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Effect of Methadone Infusion on Intraoperative Opioid Usage in a Burned Pediatric Patient: A Case Report

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Abstract

Background: Pediatric burn patients typically undergo a large number of surgical procedures, resulting in significant pain. High amounts of opioids are continuously infused both during and after surgery in these patients, which in turn confers risk of the development of opioid tolerance. We describe the intraoperative use of methadone, a synthetic opioid with unique pharmacologic characteristics, in a pediatric patient who had suffered significant thermal burns.

Case presentation: The patient was a 5 year old male who was admitted to the burn ICU with approximately 90% cutaneous burns of deep partial to full thickness burns. He underwent 27 surgical procedures over 2 years, including debridement and grafting, escharotomies, and amputations. Throughout the procedures, the patient received a variety of intraoperative analgesic drugs. The most commonly used intraoperative analgesics were fentanyl and hydromorphone. During 9 procedures, he received methadone, a synthetic opioid, alongside fentanyl and hydromorphone.

Conclusions: The objective of our analysis was to determine whether methadone infusion affected total intraoperative opioid usage in this patient. The amount of opioid product used per minute of surgery was identified for each procedure. This metric was compared between procedures where methadone was used and procedures where methadone was not used. Based on this analysis, the procedures where methadone was used resulted in decreased total intraoperative opioid usage in this patient. Use of methadone in a patient undergoing serial surgical procedures can therefore potentially decrease rapidity of opioid tolerance development via decreased intraoperative opioid use.

BACKGROUND

Opioids are widely used during surgical operations for their sedative and analgesic effects. These agents are able to help maintain effective depth of anesthesia without accompanied cardiac depression, as is seen in other classes of analgesics[2]. A common unwanted consequence of opioid administration is the phenomenon of tolerance. Opioid tolerance is a decrease in pharmacologic efficacy due to a variety of factors. Continual opioid administration results in the dose-response curve being shifted rightward, meaning increasing amounts of drug are required to maintain a similar pharmacologic effect[3]. This occurs through two major mechanisms. The first involves μ opioid receptor occupancy leading to receptor desensitization and subsequent downregulation[4]. The second involves recovery of the cyclic AMP pathway, which opioids normally inhibit5. Frequent administration of high daily doses of opioids results in rapid development of tolerance[3]. Development of tolerance then necessitates increasing opioid doses to maintain efficacy, conferring greater risk of significant adverse reactions such as respiratory depression and post-operative intestinal blockage[6].

Pediatric burn patients, especially those with >50% total body surface area as in this case, typically undergo a large number of surgical procedures, including surgical debridement, excisions, and wound care. All of these procedures result in significant pain, which is the source of immense suffering and is linked with the development of post traumatic stress disorder[7]. As such, high amounts of opioids are continuously infused both during and after surgery in these patients. This, however, confers great risk for rapid tolerance in this population. It follows that there is merit in decreasing overall usage of opioids, including intraoperative usage, in an effort to decrease the rate a patient grows tolerant. However, few other pharmacologic classes can provide similarly stable and prolonged anesthesia[8]. Another option is to explore the effects of different types of opioids. Studies have shown that opioid agonists have varying intrinsic efficacy, resulting in asymmetric cross-tolerance[9]. That is, an opioid with low intrinsic efficacy such as morphine requires higher receptor occupancy for a given analgesic effect, resulting in more rapid development of tolerance compared to an opioid with high intrinsic efficacy[9]. It was thus proposed that methadone be given in place of the usual fentanyl and hydromorphone in this patient; it has higher intrinsic efficacy and incomplete cross-tolerance with these more commonly used opioids[10,11] and is known to provide effective analgesia in pediatric surgery[12].

CASE PRESENTATION

A 5 year old male weighing 30kg was admitted to the burn ICU with approximately 90% cutaneous burns of deep partial to full thickness burns of the entire body and face, sparing the genitalia, buttocks, and lower back. The burns on his bilateral upper and bilateral lower extremities were circumferential and full thickness. There were also airway burns due to smoke inhalation which necessitated intubation on admission. A tracheostomy was later performed. Over the next 85 days, he underwent 17 surgical procedures that required anesthesia, including surgical debridement of burn wounds, escharotomies, tracheostomy, skin grafts, and amputations. He underwent 10 more similar surgical procedures over multiple separate admissions in the next 6 months. The patient progressively recovered over the following 2 years after significant debridements and multiple allografts. He is now gaining weight and is normally active. Further procedures with plastic surgery have been planned to aide with functionality and cosmetics.

RESULTS & DISCUSSION

Throughout the 27 total surgical procedures, the patient received a variety of intraoperative analgesic drugs. The most commonly used intraoperative analgesics were fentanyl and hydromorphone, along with non-opioids such as midazolam and acetaminophen. During 9 procedures, he received methadone, a synthetic opioid, alongside fentanyl and hydromorphone. Methadone is a less commonly used opioid and does not have strongly established starting doses; in this case, the initial methadone dose was chosen to be 50% of the equivalent morphine dosage used in previous procedures. The amounts of analgesics used are presented in Table 1. Morphine milligram equivalents (MME), the most widely accepted form of opioid inter-conversion[1], was chosen as a reference metric to allow for comparison of all the different opioids used. The total amounts of fentanyl, hydromorphone, and methadone were all converted into MME.

To analyze the total opioid necessary in each case, the MME was compared for each case. Differing lengths of each surgery could affect the total opioid used. The total opioid usage per surgery was calculated as a ratio between the MME used and the length of surgery in minutes, yielding a metric for comparison (MME usage / minute of surgery). This data is presented in Table 2. Using this metric, total opioid usage in all surgical procedures conducted on our patient was 5.01 MME/min. Opioid usage in surgical procedures without methadone was compared to usage in surgical procedures with methadone. Surgical procedures with only typical opioids (fentanyl, hydromorphone) in this patient yielded an average of 5.93 MME/min. Surgical procedures using methadone along with typical opioids in this patient yielded an average of 3.60 MME/min. The amount of acetaminophen, midazolam, and ketamine administered did not have any discernable affect on the amount of opioids used in this case.

There were no instances of QT prolongation or other drug reactions attributable to methadone use observed.

Table 2

	All Procedures	Procedures With Methadone	Procedures Without Methadone
Total Opioid Usage (MME)	35456	10036	25420
Total Length of Procedures (min)	7078	2790	4288
Total MME/min	5.009324668	3.597132616	5.928171642

As referenced in the case report, surgical procedures with methadone in this patient yielded 39.32% less usage of opioids per minute of surgery than in procedures without methadone. This is a remarkable reduction. Although effects of opioids vary from patient to patient, it is known that decreased surgical opioid usage leads to decreased onset of tolerance. Although there is no definitive scale, opioid tolerance is considered high-grade if the individual requires 1 M ME per hour intravenously for a period greater than 1 month[13,14]. Our patient received significantly more than that during procedures, though this report does not analyze opioid use outside of procedures. A reduction by 2.33 MME per minute of surgery is therefore significant given its magnitude in relation to the aforementioned value. It is possible that other factors affected the decreased rate of opioid usage, such as the surgical procedures performed, though breakdown of opioid dose by type of surgery results in similarly lower rates with methadone procedures. This suggests that methadone is an important variable leading to decreased overall opioid use.

The difference in rates of opioid usage exhibited in this case are likely attributable to the unique pharmacodynamic and pharmacokinetic properties methadone possesses. It is a synthetic opioid, agonizing µ and ∂ opioid receptors, and an antagonist of N-methyl-d-aspartate receptors (NMDA)[15]. These multiple different mechanisms of action allow it to provide supraspinal, spinal, and neuropathic anesthesia[16]. Studies have shown methadone provides prolonged intraoperative and postoperative analgesia in both adults and children due to its long half-life[17]. The use of opioid agonists frequently results in development of tolerance. This also occurs with methadone use, but to a reduced degree compared to the commonly used morphine18 and oxycodone. Methadone's ability to antagonize the NMDA receptor and internalize the µ receptor may contribute to this property[18].

Usage of methadone is not without risks, however. These include extreme variability in clearance kinetics in children[19], multiple drug interactions, and risk of cardiac toxicity[20]. There were no such adverse affects in our patient despite multiple procedures utilizing methadone, though the risks still exist. In addition, while methadone may have decreased overall opioid usage, this case report did not investigate depth or stability of methadone-induced anesthesia. One study has shown that methadone infusion in pediatric patients results in similar hemodynamics when compared to typical opioids[21], but few such studies have been done. Finally, while the potency of methadone is unaffected in subjects with established morphine tolerance, it is intrinsically lower than that of other opioids such as remifentanil[21]. Despite these drawbacks, the amount of reduction in opioid usage attributable to methadone in this patient warrants further investigation.

Pediatric burn patients require significant amounts of opioid products for pain, leading to opioid tolerance and subsequently elevated risk of adverse effects. Methadone can potentially provide adequate anesthesia and attenuated opioid tolerance compared to other commonly used opioid agonists, making it an enticing candidate for use in the pediatric burn population.

Table 1

Procedure #	Length (min)	Methadone (MME)	Fentanyl (MME)	Hydromorphone (MME)
1	252	0	1440	0
2	254	0	600	0
3	390	0	600	0
4	235	0	120	0
5	323	0	1320	0
6	195	0	240	20
7	330	80	720	0
8	207	60	1200	0
9	217	0	1800	0
10	239	0	2490	36
11	362	80	0	20
12	510	0	5880	400
13	266	0	1200	12
14	232	0	1200	40
15	249	0	1320	16
16	169	0	3000	108
17	455	160	3360	20
18	91	0	0	0
19	173	0	2520	8
20	417	320	2400	20
21	123	160	0	0
22	179	0	0	0
23	292	320	240	0
24	306	200	0	0
25	298	48	600	28
26	107	0	1200	40
27	207	0	360	0

LIST OF ABBREVIATIONS

Morphine milligram equivalents (MME)

N-methyl-d-aspartate (NMDA)

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