Root Causes, Clinical Effects, and Outcomes of Unintentional Exposures to Buprenorphine by Young Children

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Objective To characterize the rates, root causes, and clinical effects of unintentional exposures to buprenorphine sublingual formulations among young children and to determine whether exposure characteristics differ between formulations.

Study design Unintentional exposures to buprenorphine-containing products among children 28 days to less than 6 years old were collected from the Researched Abuse, Diversion, and Addiction-Related Surveillance System Poison Center Program and Reckitt Benckiser Pharmaceuticals' pharmacovigilance system from October 2009-March 2012. After adjustment for drug availability, negative binomial regression was used to estimate average exposure rates. Root cause assessment was conducted, and an expert clinician panel adjudicated causality and severity of moderate to severe adverse events (AEs).

Results A total of 2380 cases were reviewed, including 4 deaths. Exposures to buprenorphine-naloxone combination film were significantly less frequent than exposures to buprenorphine tablets (rate ratio 3.5 [95% CI, 2.7-4.5]) and buprenorphine-naloxone combination tablets (rate ratio 8.8 [7.2-10.6]). The most commonly identified root causes were medication stored in sight, accessed from a bag or purse, and not stored in the original packaging. Among 536 panel review cases, the most common AEs reported for all formulations were lethargy, respiratory depression, miosis, and vomiting. The highest level AE severity did not differ significantly by formulation.

Conclusions Unintentional exposure to buprenorphine can cause central nervous system depression, respiratory depression, and death in young children. Exposure rates to film formulations are significantly less than to tablet formulations. Package and storage deficiencies contribute to unintentional exposures in young children. *(J Pediatr 2013;163:1377-83)*.

Unintentional poisonings among children are an important public health problem.[1-3] One out of 180 two-year-olds visits an emergency department for a medication poisoning each year.[4] Several opioids, including buprenorphine, have been recognized for their potential to cause death in children with a single dose.[5,6] During 2010-2011, an average of 1499 children aged less than 6 years were evaluated in emergency departments in the US each year for unintentional exposure to buprenorphine.[7]

Buprenorphine, a potent partial agonist of the mu-opioid receptor, was introduced in the US in 2002 to treat opioid addiction in adults.[8,9] Buprenorphine ingestion by young children can cause central nervous system depression, respiratory depression, and death.[10] Little is known about the root causes of unintentional exposure to opioids in young children, including whether formulation and child-resistant packaging affect the risk of poisoning.[2,6,11,12]

In the US, 3 sublingual formulations of buprenorphine are available: single-ingredient tablets containing buprenorphine, buprenorphine-naloxone combination tablets, and buprenorphine-naloxone combination film. The opioid antagonist naloxone, which is poorly absorbed orally, is included in the combination formulations to deter abuse by nasal insufflation ("snorting") or injection. The tablet formulations are typically dispensed in medication bottles

AE	Adverse event
MedDRA	Medical Dictionary for Regulatory Activities
RADARS	Researched Abuse, Diversion, and Addiction-Related Surveillance
REMS	Risk evaluation and mitigation strategies
URDD	Unique recipients of a dispensed drug

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with child-resistant caps, and the film formulation, which was released in October 2010, is dispensed in child-resistant single dose foil packaging.

The purpose of this study is to characterize the rates, root causes, and clinical effects of unintentional exposure to buprenorphine sublingual formulations among young children and to determine whether these exposures and patient outcomes differ between formulations.

Methods

This is a retrospective cross-sectional study. Cases of unintentional exposure to any of 3 buprenorphine sublingual formulations involving children aged 28 days to less than 6 years were obtained from 2 sources. The date range for all events was October 1, 2009-March 31, 2012. The Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System Poison Center Program collects information from participating poison centers in the US; in the first quarter of 2012, 49 of 57 US poison centers covering more than 90% of the US population provided data. Methods for the RADARS System have been described previously.[6,13] In brief, certified specialists in poison information enter clinical information as part of patient management. After care is completed, standardized data fields and de-identified narrative notes are transmitted to the RADARS System, where a quality control process verifies products involved, exposure characteristics, and medical outcome. During the second and third quarters of 2011, this quality control process resulted in revised coding of approximately 37% of buprenorphine/naloxone tablet and oral film exposures reported by regional poison centers to the RADARS System Poison Center Program.[14] To capture reported exposures from more than 1 source, the Reckitt Benckiser Pharmaceuticals postmarketing pharmacovigilance database was also searched for eligible cases, using 4 search terms from the Medical Dictionary for Regulatory Activities (MedDRA; v 15.0, Northrop Grumman, Falls Church, Virginia), the standard taxonomy used by the Food and Drug Administration Adverse Event Reporting System: "accidental drug intake by child," "accidental exposure," "accidental overdose," and "accidental poisoning." Duplicate cases from the Poison Center Program and pharmacovigilance databases were identified and combined for analysis.

A trained researcher independently reviewed each report to identify study eligibility, buprenorphine formulation, root causes for exposure (ie, accessibility/storage, packaging, caregiver, intended recipient for the medication, and other risk factors), and adverse events (AEs). Because mandatory patient and provider education are incorporated in the buprenorphine risk evaluation and mitigation strategies (REMS) program, data about the relationship between education and the exposure were also extracted.[15] Data were passively collected by specialists in poison information for the purposes of patient care; when no information about a specific root cause was found in the record, it was impossible to determine whether the root cause was absent or not asked. Therefore, data about identified root causes were presented as the number of cases in which the root cause was mentioned.

A focused review to collect and classify AEs systematically was performed on a subset of cases with more serious outcomes. There was no attempt to differentiate between known and unexpected side effects, as this medication is not intended to be administered therapeutically to young children. Cases from the Poison Center Program were reviewed if the medical outcome was classified by the specialist in poison information as moderate effect, major effect, or death, using standard definitions established by the American Association of Poison Control Centers' National Poison Data System.[16] Cases classified by the specialist in poison information using the medial outcome codes for "not followed, judged as nontoxic exposure (clinical effects not expected)" and "not followed, minimal clinical effects possible" were excluded. Cases with a medical outcome of "unable to follow, judged as a potentially toxic exposure" were included if the level of health care facility care code or other clinical documentation indicated that the patient was admitted to the hospital. Cases from the manufacturer's pharmacovigilance database were reviewed by the panel if they met the age and date criteria and the clinical effects met the Food and Drug Administration definition of a serious AE.[17] The review panel consisted of 3 experienced clinicians: a pediatric intensivist/medical toxicologist, a pediatrician/pharmacoepidemiologist, and an emergency physician/medical toxicologist. Panel members reviewed each case to identify all documented AEs. The severity of each AE was classified by panel members using Common Terminology Criteria for AEs nomenclature.[18] The causal relationship between each AE and each drug exposure was determined using standard criteria[19,20](**Table I**; available at www.jpeds.com). Disagreements were resolved by consensus. Trained researchers then coded each AE using MedDRA taxonomy.

Exposures, root causes, and AEs were analyzed using descriptive statistics. Because the number of children potentially at risk of exposure to buprenorphine could not be estimated, we used buprenorphine prescription fulfillment data as a surrogate measure of drug availability. Prescription data were obtained from IMS Health Solutions (Parsippany, New Jersey), and the number of patients filling prescriptions for each of the 3 buprenorphine formulations in a geographic area contributing data to the RADARS System Poison Center Program during the year-quarter of the exposure (unique recipients of a dispensed drug [URDD]) was used as the denominator for rate calculations.[21] A negative binomial regression model was used to test for difference in average rates across the 3 drug groups, where URDD was an offset variable. Average rates were calculated for the year/quarters during the study period for which each formulation was available. Unintentional exposure rates, 95% CIs, and tests of significance were calculated. Two-sided tests were used for all statistical comparisons. AEs were summarized by MedDRA System Organ Class and Preferred Terms.

The operation of the RADARS System Poison Center Program is approved by the Colorado Multiple Institutional