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Case Report:
Child Death Due to Dermal Opium Application: A Case Report

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ABSTRACT

Background: Incorrect belief about opioid efficacy is a major cause of acute pediatric poisonings in Iran. We report a rare case of topical opium application that caused death in a 4-year-old child.

Case: A 4-year old girl was examined with burns over her abdominal area and lower extremities. Her parents had applied opium on burned area to relieve her pain. She was in delirium state and apnea without any evidence of infection. Immediately, she was administered a single dose of Naloxone (2 mg).

Results: While blood oxygen saturation was improving, she aspirated her vomitus into the lungs and became hypotensive and pulseless. Her condition deteriorated and the treatment team's efforts to resuscitate her failed. On her autopsy, there were no other abnormal findings, but codeine and morphine were detected in the autopsied tissue sample.

Conclusion: The plausible contributing factors may include: change in morphine pharmacokinetics in the burned skin; the low toxic dose of opium in children due to thin abdominal skin, and high blood perfusion in the burned areas.

Keywords: Dermal; Opium; Children death; Iran; Forensic toxicology

Introduction

Acute pediatric poisoning is very common in Iran [1]. Due to susceptibility of children to toxic effects of drugs, there have been several reports of drug induced pediatric death in Iran [2]. The majority of the pediatric poisoning cases are accidentally induced by parents [2] and most of them are drug related [1]. The mostly occur due to the availability of opioids and erroneous belief about efficacy of the compounds [3]. Most of the parents of drug poisoned children have low socioeconomic status or are drug addicts themselves [4]. Sedighi et al. reported two pediatric cases with opium toxicity resulted from applying opium on burned areas, both of whom were fortunately treated and survived. This article reports a child death induced by topical opium use [5].

Case

A 4-year-old girl was referred to the burns clinic at Imam Reza Hospital due to burns over her abdomen, right thigh and both forearms as a result of a gas cylinder explosion. On admission, she was in delirium, confused and hallucinating. The burned areas had been dressed by parents, who admitted that they had applied

opium to the affected areas. The dressings were clean and without excessive secretions. The child's Level Of Consciousness (LOC) was low. At the emergency room post admission, the child became apneic for which she was immediately treated with a single dose of Naloxone (2mg). Upon this treatment, her respiratory rate and blood oxygen saturation improved, but she continued to exhibit gasping respiration without any change in her LOC. At this point, she was referred to pediatric emergency room, where she vomited and aspirated some of the vomitus. Subsequently, she became hypotensive and pulseless, and her LOC deteriorated further. Upon pulse oximetry, her blood oxygen saturation level was undetectable.

The emergency room staff suctioned the aspirated secretions and provided nasal ventilation through a mask. The aspirated secretion from trachea (about 200 ml) consisted of food residues and some amount of traditional home remedy seeds (Descurainia sophia). Since her conditions continued to deteriorate, the treatment team performed Cardiopulmonary Resuscitation (CPR) on her. The standard CPR lasted for an hour; however, the child did not survive. On autopsy, the medical examiner confirmed the patient as a 4-year-old girl with appropriate weight and height, and otherwise in good bodily health. The examiner reported second and third degree burns on the abdomen, and second degree burns on the posterior of aspects of the right and left forearm, and the anterior side of the right thigh. All other findings from the autopsy were normal. Codeine and morphine were detected in the autopsied tissues through gas chromatography of the tissue samples. The child's parents signed a consent form but requested that the child identity be kept confidential.

Discussion

Small doses of opium could be lethal in young children specially those at ages less than five years old [6]. The LD_{50} of morphine in neonate is 4-5 folds less than adults [7], because the half-life of morphine elimination in neonate and young children is less than that in adults. However, some studies have suggested that the adult clearance of morphine is similar to that at ages of six to 18 months [7]. The current case is a 4-year-old girl that might have been excessively susceptible to the low dose of opium. On the other hand; it is believed that morphine safety margin is even lower in critically ill children, such as cases with large burns, than the normal ones [7].

It is known that morphine can be absorbed transdermally similar to other opioid compounds [8]. The absorption of morphine and other opiates from skin is the basis for the effects of transdermal opioid patches containing fentanyl and morphine, or naloxone used for used in the treatment of chronic pain or withdrawal, respectively [8, 9]. However, morphine with lower lipophilicity and higher molecular weight than the fast acting fentanyl and buprenorphine, offers a slower flux through the skin than the latter two agents [10]. Normal human keratinocytes and dermal fibroblasts metabolize morphine into M6G or M3G [8]. There are some evidence that the analgesic effect of topical morphine is independent of the systemic absorption of the drug, with an approximate bioavailability of 20% [8, 11, 12].

Ribeiro et al. evaluated the topical pharmacokinetics of 10mg morphine gel in 6 patients with various skin ulcers (4.5 to 60 cm^2). In this study, morphine and its metabolite, M6G (but not M3G) were detectable only in the sera of patients with large skin ulcers [11]. Further, these authors reported that the serum level of M3G in their patients was not detectable.

Application of topical morphine for the analgesic purposes in skin ulcers, such as the chronic malignant ones, has been shown to be an appropriate method without major side effects compared to the systemic administration [13, 14].

In another study, Westerling et al. [15] applied 10 mg morphine on a small area (5 mm, diameter) of iatrogenic de-epithelialized skin. They found a 75% bioavailability of morphine from the ulcerated skin. Therefore, it is likely that the bioavailability of morphine in the skin ulcers is linked to several factors, such as depth of ulcer, its acuteness or chronicity, surface area, dosage and frequency of application. Also, there is an increase in the capillary permeability in burned area, especially in the first 48 hours, resulting in increased bioavailability of the topical drugs [16].

In our case, the burned skin areas were larger and opium had been present topically for a longer duration (24 h) than those reported in the earlier studies [11, 16]. Thus, it is possible that morphine could reach a toxic level through skin absorption. Also, it can be argued that the wounds due to extensive burns are different from other types of wounds in that they affect multiple organs and may lead to a generalized disorder [16]. Moreover dehydration and hypovolemia in burns patients may alter the pharmacokinetics of drugs [5].

Westerling et al. further reported that the topical application of morphine to skin wounds resulted in lower M3G and M6G concentrations than that of the same

drug at the same dose if given intravenously [15]. It is likely that the administration of morphine to skin bypasses the hepatic first-pass, hence the increased level in the blood [17]. Skin in infants and children is thinner and much better perfused than that in adults [18]. Also, since the keratinocytes are destroyed considerably in skin wounds, these children are more susceptible to severe poisoning by topically applied drugs, because of the higher absorption rate and lower metabolic elimination, especially in burns cases.

Codeine constitutes 3%-4% of opium and has life-threatening side effects, including cadio-respiratory depression and seizure [7]. Five to 15% of codeine is metabolized to morphine by O-demethylation. The activity of this pathway up to five years of age is less than 25% of that in adults [7]. Therefore, the conversion of codeine to morphine is difficult to predict [19]. In children, the reduced clearance of codeine and its accumulation in the body occur more likely than in adults, therefore, it is not prescribed due to its safety concerns [19]. The parents of the child described in this report used raw opium; therefore, the codeine by-product might have also contributed to her fatal outcome.

Sedighi et al. have reported two children with opium toxicity following the application of raw opium to their burn wounds by their parents [5]. Fortunately, both were treated by naloxone and were discharged from the hospital in satisfactory condition. In our case, the burned areas were more extensive than those reported by Sedighi; and they were younger. There is an incorrect assumption that opium not only reduces the burns pain but also prolongs the time required for the rehabilitation [20]. The parents in both our and Sedighi's cases denied having any knowledge about the potentially fatal adverse effects of using opium in children and the possibility of its absorption from the injured skin.

Conclusions

Based on the results, we may conclude that the following factors contributed to the unfortunate fatal outcome of this pediatric case:

- The large burned areas increased the absorption rate of morphine.
- The higher surface to weight ratio of the child might have raised the toxic effect of morphine compared to adult cases.
- Avulsion of keratinocytes layer in the skin, the main site of glucuronidation of morphine in the skin, reduced the M3G level in the active metabolite of morphine, compared to other routs of administration, or if morphine had been applied to the normal skin.
- Increased vascular permeability in addition to hyperemia induced higher bioavailability rate of morphine through the burned areas.
- Bypassing the hepatic metabolism, the topical morphine administration increased the rate of its toxicity.
- The lower toxic dose of opium in children less than 5 years old (i.e. lower LD_{50}).
- Low thickness and high blood perfusion of the child's skin compared to those in adults might have made her more susceptible to the topical drug poisoning.
- Dehydration and hypovolemia secondary to burns might have contributed to the deterioration of the child's condition.
- In children less than 5 years old, the younger the child, the higher the risk of codeine toxicity, due to low activity of O-demethylation pathway.

Ethical Considerations

Compliance with ethical guidelines

The authors confirm that an informed consent was obtained from the parents of the deceased child prior to drafting this report.

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Author's contributions

Conceptualization, methodology, validation: Arya Hedjazi and Seyed Mohsen Rezazadeh-Shojaie; Writing original draft preparation: Mohammad Moshiri and Leila Etemad; Supervision: All authors.

Conflict of interest

The authors declared no conflict of interest.

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