Alfentanil as procedural pain relief in newborn infants

Elina Saarennmaa, Pirkko Huttunen, Juhani Leppäluoto, Vineta Fellman

Abstract

Aims—To assess the need for, and the suitability of, alfentanil for pain relief during tracheal suction used in assisted ventilation in newborn infants.

Methods—In a randomised, controlled, double blind, crossover trial, placebo (10 μg/kg) and 20 μg/kg alfentanil were infused in random order two minutes before three separate endotracheal suctional events, at least six hours apart, to 10 infants. Measurements were made of physiological variables, behaviour, and stress hormones.

Results—After placebo infusion heart rate significantly increased (median 14; interquartile range 12–16 beats/minute) as did behavioural pain score (5; 3–5). Alfentanil (20 μg/kg) attenuated the heart rate increase, normalised the pain score, and caused a decrease in plasma adrenaline activity (0.3; 0.2–0.7 mmol/l). Noradrenaline concentration showed a non-significant decreasing trend with increasing alfentanil dose and β endorphin was unchanged. Rigidity was noted in the placebo (n=2), 10 μg/kg (n=2), and 20 μg/kg (n=5) alfentanil groups, respectively.

Conclusions—Tracheal suction is a painful procedure. The dose of alfentanil required for pain relief (20 μg/kg) causes a high incidence of rigidity and thus should be used only with muscle relaxant.

Keywords: analgesia, opioid, rigidity, behavioural response.

The need for surgical and postoperative analgesia in newborn infants has been widely accepted in the past decade. More recently, analgesia before intubation and during assisted ventilation during the acute phase of the respiratory distress syndrome (RDS) is becoming routine. Minor procedures, however, are still usually performed without analgesia or sedation. During weaning off the ventilator, analgesia is considered necessary in older age groups, but neonates undergo common treatment procedures such as tracheal suction without pain relief. This may lead to stimulation of the autonomic nervous and neuroendocrine systems. Therefore, newborns may be subjected to the risk of deleterious haemodynamic changes and hypoxaemia in response to unrelieved pain. Moreover, activation of endogenous opiates such as β endorphin by uncontrolled pain may suppress the respiratory centre and thus exacerbate RDS.

Alfentanil, a synthetic opioid chemically related to fentanyl, with a rapid onset and brief duration of action, is used as a procedural analgesic for paediatric patients. The plasma half life is 40 minutes in children aged 4 to 8 years and 97 minutes in adults. Significantly longer half lives have been reported in preterm infants, ranging from six to nine hours. The efficacy of alfentanil for short painful events in neonates has not been evaluated.

We assessed the need for pain relief for the brief discomfort experienced during tracheal suction in newborn infants in the recovery period of assisted ventilation. Additional objectives of this randomised trial included the evaluation of the suitability and appropriate dose of alfentanil for relieving discomfort provoked by suction.

Methods

The study was performed in the neonatal intensive care unit of the Children's Hospital, University of Helsinki. The protocol was approved by the ethics committee and written informed consent from the parents was obtained before enrolment. Intubated and mechanically ventilated newborn infants were eligible. The study entry criteria were: (1) a gestational age of 24 weeks or more; (2) no chromosomal aberrations or major anomalies; (3) an indwelling arterial line for continuous blood pressure monitoring and blood sampling on clinical indications; (4) no continuous analgesic medication.

To calculate the sample size, we hypothesised that tracheal suction without pain relief would cause an increase in behavioural pain score of six points. To show a 25% reduction in the increase with either dose of alfentanil with a power of 90% (α = 0.05), a sample size of nine was needed. We decided to study 10 patients. The median birthweight of the 10 infants (six boys, four girls) was 1440 g (interquartile range 1040–3160 g) and the gestational age was 32 weeks (29–36 weeks). Eight infants had been delivered by caesarean section and two vaginally. The Apgar score was 5 (4–8) at one minute and 7 (4–8) at five minutes of age. The umbilical artery pH was 7.29 (7.24–7.31) at birth. The main diagnosis was respiratory distress syndrome in seven infants, asphyxia, immaturity, and meconium aspiration syndrome in one patient each. One infant developed necrotising enterocolitis during the study period. Nine infants received dopamine and/or dobutamine, five infants received surfactant, and five indomethacin. No neurological abnormality was observed before or during the trial.
The study was of a randomised, controlled, double blind, crossover design. Each patient received saline as placebo and two different doses of alfentanil, 10 and 20 μg/kg intravenously, in random order before three painful procedures. As standard pain stimulus we used routine tracheal suction. One nurse performed the dilution of alfentanil from commercial phials (Rapifen, Janssen) according to instructions in sealed numbered envelopes. An equal volume (0.8 ml/kg) was infused for all doses. The solution was slowly administered over two minutes by another nurse unaware of the content. The tracheal suction was started two minutes later and the severity of the pain and discomfort assessed blind by ES.

During the procedure the infant was bag ventilated, and if oxygen desaturation occurred, the FIO2 was increased. The interval between the three investigational doses was at least six hours. Arterial blood was sampled (1.5 ml blood in EDTA phials containing 15 μl of 1% sodium metabisulphite) before the investigational solution was administered and 30 minutes after the suction for determination of plasma adrenaline, noradrenaline, and β endorphin concentrations. A serum sample for determination of alfentanil concentration was obtained at the same time. The samples were centrifuged and stored at -70°C until analysis.

The severity of pain was assessed according to physiological variables, stress hormone activities, and a behavioural pain scale. Heart rate, arterial blood pressure, and oxygen saturation were continuously monitored (Hewlett Packard Neonatal Component Monitoring System). Changes associated with suction were registered and compared with baseline values before the procedure.

Noradrenaline and adrenaline concentrations were measured using a liquid chromatographic method. The catecholamines were extracted from 100-250 μl plasma into 30 mg Al2O3 in test tubes with 3,4-dihydroxybenzylamine hydrobromide (Sigma, St.Louis, Missouri, USA) as an internal standard. After washing four times with H2O the catecholamines were released into 50 μl HCIO4 solution and high pressure liquid chromatography with electrochemical detector (Esa Coulomher Multi-Electrode, model 5100 A) was used for determination of noradrenaline and adrenaline. The column was a reverse phase column and a methanol-phosphate buffer a mobile phase. The ratio of the peak height of each catecholamine to the peak height of the internal standard was used as the basis for the concentration calculations.

Detection limit of the assay was 10 pg/injection.

A radioimmunoassay was used for determination of β endorphin concentrations, with a detection limit of 2 pg/tube. Plasma samples were extracted with Gilson ASPEC automatic sample preparation system. The Sep-Pak eluates were dried in Speed-Vac, reconstituted with buffer, and measured with a β endorphin radioimmunoassay.

### Table 1 Definition of pain scale

<table>
<thead>
<tr>
<th>Facial expression:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Composed</td>
<td>0</td>
</tr>
<tr>
<td>Grimace</td>
<td>1</td>
</tr>
<tr>
<td>Cry:</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Moaning</td>
<td>1</td>
</tr>
<tr>
<td>Crying</td>
<td>2</td>
</tr>
<tr>
<td>Limbs and torso:</td>
<td></td>
</tr>
<tr>
<td>Neutral, torso is inactive</td>
<td>0</td>
</tr>
<tr>
<td>Shifting, body is arching</td>
<td>1</td>
</tr>
<tr>
<td>Movements:</td>
<td></td>
</tr>
<tr>
<td>Quiet sleep, no movements</td>
<td>0</td>
</tr>
<tr>
<td>Normal spontaneous movements</td>
<td>1</td>
</tr>
<tr>
<td>Attempt to withdraw</td>
<td>2</td>
</tr>
<tr>
<td>Complex agitation</td>
<td>3</td>
</tr>
<tr>
<td>Breath patterns:</td>
<td></td>
</tr>
<tr>
<td>Relaxed</td>
<td>0</td>
</tr>
<tr>
<td>Change in breathing</td>
<td>1</td>
</tr>
</tbody>
</table>

Alfentanil concentrations were determined by radioimmunoassay, the detection limit of which was 1 ng/ml (Janssen Research Foundation, Belgium).

Pain response before, during, and after tracheal suction was assessed by the researcher who was unaware of the dose administered. Changes occurring during the procedure were registered using a behaviour pain score ranging from zero to eight (table 1), developed from the Children’s Hospital of East Ontario Pain Scale (CHEOPS) and Neonatal Infant Pain Scale (NIPS).

Possible adverse effects of alfentanil were observed by the researcher and the nurse performing the suction. Special attention was paid to rigidity, the most common adverse effect of rapidly acting opioids. Rigidity was graded in terms of passive resistance to movement of the limbs relative to the pretreatment level in four categories: (i) muscle tone decreased or unchanged; (ii) slightly increased muscle resistance; (iii) severe rigidity; or (iv) convulsive activity. Urinary retention was evaluated clinically and at least once in each infant by ultrasound measurement.

The Wilcoxon signed rank test and Spearman’s rank correlation coefficient were used for statistical analysis. A P value of 0.05 or less was regarded as significant. Data are presented as median and interquartile range, results of comparisons as medians of the difference with 95% confidence interval (CI).

### Results

Of the 10 infants enrolled, seven completed the entire protocol. One infant received two doses (10 μg/kg and 20 μg/kg) and two infants only one study dose each (placebo and 10 μg/kg, respectively), because of removal of the arterial line. The age of the infants during the trial was 3 (2-6) days.

The serum alfentanil concentration was 21 (17-22) ng/ml after administration of 10 μg/kg and 49 (40-50) ng/ml after 20 μg/kg. Two infants had residual alfentanil concentrations of 11 ng/ml and 13 ng/ml when they received placebo as their second dose.

The changes in cardiovascular variables are shown in fig1. Heart rate and mean arterial blood pressure increased in seven out of eight infants who received placebo before the proce-
found during suction, a significant difference compared with pretreatment with placebo (fig 3).

As an adverse effect, we registered severe muscle rigidity in five out of eight infants who received 20 μg/kg alfentanil. However, two infants in the 10 μg/kg alfentanil group and two infants in the placebo group also showed some rigidity. Two of the seven infants who completed the whole protocol did not show any rigidity. Rigidity appeared immediately after the alfentanil injection before the beginning of the suction. When manual ventilation was enhanced with increased pressure and O₂ concentration, the rigidity disappeared rapidly within a few minutes, and thus muscle relaxants were not given to any infant. No other side effects were observed during the study period. Clinical and ultrasound examinations revealed no urinary retention.

**Discussion**

Assessing pain and the efficacy of analgesia in newborn and especially preterm infants is difficult because physiological, hormonal, and behavioural reactions are not necessarily specific to pain. Pain undoubtedly causes stress in critically ill newborn infants, but they may also be distressed by the basic disease, current clinical condition, or merely as a result of handling. As a measurement of behavioural pain intensity we used a pain score modified for intrubated newborns from previously published

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**Table 2** Plasma catecholamine concentrations before and after endotracheal suction in infants treated with 20 μg/kg alfentanil

<table>
<thead>
<tr>
<th>Case No</th>
<th>Adrenaline (nmol/l) Before</th>
<th>Adrenaline (nmol/l) After</th>
<th>Noradrenaline (nmol/l) Before</th>
<th>Noradrenaline (nmol/l) After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.54</td>
<td>0.36</td>
<td>1.48</td>
<td>1.73</td>
</tr>
<tr>
<td>2</td>
<td>4.41</td>
<td>0.61</td>
<td>1.16</td>
<td>0.24</td>
</tr>
<tr>
<td>3</td>
<td>0.33</td>
<td>ND</td>
<td>2.16</td>
<td>2.08</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>6.91</td>
<td>5.02</td>
</tr>
<tr>
<td>5</td>
<td>1.71</td>
<td>ND</td>
<td>9.57</td>
<td>20.30</td>
</tr>
<tr>
<td>6</td>
<td>0.62</td>
<td>ND</td>
<td>14.83</td>
<td>6.97</td>
</tr>
<tr>
<td>7</td>
<td>0.68</td>
<td>0.24</td>
<td>4.85</td>
<td>1.61</td>
</tr>
<tr>
<td>8</td>
<td>0.72</td>
<td>0.50</td>
<td>2.17</td>
<td>2.79</td>
</tr>
</tbody>
</table>

ND = less than 0.2 nmol/l.
pain scales.\textsuperscript{12, 13} Scoring of pain is always a subjective assessment, and to avoid interindividual variation all scorings were done by the same researcher (ES). Our results clearly show that brief tracheal suction led to behavioural pain that could be alleviated by the synthetic opioid alfentanil.

Plasma catecholamine concentrations have been used as indicators of pain and stress during surgery in newborn infants.\textsuperscript{1, 14} In these studies adrenaline concentration showed an immediate increase while the change in noradrenaline was delayed. Plasma adrenaline originates in the adrenal glands, but noradrenaline comes mostly from the sympathetic nerve endings in vessels. It has been suggested that a rise in adrenaline indicates a more acute stress and noradrenaline a chronic stress.\textsuperscript{16} However, in a placebo controlled morphine infusion trial of sick newborns undergoing assisted ventilation, plasma adrenaline, but not noradrenaline, was increased in the placebo group as late as 24 hours after treatment.\textsuperscript{17} Increases in both plasma noradrenaline and adrenaline concentrations during suctioning have been reported before.\textsuperscript{18}

In our study despite concentrations below the detection limit in several samples, a significant decrease in adrenaline concentration was found after 20 mg/kg alfentanil, indicating a reduction in stress. The low adrenaline concentrations may be due to the immaturity of the infants studied. With increasing maturity there is a relative increase in the proportion of adrenaline to noradrenaline in the body.\textsuperscript{16} This may be due to maturation of the enzyme (p-hylyethanolamine N-methyl transferase) which converts noradrenaline to adrenaline.\textsuperscript{16}

Results on the usefulness of β endorphin as an indicator of pain have been contradictory, some taking for granted its usefulness\textsuperscript{19} and others finding no correlation with pain score and other stress hormones.\textsuperscript{20} During cardiac surgery β endorphin increased early on; the catecholamine response occurred later.\textsuperscript{19} In our study, plasma β endorphin was measured before suction and 30 minutes later, but no changes were seen in the placebo group. The pro-opiomelanocortin system may be in an immature stage in newborns or our 30 minute blood sampling schedule did not pick up the possible changes in plasma β endorphin. The fact that we did not see any changes in plasma β endorphin in neonates treated with alfentanil supports the latter possibility.

During intensive care sick newborn infants are subjected to a variety of procedures causing pain and stress, and thus they have adverse physiological responses, which may affect outcome. Several studies have shown that potentially harmful haemodynamic changes and hypoxia occur during essential routine endotracheal suctioning.\textsuperscript{21, 22} In this study we have shown that tracheal suctioning without analgesia was associated with considerable haemodynamic changes and an increase in the pain score. Thus tracheal suctioning can be considered a painful procedure in premature infants.

After using a small dose (10 mg/kg) of alfentanil we still noticed slight increases in heart rate and mean arterial blood pressure. When pretreated with 20 mg/kg of alfentanil there was a significant fall in plasma adrenaline concentration and in heart rate, but no noticeable fluctuation in blood pressure. We noticed a trend for decreasing pain score and noradrenaline concentrations with increasing alfentanil dose. The similarity in suction provoked changes in the variables measured after placebo and 10 mg/kg of alfentanil indicate that this alfentanil dose does not relieve discomfort caused by suction. The improvements seen after 20 mg/kg of alfentanil indicate sufficient pain relief. In previous studies doses of 10–20 mg/kg with or without muscle relaxant have been used in neonates and considered efficient.\textsuperscript{2} In our trial the alfentanil concentration after 20 mg/kg was comparable with the analgesic concentrations recommended for sedation during ventilation in older age groups (35–50 ng/ml),\textsuperscript{2} which further suggest that the dose is sufficient.

The main adverse effect of alfentanil was rigidity. As rigidity has already been reported even with 9 mg/kg,\textsuperscript{23} in the present protocol attention was paid to slow administration of the trial solution. Despite this, the side effect occurred at an unacceptably high rate, 60% in the 20 mg/kg dose group. Therefore, alfentanil cannot be used as a procedural analgesic without muscle relaxant in newborn infants.

In conclusion, we found that endotracheal suction of neonates receiving assisted ventilation is a painful procedure according to the behavioural and cardiovascular criteria described. The dose of 20 mg/kg of alfentanil does relieve pain, but causes a high rate of rigidity. Therefore, alfentanil should be used only with a muscle relaxant in the neonatal period. Before elective intubation, when muscle relaxant is needed, the dose of 20 mg/kg seems to provide sufficient analgesia for premature babies. However, for safe short acting relief of brief procedural pain, such as tracheal suction, the use of other drugs should be explored.

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