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CASE REPORT

Toxicology

Pediatric poisoning management: How clinical practice can benefit from forensic approach

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Abstract

Pediatric population represents the most vulnerable and at risk for unintentional poisoning, with children younger than 6 years old accounting for nearly half of poison exposures. Poisoning is a time-dependent emergency. The need to reach a scientific agreement on diagnostic protocol and treatment seems to be crucial to reduce morbidity and mortality. Starting from a buprenorphine pediatric intoxication case, this article highlights the limits and pitfalls of the traditional diagnostic approach. Diagnosis of drug intoxication was achieved after several days when an in-depth diagnostic investigation became necessary and complete forensic toxicological analyses were performed. Results evidenced an alarming lack of an unequivocal diagnostic protocol in case of suspect intoxication in structures not provided with a forensic toxicological service/unit. Collection of biological specimens according to forensic protocols at hospitalization plays a paramount role in the definitive diagnosis of intoxication. A diagnostic algorithm that focuses on medical history and biological specimen collection timing is herein proposed, in order to unify emergency approaches to the suspected poisoned child.

KEYWORDS
biological specimen, diagnostic algorithm, diagnostic workup, drug intoxication, pediatric accidental poisoning, toxicology

Highlights

- An alarming delay of an unequivocal diagnostic protocol was found in pediatric poisoning.
- An emblematic case where the lack of a prompt specimen collection under chain-of-custody is presented.
- Consequences for clinicians not complying with forensic recommendations are presented and discussed.
- A diagnostic algorithm is proposed to improve diagnosis and outcome in pediatric intoxication.

1 | INTRODUCTION

Poisoning is the exposure of the body to exogenous substances in sufficient amounts to be considered dangerous for health, potentially harmful for life, and represent a significant global public health problem. The WHO World Health Statistics 2023 "Unintentional poisonings were responsible for about 84 000 (UI: 48 000–137 000) deaths in 2019," with a mortality rate of 1.0 per 100,000 [1]. Children younger than six represent the most vulnerable and at risk for unintentional poisoning [2]. In 2021, the US National Capital Poison

Center (NCPC) evidenced more than 2 million human exposures to toxic substances, with children younger than 6 years accounted for nearly half of poison exposures (41%), while adults accounted for 43% and teens 9% [3]. The greatest part (95.77%) of the exposures in children younger than 6 years were nontoxic, minimally toxic, or had at most a minor effect [3]. The global death rate from poisonings for children younger than 20 years is 1.8 per 100,000 population [4], meaning that, although responsible for the majority of poison events, the fatality rate is low.

A 2000–2001 survey of 16 middle-class and upper-class countries revealed that, of the different external causes of unintentional injury deaths among children between the ages of 1 and 14, poisoning was ranked fourth after car accidents, fires and drownings [5]. Chronic and an acute exposure can occur, the latest to possibly happen either accidentally or voluntarily [6].

Pediatric poisoning is a time-dependent emergency. The term accidental ingestion has now been replaced by inadvertent, unintentional and most probable, exploratory ingestion [7], since children explore their own environment without knowing the potential harm of objects often ingested. Drugs or chemicals eventually present can lead to a peculiar way of exposure, classified as "exploratory exposure" [8]. Substances can be ingested, inhaled, injected, absorbed through skin contact [9], apart from transplacental exposure [6] and breastfeeding. The tendency of children is to lick and/or suck candy-like substances, especially for those having a pleasant smell, rather than swallow them, greatly increasing the risk of toxic effects. Ingestion probability in the group of children aged 1–5 years is proportionate to their usual developmental features. In fact, toddlers are curious of their surroundings; therefore, they begin to explore them by reaching, climbing, and tasting [2, 10]. Haptman et al. [11] evidenced three main factors accounting for the higher vulnerability of children to toxic exposure: body size, personal behavior, and environment. Crawling infants and toddlers, for instance, are at higher risk to ingest chemicals laying on the floor [11]. In addition, they have a higher metabolic rate compared to adults and a major risk of adverse effects [12].

The main risk factors for children are improper storage of substances, lack of supervision, and distraction from caregivers. Other known risk factors are single parent households, parental illness or disability, accessibility to toxic agents, grandparent caretaking and a desire of the child to imitate adult behavior [6]. The top five most common exposures in children aged 5 years or less were cosmetics/personal care products (12.1%), household cleaning substances (10.7%), analgesics (9.04%), foreign bodies/toys/miscellaneous (6.87%), and topical preparations (4.69%) [13].

According to the Annual report of the American Association of Poison Control Centers, in 2018 drug identification accounted for 18.2% of all information received [13]. These data show that the substances most frequently involved in children poisoning are the most readily accessible. Trends for prescription and non-prescription medication exposure are slowly but remarkably rising, while non yet reaching the levels of other causes of poisoning [14]. The most frequent cause of pediatric fatalities reported to the American Association of Poison Control Centers' National Poison Data System (NPDS) are pain medications [13]. A cross-sectional study demonstrated that between 1999 and 2016 the mortality rate among children and adolescents due to prescription and illicit opioids increased nearly threefold [15].

Apart from correctly diagnosing and treating a poisoned child, it is mandatory to collect the most suitable biological sample when an intoxication syndrome can be suspected in the emergency department (ED). In fact, the challenge for the clinician of ED is not only to early recognize and manage pediatric poisoning [16] but also to take attention in body fluids collection for further investigation, in order to decrease the incidence of preventable injuries that depend on an inappropriate family environment. Within this contest, the availability of biological samples suitable for forensic purposes is mandatory.

Starting from results of a case of pediatric intoxication, the study is aimed to give the clinician operating in the ED a correct algorithm to be followed in case of engaged poisoning for justice finality.

2 | METHODS

2.1 | Pediatric buprenorphine intoxication

A 4-year-old boy was admitted for drowsiness at 8:00 p.m. The mother reports that the little boy was playing in the garden and suddenly became drowsy. No family history of similar episodes was reported. Referring to his personal history, he was born at 39 wg (weeks of gestation), by Cesarean section (weight at birth: 2.630 kg). All his psychomotor developmental stages were normal. An informed written consent was obtained by both parents for all treatments and analyses. During the clinical examination the child appeared sleepy and confused. The neurological evaluation evidenced tendentially sleepy state, easily aroused, with alternating agitation, myotic pupils, sometimes adequately responsive, no neurological deficits. The patient underwent intravenous hydration. A bladder catheter was positioned and urine collections for rapid toxicological examination (limited to cocaine/morphine/cannabinoids/amphetamine/methamphetamine) were performed by clinicians, resulting as negative. Toxicological analyses were asked after 12 h upon hospitalization (day 2 of hospital stay) to a clinical pharmacology unit of a local hospital. Immunoassay urinary screening test for amphetamine/methamphetamine/MDMA/barbiturates/benzodiazepines/tricyclic antidepressants/cocaine/cannabinoids/morphine/methadone/oxycodone/phencyclidine was negative. Table 1 presents results of clinical tests performed during hospital stay; Figure 1 shows the evolution of clinical signs and symptoms related to laboratory findings. Due to the child's clinical status, a complete forensic toxicological analysis was asked and performed on a urinary sample collected on day 3 of hospital stay and on a serum sample collected upon hospitalization (day 1) – residual blood after biochemical analyses. Forensic toxicological analyses evidenced a positivity to buprenorphine (BUP) and its major metabolite nor-buprenorphine (nBUP). Naloxone was administered to the patient until complete remission of the symptomatology. Forensic toxicological analyses were repeated on day 5 (whole blood tested negative and urine still positive)

and on day 7 of hospital stay (urine tested negative), as schematically reported in Table 2.

2.2 | Forensic toxicological analyses

Buprenorphine, nor-buprenorphine, and deuterated analogues (d_4-buprenorphine, d_4-BUP, and d_3-nor-buprenorphine, d_3-nBUP), used as internal standards (I.S.), were from Cerilliant (Merck KGaA, Darmstadt, Germany); β-glucuronidase/aryl sulfatase (from Helix pomatia) was from Merck. All other solvents and reagents were from Carlo Erba (Milan, Italy).

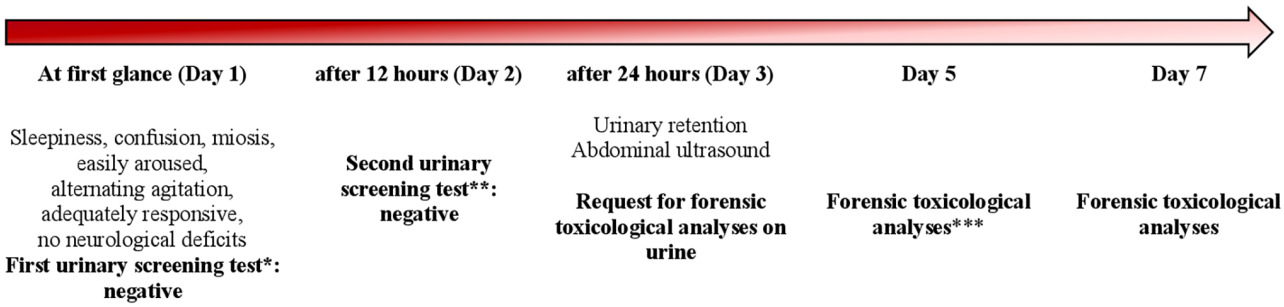
Forensic toxicological analyses were performed by using both immunoassay and ultrahigh performance liquid chromatography/mass spectrometry analyses (UHPLC-ESI-MS/MS).

Immunoassay tests were performed on a Dynex-DSX 4-plate Automated ELISA System (Dynex technology, Chantilly, VA-US), using screening tests from Abbott (Lake Forest, IL, US). In particular, the following panel was screened: cannabinoids, cocaine, barbiturates, amphetamine, methamphetamine, benzodiazepines, fentanyl, ketamine, opiates, methadone, buprenorphine, oxycodone, zolpidem, tricyclic antidepressants.

UHPLC-ESI-MS/MS analyses were performed using a TSQ_{TS} system (ThermoElectron Corporation—San Jose, CA, USA). Chromatographic separation involved the use of a Kinetex® Byphenyl (100 Å, 2.6 μm, 50 × 2.1 mm) column from Phenomenex (Torrance, CA, US) was used. UHPLC runs involve the following buffers and gradients: Solvent A, 0.25 mM ammonium formate, 0.1% formic acid in water; Solvent B, methanol. The percentage of solvent B was increased according to the following scheme: $5\%B \xrightarrow{4\ min} 100\%B \xrightarrow{1\ min} 100\%B \xrightarrow{0.1\ min} 5\%B \xrightarrow{2\ min} 5\%B$. The column was kept at 40°C, and the flow at 0.5 mL/min. The effluent was directly connected to the electrospray ion source, settled as follows: Positive Ion Voltage 3500 V, Sheath Gas 50 (Arbitrary units), Sweep Gas 1 (Arbitrary units), Ion Transfer Tube Temperature 300°C, Vaporizing Temperature 350°C. Data were acquired and processed by using Xcalibur software (2.0.7 version) from ThermoElectron.

TABLE 1 Clinical test results during hospitalization.

Day of hospital stay	Tests performed	Result
1	Electrolytes, hepatic, renal and nutritional indices, cardiological profile	Normal
	Metabolic tests (EAB, ammonium, lactate)	Normal
	Urine test and urine culture	Negative
	Skull CT	Negative
	EEG	AEC from sleep expression of diffuse encephalic suffering
2	Abdominal ultrasound	Overdistended bladder



*Drugs panel performed by Pediatricians: cocaine/morphine/cannabinoids/amphetamine/methamphetamine
**Drugs panel performed by clinical pharmacology laboratory: amphetamine; methamphetamine; MDMA; barbiturates; benzodiazepines; cocaine, morphine, cannabinoids, methadone, tricyclic antidepressants, oxycodone, phencyclidine.
***Performed on Day 5 blood and urine samples and on Day 1 serum sample residual from biochemical analyses.

FIGURE 1 Timeline of clinical signs/symptoms and laboratory findings.

TABLE 2 Results of forensic toxicological analyses performed in GC/MS-SIM.

Day of hospitalization	Matrix	[BUP] (mg/L)	[nor_BUP] (mg/L)
1	Serum	0.005	0.004
3	Urine	0.006	0.009
5	Blood	–	–
	Urine	0.005	0.008
7	Urine	–	–

Toxicological analyses were performed on serum samples collected on day 1 and residual from biochemical analyses, on urine samples collected on days 3, 5, and 7 of hospital stay and on a blood sample collected on day 5, as schematized in Figure 1.

Buprenorphine and nor-buprenorphine were determined in blood, serum, and urine samples according to procedure published by ElSohly et al. [17] slightly modified according to Seldén et al. [18] for UHPLC/MSMS analysis. In brief, 1 mL blood (0.5 mL serum) sample spiked with 50 µL of I.S. (10 ng/µL solutions) was added with 1 mL cold acetonitrile (drop-to-drop under agitation), vortexed and centrifuged (5 min, 5000 rpm) for protein precipitation. The supernatant, recovered in a clean test tube and added with 50 µL of 0.1 M ammonium acetate buffer (pH 4), was purified by liquid/liquid extraction, by adding 2 mL of methyl-t-butyl ether twice. The organic layer was recovered, evaporated until dryness under nitrogen stream and reconstituted in 100 µL for UHPLC/MSMS analysis. Urine samples (1 mL aliquots) were enzymatically digested and purified according to the procedure published by ElSohly et al. [17], then purified as for whole blood/serum samples. UHPLC/MSMS analyses of BUP and n-BUP were performed according to Seldén et al. [18].

Samples were also tested in UHPLC/MSMS for the presence of naloxone and the following benzodiazepines and neuroleptics/sedatives: alprazolam, bromazepam, clobazam, clonazepam, delorazepam, diazepam, escitalopram, estazolam, etizolam, flunitrazepam, lorazepam, lormetazepam, medazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, clotiazepam, fluvoxamine, levomepromazine, olanzapine, paroxetine, pimozide, quetiapine, risperidone, sertraline, trazodone, venlafaxina, vortioxetina, and zolpidem.

3 | RESULTS – TOXICOLOGICAL ANALYSIS

3.1 | Toxicological analyses

Results of forensic toxicological analyses performed during hospitalization are schematized in Table 2. Upon request an immunoassay ELISA screening was performed on urine samples collected on day 3 of hospital stay, obtaining a "non-negative" result toward buprenorphine. UHPLC/MSMS analysis evidenced the presence of both buprenorphine and nor-buprenorphine, at concentration of 0.005 mg/L and 0.009 mg/L respectively. Sample was positive to naloxone, while it was negative toward all other considered drugs. An aliquot of serum sample collected at arrival in ED and residual from biochemical analyses was still available and analyzed resulting positive to naloxone, BUP (at 0.005 mg/L) and nBUP (at 0.004 mg/L). Toxicological analyses were repeated on day 5 on blood and urine samples, evidencing a negativity in blood and positivity of urine to BUP (0.005 mg/L), nBUP (0.008 mg/L) and naloxone; on day 7 urine tested positive toward naloxone only. Moreover, a positivity in both blood and urine was obtained for naloxone. Since the small patient had started therapy on the third day of hospitalization with naloxone, quantitative analyses were not requested.

None of the analyzed samples presented a valid chain-of-custody nor had the serum sample been stored in a locked freezer and/or with restricted access.

4 | DISCUSSION

Presented case represents a clear example, if it were still necessary to prove it, of the fundamental importance of an effective collaboration between clinical and forensic professionals in suspicion of intoxication. Buprenorphine determination can be routinely performed in a forensic toxicological laboratory, while it can be completely absent from the panel of analytes commonly analyzed in clinical settings.

Buprenorphine is a semisynthetic, highly lipophilic opioid derived from thebaine. It is a partial µ-receptor agonist and k-receptor antagonist and is 25–50 times more potent than morphine. It has been available for many years to treat pain, however only in 2002 FDA approved it to treat pain [19]. Its pharmacokinetics have been described in detail. It is absorbed through the buccal or gastric mucosa, with an enteral bioavailability limited to 15% by first pass metabolism limits Trans buccal bioavailability is 27.8% while sublingual one is 51%. The drug is almost exclusively metabolized by the cytochrome CYP3A4 isozyme system, which is largely developed in children by 1 year of age [20]. The therapeutic dose of buprenorphine for children is between 2 and 6 µg/kg; therefore, the ingestion of a 2 mg tablet could lead to an overdose of about 10 times for a child weighing about 10 kg. An even higher risk is associated with ingestion of 4 mg, 8 mg and 12 mg formulations [21]. Unintentional ingestion of the drug can result in severe toxic manifestation also after a prompt parents' intervention, because removing buprenorphine tablets from their child's mouth is not sufficient to eliminate all risk. The time of onset of symptoms after accidental ingestion can vary significantly from case to case (from 20 min to 5 h); therefore, it is important to observe the child for at least 24 h. When buprenorphine/naloxone formulations are accidentally absorbed, patients did not experience any opioid antagonism, due to poor sublingual and enteral naloxone bioavailability [22].

No current guidelines for accidental buprenorphine ingestion in children are available [23]. Since there is no reporting of a drug ceiling effect on respiratory function, toddlers who are exposed to buprenorphine are at risk for sedation, respiratory depression, cerebral anoxia, and death [21]. By reversing respiratory depression, airway protection, and supportive care in children, buprenorphine toxicity can be managed [23–25].

Despite all these symptoms being manifested by the little patient, their non-specificity combined with the low frequency of occurrence in the pediatric population afferent to the hospital (as well as in the pediatric population in general), the physicians discharged the possibility of buprenorphine poisoning. In addition to this, the low a priori probability of buprenorphine intoxication was given by a history not suggestive of exposure. Only after the receipt of the forensic toxicological report evidencing a positive result to the drug for urine sample collected on third day of hospital stay and on

serum sampled at arrival in ED, the father admitted he was a past drug abuser currently on suboxone therapy (buprenorphine and naloxone). Consequently, an adequate therapy was administered, and the baby was discharged in good clinical condition with indications to continue neurological follow-up and EEG re-evaluation after 1 month.

Despite the positive resolution, presented clinical case highlights the following critical aspects:

1. Failure to ask for a complete forensic toxicological analysis, despite suspicion of intoxication, at the time of hospitalization;
2. Performing forensic analysis on "improper" specimens;
3. Validity of the obtained analytical result within forensic context in the event of a legal action.

With respect to point one, a more accurate anamnesis could have defined a risk of exposure to the drug through a direct investigation on both parents' recreational habits. Although in current practice, especially in pediatric emergency rooms, priority is given to patients' stabilization, a prompt assessment of family risk of exposure is crucial. The persistence of the symptomatology together with a negativity of all clinical tests performed should have induced the physicians to go further and verify the hypothesis of intoxication. During the very first hours of hospital stay physicians asked for a second screening test, maybe in consideration of the persistence of symptoms, thus recognizing the exogenous nature of the clinical status. Despite this, they decided to repeat the analyses within a clinical context, while a local forensic toxicological unit was involved only during the third day of hospital stay, to collect a further "clinical datum." This on one hand led to a critical delay in diagnosis and a negative impact on clinical management, on the other represents a clear methodological mistake. Forensic toxicological evaluation starts from the pre-analytical phase, with sample collection within chain-of-custody on specimens specifically collected, sealed, and stored for the subsequent analytical steps. This means that in a suspect of intoxication in the pediatric population, where possible judicial consequences can arise further on, physicians must promptly collect biological specimens, thus separating the clinical context from an eventual judicial one. An algorithm proposal is shown in Figure 2. In case of suspect acute intoxication, it is mandatory to collect blood sample (choice matrix to evidence the so called "current use") in test tubes provided with both EDTA and NaF and a urinary sample (to evidence a "recent use"), seal all samples with anti-burglary labels. All samples have to be stored at −20°C for any forensic toxicological evaluation, which can be decisive for the ultimate diagnosis and any other judicial purposes that can be derived.

With respect to point two, it must be underlined as, in principle and from a strictly doctrinal point of view, in the here discussed cases all samples sent for toxicological analyses were "improper," since:

- The chain-of-custody was absent at all;
- None of the test tubes presented anti-burglary labels;

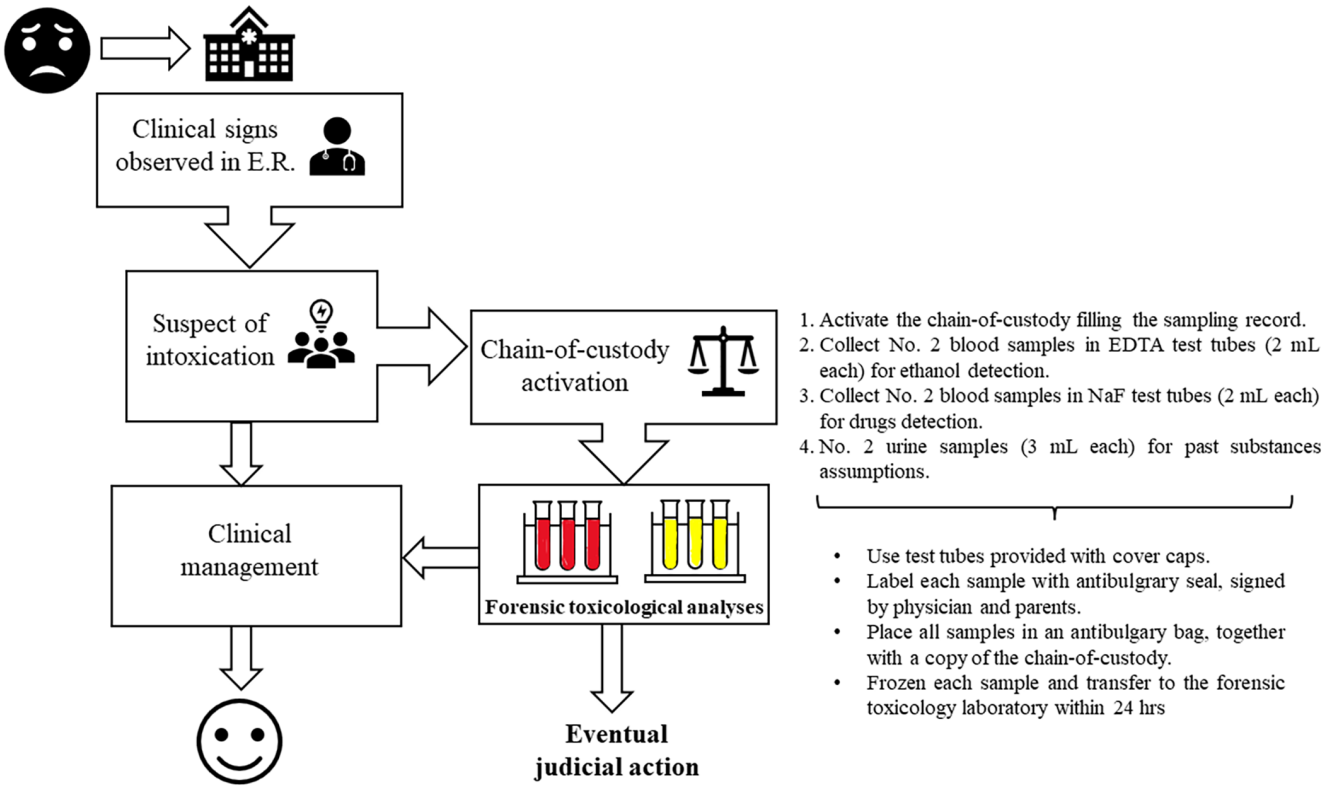


FIGURE 2 Proposed algorithm in case of suspect pediatric intoxication.

- Lack of samples collected at hospitalization (the "rescued" from the biochemical laboratory has been already processed).

A forensic toxicology laboratory cannot be involved in a "clinical diagnosis" just to improve the panel of screened analytes, ignoring its strict methodological rules in view of an emergency.

Furthermore, with respect to point three, the absence of a valid chain-of-custody undermines the possibility to use collected data as a proof in a legal context.

In conclusion, higher awareness of all risks related to immediate or future complaints in pediatric poisoning cases must be achieved. The physicians' choices could expose them to malpractice charges for not having followed the rules of forensic toxicology despite the suspicion of exogenous intoxication in a fragile patient such as a minor, even in presence of a correct clinical outcome.

5 | CONCLUSION

In a suspected exogenous intoxication in the pediatric population, where legal consequences are frequently not immediately clear and evident, it is essential to separate the clinical needs for a correct diagnosis from the judicial field. No matter the substance, a clear operational protocol could make a diagnosis easier and faster to achieve. A prompt specimen collection under chain-of-custody is mandatory to ensure a valid and irrefutable forensic datum, thus avoiding future possible allegations of misconduct for physicians.

The paucity of data on pediatric intoxication sets a need to improve the knowledge of the phenomenon, promoting a virtuous collaboration between emergency departments and forensic toxicological units.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no financial or proprietary interests in any material discussed in this article.

ETHICS STATEMENT

Both child' parents gave a written informed consent approving all performed treatments and analyses, conducted according to the World Medical Association Declaration of Helsinki. Consent has been requested and obtained for the publication of the clinical case in an anonymized form from the child's parents.

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