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Unexpected Opioid Responses in Infants: A Retrospective Case Series

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Abstract

Opioids are commonly prescribed for acute pain management. Complications such as nausea, vomiting, itch and constipation are not uncommon. Two unusual and unexpected complications that can arise in the acute setting are opioid-induced hyperalgesia (OIH) and acute opioid tolerance (AOT). The diagnostic challenges of these two entities are mainly attributed to their unpredictable onset and lack of strict diagnostic criteria. In the pediatric setting, additional confounding factors such as separation anxiety, hunger, thirst and poor verbal communication further complicate discerning between the two phenomena.

A case series was gathered from an Australian tertiary pediatric hospital to emphasize the need to consider unusual responses to opioids when dealing with unexplained pain behaviors in infants. We identified five possible OIH and AOT patients from the acute pain service database over a six year period. We were particularly interested in patients who were unexpectedly tachycardic, agitated and/or had suboptimal response to usual analgesic interventions during their stay. The cases demonstrate that OIH and AOT can occur in many clinical settings and are clinically difficult to distinguish. Greater awareness of these conditions will hopefully lead to robust diagnostic criteria and then better delineation of prevalence rates, risk factors and preventative measures.

Keywords: Acute Opioid Tolerance; Agitation; Distress; Opioid-Induced Hyperalgesia; Paediatric

List of abbreviations: AOT: Acute Opioid Tolerance; NCA: Nurse Controlled Analgesia; OIH: Opioid-Induced Hyperalgesia; OR: Opioid Receptors; PACU: Post Anesthesia Care Unit

Introduction

Opioids are commonly prescribed drugs for acute pain management [1]. Opioid tolerance, dependence and addiction are well recognized complications of extended use. Unusual and unexpected complications of acute, short-term use are now recognized. Opioid-induced hyperalgesia (OIH) and acute opioid tolerance (AOT) represent phenomena that may impact acute pain management in a hospital setting. OIH is defined as a "paradoxical condition where the intensity of pain increases rather than decreases in response to opioid administration" [2]. AOT is defined as "a requirement for increased doses of an opioid to achieve the same analgesic effect" [3]. Both conditions present diagnostic difficulties for acute pain management teams, especially in the paediatric setting.

This retrospective case series highlights these difficulties and emphasizes the need to consider unusual opioid responses when dealing with unexplained irritability in infants (<12 months). In presenting these cases, we recognize that a definitive diagnosis of OIH or AOT cannot be made. Confounding factors may have contributed to the clinical scenarios and trajectories described. However, we believe the carefully considered diagnosis of OIH or AOT may allow timely and appropriate management changes and the avoidance of unnecessary clinical interventions. The five cases presented were flagged by experienced pain clinicians in a non-systematic fashion, on the basis of unexpected responses to opioid treatment during their stay.

Case Series presentation

Ethical approval for this case series was obtained from the Sydney Children's Hospital Network Human Research Ethics Committee (2020/ETH01095). A wavier of consent was granted.

Case 1

A term 11-month-old (11kg) male with Hirschprung's disease underwent a laparoscopic-assisted ano-rectal pull-through procedure. The 8 hour anaesthesia included sevoflurane in air/oxygen, a remifentanil infusion (0.2- 0.3 mcg/kg/min- total 115mcg/kg), paracetamol (15mg/kg), morphine (91mcg/kg) and a caudal injection (6mls bupivacaine 0.25% with 1mcg/kg of clonidine). Following extubation, he was noted to be very unsettled. Nurse controlled analgesia (NCA) (morphine 20mcg/kg bolus, background of 20mcg/kg/hr) was commenced in the post anaesthesia care unit (PACU) with minimal effect. Persistent crying, facial grimace, leg withdrawal and tachycardia prompted the commencement of a ketamine infusion (100mcg/kg/hr). The patient remained unsettled while a total morphine dose of 700mcg/kg was delivered over 12 hours via a NCA, with prompt distress resolution with the cessation of Morphine background infusion. Further diagnostic anxiety and clinical interventions were avoided, with minimal Morphine usage (less than120mcg/kg/day) prior to his discharge 5 days after the procedure.

Case 2

An otherwise well ex-premature 6-month-old (7kg) female underwent sural nerve grafts to her right brachial plexus to manage a birth injury. The 6.5 hour anaesthesia involved sevoflurane in air/oxygen, a remifentanil infusion (0.08-0.2mcg/kg/min- total 60mcg/kg) and morphine (500mcg/kg). In PACU, despite being medicated with morphine incrementally (total 260mcg/kg), she remained unsettled, tachycardic and tachypnoeic. Unexplained tachycardia persisted despite regular doses of paracetamol (15mg/kg/dose) and the commencement of ketamine infusion (20mcg/kg/hr). The tachycardia resolved after a significant reduction in morphine bolus administration. Further investigations were avoided. She was discharged 7 days after admission.

Case 3

An ex-premature 4-month-old (4kg) boy had bilateral inguinal herniotomies. He underwent a 1 hour procedure, receiving remifentanil (0.2-0.23mcg/kg/hr- total 13.2mcg/kg), paracetamol (15mg/kg) and a caffeine bolus (total 20mg/kg) and regional infiltration of local anaesthetic. He was noted to be unsettled and distressed in recovery and was given fentanyl (1mcg/kg) without

effect. He remained tachycardic and irritable and was given propofol intravenously (4mg). Three hours later, after admission to the ward, a 'rapid response alert' was triggered for tachycardia and tachypnoea. He remained tachypnoeic for the next 27 hours prompting the commencement of a fentanyl NCA (total 4mcg/kg over 11 hours) with little effect. He settled gradually over the ensuing 12 hours as fentanyl doses were ceased, requiring no further investigations or interventions. He was discharged 4 days afterwards.

Case 4

A term 11-month-old (10.2kg) boy underwent a unilateral lip and partial cleft palate (anterior) repair. The 3 hour procedure included a remifentanil infusion (0.02-0.05mcg/kg/min- total 25.3mcg/kg), paracetamol (14.7mg/kg), parecoxib (1mg/kg) and morphine (100mcg/kg). In the PACU, despite a low respiratory rate suggesting residual opioid effect, the infant became unsettled and inconsolable intermittently. After recovery he remained upset, irritable and continued to display pain behaviours. Little effect was seen from administered parenteral morphine (total 520mcg/kg over 12 hours). His condition prompted multiple clinical reviews, opioid rotation (morphine to oxycodone), consideration of a ketamine infusion and possible surgical re-intervention. Before the latter two interventions became necessary and 22 hours post-op, the infant settled somewhat and became consolable. Modest oral opioid use (oxycodone 100mcg/kg) continued to the day of discharge 4 days after surgery.

Case 5

A 13-month-old (9.2kg) girl was transferred from an overseas hospital after 25 days of being intubated and ventilated for a complicated pneumonia (empyema, bronchopleural fistula and resuscitation following cardiac arrest). Sufentanil (3.3mcg/kg/hr) was the primary sedative. She remained intubated and ventilated upon admission, and was agitated, hypertensive and frequently crying resulting in ventilator dyssynchrony. Further analgesia and sedation were continued with intravenous fentanyl (continuous infusion 7mcg/kg/hr), ketamine (200mcg/kg/hr) and midazolam (4mcg/kg/min). Ongoing agitation and hypertension were managed with clonidine (1mcg/kg/hr) and propofol (1mg/kg/hr) infusions and intermittent muscle relaxation (vecuronium). On acute pain service review (day 26 of opioid treatment), methadone (0.1mg/kg/dose enterally) was commenced and fentanyl was switched to hydromorphone (50% dose reduction). Her agitation reduced significantly within 24 hours of these changes.

By day 30 of opioid treatment, she was extubated, and her sedatives and opioids were streamlined to enteral methadone (1.1mg/kg q8hrly), clonidine (3.2mcg/kg q4hrly), and diazepam (0.4mg q8hrly). She tolerated a cautious weaning regime prior to being transferred back to her previous hospital, on unsupported ventilation, 18 days after admission. Unfortunately, her clinical examination and imaging prior to discharge confirmed a significant hypoxic brain injury.

Discussion

OIH and AOT are recognized in adults with prolonged opioid exposure [1]. This case series has suggested that OIH and AOT can occur in the acute paediatric care setting including paediatric intensive care [4] and highlights the difficulties in recognizing and the importance of considering both AOT and OIH as differential diagnoses in the paediatric cohort.

Post-operative distress and irritability in infants most commonly reflects acute post-operative pain and is generally well managed with opioid analgesia [5]. Occasionally, infants unexpectedly display persistent distress and pain behaviours despite apparently adequate analgesic doses, leading to parental and clinician anxiety, thus prompting further clinical investigations. They may eventually be ascribed to factors including hunger, thirst, separation anxiety, attachment to medical equipment, and the effect of pharmacologic agents (e.g. the effect of caffeine). These confounders, however, may obscure the recognition of less familiar phenomena such as OIH or AOT. Furthermore, the cause of unusual pain behaviours remains uncertain, and clinicians are required to treat the patients with the suspicion of OIH or AOT without standardized methods to confirm a diagnosis.

The mechanisms for OIH and AOT are still unclear. Opioids work through a family of G-protein coupled receptors- mu, kappa, delta and nociceptin. Each receptor has a unique pattern of distribution throughout the nervous system and reduces neuronal excitability by inhibiting neurotransmitter release [6,7]. Prolonged opioid agonism can lead to clinical tolerance through desensitization of opioid receptors (OR) [8,9]. Desensitization is a function of uncoupling from G-proteins which results in reduced receptor synthesis and numbers within synapses [8]. In a related but distinctly different phenomenon, opioid agonism can result in increased synapse sensitivity and enhanced signal transduction [9,10].

At least four mechanisms for the development of OIH have been proposed [3,9]. It is possible that the activation of central glutamatergic systems (in particular, N-methyl D-aspartate receptors) play a critical role. This activation may be a result of increased glutamate availability within synapses secondary to inhibition of glutamate transporter systems [11]. The spinal dynorphin receptors may also play a role in OIH by increasing synthesis of excitatory neuropetides in response to peripheral nociceptive stimulation [11]. Other spinal mechanisms that may play a role are descending tracts. It is suggested that the spinal nociceptive process can be facilitated by descending facilitation. Unique responses to opioids among subsets of neurons may result in (paradoxical) descending facilitation of nociceptive processes [11]. Finally, OIH may be the result of altered neurotransmitter cycling in primary afferent fibres. Direct opioid exposure may decrease transmitter reuptake and thereby enhance nociceptive signalling [11].

In paediatric patients, the molecular mechanisms underlying OIH and AOT are yet to be defined. They may differ from adult mechanisms as a result of the well documented impact of developmental changes in drug metabolism and transport, receptor expression and function in opioid pharmacology. In addition, postnatal maturation of the developing pain pathways would continue to influence the actions of opioids on immature sensory systems. These factors may influence the likelihood OIH or AOT manifesting in infants [12].

Although the mechanisms for OIH and AOT differ, their clinical manifestations of unexpectedly poor responses to opioid dosing and/or unexplained pain behaviours [3] overlap significantly [8]. Distinguishing between 'increased opioid requirement' and 'increased pain in response to opioid doses' is particularly challenging in the rapidly changing post-operative setting.

Remifentanil and sufentanil are opioids highlighted in these cases. A meta-analysis of 27 studies published between 1994 and 2013, has shown patients receiving remifentanil consistently developed OIH [13]. Important implications were noted in a recent analysis of a large multicentre, cross-sectional study. This analysis of 7898 adults undergoing abdominal surgery, demonstrated that patients who received remifentanil also had higher post-operative pain scores and required more post-operative analgesia [14]. Several authors have highlighted AOT and OIH induced after remifentanil infusion at ≥0.1mcg/kg/min, however the exact relationship between infusion dose and the development of OIH is unclear [14,15]. Little is known about the other synthetic opioids. There is a general consensus that receiving high dose lipophilic opioids [15] or exposure to opioids for a prolonged period can induce OIH or AOT [4]. The predilection for the fentanyl group to generate OIH may relate to its potency, lipid solubility or its high receptor specificity [16]. It may also be an artefact of growing awareness of OIH since the introduction of these drugs into clinical practice.

In all the reported cases, infants appeared to have unexpected and unexplained pain behaviours such as irritability, tachycardia and tachypnoea. In each case the consulting pain physician felt the presentation to be un-usual and not fully explained by more common confounders (hunger, thirst etc). In most cases OIH/AOT symptoms resolved within 24-48 hours of the opioids being ceased or rotated. In each of the first three cases, raising the possibility of these diagnoses allowed some allaying of parental anxiety and the avoidance of unnecessary clinical investigations. The fourth case demonstrated the potential for unnecessary dose escalation and polypharmacy if the diagnosis of OIH is not entertained early.

We acknowledge that these cases were not identified in a systematic fashion. Each case was flagged by an experienced pain physician whose clinical summation was that the infant was displaying an unusual, distinct and un-expected response to an opioid medication. To date no widely accepted diagnostic criteria have been published. This makes any estimate of prevalence extremely difficult. In this tertiary paediatric hospital, approximately 250 infants under 12 months are referred to the acute pain service each year. We identified 5 infants with suspected OIH or AOT over a 6 year period. It is possible and likely that a significant number of similar cases were not flagged as OIH or AOT.

Conclusion

OIH and AOT remain elusive as clinical entities. While OIH and AOT are clearly defined, identification of clinical cases in the acute paediatric setting is more difficult. It is likely that these phenomena occur in a wide range of clinical settings- including the acute post-operative and paediatric intensive care. Greater awareness of the conditions will hopefully lead to robust diagnostic criteria and then better delineation of incidence and prevalence rates, risk factors and preventative measures.

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