Intranasal Fentanyl in the Palliative Care of Newborns and Infants

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Abstract

Context. Perinatal palliative care is an area of increasing focus among clinicians supporting newborns and their families. Although not every newborn will survive the neonatal period, assuring their comfort and quality of life remains an imperative for their care providers. It can be challenging to administer medications such as opioids in a minimally invasive yet effective manner.

Objectives. To describe the experience using intranasal (IN) fentanyl in the management of distress in a case series of 11 dying neonates.

Methods. A retrospective chart review was undertaken of 58 consecutive referrals of newborns and infants aged six months or younger between November 2006 and July 2010 to the Winnipeg Regional Health Authority Pediatric Palliative Care Service to determine how often IN fentanyl was used and review documented responses after the medication.

Results. Of 58 referrals, IN fentanyl was used in 11 patients, in all cases for concerns regarding respiratory distress. Chart documentation indicated that fentanyl was tolerated well, with no circumstances of drug-related apnea and no occurrences of chest wall rigidity. In most cases, labored breathing and restlessness settled after medication administration. The average time from administration of the last dose of fentanyl until death was 61 minutes.

Conclusion. We found IN fentanyl, which can be administered in a variety of care settings, to be a minimally invasive means of palliating distress in dying newborns and infants. No adverse events related to its use were noted. J Pain Symptom Manage 2012; —: —. © 2012 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.
Key Words
Palliative care, newborn, neonatal, perinatal, infants, fentanyl, intranasal, dyspnea

Introduction

In spite of ongoing progress in treating newborns affected by life-threatening conditions, some will not survive the neonatal period. Optimal care of such infants requires a palliative approach, focusing on comfort, while avoiding burdensome interventions, enabling meaningful connection with family in the short time they have left.

Opioids are typically used for addressing pain or dyspnea and in the context of an imminently dying newborn, and there is compelling urgency to ensure that the selected medication has a rapid onset of action by the chosen route of administration. However, the IV route is invasive, may be technically challenging to secure in a severely premature or malformed neonate, and takes precious time away from the newborn being with family. The nasogastric route also is burdensome and takes time to establish, and the relatively slow onset of effect with medications administered by the nasogastric route is not satisfactory for rapidly addressing symptoms. It is, therefore, important to explore alternative routes of medication administration in this patient population.

Sublingual morphine is one consideration for noninvasive administration of opioids in newborns. However, morphine is poorly absorbed by this route and likely undergoes gastrointestinal absorption after being swallowed rather than absorption through the oral transmucosa. The $T_{\text{max}}$ (time after administration of a drug when maximum plasma concentration is reached) of sublingual morphine has been found to be 138 minutes, which is unacceptably long in the context of proximate death and pain or respiratory distress. Although buccal or sublingual fentanyl may be an alternative route for fentanyl, there is little information published on the use of these routes in children, in contrast to the expanding literature on intranasal (IN) fentanyl.

IN administration of the highly lipid soluble drug fentanyl in adults has been found to result in therapeutic levels in as short as two minutes, and $T_{\text{max}}$ ranges from five to 15 minutes. Striebel et al. found the bioavailability of nasal fentanyl to be 71%, and, more recently, Foster et al. found it to be 89%. The onset of the effect is within five minutes, and it has not been found to be irritating to the nasal mucosa.

In adults, IN fentanyl has been found to be effective for breathlessness and pain management. In a randomized study of IN fentanyl for dental extraction pain ($N=24$ patients; total of 47 extractions), Christrup et al. found that “differences in the onsets and durations of analgesia after IN and IV administration of single doses were not significantly different and neither was the difference in overall analgesia.”

Although the literature on IN fentanyl specifically in neonates is lacking, research indicates that it is safe and effective in children aged as young as 12 months. There is an expanding evidence base documenting its effectiveness for pain management in children, in the context of an emergency department, surgery, and procedures. Initial dosages varied from 1.43 to 2 mcg/kg in these studies, with an average of 1.6 mcg/kg. In a recent review, IN fentanyl was considered “a safe and effective method of pain management for children in a variety of clinical settings.”

A protocol was developed by the Pediatric Palliative Care Service (PPCS) of the Winnipeg Regional Health Authority to standardize an approach to the preparation and administration of IN fentanyl and provide policy/procedure support to nursing and medical staff. IN fentanyl dosing was based on established IV doses of fentanyl for newborns, providing a degree of conservatism because of the incomplete bioavailability by the nasal route. Although ideal IN volumes for children in general have been described as ranging from 0.2 to 0.5 mL per dose, no specific recommendations exist for neonates. Our practice is to use 0.1–0.3 mL IN per dose in a single
nostril; higher volumes would be divided between nostrils.

The purpose of this article was to present our experience using IN fentanyl in the palliative management of distress in dying neonates. The aim of this study was to determine the frequency and circumstances under which IN fentanyl was used to address distress in palliative newborns and infants seen in the context of a pediatric palliative care consultation service. Documentation regarding therapeutic response and potential adverse effects also was reviewed.

Patients and Methods

Design

PPCS offers consultative services throughout the trajectory of a child’s illness. These services are provided in one tertiary care children’s hospital, two neonatal units, two hospitals that provide labor and delivery services, and the community.

This study was a retrospective chart review of patients who were aged six months or younger and referred to PPCS between November 2006 and July 2010, to determine if IN fentanyl was administered by the involved health care team following recommendations of PPCS. Data extraction included diagnosis, gestational age at birth, age at death, location of birth, location of death, details of fentanyl dosing, and a synopsis of the newborn’s response, as it appeared in the chart.

Prenatal Preparation

When involved prenatally in circumstances of lethal fetal anomalies, PPCS suggested that IN fentanyl be pre-drawn before delivery and available for immediate use, ensuring timely symptom management. Recommended doses were generally in the 1–2 mcg/kg range based on estimated fetal weight, which is usually documented in the Fetal Assessment Unit chart, or inferred from gestational age.

For estimated fetal weights of less than 1 kg, single-dose syringes were prepared containing 1 mcg of fentanyl (0.1 mL of 10 mcg/mL solution, prepared by diluting injectable fentanyl 50 mcg/mL in normal saline). A dose of 1 mcg falls in the 1–2 mcg/kg/dose range for newborns weighing between 500 g and 1 kg.

For estimated fetal weights greater than 1 kg, single-dose syringes were prepared containing 2.5 mcg of fentanyl (0.1 mL of 25 mcg/mL solution, prepared by diluting injectable fentanyl 50 mcg/mL in normal saline). A dose of 2.5 mcg falls in the 1–2 mcg/kg/dose range for newborns weighing between 1.25 and 2.5 kg.

Preparation After Delivery

When PPCS was initially involved after delivery, the starting dose of IN fentanyl was based on the measured weight of the newborn, usually beginning with 1 mcg/kg and adjusting if needed.

IN fentanyl could be repeated every five to 10 minutes as needed, up to three doses within 30 minutes. If three doses within 30 minutes were ineffective, a physician was required to reassess the circumstances, with a possible view to increasing the dose.

Main Outcome Measures

In our experience, respiratory distress accompanying progressive respiratory compromise is the predominant threat to comfort in the dying newborn; our primary outcome was the alleviation of respiratory distress. In the absence of existing tools for measuring dyspnea in newborns, involved health care teams were asked to be vigilant for 1) increased work of breathing: tachypnea, nasal flaring, grunting, use of accessory muscles, chest wall retractions and 2) evidence of distress: restlessness, irritability, crying.

IN fentanyl was not considered to be indicated for newborns demonstrating signs of increased work of breathing in the absence of apparent distress or for newborns with progressive apneic episodes (as may be seen in those with lethal central nervous system abnormalities). Narrative charting was used to document the presence and degree of distress, the observed response with the use of fentanyl, and potential adverse effects.

Ethical Review

This study was approved by the Health Research Ethics Board, Bannatyne Campus, at the University of Manitoba and the Institutional Review Boards at the two Winnipeg hospitals where data collection took place (Health
Results

Fifty-eight patient charts met entry criteria for review; IN fentanyl was used in 11 cases. In all cases, the indication for fentanyl administration was the concern on the part of clinical staff or family about respiratory distress. Nursing staff administered the IN fentanyl in all cases with the exception of Patient #11, whose parents administered the medication. Patient information is described in Table 1, and details of fentanyl administration are described in Table 2.

The lowest starting dose was 0.24 mcg/kg in an extremely low birth weight triplet at a time that our program was just becoming familiar with IN fentanyl and was somewhat conservative in prescribing. The highest starting dose was 3.8 mcg/kg, in an opioid-tolerant patient who had been receiving an IV infusion of fentanyl 3 mcg/kg/hour when venous access was lost at the time of withdrawal of ventilatory support. The mean initial dose was 1.3 mcg/kg, and the median was 1 mcg/kg.

The average number of doses administered was 4.5, with a range of one to 17, a median of three, and a mode of one dose. The newborn who received 17 doses had a diagnosis of Potter’s Syndrome and over 21 hours of life experienced episodes of respiratory distress for which clusters of repeated fentanyl doses were administered with good effect.

Charted descriptions of observed responses are noted in Table 2. Documentation was not consistently available regarding indications for use or specific comments regarding effectiveness; often there would be general comments such as “baby is comfortable.”

Table 1
Patient Descriptions

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trisomy 18 with cardiac defect</td>
</tr>
<tr>
<td>2</td>
<td>Potter’s syndrome with renal agenesis; gastrochisis</td>
</tr>
<tr>
<td>3</td>
<td>Intrauterine growth retardation; oligohydramnios; prematurity</td>
</tr>
<tr>
<td>4</td>
<td>Giant ruptured omphalocele</td>
</tr>
<tr>
<td>5</td>
<td>Skeletal dysplasia (lethal form)</td>
</tr>
<tr>
<td>6</td>
<td>Severe polycystic kidney disease</td>
</tr>
<tr>
<td>7</td>
<td>Multiple brain anomalies; likely mitochondrial disorder</td>
</tr>
<tr>
<td>8</td>
<td>Perinatal asphyxia; hypoxic-ischemic encephalopathy; seizures</td>
</tr>
<tr>
<td>9</td>
<td>Extreme prematurity; NEC; sepsis</td>
</tr>
<tr>
<td>10</td>
<td>Hypoxic-ischemic encephalopathy; chromosome translocation</td>
</tr>
<tr>
<td>11</td>
<td>Spinal muscular atrophy Type 1</td>
</tr>
</tbody>
</table>

Gestational Age at Birth | Age at Death |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>41 weeks, five days</td>
<td>13 hours, nine minutes</td>
</tr>
<tr>
<td>35 weeks</td>
<td>21 hours, 23 minutes</td>
</tr>
<tr>
<td>30 weeks, four days</td>
<td>Nine hours, 21 minutes</td>
</tr>
<tr>
<td>28 weeks, six days</td>
<td>15 minutes</td>
</tr>
<tr>
<td>38 weeks</td>
<td>One hour, 20 minutes</td>
</tr>
<tr>
<td>35 weeks</td>
<td>43 minutes</td>
</tr>
<tr>
<td>39 weeks</td>
<td>43 days</td>
</tr>
<tr>
<td>34 weeks, five days</td>
<td>28 days</td>
</tr>
<tr>
<td>24 weeks</td>
<td>44 days</td>
</tr>
<tr>
<td>37 weeks, four days</td>
<td>35 days</td>
</tr>
<tr>
<td>40 weeks</td>
<td>197 days</td>
</tr>
</tbody>
</table>

Location of Birth | Location of Death |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>LDRP unit</td>
<td>LDRP unit</td>
</tr>
<tr>
<td>LDRP unit</td>
<td>LDRP unit</td>
</tr>
<tr>
<td>High Risk Labor &amp; Delivery unit</td>
<td>Postpartum unit</td>
</tr>
<tr>
<td>LDRP unit</td>
<td>LDRP unit</td>
</tr>
<tr>
<td>Rural Hospital Labor &amp; Delivery unit</td>
<td>Rural Hospital Labor &amp; Delivery Unit</td>
</tr>
<tr>
<td>High Risk Labor &amp; Delivery unit</td>
<td>Children’s Hospital ward</td>
</tr>
<tr>
<td>High Risk Labor &amp; Delivery unit</td>
<td>NICU</td>
</tr>
<tr>
<td>High Risk Labor &amp; Delivery unit</td>
<td>NICU</td>
</tr>
<tr>
<td>High Risk Labor &amp; Delivery unit</td>
<td>NICU</td>
</tr>
</tbody>
</table>

LDRP = Labor, Delivery, Recovery, Postpartum; NICU = Neonatal Intensive Care Unit; NEC = necrotizing enterocolitis.
### Table 2
Details of Fentanyl Administration

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial Fentanyl Dose</th>
<th>Total No. of Doses</th>
<th>Details of Fentanyl Administration</th>
<th>Time From Last Fentanyl Dose Until Death</th>
<th>Adverse Effects Noted</th>
<th>Therapeutic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5 mcg (1.46 mcg/kg)</td>
<td>8</td>
<td>First dose given at 58 minutes, repeated at one hour four minutes, two hours 52 minutes, and three hours 40 minutes. At nine hours five minutes, a cluster of four doses was given within 58 minutes.</td>
<td>Three hours six minutes</td>
<td>None</td>
<td>Labored, grunting respirations settled after two doses initially. Required four doses within an hour at approximately nine hours of life, which were ultimately effective and baby remained settled until dying approximately three hours later.</td>
</tr>
<tr>
<td>2</td>
<td>2.5 mcg (0.8 mcg/kg)</td>
<td>15</td>
<td>First dose given at eight minutes of life, with the second dose at 13 minutes of life. Over the next several hours, five more doses given at intervals of 90—120 minutes. Subsequently, no medications needed for approximately five hours and then three doses were given in a 25-minute time frame. For the following two hours, no medications needed and then five doses were needed at the interval of 20—40 minutes over a two-hour period.</td>
<td>33 minutes</td>
<td>None</td>
<td>Experienced intermittent episodes of labored breathing and respiratory distress. Restlessness and labored breathing settled following fentanyl administration, although repeated doses were needed.</td>
</tr>
<tr>
<td>3</td>
<td>0.1 mcg (0.2 mcg/kg)</td>
<td>3</td>
<td>First dose given at two hours 11 minutes of life, next dose at three hours 35 minutes of life, and last dose at seven hours 11 minutes of life.</td>
<td>Two hours 10 minutes</td>
<td>None</td>
<td>Restlessness and labored breathing settled</td>
</tr>
<tr>
<td>4</td>
<td>1 mcg (1.2 mcg/kg)</td>
<td>2</td>
<td>One dose five minutes after birth, followed by a second dose five minutes later</td>
<td>Five minutes</td>
<td>None</td>
<td>Restlessness and labored breathing settled</td>
</tr>
<tr>
<td>5</td>
<td>2.5 mcg (0.7 mcg/kg)</td>
<td>1</td>
<td>Single dose administered</td>
<td>65 minutes</td>
<td>None</td>
<td>Restlessness and labored breathing settled</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial Fentanyl Dose</th>
<th>Total No. of Doses</th>
<th>Details of Fentanyl Administration</th>
<th>Time From Last Fentanyl Dose Until Death</th>
<th>Adverse Effects Noted</th>
<th>Therapeutic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5 mcg (1.5 mcg/kg)</td>
<td>1</td>
<td>15 minutes after birth. Single dose of fentanyl used 15 minutes after birth</td>
<td>28 minutes</td>
<td>None</td>
<td>breathing settled</td>
</tr>
<tr>
<td>7</td>
<td>5 mcg (1 mcg/kg)</td>
<td>1</td>
<td>Used fentanyl on the 33rd day of life to respond to respiratory distress</td>
<td>10 days</td>
<td>None</td>
<td>Restlessness and labored breathing settled</td>
</tr>
<tr>
<td>8</td>
<td>2 mcg (1 mcg/kg)</td>
<td>4</td>
<td>Fentanyl given at the time of withdrawal of ventilatory support with nasal CPAP. Further fentanyl doses given 20 minutes after the initial dose, repeated 15 minutes later, followed by another dose 30 minutes after that (65 minutes after NCPAP discontinued).</td>
<td>81 minutes</td>
<td>None</td>
<td>No charting about response to fentanyl</td>
</tr>
<tr>
<td>9</td>
<td>5 mcg (3.8 mcg/kg)</td>
<td>4</td>
<td>IV infusion of fentanyl 3 mcg/kg/hour was lost at the time of withdrawal of invasive ventilatory support. Two doses of IN fentanyl administered before extubation (32 minutes prior and 14 minutes prior). Two doses administered following extubation (3 minutes and 26 minutes after extubation).</td>
<td>22 minutes</td>
<td>None</td>
<td>Restlessness and labored breathing settled</td>
</tr>
<tr>
<td>10</td>
<td>8 mcg (1.9 mcg/kg)</td>
<td>3</td>
<td>Withdrawal of invasive ventilatory support without IV access. First dose given at the time of extubation, second dose 10 minutes later, followed in 10 minutes by the third dose.</td>
<td>Five minutes</td>
<td>None</td>
<td>Restlessness and labored breathing settled</td>
</tr>
<tr>
<td>11</td>
<td>5 mcg (0.8 mcg/kg)</td>
<td></td>
<td>Four doses in the episode of severe respiratory distress 10 days before dying Home support of an infant on bi-level noninvasive ventilatory support, on a background of fentanyl</td>
<td>50 minutes</td>
<td>None</td>
<td>Difficult to assess specific response to fentanyl in the episode of respiratory distress 10</td>
</tr>
</tbody>
</table>
Two doses on the day of death, regularly scheduled morphine. Ten days before death, experienced sudden respiratory distress. Given three doses of 5 mcg at intervals of 35 minutes and 2.5 hours later given a single dose of 10 mcg. Also given three breakthrough doses of morphine over a four-hour period, followed by an increase in the regularly scheduled morphine dose. Stable for the subsequent 10 days with no fentanyl or breakthrough morphine needed. On the day of death, developed respiratory distress. Fentanyl had been increased to 15 mcg because of increased opioid tolerance, and two doses were used one hour 40 minutes apart.

days before death, as morphine breakthrough doses also were given. Restlessness and labored breathing settled. Restlessness and labored breathing settled after two doses on the day of death

CPAP = continuous positive airway pressure; NCPAP = nasal continuous positive airway pressure; IN = intranasal.
Location of Death

Medication administration for symptom management in dying newborns most commonly involves the IV route, requiring equipment and/or clinical skills that are not typically available in care settings outside of those specializing in newborn care.

In this group, seven (64%) of the newborns who received fentanyl for symptom relief at the end of life were able to be cared for in settings that would not conventionally support the care of a dying newborn: four in low-risk, family-centered birthing rooms; one in a rural labor and delivery room without on-site support by pediatric specialists; one at home in an urban setting; and one on the postpartum unit of an urban hospital, with family present.

Discussion

This is the first publication describing IN fentanyl in the palliative management of dying newborns and infants. In our experience, this is a clinically effective intervention in managing symptoms in dying newborns, and no adverse events were noted in our study population. The simplicity of administration facilitates its use in a variety of care settings.

The palliative management of newborns and infants often involves the need to address symptom distress in a manner that is noninvasive and minimally burdensome, interfering as little as possible with sharing limited time with family. Opioids are the mainstay of pharmacological treatment for pain and dyspnea in palliative care, and IN fentanyl provides a minimally invasive means of administering an opioid with a rapid onset of action.

One challenge in addressing air hunger in newborns is the reliable assessment of respiratory distress. There is no validated tool for assessing respiratory distress in the newborn, making consistent evaluation of discomfort and treatment effectiveness difficult.

Concerns exist about the potential for fentanyl to cause glottic or chest wall rigidity, compromising ventilation. It is felt that this phenomenon is related to the dose and rate of administration, and it is believed that the transmucosal route may offer some protection as a result of a slower rise in drug concentration in the blood relative to IV. We saw no evidence of this or other adverse effects with IN fentanyl.

The availability of a minimally invasive means of addressing the comfort of dying newborns facilitates care in low-tech, family-focused care settings. Deliveries can be supported in low-risk birthing rooms with family present rather than a high-risk labor floor with the baby quickly removed to a neonatal intensive care unit. Consideration can be given to discharge home for palliative and end-of-life care, while supporting symptom management in a noninvasive manner. Rather than displacing families from rural or remote settings for end-of-life care because of challenges in parenteral drug administration in dying newborns, families can remain in home communities.

Although no adverse events were noted, the small number of patients in this study limits the determination of safety of IN fentanyl as used in our protocol. The study also is limited by its retrospective nature, with the inherent potential for bias. We feel that our findings will serve as a foundation for subsequent prospective studies further examining the safety and efficacy of IN fentanyl for respiratory distress in this population.

In the absence of an established dyspnea assessment tool, we were reliant on accurate and detailed charting by the health care team regarding their clinical assessment of the indications for medication administration and their observations of therapeutic response. Hence, our future research in this area will involve the development of an assessment tool for evaluating dyspnea in newborns. This will enable us to launch a prospective study, exploring in more detail the factors influencing clinical decision making involving the administration of fentanyl in distressed newborns nearing death.

Conclusion

Our experience suggests that IN fentanyl provides a minimally invasive and clinically effective means of palliating distress in dying newborns and infants. Its simplicity of administration facilitates palliative and end-of-life care of newborns and infants in low-tech, family-focused care settings, including the home. Further research is needed in the form of
prospective studies examining the safety and efficacy of IN fentanyl in newborns for the management of respiratory distress and in the assessment and measurement of respiratory distress in newborns.

**Disclosures and Acknowledgments**

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**References**


21. Mercadante S, Popper L. Efficacy and patient preference for intranasal fentanyl spray (INFS) versus oral transmucosal fentanyl citrate (OTFC) for