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Methadone for the management of complex pain and opioid-induced hyperalgesia in a child with Spinal Muscular Atrophy Type 2

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Abstract

Presentation
We report a case of methadone rotation for the management of opioid- induced hyperalgesia and complex pain in a 10-year old child with Spinal Muscular Atrophy (SMA) Type 2 along with a review of the literature.

Diagnosis
At the time of consideration for methadone conversion he was requiring escalating opioid doses despite the introduction of other neuropathic agents to manage pain secondary to pressure sores around protruding telescopic spinal rods. Because of his underlying respiratory vulnerability it was deemed that it was too unsafe to explore surgical correction for this.

Treatment
Our patient was successfully converted to methadone after a seven-day hospital admission following a 'stop and go' approach which entailed cessation of the existing opioid and all adjunctive medications. There was no evidence of withdrawal or toxicity throughout.

Discussion
Our case is unique in that it demonstrates a safe and efficacious rotation to methadone for the management of pain in a child with a significant underlying neuromuscular condition. Conversion to methadone should be highly individualised and supervised by a consultant experienced in its use.

Introduction

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Methadone is a synthetic opioid and is regarded predominantly as a mu-receptor agonist [1,2]. It has moderate delta-receptor agonism and minimal kappa-receptor agonism[1,3,4] . It also acts as a N-methyl-D-aspartate (NMDA)- channel antagonist and also blocks pre-synaptic re-uptake of serotonin and noradrenaline [5-8]. These properties make it a useful alternative in the management of neuropathic and nociceptive pain in patients with life-limiting conditions. It has several advantages in that it is available in liquid formulation which may be useful in patients who cannot swallow or require administration of medications via an enteral route[9]. It may also prevent or reverse opioid tolerance and opioid-induced hyperalgesia (OIH)[9,10]. There are some challenges associated with its complex pharmacokinetics that limit its use as a first- line analgesic agent in children and adolescents[9]. It has a highly lipophilic profile which results in a high volume of distribution and it is also extensively protein-bound. A result of the large volume of distribution is that when methadone is administered repeatedly, an accumulation occurs in tissues resulting in a considerable reservoir. The slow release from these tissue sites may prolong its duration of action despite low plasma concentrations and along with protein-binding contribute to a long and variable elimination half-life[8,9]. When the reservoir sites become saturated there may be a resultant sudden shift causing high serum concentrations which could result in death or life-threatening adverse events including respiratory depression or cardiac arrhythmia[11]. Methadone also undergoes hepatic metabolism through the cytochrome P450 system and this potentiates the risk of drug-drug interactions[6,8,9]. Furthermore there is the potential to cause cardiac toxicity through prolongation of cardiac conduction with a risk of causing Q-T interval prolongation and torsade de pointes[12]. Because of these complex pharmacokinetics, it is pertinent that when initiating methadone it is preferable for the patient to be admitted to an in-patient setting for close observation and that the clinician should have sufficient clinical experience in its use.
Methadone as an analgesic is well-established in children and adolescents with cancer[9]. There is however limited evidence for its use in children and adolescents with other life-limiting conditions. We report a case of methadone rotation for the management of complex pain and OIH in a child with Spinal Muscular Atrophy (SMA) Type 2.

Case report

We present the case of a 10 – year old male with SMA Type 2 with a background significant for a C-shaped neuromuscular curve caused by the underlying neuromuscular condition. Reduced muscle mass and tone resulted in an acquired scoliosis with a requirement for telescopic rods placement. His history was also significant for recurrent respiratory tract infections and respiratory failure secondary to his advancing neuromuscular condition. He had been requiring over 18 hours per day non-invasive BiPAP ventilation for more than 12 months. He also required percutaneous endoscopic gastrostomy (PEG) feeding. Over the

course of a number of years it was noted that the telescopic rods were becoming visibly prominent. He was reviewed by orthopaedics and deemed too high-risk for surgical intervention. At age 9, one of the metal rods became exposed and he developed a pressure area at the angle of the scoliosis on his left side. The pressure area was managed with extensive input from the tissue viability team. As he is non-verbal, his pain was interpreted via the frequency and intensity of his teeth-grinding, which was an indicator that he was uncomfortable or less content. There were challenges to being definitive regarding the aetiology of his pain due to communication limitations. However, pain episodes appeared to be arising from back pain associated with the spinal rods and open wound and pain was certainly exacerbated by movement suggesting a physical pain. Over time despite up titration of the baseline opioid and optimisation of neuropathic adjuncts, the patient exhibited signals of pain and his utilisation of opioids and adjuvant agents increased. In the preceding twelve months prior to consideration for methadone rotation, he had required monthly increases in his baseline opioid dose. He was requiring up to 6 doses of immediate release opioid daily. Rotation to alternative slow release enteral medication was precluded due to the route of administration (the gastrostomy tube) with MST Sachets being the only viable sustained release opioid option. Due to the significant escalation of opioid dose, the limitations to perform a therapeutic opioid rotation (although the transdermal route was also considered), use of neuropathic adjuvant agents and alongside a clinical impression of OIH, rotation to methadone was then considered. Following discussion with the patient's parents, an elective hospital in-patient admission was planned to undertake rotation to methadone.
At the time of the elective admission he was taking MST Continus ® 210mg BD, amitriptyline 10mg nocte, pregabalin 200mg BD, paracetamol 660mg QDS and chloral hydrate 250mg TDS. He was also prescribed ibuprofen 330mg TDS/PRN and Oramorph ® 70mg 4-6 hourly/ PRN for breakthrough pain.

There are a number of opioid rotation to methadone conversion protocols in adults[13] however these are not evidence-based in children[14]. The Association for Paediatric Palliative Medicine (APPM) Master Formulary suggests two methods – the first involves a period of opioid 'switchover' in which the existing opioid is reduced but is continued alongside a reduced dose of methadone over a period of three days (3-day switch /3DS)[15,16]. The second is a 'Stop and Go'[16] approach in which the existing opioid is stopped and a fixed methadone dose at variable dose intervals is commenced. This may be subdivided into a rapid conversion and 'ad libitum' approach[16]. It was decided in this case to make a complete switch to methadone using a modified and highly individualised rotation using the 'Stop and Go' approach, stopping MST Continus ® and all adjuncts simultaneously (see table 1 for the methadone calculations considered for this conversion). A loading dose of 1/15th the OME was prescribed and the q3h/PRN dose was calculated as 1/30th of the OME (both doses were reduced by 50% to allow for incomplete cross tolerance).

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Regular medications were administered on the day of the admission and from midnight MST Continus®, paracetamol, chloral hydrate, pregabalin and amitriptyline were stopped. The following morning a loading dose of methadone 14mg was administered. Thereafter methadone 7mg q3h/PRN was prescribed. In addition Oramorph® 35mg was prescribed for breakthrough pain (50% dose reduction of original breakthrough dose). He was monitored closely for withdrawal symptoms as well as signs of opioid toxicity. In the initial 24 hours he required x 3 methadone 7mg in addition to the loading dose. He experienced some sleep disturbance but appeared comfortable on review the following morning. The admission was complicated by a temperature spike and brief episodes of tachycardia whilst remaining clinically well. This was initially suspected to be an evolving concomitant viral infection and a nasopharyngeal swab was taken. Later an episode of acute deterioration on the ward occurred with increased work of breathing and oxygen desaturation to the mid-80s. Supplemental oxygen therapy was administered via BiPAP and nebulised hypertonic saline. Chest physiotherapy was performed using a cough assist device and suctioning which appeared to dislodge a mucus plug. He stabilised following these interventions. An extended nasal swab panel was negative. He was treated empirically with antibiotics. There was no evidence of withdrawal or toxicity throughout. On Day 7 of his admission (day 6 post methadone rotation) he appeared comfortable. In the preceding 48 hours he required eight doses of PRN methadone 7mg. Because he had been less well with a possible intercurrent infection a conservative approach was taken to convert to regular methadone. Methadone 10mg BD was prescribed. For breakthrough pain he was prescribed methadone 2mg q3h/PRN and continued Oramorph® 35mg PRN. He was discharged home the following day on methadone 10mg BD, on Day 8 of methadone administration. A 14-day admission had been anticipated (as it is during this time period that the reservoir sites become saturated and there may be a resultant sudden shift causing high serum concentrations resulting in serious life-threatening adverse events). An earlier than anticipated discharge was enabled following examination and discussion of the benefit versus burden and risk. Considerations included risk of respiratory depression, risk of hospital acquired infection and patient preference for care at home, and parent preference for care at home. The availability of an in-home nursing care package providing 100 hours per week one-to-one nursing care, who continued to monitor for evidence of withdrawal/toxicity alongside his parents facilitated close monitoring to mitigate the risks. The use of non-invasive ventilation circuit and a respiratory care plan was considered to mitigate the effects of toxicity and allowed for in home stabilisation should toxicity be suspected.

For breakthrough pain single agent Oramorph® 35mg was further reduced to Oramorph® 20mg q2h/PRN. His pain remains well-controlled.

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Discussion

SMA type 2 is a life-limiting condition for which there have been significant treatment advances in recent years. Prior to these treatments, therapies aimed at optimising respiratory health, seating and social interaction, as well as prolonging life, were employed to optimise quality and longevity of life. While long-term outcomes are awaited for the children and young people receiving newer treatments since diagnosis, they show promising results[19]. Other potential complications include respiratory failure, scoliosis and joint contractures[20]. Children with neuromuscular conditions are at risk of pain resulting from these complications. Optimal treatment will meet the analgesic needs of the child with the least side effects, and the benefits and burdens of all modalities of treatment options (e.g. non-pharmacological, pharmacological, surgical etc) separately, and in combination, should be considered.

In this case there was a clinical impression of OIH as the underlying aetiology for the escalation in pain and this was positively reflected in the successful rotation to methadone with significantly smaller doses of PRN Oramorph® to achieve adequate pain management. Methadone may prevent or reverse opioid tolerance OIH. Opioid tolerance refers to the reduced responsiveness to an opioid agonist i.e. increasing opioid doses required to produce the same analgesic effect. It may be caused by the desensitisation and downregulation of opioid receptors. Methadone is primarily a mu-receptor agonist, it also demonstrates affinity for the delta-receptor which is similar to morphine[1]. In contrast to morphine however it has been shown to induce delta-receptor desensitisation[22] which may underlie the differences between it and morphine in terms of tolerance. OIH refers to patients who demonstrate the paradoxical effect of increased sensitivity to painful stimuli[23]. This may be as a result of increased sensitisation facilitating nociception thereby counteracting the analgesic effect of the opioid. One proposed mechanism of action of OIH is the glutamate-associated activation of NMDA receptors[23]. Methadone demonstrates antinociceptive effects through the antagonism of NMDA receptors which may underlie its use in the management of OIH.

Opioid dose conversion ratios are not static and may depend on previous opioid exposure and may also be highly variable and unpredictable amongst individuals[9,21]. For individuals on long-term morphine the potency of methadone is ten times that of morphine. However in patients on higher doses of morphine this may reach a potency of thirty times that of morphine[14]. Conversion to methadone should be highly individualised and supervised by a consultant experienced in its use.

Methadone is a safe and efficacious analgesic agent that may be used in children and adolescents with cancer [1,9] who experience neuropathic, nociceptive or mixed neuropathic and nociceptive pain. There is however very limited evidence pertaining its use in children

and adolescents with life-limiting conditions outside of cancer. We conducted a rapid review of the literature and identified 14 studies examining its use for the management of pain in children or adolescents with life-limiting conditions (summarised in Table 2). One retrospective review[24] included three patients with an underlying neurological diagnosis and one patient with an underlying cardiac diagnosis. In this review most of the patients underwent rapid conversion (12 patients) and the conversion ratios from PO morphine to PO methadone ranged from 2: 1 - 150:1.

*Other: neuroblastoma, undifferentiated sarcoma, Wilms tumour, adrenocorticoid carcinoma, alveolar soft part sarcoma, angiosarcoma, and hepatoblastoma

Ψ Unclear from article if these patients had advanced cancers

OIH can complicate pain management and identification of the phenomenon, as well as explanation to the child or young adult (and family where appropriate) is key to making a management plan. Various options for opioid rotation exist, and in this case methadone was selected for its antinociceptive effects through the antagonism of NMDA receptors and its liquid preparation. There is limited evidence to the use of methadone in children and adolescents with life-limiting conditions outside of cancer. Our case report demonstrates a successful, safe and efficacious rotation to methadone for the management of OIH and complex pain in a patient with advanced SMA type 2.

Declarations of Conflicts of Interest:
None declared.

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List of abbreviations:
NMDA = N-methyl-D-aspartate
SMA = Spinal Muscular Atrophy

OIH= Opioid induced hyperalgesia
PEG = Percutaneous endoscopic gastrostomy
BiPAP = Bilevel Positive Airway Pressure
APPM = Association for Paediatric Palliative Medicine
PRN = pro re nata (as required)
BD = twice daily
TDS = three times per day
QDS= four times per day
OME = oral morphine equivalent

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Table 1- Methadone conversion ratio methods considered for the 'Stop and Go' approach

Name of method		
Morley and Makin model [17]	Calculate the total OME Give q3h/PRN doses of methadone *1/10* of the previous 24h PO morphine dose, up to a maximum of 30mg	MST 210mg BD = 420 mg OME 420mg ÷ 10 = 42mg (maximum dose = 30mg) Reduce by 50% for incomplete opioid cross tolerance = 15mg

	Reduce the total oral daily dose OME by 30-50% to account for incomplete cross tolerance. On Day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular q12h dose	
APPM [14] – modified	Calculate the total OME Reduce the total oral daily dose OME by 30-50% to account for incomplete cross tolerance. Convert the final calculated oral morphine daily dose to oral methadone daily dose by dividing by *15* Divide this into three daily doses. (As a rule, the initial dose should not usually exceed 10 mg 3x per day in an adult/patient over 50 kg, 5 mg 3x per day in child/patient under 50 kg). Initially give either 2 or 3 doses/24 hours.	MST 210mg BD = 420mg OME 420mg ÷ 15= 28mg Reduce by 50% for incomplete opioid cross tolerance = 14mg
Palliativedrugs.com [18]	Calculate the total 24 hour OME dose Give a single loading dose of oral methadone *1/10* of the	MST 210mg BD= 420mg OME 420mg ÷ 10 = 42mg (maximum dose =30mg)

	total 24 hour OME dose (up to a maximum of 30mg of methadone) A q3h/PRN dose of methadone *1/30* of the total 24 hour OME dose is prescribed (up to a maximum of 30mg of methadone) If additional analgesia is required for breakthrough pain, i.e. for patients in severe pain, an alternative opioid may be prescribed 'as required' for second line use. This dose should be 50–100% of the PRN dose used before switching, and can be administered hourly. On day 6, the amount of methadone taken in total over the previous 48 hours is calculated and divided by 4 to give a regular twice daily dose	Q3h/PRN dose = 14mg

Table 2- Full-text data extraction

Reference	**Study type**	**Primary diagnosis**	**Clinical indication for methadone**
Anghelescu et al, 2011 [6]	Retrospective review	Leukaemia/lymphoma Solid tumours	Control of neuropathic pain

		Haematologic or congenital disorders	Control of nociceptive pain Opioid weaning/prevention of withdrawal End-of-life pain management
Bonertz et al, 2007 [25]	Case report	Metastatic liver cancer	Control of neuropathic pain
Crews et al, 1993 [26]	Case series	Terminal metastatic hepatoblastoma Refractory acute lymphoblastic leukaemia	End-of-life pain management "Joint-related" pain
Davies et al, 2008 [2]	Retrospective review	Advanced cancers including : Solid tumours Haematological malignancies Brain	"Advanced cancer" Specified in two patients as "all over pain presumed secondary to widespread bony infiltrates"
Fife et al, 2016 [27]	Retrospective review	Unclear- majority of patients in NICU or PICU	"Patients converting from primary opioid therapy"
Martinson et al, 1982 [28]	Retrospective review	Advanced cancers	End-of-life pain management
Miser and Miser, 1985 [29]	Prospective interventional study	Advanced cancers	Control of neuropathic pain Control of nociceptive pain
Mott et al, 2018 [24]	Retrospective review	Advanced cancers Non-malignant diagnoses including: Meningococcal septicaemia with brain injury and four limb amputation	"Inadequate analgesia" "Increasing drowsiness" "Loss of central venous access and unable to maintain SC route"

		Epileptic encephalopathy Cerebral palsy with a spastic quadriplegia, parental nutrition Pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries	"Side effects with morphine-inadequate analgesia and itch" "Methadone only alterbative slow release opioid that comes as elixir" "Irritability" "Myoclonus" "Experienced pruritis with morphine" "Seizures (neurotoxicity) possibly due to hydromorphone" "Complex pain" "Neuropathic pain" "Neurotoxicity. Severe dyspnoea. Chest pain. Required elixir" "Agitation"
Richlin at al, 1987 [30]	Case series	Advanced cancers	Described "site of pain" as opposed to clinical indication
Rogers, 1986 31	Case report	Advanced neuroblastoma	Control of neuropathic and nociceptive pain
Sabatowski et al, 2002 [32]	Case report	Advanced neuroblastoma	Control of neuropathic and nociceptive pain
Shir et al, 1998 [33]	Case series	Metastatic nephroblastoma Burns pain	

		Post amputation Acute lymphoblastic leukaemia Osteopetrosis	
Shir et al, 2001 [34]	Retrospective review	Cancer pain Ψ Burn pain 'Other' non-malignant pain	Control of neuropathic pain Control of nociceptive pain
Sjogren et al, 1994 [35]	Case series	Astrocytoma	Control of nociceptive pain