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REVIEW ARTICLE

Clinical Pharmacology of Fentanyl in Preterm Infants. A Review

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Fentanyl is a synthetic opioid that is very important in anesthetic practice because of its relatively short time to peak analgesic effect and the rapid termination of action after small bolus doses. The objective of this survey is to review the clinical pharmacology of fentanyl in preterm infants. The bibliographic search was performed using PubMed and EMBASE databases as search engines. In addition, the books *Neofax: A manual of drugs used in neonatal care* and *Neonatal formulary* were consulted. Fentanyl is N-dealkylated by CYP3A4 into the inactive norfentanyl. Fentanyl may be administered as bolus doses or as a continuous infusion. In neonates, there is a remarkable interindividual variability in the kinetic parameters. In neonates, fentanyl half-life ranges from 317 minutes to 1266 minutes and in adults it is 222 minutes. Respiratory depression occurs when fentanyl doses are >5 μg/kg. Chest wall rigidity may occur in neonates and occasionally is associated with laryngospasm. Tolerance to fentanyl may develop after prolonged use of this drug. Significant withdrawal symptoms have been reported in infants treated with continuous infusion for 5 days or longer. Fentanyl is an extremely potent analgesic and is the opioid analgesic most frequently used in the neonatal intensive care unit.

1. Introduction

The mainstay of systemic analgesia for moderate to severe pain is the use of opioid therapy. Opioids provide both sedation and analgesia, have a wide therapeutic window, and decrease hemodynamic and metabolic stress response.[1] As pain is a major stressor that may increase morbidity and mortality in critically ill neonates,[2] sedation and analgesia are widely used in infants.[2] Fentanyl is the most used analgesic opioid in the neonatal intensive care unit. Fentanyl acts as an agonist binding to μ and κ opioid receptors and has the properties of an analgesic, sedative, and anesthetic.[3] This drug has a rapid onset of action of 2—3 minutes, a short duration of action of 60 minutes with

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bolus doses and minimal hemodynamic effects.[4] It is widely used to provide rapid short-lived pain relief during surgery.[5] This drug is 50—100-times more potent than morphine on a weight basis.[3] In the literature, there was no survey on the clinical pharmacology of fentanyl in preterm infants, although this drug is often used in neonates. This prompted us to review the published data on the effects and fate of fentanyl in neonates, and to write the present article. The objective of this study is to review the clinical pharmacology of fentanyl in preterm infants.

2. Bibliographic search

The bibliographic search was performed electronically using PubMed and EMBASE databases as search engines. The following keywords were used: "fentanyl pharmacokinetics neonate", "fentanyl metabolism neonate", "CYP3A4 fentanyl neonate", "fentanyl adverse effects neonate", "chest wall rigidity fentanyl neonate", "muscle rigidity fentanyl neonate", "urinary retention fentanyl neonate", "hypothermia fentanyl neonate", "pharmacodynamic-pharmacokinetic fentanyl neonate", "tolerance fentanyl neonate", and "adverse effects fentanyl neonate". In addition, the books *Neofax: A manual of drugs used in neonatal care* by Young and Mangum[6] and the *Neonatal formulary*[7] were consulted. Drug use in pregnancy and the first year of life.

3. Results

3.1. Effects of fentanyl in neonates

Fentanyl is an extremely potent analgesic, maintains hemodynamic stability, blocks endocrine stress responses, and prevents pain-induced and increased pulmonary vascular resistance.[2,8] Muscle rigidity appears after high doses of fentanyl used in anesthetic induction.[9—12] Rigidity and respiratory depression can be treated with naloxone (10 μg/kg).[3] High doses of fentanyl can cause neuroexcitation and, rarely, seizure-like activity.[9]

Guinsburg et al[13] studied the response of 22 ventilated preterm infants prior to and after a single dose of 3 μg/kg fentanyl or placebo, and evaluated the physiologic and behavioral measures for the assessment of pain in intubated and ventilated preterm infants, and also studied their physiologic and behavioral pain responses occurring after fentanyl analgesia. The work by Guinsburg et al[13] suggests that opioid use may decrease catabolism, divert energy sources to growth and healing, and have a beneficial effect on the clinical stability of critical ill preterm infants. Single doses of fentanyl analgesia can reduce the physiologic/behavioral measures of pain and stress associated with mechanical ventilation in preterm infants.

Recently, attention was drawn to the pharmacokinetic/pharmacodynamic (PK/PD) relationship for fentanyl. A predictive PK/PD model of fentanyl that includes growth and maturation physiologic changes for fentanyl in neonates was developed.[14] The final model was evaluated by predicting the time course of plasma concentrations and the effect of a standard regimen of 10.5 μg/kg, followed by 1.5 μg/kg/hour for 48 hours. Systemic clearance, volume of distribution of the central compartment, and steady-state volume of distribution were 0.028 L/minute, 1.26 L, and 22.04 L, respectively. The model could be used in optimal design of clinical trials for this vulnerable population.

The PK/PD correlation of intranasal and intravenous fentanyl in opioid-naïve patients has been studied.[15] Bioavailability of intranasal fentanyl was 89%, with a lag of approximately 5 minutes and a half-life of about 6.5 minutes. Interindividual variability of fentanyl was about 30% for all absorption parameters. Intranasal versus intravenous administration of fentanyl lead to a delayed mean fentanyl time to maximum concentration (13 minutes vs. 6 minutes) and lower maximum concentration (1.2 ng/mL vs. 2.0 ng/mL). Dosing of intranasal fentanyl can be variable and the duration of effect was directly related to the intranasal fentanyl dose. The standard dose of intravenously administered fentanyl is 1—2 μg/kg.

Changes in plasma fentanyl concentrations were measured in 15 infants undergoing cardiac surgery using a low-volume bypass circuit.[16] Intravenous anesthesia was induced with 30 μg/kg of fentanyl, followed by a continuous infusion of 0.3 μg/kg fentanyl/hour until skin closure. Minimal changes in fentanyl concentration occur during infant cardiac surgery when a low-volume circuit and a fentanyl technique that includes an initial bolus followed by a continuous infusion of fentanyl are used.

3.2. Metabolism of fentanyl in neonates and adults

Fentanyl is metabolized by CYP3A4,[3] which appears during the 1st week of life.[6,7] Studies with the human adult liver microsomes revealed that fentanyl is N-dealkylated to give the inactive norfentanyl.[17] Fentanyl is also N-hydroxylated by CYP3A4, but N-hydroxylation is a minor metabolic pathway of fentanyl.[18]

Tramodol (M) is N-demethylated to N-demethyl tramadol (M2) by CYP3A4. The log M/M2 ratio was assessed in 24-hour urine collection and found to be 1.44 ± 0.46. There was an inverse correlation with the postmenstrual age ($r^2 = -0.43$)[19] and the maturational half-life of the log M/M2 ratio was 16—20 weeks. The postmenstrual age was found to be the most important maturational change determining the *in vivo* activity of CYP3A4.[19]

3.3. Pharmacokinetics following bolus administration of fentanyl to neonates

The pharmacokinetic parameters of fentanyl are summarized in Table 1.

Fentanyl is well absorbed by the gastrointestinal tract, but bioavailability is limited by rapid liver metabolism.[5,20] The pharmacokinetics of fentanyl, administered intravenously at the doses 10—50 μg/kg, were studied in 14 neonates aged 1—14 days, undergoing major surgical procedures.[18] Pharmacokinetics of fentanyl were influenced neither by the dose, nor by the infant age. Doses of 25—50 μg/kg fentanyl given to infants aged 0.5—1 day yielded plasma concentrations of 1.1—3.8 ng/mL 3—16 hours after fentanyl injection.[18]

The pathology and/or the surgical lesion lengthen half-life of fentanyl.[18] Three infants with increased intra-abdominal pressure had a fentanyl half-life 1.5—3 times the population