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Tramadol Intoxication in an 8-Months-Old Infant through Breastfeeding: A Case Report

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Abstract

Tramadol is a widely used, synthetic centrally acting opioid analgesic commonly used for the treatment of moderate to severe pain. Very few reports about its excretion into breast milk were published and most of them suggested that short-term maternal use of tramadol is compatible with breastfeeding. No available data about its chronic daily use in addict lactating mothers. To date, there are no published reports of tramadol poisoning through breastfeeding. We report a case of tramadol intoxication in 8-month-old infant through breastfeeding as her mother was an addict on tramadol. The infant presented to the Emergency Department (ER) of the Poison Control Center (PCC) of Ain Shams University Hospital twice with 36 h apart. The first time, the infant was discharged from the hospital with no sequelae after receiving the appropriate management. The second time, the infant deceased due to cardiac arrest three days after tramadol poisoning. This case report highlights the dangers of excretion of tramadol in milk and the severity of complications that can even be near fatal to infant.

Keywords: Tramadol; Intoxication; Infant; Breastfeeding; Death

Introduction

Tramadol is a widely used, synthetic centrally acting opioid analgesic for the treatment of moderate to severe pain. It has a weak μ-receptor agonist activity that blocks the pain pathways as well as the inhibition of the reuptake of the biogenic amines especially serotonin and norepinephrine in central nervous system [1]. The Manufacturer's Product Information on tramadol gives very limited data on the transfer of tramadol and its active O-desmethyl metabolite (M1) into breast milk, with unpublished information reported that very small amounts (0.12%) are excreted in the breast milk within 16 h after single 100 mg intravenous dose [2,3] found that tramadol and its active metabolite (M1) can transfer from maternal plasma to milk with mean steady-state M: Ps of 2.2 and 2.8 respectively which is considered low. The absolute infant dose was about 112 μg/kg/day when compared with analgesic doses used for postoperative pain in children (1000 μg/kg of tramadol); this represents about 14% of the pediatric therapeutic dose for tramadol. They suggested that short-term maternal use of tramadol is compatible with breastfeeding. This data is related to single-dose therapy or short-term treatment, no available data about its chronic daily use in addict lactating mothers. Severe pediatric cases of tramadol intoxication through breastfeeding are rarely reported. We report a case of tramadol intoxication in 8-month-old infant through breastfeeding as her mother was an addict on tramadol.

Case Report

An 8-month-old infant was presented to the Emergency Department (ER) of the Poison Control Center (PCC) of Ain Shams University Hospital with cyanosis and altered mental status referred from general pediatric hospital. There was no specific report that anyone witnessed the infant ingest any medications. The night before, her parents reported that they were in the wedding party of one of their relatives after that they returned home and put the infant to bed after breastfeeding, 5 h later the mother found her infant bluish and unresponsive.

Upon arrival at the Emergency Department, the infant's vital signs included a temperature of 37°C, heart rate at 138 beats/min, a respiratory rate of 10 per min, blood pressure at 90/50 mmHg, and 88% finger probe pulse oximetry. Her skin was pale but not diaphoretic. She had vomiting but did not exhibit diarrhoea. Her neurologic examination was significant for constricted pupils, ataxia, episodic agitation alternating with drowsiness with a Glasgow Coma Scale of 10, and a global increase in her lower limb tendon reflexes. Examination of other systems was unremarkable.

Laboratory investigations, including blood gas analysis showed respiratory acidosis (Ph: 7.21, PCO_2: 56 mmHg, HCO_3: 22.7 mmol/l, PO_2: 61 mm Hg and O_2 saturation 81%). Blood Hemoglobin was 8.6 gm/dl and Hematocrit 28.1% (normal range:33-39%), with indices compatible with iron deficiency anemia. Electrolytes, blood urea nitrogen, creatinine, glucose, AST and ALT were normal. Computed tomography of the brain also produced normal results. An electrocardiogram revealed no abnormalities except for sinus tachycardia (140 per min). A drug screen for tramadol produced positive results. A urine immunoassay for cannabinoid and opiates produced negative results. Being tramadol positive, detailed history was taken from the mother who confirmed that she is tramadol addict. We advise her not to breastfed her child again all through she takes tramadol as it is excreted in milk and cause harmful effect to her child even death and she should shift to artificial formula.

The child was admitted to ICU where she was attached to cardiac monitor and put on nasal O_2, hence tramadol overdose, was suspected and naloxone (twice 0.4 mg intravenous) was given on which the child was responding appropriately, her respiratory rate increased to 25

breath/ min with improvement of her ABG (pH: 7.36, PCO_2:40 mmHg, HCO_3:24.3 mmol/l) and 100% finger probe pulse oximetry.

Within the next 2 days, her neurologic status improved, she did not experience seizures or myoclonus, and the initial disturbances disappeared 24 h after admission. On day 1, her blood pressure increased to 120/100 mmHg. Her pulse returns to normal value. Family and social history was notable for a history of tramadol addiction in her parents. We advise the mother not to breastfed her child again all through she takes tramadol as it is excreted in milk and cause harmful effect to her child even death and she should shift to artificial formula. She was discharged from the hospital on day 3, with no sequelae.

Thirty six hours later, the infant presented again to our Emergency Department but this time with cardiopulmonary arrest, cardiopulmonary resuscitation (CPR) was initiated and airway was secured with endotracheal intubation and boluses of atropine, and epinephrine were given, normal cardiac rhythm were restored. She was transported to ICU, There she had a Glasgow Coma Scale score of 4 and generalized tonic-clonic seizures treated with IV diazepam which stopped the seizure. The child was mechanically ventilated. She developed recurrent seizure activity; on which she was given midazolam with resolution of the seizure.

The infant's vital signs included a temperature of 36°C, heart rate at 150 beats/min, blood pressure at 50/20 mmHg, and 75% finger probe pulse oximetry. She was shocked (blood pressure 50 mmHg) on which kept on dopamine support (10 μg/kg/min). On physical examination, slight reactive double mydriasis was observed, Chest auscultation revealed scattered rales all over the lung and the heart presented no arrhythmia. Electrocardiogram showed a sinus tachycardia.

Arterial blood gases revealed metabolic acidosis (pH:7.10, PCO_2:41 mmHg, HCO_3:12.7 mmol/l, PO_2:51 mmHg and O_2 saturation 72%). Blood Hemoglobin was 6.6 gm/dl and Hematocrit 22.1% (normal range:33-39%), with indices compatible with iron deficiency anemia, blood transfusion was given. Initial serum Na:135 mmol/l, K:4.5 mmol/l, glucose: 94 mg/dl. Serum urea: 60 mg/dl, serum creatinine: 2.4 mg/dl. AST (428 U/L), ALT (436 U/L). Chest X ray revealed aspiration pneumonia. A drug screen for tramadol produced positive results.

Thirty mins later, the girl was arrested again with successful cardiopulmonary resuscitation. Within the next 2 days, she received anticonvulsants, antibiotics, and dopamine- norepinephrine infusion, in addition to routine management. Furthermore, several neurological consultations were performed. She was considered for dialysis but it was not performed because of sever hypotension.

The infant had poor condition and showed many complications (coagolative disorders, renal failure, and de-cerebrate position). Finally, the infant deceased due to cardiac arrest three days after tramadol poisoning. The mother later reported that she breastfed her child after she discharged from the hospital at the first time.

Discussion

The clinical and toxicological pictures in this case are consistent with tramadol toxicity leading to infant death. The infant in this case developed tramadol toxicity through breastfeeding by multiple factors. The amount of any drug to be excreted from maternal plasma into breast milk and the rate at which this occurs depends on multiple factors; factors related to the drug, factors related to the mother and factors related to the infant. Regarding the drug factors; it depends on its chemical properties such as molecular weight, plasma protein binding, ionization, and lipid solubility. For a drug to be transferred into human milk, it must has the following characteristics; smaller molecular weights, low protein binding, weak base and lipid soluble [4-6]. Tramadol and its active metabolite; M1 (O-desmethyl tramadol) are small, lipid soluble molecules with low protein binding and low volume of distribution sharing a high membrane permeability. These chemical properties facilitate drug excretion into human milk [7].

In addition to pharmacokinetic or chemical properties of the drug, the infant's expected drug exposure is affected by infant and maternal factors. Maternal pharmacokinetics may determine the availability of the drug in the blood and therefore, its availability to the mammary alveolar membrane and human milk. Maternal genetic polymorphism may affect the toxic effects of tramadol by increasing metabolism to an active metabolite; M1 (O-desmethyl tramadol). This active metabolite (M1) has a 300-400 times higher affinity to μ opioid receptors than the parent compound and has an elimination half-life of nine hours [8-10].

Tramadol is metabolized by the cytochrome P450 (CYP) 2D6 into the only active metabolite; M1 (O-desmethyl tramadol). The gene encoding for CYP2D6 is polymorphic resulting in three phenotypes: poor (PM), extensive (EM) and ultra-rapid (UM) metabolizer phenotypes. There is a large individual variation in the activity of CYP2D6 enzyme within a population and between ethnic groups [10-13]. The ethnic groups from the Middle East and East Africa are more likely to be ultrarapid metabolizers compared with those from Middle Europe and North America (incidence 21%-29% *vs.* 0.5%-1% respectively) so people in the Middle East are more susceptible to opioid effects, including dependency, seizure, sedation, and respiratory depression [10-16]. Ultrarapid metabolizer (UMs) have increased CYP2D6 enzymatic activity and may experience different degrees of pain relief and side effects of tramadol by converting it into its active metabolite; M1(O-desmethyl tramadol) more rapidly and completely than other people. This rapid conversion results in higher than expected toxic levels [17,18, 20].

The presence of maternal ultrarapid metabolism of CYP2D6 can be life threatening for some breastfed infants as what occur in this infant. It is not practical to identify these ultrarapid metabolisers by genotyping as this assay is complex and expensive so we can only rely on close monitoring of breastfed infants to detect any problems [20]. This case of infant' death resulting from tramadol poisoning as her mother abused tramadol is alarming, considering that the mother could be an ultrarapid metabolizer of cytochrome CYP2D6.

Once the drug reaches human milk, several additional factors determine if it will affect the infant absorption, metabolism, and body composition. The infant has limited metabolic capacity leading to prolonged half-lives and accumulation of the drug with repeated exposure on successive days. Administration of a highly lipid soluble drug such as tramadol to an infant with a lower body fat composition may allow more of it to accumulate in the brain leading to more CNS symptoms per dose [17,20].

The lower total body clearance which is observed in infants is attributed to their lower metabolic capacity as well as lower glomerular filtration rate and less effective tubular reabsorption/excretion so elimination of M1 from the infant was prolonged, resulting in substantial increase in her exposure to M1 [20]. When assessing this infant with tramadol intoxication, we should consider that the source of tramadol may be from the infant's ingestion of the maternal

medication in addition to the breast milk as the mother could continue taking tramadol and breastfed her child after discharging from the hospital at the first time in spite of warning her.

Conclusion

This case report highlights the dangers of excretion of tramadol in milk and the severity of complications that can even be near fatal to infant. With the increasing abuse of tramadol, it is important for physicians to be aware of tramadol intoxication through breastfeeding in severe pediatric cases.

Recommendations

Caution should be taken when tramadol is administered to nursing mothers. Some women are ultrarapid metabolizers of tramadol having higher than expected serum levels of its active metabolite (M1) leading potentially dangerous effects including death in their breastfed infants.

Breastfeeding is generally discouraged in mothers who are actively abusing tramadol.

When the human milk is suspected to be the source of tramadol poisoning, tramadol concentrations in infant blood, maternal blood, and milk should all be collected as soon as possible after toxicity appears.

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