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 >5μg/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. Copyright © 2014, Taiwan Pediatric Association. Published by Elsevier Taiwan LLC. All rights reserved.

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. As pain is a major stressor that may increase morbidity and mortality in critically ill neonates, sedation and analgesia are widely used in infants. 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. This drug has a rapid onset of action of 2–3 minutes, a short duration of action of 60 minutes with
bolus doses and minimal hemodynamic effects. It is widely used to provide rapid short-lived pain relief during surgery. This drug is 50–100-times more potent than morphine on a weight basis. 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 and Neonatal formulary 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. Muscle rigidity appears after high doses of fentanyl used in anesthetic induction. Rigidity and respiratory depression can be treated with naloxone and respiratory depression can be treated with naloxone. Single doses of fentanyl analgesia can reduce the physiologic and behavioral pain responses occurring in ventilated and ventilated preterm infants, and also studied behavior measures for the assessment of pain in intu-

3.2. Metabolism of fentanyl in neonates and adults

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

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 (r² = −0.43) 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.

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. 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. 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. The pathology and/or the surgical lesion lengthen half-life of fentanyl. Three infants with increased intra-abdominal pressure had a fentanyl half-life 1.5–3 times the population...
mean of 317 minutes. An infant, treated with 25 μg/mL and undergoing an exploratory laparotomy, had a fentanyl half-life of 750 minutes. Another infant, who received 50 μg/kg fentanyl, and was undergoing a repair of a large omphalocele, had a fentanyl half-life of 463 minutes. Neoneates with increased abdominal pressure had longer half-life than healthy infants. Fentanyl has a high hepatic extraction ratio, and clearance is primarily dependent on hepatic perfusion. The transient rebounds in fentanyl plasma levels that occurred in some patients may reflect sequestering and subsequent release of fentanyl. Rebounds in fentanyl plasma levels have been reported in adults. Fentanyl was administered at the dosage of 54.1 ± 2.3 μg/kg to 14 infants aged from 1 day to 71 days. Clearance was not measurable in two neonates aged 1 day and 3 days. In the remaining 12 neonates, clearance ranged from 9.0 mL/kg/minute to 32.8 mL/kg/minute [mean ± standard deviation (SD), 19.2 ± 11.0 mL/kg/minute] and was correlated with the infant age (r = 0.5642; p = 0.0356). Mean ± SD half-life was 279 ± 204 minutes and distribution volume was 8.2 ± 2.5 L/kg. Neither parameter was correlated with the infant’s age.

Fentanyl (30 μg/kg) was administered to nine preterm infants. The fentanyl plasma concentration was 10.6 ± 1.9 ng/mL, 30 minutes after dosing. After 2 hours, it was 9.6 ± 1.6 ng/mL suggesting that fentanyl plasma concentration reduces slowly in infants yielding a half-life of 1062 ± 558 minutes. A gradual increase in heart rate from 159 ± 12 beats/minute, at the time of skin incision, to 173 ± 15 beats/minutes (p < 0.05), at the time of skin closure, was observed after fentanyl injection. A 30-μg/kg dose of fentanyl may not be adequate to cover the increased stimulus of skin closure in preterm infants after closure of a patent ductus arteriosus. A dose of 50 μg/kg or a continuous infusion of fentanyl are more reasonable. The unbound fentanyl fraction is 0.23 in neonatal plasma and 0.16 in adult plasma. The modest difference in the unbound fraction of fentanyl between infants and adults cannot explain the large difference observed in distribution volume between neonates and adults. The rapid and cumulative redistribution of fentanyl into fat and muscle depots may be the cause of the large distribution observed in neonates.

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### Table 1 Pharmacokinetic parameters of fentanyl in neonates.

<table>
<thead>
<tr>
<th>Age (d)</th>
<th>No. of cases</th>
<th>Dose (μg/kg)</th>
<th>Half-life (min)</th>
<th>Clearance (mL/min/kg)</th>
<th>Distribution volume (L/kg)</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–14</td>
<td>14</td>
<td>10–50 Bolus</td>
<td>317 ± 70</td>
<td>17.9 ± 4.4†</td>
<td>5.1 ± 1.0†</td>
<td>18</td>
</tr>
<tr>
<td>1–71</td>
<td>14</td>
<td>54.1 ± 2.3 2.3 Bolus</td>
<td>279 ± 204</td>
<td>19.2 ± 11.0</td>
<td>8.2 ± 2.5</td>
<td>25</td>
</tr>
<tr>
<td>31.8 ± 4.7 weeks</td>
<td>9</td>
<td>30 Bolus</td>
<td>1062 ± 558</td>
<td>NA</td>
<td>NA</td>
<td>26</td>
</tr>
<tr>
<td>26–42 weeks</td>
<td>38</td>
<td>Infusion</td>
<td>NA</td>
<td>11.5 ± 4.0</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>32 ± 4 weeks</td>
<td>7</td>
<td>1.28 ± 0.58 μg/kg/h</td>
<td>570 ± 156</td>
<td>19.2 ± 8.2</td>
<td>17.0 ± 9.0</td>
<td>31</td>
</tr>
<tr>
<td>18 days–14 years</td>
<td>19</td>
<td>Bolus + infusion</td>
<td>1266†</td>
<td>13.2</td>
<td>15.2†</td>
<td>27</td>
</tr>
<tr>
<td>Adults</td>
<td>—</td>
<td>—</td>
<td>222 ± 24</td>
<td>13.2 ± 2.0</td>
<td>4.0 ± 0.4</td>
<td>28</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation unless otherwise indicated.

† Data are the mean ± standard error of the mean.

2. Continuous infusion of fentanyl of 10.5 μg/kg over a 1-hour period was followed by an infusion of 1.5 μg/kg/hour for 2–3 days.

3. Value is presented as mean ± standard deviation was not available.

4. Loading dose of 5 μg/kg fentanyl, immediately followed by a constant infusion at 0.47–10.3 μg/kg/hour.

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### 3.4. Pharmacokinetics following continuous infusion of fentanyl to neonates

Thirty-eight infants with a gestational age of 26–42 weeks received a fentanyl bolus dose of 10.5 μg/kg, followed by an infusion of 1.5 μg/kg/hour, which lasted for 2–3 days. The steady-state fentanyl concentration (mean ± SD, 2.5 ± 1 ng/mL) negatively correlated with the pain score (r = −0.57; p < 0.01). The clearance of fentanyl (mean ± SD, 11.5 ± 4.0 mL/kg/minute) correlated with gestational age (r = 0.46; p < 0.01) and with birth weight (r = 0.48; p < 0.01). The pharmacokinetics of fentanyl was studied in seven preterm infants who had undergone mechanical ventilation. They received a continuous infusion of fentanyl (mean ± SD, 1.28 ± 0.58 μg/kg/hour). The mean half-life, clearance, and distribution volume were 570 ± 156 minutes, 19.2 ± 8.2 mL/minute/kg, and 17.0 ± 9.0 L/kg, respectively. A significant correlation was observed between postnatal age and clearance (r = 0.80; p = 0.03). Nineteen children, aged from 18 days to 14 years, undergoing mechanical ventilation, received a loading dose of 5 μg/kg fentanyl, followed by a continuous infusion of 3.6 μg/kg/hour. Clearance was 13.2 ± 2.0 mL/minute/kg and correlated with infant age. Patients aged between 6 months and 6 years had a mean clearance of 18.8 mL/minute/kg and patients aged <6 months and >6 years had a clearance of 8.0 mL/minute/kg and 8.1 mL/minute/kg, respectively. The mean terminal half-life was 1266 minute and distribution volume was 15.2 L/kg. Patients seen in a pediatric intensive care unit required a 10-fold variability in fentanyl infusion rates to achieve similar levels of sedation.

### 3.5. Analgesic effects of fentanyl following bolus or continuous infusion to neonates

Ancora et al studied the analgesic effect of fentanyl in 64 preterm infants. There were 67 controls and the study lasted 7 days. The analgesic efficacy was evaluated by the Echelle Douleur Inconfort Nouveau-Né scale, with scores >6 for 6.8% (fentanyl) and 10.6% (placebo; p = 0.003). The median premature infant pain profile score was statistically higher in the placebo group than in the fentanyl...
group on Day 1, Day 2, and Day 3 after treatment ($p < 0.05$). Mechanical ventilation was required in 42.2% and 25.4% ($p = 0.042$) in the fentanyl group and placebo group, respectively. The median duration of the mechanical ventilation cycle was 151 hours and 110 hours ($p = 0.019$) in the fentanyl group and placebo group, respectively. In preterm infants on mechanical ventilation, continuous fentanyl infusion, plus open-label boluses of fentanyl, does not reduce prolonged pain, and increases adverse effects compared with open-label boluses of fentanyl alone. Vaughn et al.\textsuperscript{33} compared the continuous infusion of fentanyl with bolus dosing in infants. Apenia occurred in eight of nine (89%) patients receiving fentanyl as a bolus compared with one of seven patients receiving fentanyl as a continuous infusion (14%; $p < 0.009$). Apenia was less likely to be severe in the continuous infusion patients (11%) than in the bolus patients (73%). Bolus fentanyl dosing may be appropriate for analgesia and sedation during minor procedures, but is not appropriate for postoperative analgesia in high-risk neonates. Continuous infusion of fentanyl is not a therapy without risk, but it may be associated with less severe respiratory depression as compared with intermittent treatment. The results by Ancora et al.\textsuperscript{32} do not accord with those by Vaughn et al.\textsuperscript{31}

Gruber et al.\textsuperscript{34} evaluated whether the administration of midazolam has some beneficial effects compared to that obtained with large-dose fentanyl. These authors were unable to demonstrate any additional suppression of the stress response in the midazolam group, or advantages in hemodynamic stability or total duration of mechanical ventilation and intensive care unit stay.

3.6. Plasma levels of fentanyl during extracorporeal membrane oxygenation in neonates

Extracorporeal membrane oxygenation (ECMO) therapy is a form of prolonged cardiopulmonary bypass used to support patients with life-threatening respiratory or cardiac failure.\textsuperscript{35} Fentanyl has rapid onset of action, relative hemo-dynamic effects, and short half-life, and is frequently used to provide analgesia and sedation for patients undergoing ECMO therapy. Tolerance to opioid-induced sedation has been described in neonates sedated with fentanyl by continuous infusion while undergoing ECMO.\textsuperscript{36} Eight neo-nates, with a birth weight of 3160 ± 620 g, received a fentanyl dose of 10–20 μg/kg, followed by continuous fentanyl infusion (9.2 ± 1.9 μg/kg/hour), which lasted 5.9 ± 3.0 days. The mean fentanyl infusion rate increased 238% during the 6 days of infusion. The assessment of adequacy of sedation in critically ill newborn infants undergoing ECMO is a difficult process because of the alterations that occur in infant fentanyl pharmacodynamics.

The neonates who had opioid withdrawal after ECMO, had significantly higher peak infusion rates of fentanyl, larger total doses of fentanyl, and longer ECMO therapy than the neonates who did not have withdrawal after ECMO ($p < 0.001$, $p = 0.003$, and $p = 0.009$, respectively). Neonates who received a total fentanyl dose >1.2 mg/kg during ECMO were 13 times more likely to experience opioid withdrawal after ECMO (Fisher exact test, $p = 0.003$) than were neonates who received a smaller total dose of fentanyl. Total fentanyl dose during ECMO had a sensitivity of 85% and a specificity of 70% for predicting the occurrence of withdrawal after ECMO. Tolerance and physical dependence are thought to develop more rapidly with continuous infusion than with intermittent administration, because of the greater duration of receptor occupancy.\textsuperscript{37}

3.7. Adverse effects of fentanyl in neonates

Fentanyl citrate is incompatible with thiopental sodium, methohexital sodium,\textsuperscript{38} azithromycin, pentobarbital sodium, and phenytoin.\textsuperscript{1} Ketoconazole and erythromycin are potent inhibitors of fentanyl metabolism\textsuperscript{17} and must not be used in association with fentanyl.

Nausea, vomiting, and itching can be observed after fentanyl administration. Muscle rigidity appears to be more common after high doses used in anesthetic induction. High doses of fentanyl can cause neuroexcitation and, rarely, seizure-like activity.\textsuperscript{39} Urinary retention may occur with fentanyl continuous infusion.\textsuperscript{3} Respiratory depression occurs when fentanyl doses >5 μg/kg are used, and it may also occur unexpectedly because of redistribution.\textsuperscript{3,39} Respiratory depression responds to naloxone (10 μg/kg).\textsuperscript{3} Atropine (10–30 μg/kg)\textsuperscript{3} may be used to block the vagal effects of fentanyl such as bradycardia.

A study on chest wall rigidity, with occasional laryngospasm, has been reported in preterm and term infants.\textsuperscript{9} Eight out of 89 neonates receiving fentanyl over a 1-year period showed chest wall rigidity.\textsuperscript{12} Fentanyl dosage ranged from 2.2 μg/kg to 6.5 μg/kg and was administered as a slow intravenous bolus.\textsuperscript{12} Seventy-five percent of patients received naloxone 10–105 μg/kg (mean dose 45 μg/kg), resulting in improvement and recovery from respiratory distress with good thoracic expansion after 1 minute.\textsuperscript{40}

Fentanyl analgesia increases the incidence of postoperative hypothermia in neonates.\textsuperscript{41,42} Nine neonates with a mean age of 35 weeks received fentanyl intravenously (median 5.9 μg/kg). The decrease in temperature was 1.8–2.8°C. Hypothermia can increase the risk of postoperative complications by inducing peripheral vasoconstriction, increasing anaerobic metabolism, pulmonary vasoconstriction, and right-to-left shunting. Morphine or bupivacaine did not yield hypothermia.

Tolerance is an adverse effect of opioids and may develop to high analgesic doses with prolonged use.\textsuperscript{36,41} Significant withdrawal symptoms have been reported in patients treated with continuous infusion receiving 10–20 μg/kg fentanyl for 5 days or longer.\textsuperscript{1} Arnold et al.\textsuperscript{31} reported the uniform development of tolerance and high incidence of opioid dependence in neonates receiving prolonged fentanyl infusion during ECMO. Mean infusion rate increased steadily during ECMO therapy, from a mean ± SD of 11.6 ± 6.9 μg/kg/hour on Day 1 to 52.5 ± 19.4 μg/kg/hour on Day 8; the increase was 452%.

4. Discussion

Fentanyl provides rapid analgesia, maintains hemostatic stability, blocks endocrine stress responses, and prevents pain-induced increases in pulmonary vascular resistance.
Fentanyl causes less histamine release than morphine and is therefore more stable in patients with congenital heart or chronic lung disease.5

Muscle rigidity appears to be more common after high doses in anesthetic induction.42–49 Chest rigidity and laryngospasm are reversible with 10 μg/kg naloxone.3 It has been postulated that the rigidity is mediated in part by the modulation of γ-aminobutyric acid pathways at the spinal cord and basal ganglia levels via fentanyl binding to μ, and κ opioid receptors.44

Sustained administration of an opiate agonist leads to progressive loss of drug effect. Tolerance is reflected by a reduction in the maximum achievable drug effect. It develops rapidly, especially with infusion compared to boluses because of the greater duration of receptor occupancy.50

A remarkable variability of the pharmacokinetic parameters of fentanyl has been described in neonates.18 Half-life ranged 12-fold, and distribution volume and clearance ranged 12-fold and 11-fold, respectively. The longer half-life of fentanyl in neonates, and the consequent lower rate of fentanyl elimination, are due to the lower expression of CYP3A4 in neonatal liver, which metabolizes fentanyl.7,51 The pathology and/or surgical lesion lengthens half-life of fentanyl in neonates.

Guinsburg et al13 suggested that preterm neonates experience some degrees of pain or stress associated with mechanical ventilation. Opioid use has a beneficial effect on the clinical stability of critically ill preterm neonates.5,41

Ancora et al52 found that fentanyl administrated as a bolus is safer that the continuous administration of fentanyl. In contrast, Vaughn et al33 reported opposite results: a lower frequency of apneic spells after continuous infusion than after bolus administration of fentanyl.

Tolerance to opioid-induced sedation has been reported in neonates sedated with fentanyl by continuous infusion while undergoing ECMO.61 An average of 8 days duration of ECMO therapy determined an infusion rate increase of 452%. The mean plasma fentanyl concentrations increased 448% in 6 days of infusion. Although much about analgesics in neonates is already known, further research is required to ensure that the doses recommended for the treatment of analgesia in neonates are evidence-based.

Schmidt et al52 compared the sufentanil versus fentanyl in ventilated term neonates. These authors compared the weaning time between fentanyl and sufentanil group. Mean ± SD weaning time of the fentanyl group was 520 ± 381 minutes and of the sufentanil group was 585 ± 531 minutes. No difference was observed for weaning time between the fentanyl group and sufentanil group. The mean opioid dose resulted in a 10:1 ratio (fentanyl 4.11 μg/kg/hour vs. 0.41 μg/kg/hour). These authors found no difference in sedation levels, blood pressure, heart rate, oxygenation index, comedication, or urinary cortisol levels. In both groups similar adverse effects were assessed including respiratory depression, mild withdrawal symptoms, or decrease of gastrointestinal motility.

Conflicts of interest

The author has no conflicts of interest relevant to this article.

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