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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

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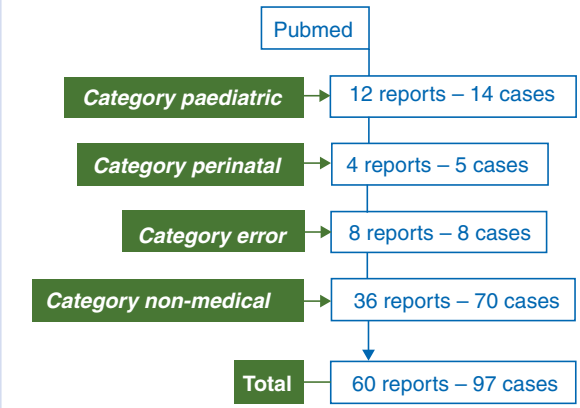

Fig 1 Flow chart of the extraction of case reports on paediatric cases of OIRD from PubMed.

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 (adeno)tonsillectomy 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 uremic 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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Table 1 Case reports on OIRD in the paediatric population. ?, data unavailable; m, male; f, female

Study	Age, weight, sex	Underlying disease	Opioid	Treatment/outcome	Comments
Wilkes and colleagues[2]	3 months, 3 kg, m	Upper airway infection	Codeine	Naloxone bolus/full recovery	
Krane[3]	2.5 yr, ?, m	Surgical repair of penile hypospadia	Caudal epidural morphine	Naloxone bolus+infusion/full recovery	Late respiratory depression after caudal morphine
Hasselström and colleagues[4]	7 yr, 27 kg, f	Peritoneal catheter placement in a child with renal impaired from haemolytic uremic syndrome	Morphine for postoperative pain relief	Naloxone infusion/ full recovery	Respiratory depression induced by morphine's metabolite M6G
Yaster and colleagues[5]	14 months, 13 kg, ?	Bone marrow aspiration in a child with an astrocytoma	Midazolam–fentanyl i.v. sedation	Naloxone bolus/full recovery	Sedation performed by a non-anaesthesiologist
Gourlay and Boas[6]	7 months, 9 kg, m	Nephrectomy in a child with hypertension from renal vein thrombosis	Rectal morphine for postoperative pain relief	Resuscitation/ deceased	
Richtmeister and colleagues[7]	12 yr, 30 kg, m	Nephrectomy in a child with hypertension from renal failure	Patient-controlled analgesia with morphine	Multiple naloxone injections and haemodialysis/full recovery	Respiratory depression induced by morphine's metabolite M6G
Magnani and Evens[8]	29 days, ?, ?	Cough, bronchitis, bronchiolitis	Codeine-containing syrup	Resuscitation/ deceased	
Tong and Ng[9]	17 days, ?, f	Cough	Codeine-containing syrup	Resuscitation/full recovery	
Voronov and colleagues[10]	29 months, 13.7 kg, m	Elective adenotonsillectomy for recurrent tonsillitis and sleep apnoea	Acetaminophen+codeine	Naloxone/ischaemic brain injury	Ultra-rapid metabolizer of codeine
Ciszkowski and colleagues[11]	2 yr, 13 kg, m	Elective adenotonsillectomy for recurrent tonsillitis and sleep apnoea, bronchopneumonia	Acetaminophen+codeine	Resuscitation/ deceased	Ultra-rapid metabolizer of codeine (*CYP2D6* gene duplication)
Madadi and colleagues[12]	5 yr, 35 kg, f	Seizures since birth, upper respiratory tract infection, hypothermia	Hydrocodone, clarithromycine	—/deceased	Reduced metabolic capacity due to impaired *CYP2D6* allele and 2D6 inhibition by clarithromycine
Kelly and colleagues[13]	4 yr, 28 kg, m	Elective adenotonsillectomy for recurrent tonsillitis	Codeine	—/deceased	Ultra-rapid metabolizer of codeine (*CYP2D6* gene duplication)
Kelly and colleagues[13]	3 yr, 14.4 kg, f	Elective adenotonsillectomy for obstructive sleep apnoea syndrome	Codeine	Resuscitation, naloxone/full recovery	Extended metabolizer of codeine
Kelly and colleagues[13]	5 yr, 29 kg, m	Myringotomy and adenotonsillectomy for recurrent tonsillitis and snoring	Codeine	—/deceased	Likely an ultra-rapid metabolizer of codeine

given the pill container to play with, the intake of hidden heroin found by a playing child).[31 32] One case described OIRD in a body-packing child, a form of child abuse.[33] A full list of references of these non-medical cases may be obtained from the authors.

Discussion

We retrieved 24 reports from the literature on OIRD in 27 children aged 12 yr or younger receiving, either directly for medical reasons or indirectly via their mother. Of the 27 children who developed OIRD, seven died and one developed ischaemic brain injury. In none of the current reports, OIRD was predefined, but in 23 of the 27 cases, an intervention was performed to attempt to resuscitate the child (successful in 20/23 cases); in four of the 27 cases, the child was dead upon discovery. The interventions were the injection of multiple naloxone doses, the continuous infusion of naloxone, and/or tracheal intubation, often followed by admittance to

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Table 2 Case reports on OIRD in the perinatal population due to maternal opioid intake. ?, data unavailable; m, male; f, female; *it seems unlikely that 300 mg was given; probably a dose of 300 μg was injected

Study	Age, weight, sex	Setting	Opioid	Symptoms	Comments
Lindemann[14]	Newborn, 1.4 kg, m	Caesarean section	Morphine (7.5 mg) and fentanyl (300 mg)* given to the mother during surgery (additional drugs ketamine, diazepam, scopolamine, vecuronium)	Apgar score=3 upon delivery with the absence of respiratory movements. Inability to inflate chest after mask ventilation and intubation despite high-inspired pressures	Chest wall movements were achieved 8 min after delivery. No naloxone or neuromuscular blocking agents given. Full recovery
Kumar and Paes[15]	Full-term newborn, 3.2 kg, m	Patient-controlled epidural labour analgesia	400 μg of fentanyl epidurally received during labour	No respiratory effort at birth (APGAR 3–8)	Naloxone i.m. (0.4 μg) caused full recovery
Kumar and Paes[15]	Full-term newborn, 3.5 kg, m	Patient-controlled epidural labour analgesia	260 μg of fentanyl epidurally received during labour	Respiratory depression after a reasonably good start (APGAR 6–9)	Naloxone i.m. (0.4 μg) caused full recovery
Meyer and Tobias[16]	5 weeks, 3.8 kg, f	Mother breastfeeds while taking opioids for migraine headaches	Mother uses methadone and hydrocodone	Child developed cyanosis and respiratory depression requiring resuscitation	I.V. naloxone, full recovery
Koren and colleagues[17]	13 days, ?, m	Mother breastfeeds while taking opioid for episiotomy pain	Mother uses codeine/ paracetamol	Found dead after failure to thrive	The mother is an ultra-rapid metabolizer of codeine (*CYP2D6* gene duplication) with high concentrations of morphine in the mother's milk

the emergency ward or paediatric ICU. We believe that the presented cases represent just the tip of the iceberg when estimating the prevalence of OIRD. The retrieved cases describe only very serious cases of OIRD that without an intervention would have resulted in the death of all 28 children. Clearly, this is related to the fact that case reports are published based on the policy of the editorial team, and consequently, the majority of cases do not reach the medical literature. Bias of the editorial team towards the more severe cases but also the lack of will of the physician to publish their 'failures' and 'complications' of opioid therapy will restrict publication. We are aware of these restrictions and of the fact that case reports represent a low level of evidence. Still, because of the lack of good quality randomized controlled trials on OIRD in the paediatric population, we believe that the analysis of our current set of 28 cases is of importance to the medical audience. Specific patterns are visible in the data that may lead to the prevention of serious OIRD in future patients.

Clear and useful definitions of respiratory depression are lacking.[34] All providers of opioids are (or should be) aware that there is a narrow transition from mild to moderate to severe OIRD. Mild-to-moderate transient respiratory depression from opioids (bradypnoea and/or upper airway obstructions requiring interventions such as coaching, supplemental oxygen, chin lift) is part of daily clinical practice. Severe OIRD requires naloxone injections and/or tracheal intubation to restore ventilation and gas exchange in the lungs, or cardiac resuscitation in the case of a cardiac arrest secondary to hypoxia. It is evident that the transition from moderate-to-severe OIRD should be prevented at all cost. One important question then is why in some patients severe OIRD develops and in others not. Apart from the (un)-intentional overdoses (as presented in categories errors and non-medical), our data do provide important insights that may explain at least part of the mechanisms behind the occurrence of serious OIRD in otherwise healthy patients that are treated according to accepted guidelines.

Morphine and renal failure

In three patients with renal complications, severe OIRD after morphine treatment occurred.[4 6 7] About 10% of morphine is metabolized into the active μ-opioid receptor agonist morphine-6-glucuronide (M6G), while 80% is metabolized into the inactive morphine-3-glucuronide, which is devoid of opioid activity. M6G is eliminated via the renal pathway and consequently renal failure will enhance the risk of OIRD. In a simulation study in healthy young adults, we showed that the probability of respiratory depression during morphine treatment increases by a factor 6 during the first 48 h of morphine therapy in patients with renal failure due to the accumulation of M6G.[35] Hence it is advisable either to use opioids that are eliminated via non-renal dependent pathways or to reduce the morphine dose (coupled to less frequent dosing) in patients with compromised renal function. Practitioners should be aware that codeine is metabolized into morphine and that renal failure will also enhance the possibility of codeine toxicity.

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Table 3 Errors in medication administration causing OIRD in the pediatric population. ?, data unavailable; m, male; f, female

Study	Age, weight, sex	Setting	Opioid	Symptoms	Comments
Gober and colleagues[18]	4 weeks, 3.3 kg, m	CT scan for evaluation of macrocephaly due to acquaductal stenosis under sedation	Morphine	Apnoea developed 50 min after opioid administration, requiring naloxone, full recovery	Morphine 4 mg instead of meperidine 4 mg was injected i.m.
Ryan and Meakin[19]	25 days, 3.9 kg, m	Pyleromyotomy	Fentanyl during surgery	Absent respiratory effort after surgery required a naloxone infusion, full recovery	Instead of 2 μg kg^{-1} fentanyl, 26 μg kg^{-1} was given i.v.
Keyes[20]	2 months, ?, m	Pyleromyotomy	Subcutaneous morphine	Respiratory arrest within minutes after injection treated with naloxone, full recovery	Ten-fold morphine overdose (0.4 ml instead of 0.04 ml)
Chisholm and Klanduch[21]	15 months, ?, m	Admitted for seizures. Lumbar puncture for which sedation is given	Fentanyl (plus midazolam)	Rapid development of apnoea treated with naloxone and flumazenil, full recovery	Inadvertent replacement of fentanyl by sufentanil syringes in the narcotic drawer
Brown and colleagues[22]	2 months, 6.2 kg, m	Scrotal hernia that required reduction under sedation	Meperidine (plus promethazine and chlorpromazine)	Immediate apnoea and cardiac arrest requiring resuscitation, naloxone, full recovery	Ten-fold the expected dose was inadvertently administered via i.v. route instead of i.m.
Meyer and Tobias[16]	8 months, 3.7 kg, ?	Cough and fever in a child with Pierre–Robin syndrome and a tracheostomy	Codeine	Acute development of apnoea treated with rescue breathing with an Ambu bag, full recovery	Inadvertently acetaminophen with codeine given to the child rather than just acetaminophen
Deshpande and Grill[23]	Preterm neonate (27 weeks+3 days), 485 g, f	Hyaline membrane disease requiring respiratory support/ ventilation	Morphine	Ten-fold overdose treated with naloxone, full recovery	Naloxone (100 μg kg^{-1}) caused cardiac arrest requiring resuscitation
Lynch and Hack[24]	6 weeks, 2 kg, m	Respiratory distress from RS virus infection requiring respiratory support	Methadone	Slow-onset respiratory depression and apnoea with rigid-chest syndrome after methadone overdose	Ten-fold methadone overdose. Symptoms resolved after i.m. naloxone. No neuromuscular blocking agent needed

CYP2D6 genetics

Genetic polymorphism in metabolic enzymes has an important impact on the effect of the parent drug through either excessive creation of active metabolites or inability to produce inactive metabolites. In our data set, seven cases of OIRD were linked to the *CYP2D6* metabolic gene (Fig. 2).[10–13 17] The metabolizing system can either be overactive or less *cq.* inactive. An overactive system occurs in the case of gene duplication which causes the extended or ultra-rapid metabolizer phenotype (occurring in 1% of whites, 10% of people from Mediterranean descent, and 30% of people from Asian or Middle Eastern origin). Alternatively, drug- or food-induced CYP2D6 enzyme induction may increase the turnover in the metabolic pathway. A less active system is related to enzyme inhibition, or a defect in one of the alleles causing the poor metabolizer phenotype (occurring in 5–10% of whites and 1% of people of Asian origin). This will cause the accumulation of the parent drug. In the case of codeine, an ultra-rapid metabolizer with multiple copies of the *CYP2D6* gene will produce large quantities of the active morphine, thereby enhancing the risk of OIRD. In our data set, seven patients suffered from OIRD after intake of codeine (six by the patients, one by the breastfeeding mother).[10 11 13 17] Codeine is metabolized in the liver into the active compound morphine (via CYP2D6), norcodeine (via CYP3A4), and codeine-6-glucuronide (via UGT). In infants (<6 months of age), the metabolic pathways of codeine are not fully developed and the CYP2D6-dependent conversion into morphine is predominant. Extensive and ultra-rapid metabolizers will produce large quantities of morphine and hence carry a greater probability of OIRD. An important and illustrative case is described by Koren and colleagues,[17] in which a mother with the ultra-rapid metabolizer phenotype breastfeeds a neonate while ingesting codeine daily for episiotomy pain. The resultant high maternal morphine serum levels transferred to the infant in breast milk were fatal to the child. Recently, new guidelines for the use of codeine in the context of the cytochrome CYP450 2D6 genotype have been published.[36]

Complete or partial loss of gene function as characterized by the poor metabolizer phenotype may also be a risk factor

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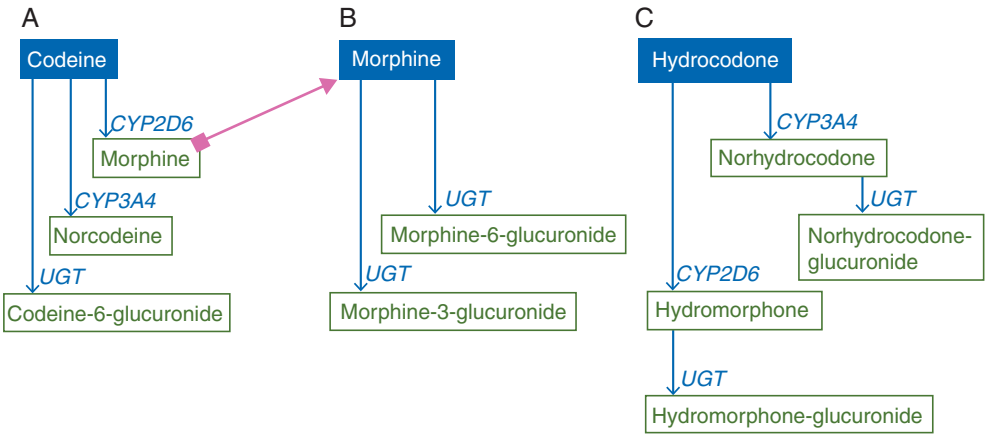

Fig 2 Metabolic pathways of codeine, morphine, and hydrocodone. UGT, uridinediphosphate-glucuronosyltransferase.

for OIRD. The primary route of metabolism of hydrocodone is by the CYP2D6 system and a secondary route by CYP3A4. In one report, hydrocodone toxicity arose in a child with an impaired CYP2D6 system that was treated simultaneously with clarithromycine.[12] Clarithromycine blocked the alternative pathway (by CYP3A4 inhibition) and the failure of both CYP systems led to a fatal OIRD.

Adenotonsillectomy, obstructive sleep apnoea

Five cases relate to OIRD in children who received an (adeno)tonisillectomy for recurrent tonsillitis and obstructive sleep apnoea. There is ample evidence that upper airway obstructions cause hypoxic episodes during sleep.[37] Recent animal studies indicate that recurrent hypoxic episodes may enhance opioid respiratory sensitivity and in children opioid analgesic sensitivity increases after previous episodes of recurrent hypoxia.[38 39] These data explain the increased risk of OIRD in children with sleep disordered breathing and mandate very careful opioid dose titration. Furthermore, young children with obstructive sleep apnoea treated with adenotonsillectomy remain symptomatic in 30% of cases and the risk of OIRD may persist.[37]

Errors

Eight reports of OIRD were due to faults or errors in drug administration (either the wrong opioid was administered or the drug was too high). All of them were related to human error. In our experience, errors are difficult to eliminate and additional safety precautions should be mandatory to prevent these problems, including the use of checklists, double checks, and proper education (how to prepare and how to administer a drug).

Naloxone

An important finding in these reports is that the use of naloxone is effective in treatment of OIRD when used as a continuous infusion (or by repetitive injections). This is in agreement with earlier observations showing the need for long-term naloxone exposure to prevent return of OIRD (renarcotization).[1] This is related to the fact that naloxone has a short elimination half-life (15–30 min), and consequently, the opioid effect will outlast the naloxone effect.[1] Another issue is that the speed of naloxone-induced reversal of OIRD is related to opioid receptor kinetics. An opioid that has a high affinity for the opioid receptor (such as buprenorphine and to a lesser extent morphine) has a fixed (relatively slow) speed of reversal, irrespective of the naloxone dose.[40 41] This indicates that naloxone effect is not immediate and that additional measures are required (e.g. bag ventilation) before naloxone effect sets in.

In conclusion, we extracted case reports on OIRD from the literature to describe specific patterns and factors in the development of OIRD in the paediatric population. We agree that our approach is unable to quantify the occurrence of OIRD in this population and assess all possible risk factors. A more proper approach would be to systematically extract data from high-quality prospective trials. However, such trials are currently unavailable and the literature on OIRD is sparse.[1 42] Irrespectively, our current approach does yield an important insight in the development of OIRD. Three factors in these case reports are evidently related to paediatric OIRD: renal impairment, *CYP2D6* polymorphims (with either poor metabolizer or ultra-rapid metabolizer phenotypes), and recurrent hypoxic episodes from tonsillitis and obstructive sleep apnoea. Clearly, it is important to recognize these factors, although some (e.g. CYP polymorphisms) are often not known at the time of opioid treatment. Still, in the case of renal impairment, a wise choice in analgesic treatment should be made avoiding the accumulation of toxic metabolites. And in the case of a history of recurrent tonsillitis, adenotonsillectomy, and obstructive breathing, a non-opioid analgesic regimen is best chosen.

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Appendix: PubMed search strategy

{('Analgesics, Opioid'[Pharmacological Action] or 'Narcotics' [Pharmacological Action] or opiate[tiab] or opiates[tiab] or opioid[tiab] or narcotic[tiab] or narcotics[tiab]) and ('poisoning'[Subheading] or 'toxicity'[Subheading] or intoxication[tiab] or toxicity[tiab] or poisoning[tiab] or 'adverse effects'[Subheading] or adverse[tiab])} or 'Analgesics, Opioid/poisoning'[Mesh] or 'Analgesics, Opioid/toxicity'[Mesh] or 'Analgesics, Opioid/adverse effects'[Mesh] or {('Analgesics, Opioid'[Pharmacological Action] or 'Narcotics' [Pharmacological Action] or opiate[tiab] or opiates[tiab] or opioid[tiab] or narcotic[tiab] or narcotics[tiab]) and ('respiratory arrest' or 'respiratory arrests' or 'respiratory depression' or 'Respiration Disorders/chemically induced'[mesh])} and {case report or case reports or case series or case[ti] or cases[ti] or [(case or cases) and (report or reports or series)]}.

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