

REVIEW ARTICLES

 **Opioid-induced respiratory depression in paediatrics: a review of case reports**

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Editor's key points

- Not much has been published on opioid-induced respiratory depression in children.
- The authors undertook an unusual approach of reviewing case reports.
- Importantly, this review has identified some predisposing patterns and clinical conditions.
- These conditions are renal failure, patients undergoing adenotonsillectomy, and those having *CYP2D6* gene polymorphism.

Summary. Opioids remain the cornerstone of modern-day pain treatment, also in the paediatric population. Opioid treatment is potentially life-threatening, although there are no numbers available on the incidence of opioid-induced respiratory depression (OIRD) in paediatrics. To get an indication of specific patterns in the development/causes of OIRD, we searched PubMed (May 2012) for all available case reports on OIRD in paediatrics, including patients 12 yr of age or younger who developed OIRD from an opioid given to them for a medical indication or due to transfer of an opioid from their mother in the perinatal setting, requiring naloxone, tracheal intubation, and/or resuscitation. Twenty-seven cases are described in 24 reports; of which, seven cases were fatal. In eight cases, OIRD was due to an iatrogenic overdose. Three distinct patterns in the remaining data set specifically related to OIRD include: (i) morphine administration in patients with renal impairment, causing accumulation of the active metabolite of morphine; (ii) codeine use in patients with *CYP2D6* gene polymorphism associated with the ultra-rapid metabolizer phenotype, causing enhanced production of the morphine; and (iii) opioid use in patients after adenotonsillectomy for recurrent tonsillitis and/or obstructive sleep apnoea, where OIRD may be related to hypoxia-induced enhancement of OIRD. Despite the restrictions of this approach, our analysis does yield an important insight in the development of OIRD, with specific risk factors clearly present in the data.

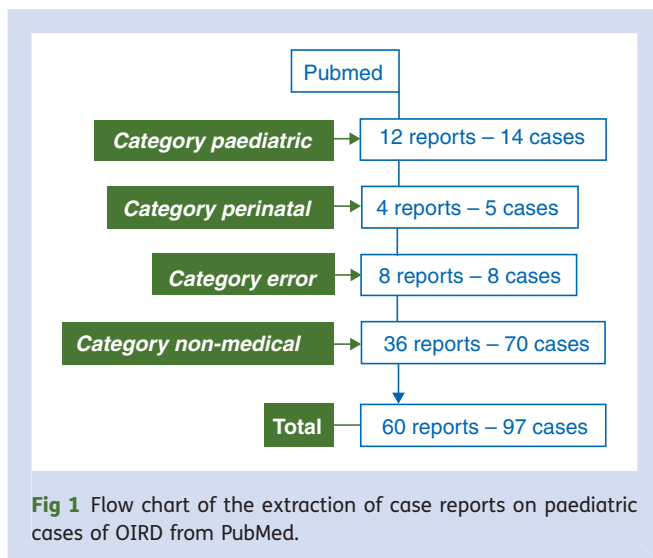
Keywords: case reports; codeine; opioid; opioid-induced respiratory depression; paediatrics

Most physicians would agree that moderate-to-severe pain deserves an aggressive treatment approach. Most effective treatment of pain is with opioid analgesics. Opioids act through activation of endogenous opioid pathways and produce relief of pain perception and various side-effects. Opioid-induced respiratory depression (OIRD) is among the most serious of these side-effects as it is potentially life-threatening.¹ Most (if not all) prospective studies on the effect of opioids on the ventilatory control system are performed in adults (mostly men). Little information is available on the occurrence of OIRD in the paediatric population, and no comparative data on the effect of different opioids on breathing are available in children. Since we believe that knowledge on the occurrence of OIRD is important to physicians and opioid manufacturers alike, and no randomized (case) controlled trials are available on OIRD in the paediatric population, we performed, as part of a much larger systematic review of the literature, a search of case reports that describe OIRD in children aged 12 yr or younger. Our aims were to review these cases and assess whether we could find

obvious risk factors for OIRD in the paediatric population. We focus on OIRD induced by opioid taken by or given to patients for a medical indication (pain, sedation, and cough) or OIRD due to transfer of an opioid from mother to child when the opioid is prescribed or given to the mother in the perinatal setting.

Methods

In May 2012, we searched the electronic database PubMed (www.ncbi.nlm.nih.gov) for 'case reports' on OIRD related to opioid intake for a medical indication in the patient (e.g. pain, sedation, cough) or perinatal OIRD due to transfer of an opioid from mother to child (see Appendix for the PubMed search strategy). Also case reports mentioned in the retrieved papers were taken into account, and we retrieved case reports on OIRD by systematically scanning several case report journals (*Case Reports in Anesthesiology*, *BMJ Case Reports*, *Journal of Medical Case Reports*, *International Medical Case Reports Journal*). Finally, case reports in our local literature databases were searched for additional



papers from journals not listed by PubMed including the *Dutch Journal of Anesthesiology*. All relevant papers were read in full and a separation was made between OIRD in patients >12 and 12 yr and younger. Only case reports on OIRD in patients of 12 yr and younger were considered in the current report (Fig. 1).

We did not predefine OIRD *a priori* but searched within the case report whether the authors had linked the medically prescribed opioids to the occurrence of respiratory depression (irrespective of the outcome). If so, the paper was considered for further analysis. Excluded were papers in languages other than English, French, German, or Dutch. All relevant papers were read in full and the link between opioid use and endpoint (OIRD, death, hospital admittance because of respiratory events) was made by A.D. and M.N.

The data set was *post hoc* divided into three distinct categories: (i) Category 'paediatrics', which describes patients (age 0–12 yr), receiving opioids for acute pain, chronic pain, sedation, or cough; (ii) Category 'perinatal' where opioid administration to a (breastfeeding) mother led to respiratory depression in her child; (iii) Category 'error', where OIRD occurred due to an error of medically trained personnel; and (iv) finally, our search identified a large number of cases that are best described as OIRD due to a non-medical intervention (Category 'non-medical'). Since physicians or other medical personnel were not involved in these cases, they were not included in our intended analysis, but a short summary of the data will be given. Taken the nature of the reports, we performed a narrative review of the data.

Results

Category paediatrics

Since 1981, 14 patients are discussed in 12 reports (Table 1).^{2–13} The youngest child was 17 days, the oldest 12 yr of age; the earliest publication dates from 1981,² the latest from 2012.¹³ Eight patients had received codeine, four morphine, one fentanyl, and one hydrocodone. The number of fatal outcomes was 6, while

near-fatal respiratory depression occurred in the remaining eight cases. Five patients on codeine received this opioid for postoperative pain relief after they underwent an elective (adenotonsillectomy because of recurrent tonsillitis and obstructive sleep apnoea. All five were diagnosed (or suspected of being) an ultra-rapid or extended metabolizer with CYP2D6 gene duplications. Three patients received codeine for persistent cough. All three had a pulmonary or upper airway infection. Three (of five) patients on morphine received the drug after operation and were diagnosed with renal complications, ranging from renal failure to renal vein thrombosis and haemolytic uraemic syndrome. Finally, the one child on hydrocodone had a reduced metabolic capacity due to an impaired CYP2D6 allele.

Category perinatal

Four reports describe five cases, two of which regard the use of opioids by a breastfeeding mother, two the use of epidural fentanyl in a parturient, and one the administration of fentanyl during a Caesarean section (Table 2).^{14–17} Three children survived serious respiratory depression after receiving i.v. naloxone.^{15 16} One child died after receiving breast milk from a mother treated with codeine for episiotomy pain who was also diagnosed as an ultra-rapid metabolizer with CYP2D6 gene duplication.¹⁷ Finally, a preterm infant developed immediate postnatal respiratory depression and muscle rigidity due to fentanyl administration to his mother during the performance of a Caesarean section. He had an Apgar score of 3 without respiratory movements.¹⁴ After intubation and despite high pressures initially, no chest wall movements were achieved. The child survived as respiratory movements were achieved without naloxone or neuromuscular blocking agent administration.

Category error

Eight reports describe eight cases, all of which were medication errors (Table 3).^{16 18–24} sufentanil injected rather than fentanyl, morphine instead of meperidine, codeine plus acetaminophen given rather than just acetaminophen, or an opioid overdose ($n=5$). In one case, methadone-overdose resulted in rigid-chest syndrome.²⁴ No fatalities were reported related to the overdose.

Category non-medical

Thirty-six reports describe 70 children (≤ 12 yr) who developed severe OIRD due to a non-medical intervention and who required immediate medical attention [e.g. admittance to the paediatric intensive care unit (ICU) and/or the injection of naloxone]. In one-quarter of cases, the child did not survive. These cases included the inadvertent administration of an opioid by proxy (such as the unintentional transfer of a fentanyl patch from grandparent to child, parent self-medicating the child with opioid-containing cough medication),^{25–27} intents to deliberately harm the child (homicide, sexual abuse),^{28–30} and most common the self-intake of illicit drugs or of opioids prescribed to others (e.g. ingestion of legally prescribed opioids after being

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