. For the remaining variables, we used the same cutoffs used in adults (QTc ≥ 500 ms, and serum bicarbonate < 20 mEq/L). The method used for QTc correction was Bazett’s formula in > 99% of data. Records missing serum bicarbonate and/or QTc data were excluded from the analysis. All data analyses were performed using SAS software (Version 9.4, Cary, NC).
Results

Study population characteristics

Among the 13,097 pediatric patients enrolled in this registry in the study period, 58.5% were female with the following age distribution:< 2 years, 1704 patients (13.0%), 2–6 years, 2310 patients (17.6%), 7–12 years, 1090 patients (8.3%), and 13–18 years, 7993 (61.0%). Patient characteristics are outlined in Table 1.

Incidence and distribution of ACVEs

The incidence of any ACVE was 2.1%, with shock being the most common event, occurring in 69.8% of all ACVEs (Table 2). Death occurred in 39 (0.3%) patients overall, and in 23 (8.3%) patients with an ACVE. Of note, no deaths occurred within the 7–12-year-old age category.

Unadjusted analyses of ACVEs

On unadjusted analyses, there were no significant differences between the ACVE and non-ACVE groups with regards to sex, race, ethnicity, or history of cardiac disease. Patients from the 13–18-year-old age category had higher odds of ACVE compared to other age groups (OR: 2.3, p < .001). We observed a lower frequency of ACVEs when the medical toxicology consultation was initiated in the Emergency Department (ED) and increased frequency of ACVEs when the medical toxicology consultation was made by an admitting service.

Unadjusted analyses of drug class and outcomes

The five most common drug classes in the cohort were non-opioid analgesics (23.2% of total cohort), antidepressants (14.1%), anticholinergics (11.4%), cardiovascular drugs (8.7%), and sedative hypnotics (8.6%). These five categories made up 66% of all exposures, and 78% of ACVE outcomes. Among these drug classes, cardiovascular drugs (OR: 3.48, p < .001) and antidepressants (OR: 1.59, p < .01) were significantly associated with an increased risk of ACVE, while non-opioid analgesics (OR: 0.58, p < .01) were significantly associated with a decreased risk of the primary outcome (Supplemental Table 1). None of these drug classes were significantly associated with death.

While not among the five most common drug class categories, two drug classes of recent clinical interest [16,17] were associated with mortality: opioids and sympathomimetics. These two classes comprised 5.9% and 6.6% of patients, respectively (Supplemental Table 1). Opioid exposure was significantly associated with both ACVE (OR: 2.77, p < .001) and death (OR: 4.8, p < .001), while sympathomimetic exposure was associated with only death (OR: 2.6, p = .03) but not ACVE (OR: 1.1, p = .66).

Opioid subgroup analysis and outcomes

Because of the correlation of opioids with both the primary and secondary study outcomes and the
contemporary interest in the effects of the current opioid crisis, a series of post hoc subgroup analyses were performed to evaluate the effect of specific opioids on AVCE and death. Patients with opioid exposures made up 5.9% of the total cohort but 14.4% of all ACVEs and 23% of deaths (Table 3). Buprenorphine was the most frequent opioid implicated, followed by oxycodone. Oxycodone was associated with the highest number of ACVEs and deaths, but only its relationship with death was significant. Buprenorphine exposure was less frequently complicated by ACVE compared to all other opioids (0.7% compared to 6.1%, p = .01).

**Cardiovascular drug subgroup analysis and outcomes**

Because of the statistical and clinical association of cardiovascular drugs with the primary outcome, a series of post hoc subgroup analyses were also performed to evaluate the effect of specific cardiovascular drug classes on AVCE and death. Patients with cardiovascular drug exposures made up 8.7% of the total cohort but 24% of all ACVEs and 15.4% of deaths (Table 4). Centrally acting alpha receptor agonists (e.g., clonidine, guanfacine) were the most frequently implicated class, followed by beta blockers and calcium channel blockers. Calcium channel blockers and antiarrhythmics were significantly associated with increased rates of AVCE, while centrally acting alpha agonists were associated with lower rates of ACVE (3.9% compared to 9.1%, p = .001).

**Independent predictors of the primary outcome (ACVE)**

Results for logistic regression models examining independent predictors of ACVE are reported in Table 5. Adolescent age group was associated with increased odds of ACVE compared with all other age groups. Exposures to either cardiovascular drugs (OR: 4.63, 95% CI: 3.30–6.50) or opioids (OR: 3.53, 95% CI: 2.33–5.35) independently predicted occurrence of ACVE. Sex, race, the presence of intent (intentional vs. unintentional exposure), and number of unique drugs in exposure were not independent predictors of ACVE.

**Independent predictors of the secondary outcome (mortality)**

Results for logistic regression models examining the independent predictors of mortality are also reported in Table 5. Black race (OR: 3.3, 95% CI: 1.17–9.33), cardiovascular drug exposures (OR: 3.25, 95% CI: 1.17–9.05), and opioid exposures (OR: 5.54, 95% CI: 1.94–15.79) were all independent predictors of mortality. Age group, sex, presence of intentional exposure, number of unique drugs in exposure were not predictors of mortality.

**Replication of adult ACVE model**

After listwise deletion, the necessary data points for the model (QTc interval and serum bicarbonate concentration) were available for 1827 patients. Of these, there were 100 ACVEs and six deaths. Characteristics of patients included and excluded from this analysis are outlined in Supplemental Table 2. After adjusting for age, both QTc ≥500 ms (OR: 2.83, 95% CI: 1.67–4.78) and serum bicarbonate concentration <20 mEq/L (OR: 2.31, 95% CI: 1.48–3.61) were significantly associated with an increased risk for ACVE (Wald test: $\chi^2 = 35.5$, p < .001; Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 1.50$, p = .47). Age was not associated with increased risk (OR: 1.38, 95% CI: 0.71–2.71). We were not able to build a logistic regression model for mortality due to the low number of deaths (N=6) with complete data.

**Discussion**

Our data show that clinical predictors of ACVE in pediatric acute drug exposures are similar to those of adults, but with
unique characteristics in terms of age and specific drug classes. While ACVE incidence was relatively low overall (2.1%), novel clinical risk factors included the following: adolescent age, opioid drugs, and cardiovascular drugs. Importantly, these results confirm that the initial serum bicarbonate and initial ECG are crucial clinical tests in the evaluation of pediatric acute drug exposure. Clinicians should consider these clinical and diagnostic factors when evaluating children with acute drug exposure, and use this information to guide the diagnostic work-up from the ED.

Though opioids accounted for less than 5% of exposures, they were significant risk factors for ACVE and responsible for nearly 25% of all deaths. The opioid epidemic has been declared a national emergency in the US [18,19], and overdose deaths from opioids continue to increase, with more than 350,000 deaths from 1999 to 2016 [20]. Across the US, the prevalence of opioid use disorder and the rates of opioid overdoses have risen precipitously in recent years. High-risk opioid use in young people is increasing alarmingly in recent years [5], and pediatric opioid exposures are rising in parallel with availability of opioids though adult prescriptions in the home [21]. Opioid overdose induced respiratory failure is a common cause of cardiovascular collapse in otherwise healthy children, which may explain the findings of the present study. In the midst of this crisis, these findings urgently warrant further investigation to combat pediatric opioid overdose morbidity and mortality.

Buprenorphine exposures in this cohort were consistent with, and build upon, prior literature from pediatric drug exposures. Buprenorphine in this cohort was significantly less likely to be complicated by ACVE compared to all other opioids (0.7% compared to 6.1%, \( p = .01 \)). Theoretically buprenorphine should be associated with lower risk of ACVE and death, given its ceiling effects on respiratory depression in adults [22,23]. Although previous studies have found that pediatric patients exposed to the partial opioid agonist buprenorphine do commonly exhibit signs of opioid toxicity [24], our findings suggest it is lower risk with respect to ACVE and death than other opioid subclasses. Oxycodone may be associated with mortality given the availability and widespread use of extended release preparations and risks of delayed symptom onset after exposure, and possible QTc prolongation [25], which may have an impact on cardiac morbidity as well.

The association between adolescent age and ACVE in the present study is a novel finding. Adolescents are more likely to present after recreational drug use and/or self-harm attempts. These exposures differ from exploratory ingestions in younger children, which are typically low dose, oral exposures [4]. By comparison, intentional exposures in adolescents are more likely to involve larger doses and potentially dangerous routes of administration (injection, insufflation). Further study should focus on this population in terms of strategies to identify and prevent drug overdose.

A significant strength of this study is confirmation of toxicological exposure based on bedside evaluation by experts in medical toxicology, rather than reliance on toxicology screens. Standard toxicology screens were not used to determine eligibility because these tests are incomplete, fraught with false positives/negatives, and typically do not change the acute management in the ED [26]. Thus, patients with no toxicological exposure, who had symptoms unrelated to a drug exposure, were accurately excluded. This adds substantially to the validity of the study and enhances generalizability to “real-world” ED patients.

Interestingly, ACVE was associated with toxicology referral by an admitting service while non-ACVEs were more likely to receive a toxicology referral from the ED. This may suggest that delayed symptom onset carries greater risk of adverse outcome, or that prompt recognition and referral from the ED is protective; however, this is a matter of speculation and further study is warranted. It is also logical that single drug and unintentional exposures were associated with lower incidence of ACVE, as these types of exposures tend to be less

Table 5. Logistic regression models for ACVE and death.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Regression coefficient</th>
<th>OR 95% CI</th>
<th>Regression coefficient</th>
<th>OR 95% CI</th>
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<td>0.21–0.80</td>
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<td>0.51</td>
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<tr>
<td>13–18</td>
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<td>0.70–5.55</td>
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<td>0.67–2.25</td>
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<td>Intent of exposure</td>
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<td>0.43–1.47</td>
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<td>0.94–1.8</td>
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<td>3.53</td>
<td>2.33–5.35</td>
<td>1.71</td>
</tr>
</tbody>
</table>

*Denotes referent category.

Excluded from model, no deaths in this age group.

Includes nonpharmaceutical exposures, withdrawal, and other.
severe [4]. However, these associations did not remain significant on multivariate analyses.

The association between cardiovascular drugs and ACVE is unsurprising, as these have obvious effects on physiologic parameters such as blood pressure, cardiac contractility, and cardiac conduction. Cardiovascular drug systemic effects, coupled with failure of compensatory mechanisms, could lead to distributive or cardiogenic shock. Cardiovascular drug toxicity may also cause myocardial injury through a variety of mechanisms, including decreased myocardial supply (e.g., vasospasm), increased myocardial demand (e.g., tachycardia), or myocardial cell death (e.g., inhibition of oxidative phosphorylation). Finally, sudden cardiac death from dysrhythmia in a young healthy population is epidemiologically most likely to be drug-related [27,28].

Existing models to predict ACVE in adults may be applicable in pediatric patients, aside from prior heart disease. Our replication of the adult model [6] was somewhat hampered by incomplete capture of these variables, particularly absence of ECG data. Furthermore, both ECG and serum bicarbonate concentration were more likely to be captured routinely in older children, females, cardiovascular drug exposures, and in patients with vasopressor requirement and/or myocardial injury (Supplemental Table 2). These data suggest severe underutilization of the initial ECG as part of the basic ED management of the poisoned pediatric patient. Our heterogeneous dataset included children with unintentional and asymptomatic exposures, supporting the importance of ECG screening for QT interval in children with acute exposures. Further studies are required to evaluate barriers and facilitators to implementation of routine ECG screening as part of the routine ED evaluation for pediatric patients with acute drug exposures.

**Study strengths and limitations**

This multicenter cohort was leveraged from a large data registry, providing an opportunity to study the relatively rare phenomenon of pediatric ACVE and death after drug exposures. As a requirement of the registry, all patients received bedside evaluation by an attending medical toxicologist. This is expected to increase the diagnostic accuracy of the clinical data entered, but may skew the registry towards more severe drug exposures on a population level [29]. In addition, by virtue of using registry data, certain elements are subject to misclassification bias (such as racial and ethnic assignment) because methods to ascertain these variables were not standardized across all hospitals; however, data used for the final model were extremely objective (i.e., serum and ECG data) and not as vulnerable to misclassification. Also inherent to registry studies is the dilemma of missing data, which in our case was more common in some variables that others. Finally, generalizability to hospitals without medical toxicology expertise (e.g., community non-teaching hospitals) is another potential limitation which requires further study.

**Conclusions**

In this large multicenter cohort of pediatric drug exposures, the incidence of ACVE was much lower than that of adults with acute drug overdose. Several previously derived clinical predictors of ACVE from an adult drug overdose population were successfully extrapolated to a pediatric population of drug exposures. Existing models to predict ACVE in adults may be applicable in pediatric patients, aside from prior cardiovascular disease. Clinicians should consider these clinical and diagnostic factors when evaluating children with acute drug exposure. Novel associations with ACVE and death included adolescent age and opioid drug exposures. In the midst of the opioid crisis, these findings urgently warrant further investigation to combat adolescent opioid overdose morbidity and mortality.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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