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Clinical effects of unintentional pediatric buprenorphine exposures: experience at a single tertiary care center

Michael S. Toce, Michele M. Burns and Katherine A. O'Donnell

ABSTRACT
Context: Exploratory buprenorphine ingestions in young children have been associated with clinically significant toxicity. However, detailed data on the clinical presentation and management of these patients are lacking. In an attempt to obtain more comprehensive data, we sought to examine a single center cohort of patients with report of buprenorphine exposure and provide descriptive analysis of rates of respiratory depression, time to respiratory depression, interventions, disposition, and outcomes.

Study design: We performed a retrospective cohort study at a single pediatric tertiary care center of children between the age of 6 months and 7 years of age hospitalized between 1 January 2006 and 1 September 2014 with report of buprenorphine or buprenorphine/naloxone exposure. Patients with possible exposure to more than one agent were excluded. We extracted clinical findings, including time to respiratory depression, interventions, and disposition from the medical record.

Results: Eighty-eight patients met the inclusion criteria. Seven patients were excluded. The median age was 24 months (IQR 18–30). 20 patients (23%) received activated charcoal while 48 (55%) were treated with naloxone. 36 (41%) patients were admitted to the ICU. Observed clinical effects included respiratory depression (83%), oxygen saturation by pulse oximetry (SpO2) < 93% (28%), depressed mental status (80%), miosis (77%), and emesis (45%). Median time from exposure to respiratory depression was 263 min (IQR 105–486). The median hospital length of stay was 22 h (IQR 20–26) and was positively associated with estimated exposure dose (p = 0.002).

Conclusion: Pediatric patients exposed to buprenorphine are likely to exhibit signs and symptoms of opioid toxicity, including respiratory depression, altered mental status and miosis. Although the majority of patients developed signs of clinical toxicity within 8 h of reported exposure, the optimum duration of monitoring remains unclear.

Introduction
Mortality rates for heroin overdose in the United States doubled between 2010 and 2012.[1] These findings mirror the overall trend in the country of increased non-medical use of opioid pain relievers and heroin.[2,3] Buprenorphine is a highly lipophilic, partial μ-opioid agonist and κ-opioid antagonist that reduces illicit opioid use.[4,5] Buprenorphine has a high affinity for the μ-receptor (more than 1000 times that of morphine) and has a long half-life (mean half-life = 37 h).[6] Buprenorphine has a “ceiling effect” limiting rates of euphoria and respiratory depression in adults, although the ceiling effect may be mitigated in cases of co-ingestion of benzodiazepines.[7–10] These pharmacokinetic and pharmacodynamic properties make buprenorphine an effective drug to treat opioid addiction.[6,11,12]

However, unintentional buprenorphine exposures in children can cause significant morbidity and rarely mortality, with multiple case reports and case series highlighting this danger.[13–15] Children are susceptible to adverse effects including respiratory depression, emesis, and paradoxical agitation when unintentionally exposed to buprenorphine.[16–18] In a recent national surveillance study, nearly 8% of all unsupervised oral prescription medication ingestions by children <6 years of age presenting to emergency departments and resulting in hospitalization were due to buprenorphine, the highest percentage of any single agent examined.[19] This trend is particularly concerning in the context of increasing buprenorphine prescriptions,[20–22] increasing overall prescription drug use and increasing polypharmacy.[23]

The aim of our study was to expand on previous research by identifying a large single center cohort of children evaluated at the bedside by a medical toxicologist in the setting of buprenorphine exposure. By using a single center cohort at a pediatric tertiary care center with well-utilized consulting and admitting toxicology services as opposed to poison center data, we had access to detailed information present in the electronic health record on the presenting signs and symptoms of toxicity, time to respiratory depression and interventions, disposition, and length of stay.
Patients and methods

Study design

We performed a single center retrospective cohort study of children between the age of 6 months and 7 years admitted to a large, urban, tertiary care center between 1 January 2006 and 1 September 2014 with concern for buprenorphine exposure. The study protocol was approved by the institutional review board with a waiver of informed consent.

Patient identification

We identified patients using a list maintained by the hospital’s toxicology service of all patients in whom the admitting diagnosis was buprenorphine exposure and the toxicology team was consulted. Primary author performed chart review. We entered data into a standardized spreadsheet for all patients. The data abstractor was not blinded to study purpose. For inclusion, patients had to be between the ages of 6 months and 7 years at the time of presentation with report of buprenorphine or buprenorphine/naloxone exposure and be evaluated at the bedside by the medical toxicology service. We excluded patients with possible exposure to multiple medications. Given the nature of pediatric unintentional exposures, polysubstance exposures are relatively rare.

Patients were examined in the emergency department (ED), medical floor or the intensive care unit (ICU). To ensure that no patients who met inclusion criteria were missed, a separate search of hospital administrative data utilizing ICD-9 codes (965.00, 965.09, E850.2, 970.1) and subsequent chart review was performed. No additional patients who met inclusion criteria were identified.

Data collection

We reviewed the medical records of all eligible patients and abstracted the following: age, sex, weight, time of exposure, estimated exposure dose, time to respiratory depression, heart rate, blood pressure, oxygen saturation, disposition (floor or ICU), length of stay, medication exposure (buprenorphine versus buprenorphine/naloxone), medication preparation (tablet versus film), medication source (mother, father, other relative, parent’s partner, parent’s friend, unknown), interventions (naloxone, activated charcoal, and/or intubation), presenting hospital, and time from exposure to presentation at our institution. Our primary outcomes included rates of respiratory depression, hypoxia, and the use of naloxone, while our secondary outcomes included examining factors that were associated with length of stay, and exploring the relationship between estimated exposure dose and the development of respiratory depression. We calculated time to presentation at our institution by recording the time of presenting vital signs obtained in triage in the emergency department, or upon arrival to the floor/ICU and subtracting the documented time of exposure. Hours were then converted to minutes for statistical analysis. Similarly, we calculated time to respiratory depression by determining the time of first occurrence of respiratory depression (defined below) by reviewing available vital sign data in outside hospital documentation and the electronic health record and subtracting the documented time of exposure. Estimated exposure dose based on documentation; no confirmatory levels were obtained for the majority of patients. In the event a pill fragment was removed from a patient’s mouth, we relied on documentation to estimate the exposure dose. For example, if one-half of an 8 mg tablet was removed, we estimated the exposure dose to be 4 mg. If a pill was “licked” or “removed intact,” we estimated exposure dose to be 1/10th of the total dose, similar to previous reports.

For the purposes of medication source, primary caregiver was defined as mother, father, or parent’s partner. In addition to our institution’s electronic medical record, we had access to outside hospital documentation in the form of scanned records. We included interventions prior to arrival at our institution in analysis.

Adverse events

We defined miosis as at least one provider documenting a pupillary diameter of 2 mm or less, or documentation of “miosis” or “miotic pupils.” We defined respiratory depression as any recorded respiratory rate below the first percentile for age. We defined hypoxia as an oxygen saturation by pulse oximetry (SpO2) < 93% on room air.

Statistical analysis

We used STATA version 13.0 for all statistical analysis (College Station, TX). When appropriate, we calculated medians and interquartile ranges (IQR). To examine the relationship between estimated dose ingested and the development of respiratory depression, we performed a logistic regression model with respiratory depression as the dependent variable and dose as the independent variable. We performed a multivariate quantile (median) regression with length of stay (in hours) as the dependent variable and sex, age (in months, modeled as continuous variable), dose (in mg/kg), and time to presentation (in minutes) as the independent variables. These predictors were chosen based on previous literature and clinical expertise.

All tests were two-tailed with a cut-off p value of < 0.05.

Results

We identified 95 children with concern for buprenorphine exposure, of whom 88 (93%) met inclusion criteria (Table 1). Five patients were excluded due to possible exposure to more than one substance and two patients were excluded for being less than 6 months of age at time of presentation. Data on estimated exposure dose and time to presentation at our institution were available on 78 and 85 patients, respectively. The majority of patients (89%) initially presented to another health care facility and were transferred to the study institution (median time from exposure to arrival at the study institution was 232 min [IQR 178–331]). 86 patients were exposed to buprenorphine/naloxone and 2 patients were exposed to buprenorphine alone. Of the patients who...
were exposed to buprenorphine/naloxone, 80 (93%) of them were exposed to a tablet formulation while 6 were exposed to a strip/film formulation. The median reported buprenorphine exposure dose was 4 mg [IQR 2–8], or 0.29 mg/kg [IQR 0.18–0.53].

In terms of clinical effects (Table 2), 83% of patients exhibited respiratory depression based on our definition and 28% became hypoxic. Furthermore, 27 patients had a respiratory rate that was more than 5 breaths per minute below the first percentile for age. Of the 73 patients who developed respiratory depression, data on time to respiratory depression were available on 69 patients. Median time from exposure to respiratory depression was 263 min [IQR 105–486]. 70 patients (80%) had depressed mental status (i.e., lethargic, somnolent, sleepy, drowsy) and 4 patients (5%) were paradoxically agitated. 65 patients (77%) had miotic pupils. 40 patients (45%) had at least one episode of emesis. Respiratory depression was not associated with estimated exposure dose \( (p = 0.134) \).

Interventions included activated charcoal (23%) and naloxone (55%). Within the group that received naloxone, 32 (67%) patients received multiple doses of naloxone with a range of 2–10 doses and 13 (27%) patients received naloxone infusion. One patient received naloxone infusion without receiving a bolus. The median dose of naloxone given to patients receiving a single dose \( (n = 15, \text{ data available on 14}) \) was 0.09 mg/kg [95%CI 0.07, 0.11]. In patients who received multiple doses of naloxone but not placed on continuous infusion \( (n = 20, \text{ data available on 19}) \), the median total amount received was 0.19 mg/kg [95%CI 0.07, 0.31]. We omitted patients receiving continuous naloxone infusion from the analysis of median dose received due to the fact that infusions were often started at outside institutions and compared to other extracted data, documentation rarely included starting time. Additionally, infusions were occasionally discontinued during transfer or upon arrival to our emergency department, leading to challenges in obtaining accurate data regarding duration of infusions. Of the 48 patients that received naloxone, time to administration of the first dose was available on 37 patients. 32 (86%) received naloxone within 4 h of exposure. Of that group, 5 (16%) received naloxone within an hour. Three (8%) received naloxone between 4 and 8 h of exposure, one patient received naloxone between 8 and 12 h of exposure, and one patient received naloxone greater than 12 h after exposure. One patient was intubated and received vasopressors. He was found by his family at 5 o’clock in the morning unresponsive and apneic. He was taken to an outside hospital where he was intubated and started on dopamine and epinephrine for refractory hypotension with a systolic blood pressure of 50 mmHg. He remained intubated for 2 days and upon extubation, continued to experience respiratory depression that was resolved with naloxone administration. There were no fatalities. One patient was discharged from the ED. 36 (41%) patients received ICU level of care. All patients were discharged in the care of their primary caregiver and no patient was placed in Department of Children and Families custody.

In multivariate regression analysis, reported exposure dose was significantly associated with an increase in length of stay \( (p = 0.002) \) (Table 3). Age, sex, and time to presentation were not statistically significantly associated with length of stay.

### Discussion

In this single center cohort of pediatric patients with reported buprenorphine exposure, the majority of patients demonstrated clinical evidence of opioid intoxication and received antidotal therapy (naloxone). Unlike previous studies, we had access to each patient’s electronic medical record and, in most cases, outside hospital documentation.\[16–18\] Documentation included bedside histories, physical examinations, and assessments by a fellowship-trained medical toxicologist. As such, we were able to extract and analyze data not available to previous groups.

Compared to previous reports, a larger percentage of our patients presented with typical signs and symptoms of opioid toxicity, namely miosis, depressed mental status, and respiratory depression and a larger proportion of our patients received antidotal therapy.\[16–18\] There are several reasons for these clinical findings. First, Hayes et al. and Lavonas et al. queried a national poison center database (RADARS System) to obtain their data, while Thomas et al. used data obtained from the Utah Poison Control Center.\[16–18\] As such, these studies were limited by cases that were

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### Table 1. Demographics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male 45 (51)</td>
</tr>
<tr>
<td>Medication source</td>
<td>Primary caregiver 57 (65)</td>
</tr>
<tr>
<td></td>
<td>Other relative 15 (17)</td>
</tr>
<tr>
<td></td>
<td>Parent’s friend 12 (14)</td>
</tr>
<tr>
<td></td>
<td>Unknown 4 (5)</td>
</tr>
</tbody>
</table>

### Table 2. Clinical effects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory depression</td>
<td>83</td>
</tr>
<tr>
<td>( \text{SpO}_2 ) &lt; 93% [^a]</td>
<td>28</td>
</tr>
<tr>
<td>Depressed mental status</td>
<td>80</td>
</tr>
<tr>
<td>Agitation</td>
<td>5</td>
</tr>
<tr>
<td>Miosis [^b]</td>
<td>77</td>
</tr>
<tr>
<td>Emesis</td>
<td>45</td>
</tr>
</tbody>
</table>

\[^a\] n = 87.

\[^b\] n = 84.

### Table 3. Multivariate analysis of factors associated with length of stay.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.545</td>
<td>[–3.14, 4.23]</td>
</tr>
<tr>
<td>Age, months</td>
<td>0.002</td>
<td>[–0.161, 0.165]</td>
</tr>
<tr>
<td>Dose, mg/kg</td>
<td>3.39</td>
<td>[1.27, 5.51]</td>
</tr>
<tr>
<td>Time to presentation, minutes</td>
<td>–0.0002</td>
<td>[–0.012, 0.011]</td>
</tr>
</tbody>
</table>
voluntarily reported and by the information provided by the caller. Key information, including time of exposure, time to respiratory depression, respiratory rate, and interventions, was frequently unavailable. Poison center databases are a valuable source of data that are easily accessible and provide large sample sizes for a given exposure, but limitations do exist.[30,31] In contrast, we had access to recorded vital signs (by hospital policy, vital signs are recorded at least every 4–8 h while on the floor and every 1–2 h while in the ICU), an electronic medication administration record which records dose and timing of all administered medications, bedside nursing assessments and documentation, as well as bedside physician documentation.

Second, 99% of our cohorts were admitted and 100% were evaluated at the bedside by a medical toxicology attending. In the cohort studied by Hayes et al., 26% of patients were managed at home while in the cohort studied by Thomas et al., 46.5% were managed outside of a health care facility.[17,18] Such findings suggest that these two studies included less sick patient populations compared to our study. Third, the estimated median buprenorphine exposure dose in the Hayes et al. study was 2 mg.[17] In this study, the estimated median buprenorphine exposure dose was 4 mg. While we did not find a statistically significant association between estimate exposure dose and respiratory depression, this could be due to the small number of patients in our study that did not fit our definition of respiratory depression. Finally, the majority of patients in our cohort were transferred from an outside hospital for a tertiary level of care, likely selecting for a more symptomatic patient population and also explaining the higher proportion of patients receiving naloxone.

An additional explanation for the large discrepancy in the proportion of patients developing respiratory depression is due to the difference in the definition of respiratory depression. Similar to Hayes et al., Lavonas et al. found respiratory depression in 43% of patients whose cases underwent a focused adverse event review, which is approximately half of the percentage we presented in this study.[16,17] Thomas et al. found respiratory depression in only 19% of patients.[18] Hayes et al. defined respiratory depression as a "decreased rate of respirations, decreased depth of respirations, decreased oxygen saturation, or evidence of cyanosis" while Lavonas et al. and Thomas et al. did not define respiratory depression.[16–18] In our study, we defined respiratory depression as a respiratory rate below the first percentile for age. This value was based on research that has examined age appropriate vital signs.[26] When we examined our patients with respiratory depression, 48 (66%) were either hypoxic, received naloxone, or both, suggesting that our definition of respiratory depression captured the majority of patients with clinically significant toxicity. Additionally, more than a third of our cohort had a documented respiratory rate more than 5 breaths per minute below the first percentile for age, again supporting the findings that our patient population represents a sicker cohort than has previously been described.

While 83% of patients developed respiratory depression, only 28% became hypoxic. Most patients admitted with concern for buprenorphine exposure were placed on continuous pulse oximetry, but few were placed on continuous waveform capnography. Seeing that hypoventilation is the primary respiratory finding, and hypoxia occurs in relatively few patients, providers should consider continuous waveform capnography in patients exhibiting signs of opioid intoxication, although further studies are needed to determine the significance of transient hypoventilation in the pediatric population.

Although we observed only one intubation and no deaths, buprenorphine exposure may have morbidity and mortality. Geib et al. presented a case series of five patients with buprenorphine exposure, one of whom required intubation and mechanical ventilation.[14] Bellot et al. describe a 2-year-old child who suffered from acute leukoencephalopathy after unintentional ingestion.[13] Kim et al. reported a pediatric fatality after a 13-month-old boy ingested an 8 mg tablet of buprenorphine/naloxone. The pill was found in his mouth after he was given the pill bottle to use as a rattle. It was then removed, and he was allowed to sleep. The following morning he was found unresponsive and subsequent resuscitation efforts were unsuccessful.[15] Thomas et al. described 462 exposures that resulted in 3 deaths.[18] Finally, Lavonas et al. examined 2380 cases of unintentional pediatric buprenorphine exposures and identified four pediatric fatalities.[16] These reports highlight the need for monitoring and medical evaluation after suspected buprenorphine exposure.

Previous research suggests a "ceiling effect" of buprenorphine in adults such that higher doses do not induce respiratory depression.[10] As the present study demonstrates, the ceiling effect is not seen in pediatric buprenorphine exposures. One possible explanation involves the development of P-glycoprotein (P-gp) in pediatric brains. P-glycoprotein is a protein that functions to move substrates across the blood–brain barrier. Norbuprenorphine, a major metabolite of buprenorphine, is a substrate for P-gp, and blockade of P-gp leads to increased respiratory depression in norbuprenorphine-exposed mice.[32,33] The development of P-gp occurs in time-dependent manner, with limited P-gp present in the newborn.[34–36] It is possible that the limited availability of P-gp in the pediatric brain leads to an increase in cerebral norbuprenorphine, with the result being respiratory depression.

Due to the long half-life of buprenorphine and concern for delayed respiratory depression, our current practice is to admit all young children with potential buprenorphine exposure. In spite of our rates of clinical symptoms and antidotal therapy, the median length of stay of our cohort was 22 h. 84 (95%) patients developed clinical signs and symptoms consistent with opioid exposure (CNS depression, respiratory depression, and/or miosis). The median time from reported exposure to documented respiratory depression was roughly four and a half hours; however, approximately a quarter of patients who developed respiratory depression did so more than 8 h after reported exposure. Despite the number of patients who had delayed onset respiratory depression documented, only two patients received their first dose of naloxone eight or more hours after reported exposure. Estimated dose of exposure was the only measured variable
that was significantly associated with length of stay, with every 1 mg/kg increase in reported exposure dose associated with an increase in length of stay by 3.39 h. Although estimated dose is thought of as an unreliable measure, these data suggests that it might have some prognostic relevance in this particular exposure.

This study has several limitations. As a retrospective cohort study, we were limited by the information included in the patient’s electronic medical record. Similarly, there were patients whose outside medical records were incomplete. Additionally, because buprenorphine serum or urine concentrations were not obtained in the majority of patients, it is impossible to confirm that exposures actually occurred, or that symptoms were due to buprenorphine as opposed to some other agent. Similarly, it is important to stress that all reported exposure doses are estimates provided by the family or caregiver and subject to recall bias as parents or caregivers are often emotionally distressed due to the exposure and may not always provide accurate exposure estimates. This historical information is further complicated when an exposure was documented as “the patient spit out the tablet” or “a fraction of the tablet was removed.” In these instances it was necessary to estimate the exposure based on information available in the electronic health record. Finally, a large number of patients were referred to our hospital from an outside institution, presumably because our hospital houses both the regional Poison Control Center as well as an admitting toxicology service. It is likely that there was a cohort of asymptomatic patients evaluated and discharged from outside hospitals while other, presumably sicker patients, were transferred to our institution for admission. This practice may introduce referral bias for a sicker or symptomatic patient population.

**Conclusion**

In this pediatric tertiary hospital cohort, we found that exposure to buprenorphine-containing products in young children frequently caused respiratory depression and CNS depression. Exposed children often received repeated doses of naloxone and naloxone infusion. Symptoms generally became apparent within the first 8 h after exposure. Respiratory depression, altered mental status, and antitodal treatment were more frequent than in previous studies.

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**Disclosure statement**

None of the authors have any conflicts of interest.

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