Prolonged Apnea and Sedation in Premature Babies with the Use of Oral Tramadol

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Abstract

Clinical studies have shown that premature infants may experience pain in spite of the immaturity of anatomical and functional pathways transmitting nociceptive stimuli [1]. Over the past decade, survival rates for pre-term neonates have increased markedly [2]. The increase in premature birth and survival is provided by O2 therapy and ventilatory management. Oxygen therapy is directly related to Retinopathy of Prematurity (ROP). Screening examination for ROP is a very brief painful procedure and requires long-term follow-up [3]. Although the management of neonatal pain from major single procedures (eg, postoperative pain) has improved significantly, pain management for multiple and repetitive diagnostic and therapeutic procedures (eg, heel lances, suctioning) have not kept pace [2]. Multiple invasive procedures in premature infants caused marked fluctuations in intracranial pressure, possibly leading to early intraventricular haemorrhage and periventricular leucomalacia. Premature infants tend to be more unstable systemically than full term infants of the similar postnatal age, and are more susceptible to apnea and bradycardia [3]. Tramadol was being used in paediatric surgery department even in newborn babies undergoing surgery under general anesthesia, we thought that it could be safe and effective for ROP examination also [4-7].

Here we would like to present 3 cases who had heavy sedation and respiratory depression with the use of tramadol 2 mg/kg (one drop/kg) in premature infants for pain relief and sedation during ROP examination.

Keywords: Apnea; Tramadol; Premature infant

Introduction

Over the past decade, survival rates for pre-term neonates have increased markedly. However, this improvement has been accompanied by a corresponding increase in the incidence of NICU stays and increased incidence of surgery. Although the management of neonatal pain from major single procedures (eg, postoperative pain) has improved significantly, pain management for multiple and repetitive diagnostic and therapeutic procedures (eg, heel lances, suctioning) have not kept pace [2].

The increase in premature birth and survival is provided by O2 therapy and ventilatory management. Oxygen therapy is directly related to Retinopathy of Prematurity (ROP). Screening examination for ROP is a very brief painful procedure and requires long-term follow-up. In the institution where these incidents took place, the examinations are performed in a special room equipped with anaesthesia machine and an anaesthesiologist stay standby during the examination in order to resuscitate the neonate in emergency because premature infants tend to be more unstable systemically than full term infants of the similar postnatal age, and are more susceptible to apnea and bradycardia [3].

Tramadol is a synthetic opioid with a low affinity for opiate receptors, unlike morphine. Besides mu-agonistic activity, tramadol exerts its effects by inhibition of serotonin and noradrenaline re-uptake. It is a potentially useful analgesic drug in pediatrics, compared with morphine when the incidence and magnitude of respiratory depression are considered [4]. Tramadol had been used in paediatric surgery department even in newborn babies undergoing surgery under general anesthesia for last few years in the institution. With this experience and following the reports by Allegaert’s study group we thought that it could be safe and effective for ROP examination also [5-7]. Here we would like to present 3 cases who had late heavy sedation and respiratory depression with the use of tramadol 2 mg/kg (one drop/kg) in premature infants for pain relief and sedation during ROP examination.

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Results

Case 1

Baby (EHH) was born at 32 weeks of gestation, with a birth weight of 1.370 kg and APGAR score of 0. He had been resuscitated and intubated and admitted to NICU and artificial ventilation was performed and discharged from hospital in one month. The incident occurred when the babies’ postconceptual age was 39 weeks (1760 g). He was brought to the hospital from home at 8:00 and given 1 drop of oral tramadol and admitted to the examination room 30 min-1 hr after. His NIPS were 0,0,7,7,7,7, and 0.0 at times arrival, 1 min after, PS1, RD1, PS2, RD2, 1 and 2 min after the procedure consecutively. His NIPS was 0 when he was leaving hospital 2 hours after the procedure and sedation level was as all babies sleeping but arouses when stimulated. His parents took him to their previous private hospital when they observed apnoea after long hours of sleeping (at midnight). According to the report of the neonatologist in the private hospital (approximately 15 hours after tramadol) the baby was having shallow breathing, frequent apnoea, cyanotic and hypotensive. His reflexes were weak, fontella normal, temperature 36.1°C, heart rate 137/min and blood pressure 58/35 mmHg. His body was soft, chest x-ray normal and blood gases pH 7.30, PCO2 57 mmHg, PO2 42.9 mmHg, bases excess 27.7 mmol/L. He was started CPAP and given antibiotic and fluid replacement 60 ml/kg. Later he had severe apnoeas and generalized tonic convulsion 3 times and developed bradycardia. Four hours after admission he was intubated the baby and initiated SIMV and given phenobarbital. He was found anemic (Hematocrit level 25%) and blood transfusion performed. All of his functions, neurologic examination and ultrasound found normal the next day and extubated and stayed in O3 hood another day. He was discharged from the hospital 5th day in perfect status and breast fed.

Case 2

Baby (ASD) born at 32 weeks of gestation, with a birth weight of 1.460 kg. He had developed neonatal icterus and had been admitted to NICU in a private hospital with the diagnosis of sepsis. He had been discharged from NICU in 7 days. The baby had been examined several times for ROP. The incident took place when her postconceptual age was 37 weeks and weight 2.200 kg. Similar to others she was given 2 drops of oral tramadol when she arrived from home. Her NIPS in the examination room were 0,6,7,7,7,7, and 0.0. Her NIPS was 0 when she was leaving hospital 2 hours after the procedure and sleeping but arousing when stimulated. The parents reported that she slept in the rest of the day and while she cannot breastfeed, the parents gave her mother’s milk very carefully. All the parents of premature infants were encouraged the use of tramadol for us. In Allegeart’s studies tramadol was one option. Several reports by Allegeart’s group had encouraged the use of tramadol for us. In Allegeart’s studies tramadol was administered with IV bolus 1 mg kg and maintenance infusion of tramadol hydrochloride 0.09 mg kg \( \text{h}^{-1} \) (target concentration of 300 mg litre \(^{-1} \)) to infants as low as 25 weeks gestational age weeks with no complications in NICU settings for performing pharmacokinetic studies. Allegeart et al. [10] observed a lag time of 4 hours in a full term newborn between intravenous administration of tramadol and plasma/cerebrospinal fluid equilibration. In a case report where 100 mg of rectal tramadol administered to a 6 month old infant the CSF concentration of tramadol showed the exactly similar elimination curve as intravenous administration and equilibration between the plasma and central compartment achieved in 17 h after rectal administration of the drug [11]. In all three cases heavy sedation observed in the early afternoon (more than 4 hours after oral tramadol administration) coincides with the information in the literature. The presence of anaemia in two premature infants presented here should have triggered apnea in conjunction with the peak central effects of tramadol. Anaemia is also directly related to apnea of prematurity [12].

In the literature it is stated that the premature babies with the high risk of ROP are screened in the NICU by ophthalmologist. In the country where the incidents took place is a huge inhabitant area of 10 million people and in which hundreds of hospitals are located. The eye clinic of the university is a referral centre for screening of ROP. Because the number of babies were high, a special room was designed directly related to apnea of prematurity [12].

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Discussion

After these three cases of heavy sedation and apnea as a result of tramadol usage, we quit using tramadol drops for pain relief in ROP examination.

Several techniques such as use of local anesthetics, general anesthesia, sedation/ analgesia by sucking sucrose or use of several sedative drugs orally or intravenous drugs are defined for analgesia in babies [8, 9, personal discussion Josef Jolzi]. In the search of best pain treatment for these premature babies with no intravenous line, use of oral tramadol was one option. Several reports by Allegeart’s group had encouraged the use of tramadol for us. In Allegeart’s studies tramadol was administered with IV bolus 1 mg kg and maintenance infusion of tramadol hydrochloride 0.09 mg kg \( \text{h}^{-1} \) (target concentration of 300 mg litre \(^{-1} \)) to infants as low as 25 weeks gestational age weeks with no complications in NICU settings for performing pharmacokinetic studies. Allegeart et al. [10] observed a lag time of 4 hours in a full term newborn between intravenous administration of tramadol and plasma/cerebrospinal fluid equilibration. In a case report where 100 mg of rectal tramadol administered to a 6 month old infant the CSF concentration of tramadol showed the exactly similar elimination curve as intravenous administration and equilibration between the plasma and central compartment achieved in 17 h after rectal administration of the drug [11]. In all three cases heavy sedation observed in the early afternoon (more than 4 hours after oral tramadol administration) coincides with the information in the literature. The presence of anaemia in two premature infants presented here should have triggered apnea in conjunction with the peak central effects of tramadol. Anaemia is also directly related to apnea of prematurity [12].

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Conclusion

Although the pharmacokinetics of tramadol for premature infants were studied and had been proven safe it should be used when the infants are closely observed and/or monitored in hospital settings. The use of oral tramadol is insecure in premature babies for outpatient sedation and analgesia.
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