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CASE REPORT

Probable association of neonatal death with the use of tramadol to treat labour pain

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ABSTRACT

Tramadol is often used in obstetrics for the relief of labour pain. It has a dual mechanism of action, a monoaminergic effect of tramadol itself and an opioid effect, primarily mediated by its metabolite O-desmethyl tramadol, formed by genetically polymorphic cytochrome P450 2D6. In newborns, elimination of O-desmethyl tramadol is prolonged due to immature renal function. We report on a case of neonatal death following rectal administration of tramadol to treat labour pain to a birth-giving mother. An objective causality assessment using the Naranjo probability scale revealed that the likelihood of tramadol causing respiratory depression was probable. We hypothesize that neonatal death was associated with an increased exposure to O-desmethyl tramadol due to ultrarapid metabolizer cytochrome P450 2D6 genotype of the mother. More evidence is needed to support this association. Nevertheless, in obstetric analgesia, tramadol should be used with more caution until more safety data are available.

Key words: opioid analgesics, tramadol, O-desmethyltramadol, labour, drug toxicity, respiratory depression

Introduction

Tramadol is a centrally acting analgesic. In humans it is extensively metabolized, with major metabolites being O-desmethyl (M1) and N-desmethyl (M2) tramadol. Both, tramadol and its metabolite M1 are agonists of the μ opioid receptor. Compared to parent tramadol, M1 has approximately 700 fold higher affinity for the μ-receptors. (1) Consequently, M1 metabolite is predominantly responsible for the μ-receptor mediated analgesic effect of tramadol, although nonopioid mechanisms of action potentiate opioid effects. (2) The dual mode of action of tramadol by inhibition of noradrenaline and serotonin reuptake, besides agonism at the opioid receptors, causes decreased risk of respiratory depression. (3,4) In obstetrics it is used to treat labour pain. (5) It was demonstrated that tramadol (50-100 mg) in the first stage of labour is as effective as pethidine (50-75 mg), but has a superior safety profile. (6)

In vitro it was demonstrated that formation of M1 is catalyzed by the liver enzyme cytochrome P450 (CYP) 2D6. (7) The gene encoding for CYP2D6 is polymorphic resulting in functionally different enzymes, characterized in poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM) metabolizer phenotypes. Tramadol and M1 pass the placental barrier. (8) Depending on the

postmenstrual age, neonates possess almost complete hepatic capacity of tramadol metabolism to M1; however, compared to mothers, the renal elimination of M1 is notably prolonged. (8,9) Despite its use in the treatment of labour pain for over a decade, there is no report, to our knowledge, of a fatal event with such use.

This case report suggests a probable association between fatal respiratory depression in a neonate and antenatal administration of tramadol in the mother for labour pain.

Case report

For the 28 year old female this was her third pregnancy. Four weeks before delivery (in the 36th week of gestation) she had successful external cephalic version. Finally, labour was induced with oxytocin in the 40th week, at 10.30, because of 2 hours of decelerations on cardiotocography. At 13.50 the mother was given one suppository of 100 mg tramadol hydrochloride (Tadol®, Krka, d.d., Novo mesto, Slovenia) and one suppository of 10 mg hyoscine butylbromide (Buscopan®, Boehringer Ingelheim International GmBH, Ingelheim am Rhein, Germany) for labour pain.

At 15.16 a boy (2910 g) was born with an APGAR score of 8 and 9 at 1 and 5 minutes after birth, respectively. The baby stayed with his mother, but at 16.50 he was found pulseless and apnoeic. He was cyanotic and hypotonic. The physicians started cardiopulmonary resuscitation and 0.2 mg of adrenaline was delivered through an endotracheal tube. After 2 minutes heart rate was re-established.

At the arrival of the transport team, the newborn was already intubated and ventilated by the attending physician. His pulse rate was over 100 per minute, blood pressure was 89/51 mmHg (left arm) and 86/55 mmHg (left leg). He was floppy, not reacting to any stimuli. His pupils were constricted and not reacting to light. The newborn was transported to the Level III Neonatal and Paediatric Intensive Care Unit.

A brain ultrasound was performed by an experienced paediatric radiologist. The ultrasound revealed diffuse hypoechogenic areas and small hyperechogenic areas periventricularly. Induced hypothermia (core temperature was held between 32 and 34 °C) for neuroprotection and therapy with phenobarbital was started. The Electroencephalogram (EEG) was repeatedly (3 times) abnormal and showed changes in activity, which were attributed to diffuse ischaemic lesions of the white substance. A neurologist confirmed the minimal status of consciousness of the newborn and no resuscitation was indicated. The child died 28 days after birth.

Blood samples were drawn from the mother at 5 h and from the newborn at 7 and 72 h after birth. Tramadol concentration in the serum was determined using a gas chromatography–mass spectrometry (GC-MS) assay. The lower limit of quantification (LLOQ) of the method was 0.04 mg/l. Tramadol serum concentration in the mother was 0.18 mg/l (therapeutic range 0.1-0.3 mg/l). In the newborn, tramadol serum concentration at 7 h after birth was 0.05 mg/l. A second measurement in the newborn, at 72 h was below the assay LLOQ.

Discussion

Labour pain inevitably affects maternal psychology, labour progress and foetal well-being. Consequently, adequate analgesia is essential in obstetrics. (10) Because of the lower incidence of side effects, and analgesic activity comparable to pethidine, tramadol has been recommended for obstetrical analgesia. (6,11) Additionally, in the study by Khooshideh and Shahriari the duration of labour was shorter for the first stage (190 vs. 140 min) and for the second stage (33 vs. 25 min) in women treated with tramadol compared to pethidine. (11) In a previous study by Keskin et al., however, no difference with regard to the duration of labour and APGAR score was found, while superior analgesic efficacy was observed in women treated with pethidine. (10) In general, tramadol is considered to have fewer cardiovascular, gastrointestinal and central depressant adverse effects than any other opioid drug. (2,3) The most common adverse effects observed with tramadol are: central nervous system (CNS) depression (27.4%), nausea and vomiting (21.1%), tachycardia (17.4%), seizures (13.7%), confusion (3.7%) and miosis (3.2%). (12) CNS depression can be successfully treated with naloxone and seizures with benzodiazepines. Dual mechanism of action and relatively slow metabolism of tramadol to M1 result in prolonged analgesia. Consequently, repeated doses of naloxone are necessary to antagonize the opioid adverse effects. The influence of CYP2D6 polymorphism on tramadol pharmacokinetics has been extensively studied. However, its clinical importance regarding analgesic efficacy and safety has not been elucidated, especially in patients with UM phenotype. Based on the known mechanisms of action and the identified effects of CYP2D6 genotype on drug exposure, increased incidence of serotonergic effects is expected in patients with PM phenotype, while opioid mediated adverse effects are more likely in patients with UM phenotype. Tramadol and M1 have a high placental permeability and are not lost during foetal passage. In neonates, renal elimination of M1 is considerably prolonged, especially in the first hours post-partum. (8) Based on data by Stamer et al., the plasma concentrations of M1 in adult patients with UM phenotype is increased by more than 100%, compared to EM phenotype. (13) The exposure of the neonate to M1, however, is hard to predict as it also depends on the time interval between drug administration and delivery of the child. While most people have EM phenotype, approximately 1% of people in Finland, Denmark (14) and Slovenia, (15) 2% in Germany, (16) 3.5% in Spain, (16) 10% in Greece and Portugal, (14) and 29% in Ethiopia (14) have CYP2D6 gene duplication resulting in UM phenotype.

The clinical signs presented in this case are consistent with opioid toxicity leading to respiratory depression and neonatal death. Furthermore, opioid induced respiratory depression may have

been enhanced by the anticholinergic action of hyoscine butylbromide. (17) According to the Naranjo probability scale, (18) respiratory depression was probably related to the tramadol treatment (Q1 = 0; Q2 = 2; Q3 = 0; Q4 = 0; Q5 = 2; Q6 = 0; Q7 = 0; Q8 = 0; Q9 = 0; Q10 = 1, total score = 5). The measured serum concentration of tramadol in the mother at 6.5 h after administration of tramadol suppository was within the therapeutic range and consistent with the mean observed tramadol concentration with this type of administration (approximately 0.2 mg/l). (19) However, it is the formation of M1, which is probably related to the observed respiratory depression in the neonate. Unfortunately, M1 concentration was not available, since this metabolite is not routinely measured in our toxicology lab. Some pharmacokinetic data suggest that formation clearance of M1 is a minor route in the total elimination of tramadol. (20,21) Consequently, genetic polymorphism of CYP2D6 has a more pronounced effect on the serum concentration time course of M1 than the concentration time course of tramadol. This is also supported by the study of tramadol pharmacokinetics in mothers treated for labour pain and their neonates, where the serum concentration of tramadol in neonates at the time of birth was much less variable (range 0.122-0.557 mg/l) then the serum concentration of M1 (range 0.003-0.112 mg/l). (8) Based on these data we speculate that in the presented case, the mother has a UM phenotype resulting in minor influence on the exposure to tramadol, but considerably increased exposure to M1. At the time of delivery, serum concentrations of M1 in the mother and the child were presumably near maximum. Due to immature renal function in the neonate, elimination of M1 from the child was prolonged, resulting in substantial increase in exposure of the child to M1. Again the tramadol concentration in the serum samples taken from the child did not deviate from previously reported in a group of neonates. (8) Furthermore, in the study by Claahsen-van der Grinten et al., no relationship between the concentration of tramadol and M1 in the serum of the neonate and APGAR score 1 min post-partum was detected, in concordance with the present case of the child with APGAR score 8/9. (8) At the top of the body system ranking of adverse events in neonates was the respiratory system (14.3%); the incidence was not related to the tramadol dose. (8) The possible relationship with the concentration of tramadol or M1 was not commented. However, the authors report the case of respiratory depression in a child probably related to the treatment with the highest concentration of tramadol (0.557 mg/l) and M1 (0.112 mg/l). The respiratory status in this child immediately improved with naloxone treatment. (8) In our case naloxone was not used, since association of respiratory depression with tramadol use in the mother was not immediately recognized. Our hypothesis that neonatal death could be associated with the UM phenotype of the mother is further supported by a published case report of respiratory depression associated with elevated levels of M1 in an adult patient with renal impairment and CYP2D6 gene duplication who was treated with tramadol. (22) Similar to the situation in newborns, elimination of M1 is prolonged in patients with renal impairment.

To confirm our hypothesis plasma concentration of M1 should have been measured and CYP2D6 genotype of the mother should have been identified. Nevertheless, in mothers treated for labour pain, tramadol should be administered with more caution until more safety data are available.

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