Case report

Suspected opioid-induced hyperalgesia in an infant

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Editor’s key points
- In opioid-induced hyperalgesia (OIH), increasing opioid administration can lead to an increased pain state with hyperalgesia and allodynia.
- This report describes suspected OIH in an infant receiving long term opioid infusion.
- Treatment included opioid rotation supplemented by ketamine and dexmedetomidine infusions.

Case report

A 1-day-old 35 + 6 week male neonate weighing 2410 g, antenatally diagnosed with gastroschisis, was transferred to our institution for surgical management. The patient had no other co-morbidities but developed respiratory distress requiring continuous positive airway pressure soon after birth and the trachea was intubated at 1 h of life. A laparotomy and ventilation, including a period of high-frequency oscillating ventilation, and long-term total parenteral nutrition (TPN) requirement complicated by TPN-induced liver function derangement. Renal function remained appropriate for age.

During the remainder of the inpatient admission, the patient underwent a further 21 surgical procedures. Major complications included episodes of sepsis, bowel ischaemia, coagulopathy, respiratory deterioration requiring prolonged intubation and ventilation, including a period of high-frequency oscillating ventilation, and long-term total parenteral nutrition (TPN) requirement complicated by TPN-induced liver function derangement. Renal function remained appropriate for age.

Morphine 40 μg kg⁻¹ h⁻¹ was continued until day 17 when due to increasing pain scores and irritability, the opioid infusion was changed to fentanyl 2 μg kg⁻¹ h⁻¹.

Over the ensuing days, pain scores remained high with problematic irritability requiring frequent boluses of fentanyl.

One explanation for diminished opioid analgesic efficacy is opioid-induced hyperalgesia (OIH). We report a case of OIH in an infant with gastroschisis, requiring multiple surgical interventions and prolonged sedation for ventilation. This is the first report of OIH in an infant. On day 41 of life after nine separate surgical interventions, the patient’s pain scores increased and remained elevated, despite increasing opioid administration. The patient also developed hyperalgesia, allodynia, and photophobia and became extremely irritable upon handling. Other possible causes were excluded, including interruption to opioid delivery, sepsis, acid–base and electrolyte disturbance, and ongoing surgical pathology. An opioid rotation to hydromorphone was initiated and ketamine was commenced. Sedation for ventilation was achieved with dexmedetomidine and midazolam infusions. Over a period of 24 h after opioid de-escalation, pain scores reduced rapidly and the patient became significantly less irritable with handling. All infusions were gradually weaned and eventually ceased.

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Diminished opioid analgesic efficacy or increased opioid requirements can be explained by three distinct clinical possibilities—worsening of the disease process, opioid tolerance, or opioid-induced hyperalgesia (OIH). OIH is an apparent paradox, whereby the ongoing or increased administration of an opioid leads to an unexpected state of increased pain perception and sensitivity rather than improving analgesia. This state is also characterized by the development of hyperalgesia and allodynia. This contrasts with tolerance, where increased administration of opioid is required to maintain the same analgesic effect.2–4

We report a case of suspected OIH in a neonate who underwent serial and complex repair of gastroschisis and received a long-term, high-dose opioid for analgesia and sedation.
and midazolam. Fentanyl was increased to 5 μg kg⁻¹ h⁻¹ on day 28, changed back to morphine 40 μg kg⁻¹ h⁻¹ on day 32, and increased to 50 μg kg⁻¹ h⁻¹ on day 33.

On day 34, the patient had a laparotomy and formation of jejunostomy. Intraoperative analgesia was managed with i.v. fentanyl boluses, and after operation, a fentanyl infusion was restarted at 5 μg kg⁻¹ h⁻¹ as morphine had continued to be poorly efficacious. On day 35, fentanyl was increased to 6 μg kg⁻¹ h⁻¹ and continued at this rate until day 41 of life.

On day 41 of life, pain scores increased and reached 20 on several occasions, despite regular fentanyl (2 μg kg⁻¹) boluses. The opioid was again changed to morphine and started at 100 μg kg⁻¹ h⁻¹, then increased to 150 μg kg⁻¹ h⁻¹ later the same day (Fig. 1). Pain scores continued to be high and i.v. clonidine was commenced at 0.33 μg kg⁻¹ h⁻¹.

On day 42, the pain scores remained consistently elevated (Fig. 1) and the infant was continuously distressed and difficult to settle, despite the increased opioid administration. Multiple morphine boluses (100 μg kg⁻¹) were administered and the infusion was increased to 200 μg kg⁻¹ h⁻¹, and clonidine increased to 0.45 μg kg⁻¹ h⁻¹. The patient also developed increased sensitivity to light touch and handling, sound and light, and became increasingly agitated, irritable, distressed, and tachycardic.

At this point, the acute pain service was consulted to assist with the increasingly complex nature of the pain and provision of analgesia. The analgesic regime was changed on day 43, as we suspected OIH. Morphine 200 μg kg⁻¹ h⁻¹ was stopped and i.v. hydromorphone (20 μg kg⁻¹ h⁻¹) commenced representing a 50% dose equivalent reduction (morphine:hydromorphone dose equivalence, 5:1), along with i.v. ketamine 0.1 mg kg⁻¹ h⁻¹. I.v. dexmedetomidine was started at 0.7 μg kg⁻¹ h⁻¹ in place of clonidine to facilitate sedation for ventilation. Midazolam was continued at 3 μg kg⁻¹ min⁻¹. Within 24 h, there was a dramatic improvement with pain scores reduced to single figures. Pain scores remained consistently <5 thereafter and the neonate was significantly more settled, despite undergoing further surgical procedures.

Ketamine (dose range 0.01–4.3 μg kg⁻¹ min⁻¹) was discontinued after 30 days and midazolam (0.5–3 μg kg⁻¹ min⁻¹) after 70 consecutive days. Hydromorphone (2–40 μg kg⁻¹ h⁻¹) and dexmedetomidine (0.5 μg kg⁻¹ h⁻¹) were discontinued after 46 consecutive days.

The trachea was extubated 60 days after admission and the infant eventually discharged from hospital after 206 days.

**Discussion**

This case is the first known report of OIH in an infant and was successfully managed by opioid de-escalation and rotation, facilitated by ketamine and dexmedetomidine infusions. The use of dexmedetomidine for 46 consecutive days is the longest reported use of the drug in an infant.

The differential diagnosis in the setting of reduced opioid efficacy includes OIH, worsening of the disease process, and the development of tolerance. Although this patient did have major ongoing surgical problems throughout the admission, the observed increase in PAT scores, hyperalgesia, allodynia, and extreme irritability all occurred during a surgery-free period and the patient had been otherwise medically stable.

The other possibility considered was the accumulation of products of morphine metabolism. Morphine is metabolized to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in the liver, both of which are renally excreted. M3G in particular and to a lesser degree M6G can cause behavioural excitation and both may be implicated in the development of OIH. However, since the infant's
renal function was normal at the time and changing to fentanyl previously had not helped, this was considered unlikely.

The diagnosis of OIH can be difficult, especially in an infant. Alldynia was clearly present with the infant startling and withdrawing with any light touch. While hyperalgesia was more difficult to assess, due to the presence of allodynia, the abdomen was generally more tender than elsewhere on the infant.

Differentiating OIH from tolerance clinically starts with being able to overcome reduced opioid efficacy by delivering an increased dose of the drug, which is a feature of tolerance and not OIH. OIH does not respond to increased opioid administration and a paradoxical situation arises where the pain state actually worsens and features of central sensitization occur. Our patient developed hyperalgesia and allodynia, which are features of OIH and not tolerance. Most importantly, the symptoms improved dramatically with rapid opioid de-escalation, which would not have occurred with tolerance.

The precise mechanisms that underlie OIH remain largely unknown. However, three important mechanisms are thought to occur: (i) activation of the central glutaminergic system [N-methyl-D-aspartate (NMDA) receptor activation], (ii) increased production and release of spinal dynorphins (excitatory neuropeptides), and (iii) activation of descending facilitation pathways. Overall, the activation of the NMDA neuroexcitatory receptors is proposed to be one of the most important cellular mechanisms in the development of OIH. It was for this reason that we chose to introduce ketamine, a non-competitive NMDA-receptor antagonist as part of our regime.

The use of ketamine in the developing child, however, is controversial as it has been implicated to cause programmed cell death or apoptosis of neurones in the central nervous system. Systemically administered ketamine has been demonstrated to trigger dose-dependent neuronal apoptosis and neurodegeneration in the brains of neonatal rats and monkeys during early development leading to potential problems with learning, memory, and behaviour and other neurocognitive deficits.

We believed that the potential long-term consequences of ketamine administration in this patient were outweighed by the risks of prolonged uncontrolled pain and extreme irritability in this situation. Poorly controlled or uncontrolled pain can also have negative physiological and pathological consequences and potentially impact on normal neonatal development.

In order to achieve adequate sedation for ventilation, dexmedetomidine, a potent α₂-adrenoceptor agonist, was used. Clonidine had been introduced earlier without any observable benefit. A previous case report had described the use of dexmedetomidine for sedation during mechanical ventilation where midazolam and fentanyl had failed. Activation of α₂ post-synaptic adrenoceptors by dexmedetomidine leads to sedation, anxiolysis, and analgesia by inhibition of norepinephrine release and increased firing of inhibitory neurones such as the γ-aminobutyric acid system, thus facilitating opioid detoxification.

Dexmedetomidine is currently licensed for sedation in adults >18 yr for <24 h in Australia. A recent review identified five paediatric trials where dexmedetomidine was used for longer than 24 h without adverse consequence. The off-label use of dexmedetomidine in our patient proved to be efficacious and no significant haemodynamic disturbances were observed in association with prolonged infusion or bolus administration.

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**Declaration of interest**

None declared.

**References**

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