Narrative Review

Methadone in Cancer Pain

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Abstract

Methadone has been an unique, versatile, cost effective, synthetic opioid utilized in nociceptive as well as neuropathic pain. Pain and palliative care physicians started accepting methadone in treatment of complex pain associated with advanced cancer and neuropathic pain syndromes in which conventional opioids were no longer effective. The challenge is in accepting methadone as a main stream first line opioid , from being considered as a second line replacement/substitution drug all these years. Methadone has a significant role as opioid rotation in refractory cancer pain, especially when started early leading to successful conversion. Advantages of methadone in paediatric patients with advanced cancer were its safety and efficacy as a first-choice opioid, availability as a liquid formulation and its infrequent dose requirements. Methadone is neither recommended nor justified to be used as an anti-cancer drug and its role as an anti-cancer agent is a misconception. Many guidelines were proposed after 2008 to address methadone safety. Most of them emphasized on prevention of cardiac arrhythmia and association of methadone with QTc prolongation rather than address the real issue. Methadone has been established to be safe when used in opioid naïve patients with careful titration instituted in an ambulatory setting and has equal success in opioid rotation in outpatient setup. Methadone prescription should be carried out by experienced pain and palliative care providers with careful dose titration and clinical monitoring.

Keywords: Methadone, refractory cancer pain, QTc interval, opioid rotation

Introduction

The quest for conquering pain historically dates back centuries and the search for ideal opioid in cancer pain management has continued. Methadone has been an unique, versatile, cost effective, synthetic opioid utilized in nociceptive as well as neuropathic pain.[1,2] Initially limited to de-addiction centers as a drug assisted rehabilitation for treatment of opioid dependence and substance abuse to heroin, it gradually paved way in cancer pain practice by utility as a second line drug and in opioid rotation.[3,4] It started having a strong foothold in opioid refractory cancer pain, opioid tolerance and opioid induced hyperalgesia.[5,6] Pain and palliative care physicians started accepting methadone in treatment of complex pain associated with advanced cancer and neuropathic pain syndromes in which conventional opioids were no longer effective.[7,8] Methadone started being accepted as a first line strong opioid gradually and incorporated in WHO ladder as step 3 opioid.[9,10,11] Low dose methadone became more versatile in palliative medicine practice.[4,12-14] Being also available in a liquid preparation, it was more acceptable in paediatric pain.[15-20] The complexity of pain in terminal cancer and need for improving quality of life paved way for its use in end of life care.[7,8,13,21] The journey of methadone in cancer pain which had its initial safety reservation and prescription concerns, to overcoming the stigmatic barriers has been the subject for its review.

Discussion

Methadone as a pharmacological formulation

Methadone is a synthetic opioid, structurally belonging to diphenyl propylamine class, developed way back in 1937 in Germany. A racemic mixture with levo (R) and dextro (S) rotatory enantiomers having discrete action on Mu receptor (supraspinal analgesia) and delta receptor (spinal) for nociceptive pain pathway as well as NMDA and epinephrine/serotoninergic reuptake inhibitory neuropathic pain pathway.[1]

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Methadone being a lipophilic hydrochloride salt-based formulation is available as a liquid suspension (5mg/ml) and oral tablet (5mg, 10mg) which is administered by oral, buccal, sublingual routes and less preferred being rectal, intravenous, subcutaneous and intrathecal routes. Oral methadone attains plasma levels within 30 mins owing to high oral bioavailability, peak levels at 4hours with long elimination half-life beyond 24 hours, metabolized by auto-inducing hepatic microsomal enzymes by oxidative biotransformation and excreted after renal N-demethylation with no active metabolites.[1,7,22-25] Renal impairment does not hinder methadone elimination and is considered safe in this subset of patients. Dose escalation needs to be gradual and low incremental due to its enzymatic auto-induction on chronic usage.[3,22,26,27]

Favourable profile of methadone include versatility in treating central sensitization, opioid tolerance, opioid induced hyperalgesia and complex pain owing to its extra-opioid analgesic action and anti-hyperalgesic properties.[3,21] Methadone has non-existing tolerance as there is no ceiling effect described in pharmacological literature.[9,28] The efficacy of methadone is similar and equianalgesic to that of morphine in cancer pain management, with an added advantage of low cost and an ideal therapeutic option to initiate opioid therapy in progressive cancer pain.[9,22]

At the same time, methadone has its disreputation for its drug accumulation due to its complex pharmacodynamic, pharmacokinetic and pharmacogenomic modulation brought amongst the inter-individual population, leading to therapeutic variations seen as an end effect clinically.[9,22] The dose initiation, titration, escalation and opioid conversions are extremely variable and should be individualized to each patient. The complexity of methadone dosing demands an expertise in its prescription by a pain and palliative care provider.[22] The risk of toxicity exists with repeated administration.[22] The most important concerns regarding methadone prescription are its drug interactions and prolongation of QTc interval predisposing to arrhythmias.[29-34] Many confounders exist in causation of methadone related adverse effects due to enzyme activation by alcohol, benzodiazepines, anticonvulsants, antidepressants, anti-retroviral therapy, substance abuse which may predispose to toxicity.[1]

Methadone as a first line opioid in cancer pain management

Methadone as a first line opioid was put forth by Bruera *et al*. in 2004 where the comparison was drawn with oral morphine which was the existing gold standard and concluded that methadone in a dose of 15mg/day was not superior to 60mg/day modified release morphine, both groups attaining and achieving > 20% improvement in pain scores.[1,11] Later, Mercadante *et al*. in 2008 compared methadone with oral morphine and transdermal fentanyl in which no differences were reported in pain intensity, mean pain scores, reporting no worse than mild pain and found similar efficacy with >30% pain reduction among the groups.[1,22,35,36] Both the studies found methadone to be equianalgesic and producing similar opioid related adverse effects. Methadone did not produce superior analgesic efficacy in comparison to morphine as a first line strong opioid in cancer pain management though.[11]

The conclusions put forth by Nicholson *et al*. in the Cochrane review were that the evidence from randomized control trials establishing efficacy of methadone as a first line opioid in the management of severe cancer pain is low and unlikely to be considered, based on difficulties around dose titration as well as the adverse effect profile of methadone.[1] Although studies have established safety as well as non-inferiority of methadone compared with its opioid counterparts when used as first line opioid in cancer pain, evidence is not yet robust to recommend it.[1,37] The challenge is in accepting methadone as a main stream first line opioid, from being considered as a second line replacement/substitution drug all these years.[7,26] This can become practical by identifying methadone by its unique pharmacology, carefully done low dose initiation and gradual dose titration by an experienced palliative care clinician, vigilant monitoring for QTc prolongation and respiratory depression, proper patient selection, minimizing drug interactions, advocating a safety checklist and formulating opioid rotation protocols could go a long way in establishing safety of methadone as a first line opioid in cancer pain management.[1,7,23,29-34]

At the same time, methadone may have a role if other strong opioids are not tolerated.[1] Methadone needs to be considered early in cancer pain management rather than to reserve it for later stages when opioid tolerance has already set in, needing consideration for undertaking an opioid rotation.[37] It has been reported that 50-80% patients with cancer pain demonstrated improved pain control after addition of methadone.[38-40] Methadone has been a revelation in the management of complex pain, which usually is a combination of nociceptive and neuropathic components occurring towards end of life care, where poor pain control is often associated.[41]

Methadone initiation guidelines

i. Opioid naïve patients with moderate to severe cancer pain: European association for palliative care recommends methadone initiation as first line step 3 opioid by experienced practitioners. American pain society has recommended methadone initiation in opioid naïve not to exceed 7.5 mg/day (2.5mg every 8 hourly). Society for hospice and palliative care has recommended low dose

Table 1: Methadone conversion ratios

Daily oral morphine equivalent (mg)	Conversion ratio of oral morphine:Oral methadone
30-100	3:1
101-300	5:1
301-600	10:1
601-800	12:1
801-1000	15:1
>1000	20:1

initiation 2-7.5mg/day with dose escalation no sooner than 5-7 days and not more than 5mg/day[12,42-44]

ii. Opioid tolerant patients needing opioid rotation: Cancer patients receiving less than 60 mg/day oral morphine when rotated to methadone are considered at par with opioid naïve group described above. Society for hospice and palliative care has recommended 10:1 or 20:1 dose conversion respectively in-patient group less than 65 years receiving morphine equivalent dose of 60-199mg/day and in-patient group receiving more than 200mg/day above 65 years. Dose escalation limits not exceeding 5mg/day irrespective of the previous opioid dose.[12,43] A simpler way to methadone switch from oral morphine [Table 1] had been recommended by Ayonrinde and Bridge[45]

iii. Pediatric pain: American pain society recommends starting dose 100 microgram/kg with maximum limit 5mg/dose given every 6-8 hours promptly withholding if sedation manifests although World Health Organisation suggested higher dosing at 100-200 microgram/kg[43]

iv. Methadone re-initiation: Patients previously prescribed methadone, but currently not on any opioids over the past 1-2 weeks, should be considered at par with opioid naïve patients.[43]

Methadone in neuropathic pain

The Cochrane review by McNicol on methadone in neuropathic pain concluded that there was very low-quality evidence on its efficacy and safety.[2] The review stated that no conclusions could be made regarding the safety and efficacy of methadone in the management of neuropathic pain. Further, evidence-based studies in future may provide a clear distinction of the role of methadone in neuropathic cancer pain.[2,13,46]

Methadone as the choice of opioid rotation in refractory cancer pain

Opioid rotation in chronic cancer pain is therapeutically considered when inadequate analgesia and/or intolerable side effects are encountered.[47] This has been encountered in upto 30% patients prescribed on strong opioids. The success of opioid rotation is assessed by improved analgesia, improved patient satisfaction and acceptance but may not necessarily reduce the frequency of opioid related adverse effects. Opioid rotation may become necessary in 20-44% cancer pain patients which could lead to clinical improvement in about 40-80% of them upon rotation.[48,49]

The dose of the new drug introduced in opioid rotation is always greater than the ongoing dose calculated by an opioid conversion ratio, with the exception of methadone. Methadone has a significant role as opioid rotation in refractory cancer pain, especially when started early leading to successful conversion. Patients when switched over from oral morphine to methadone preferred to stay in the methadone regime with comparable quality of life.[23,36,50] Opioid conversion to methadone should be done under clinical supervision with individualized dose titration to prevent serious adverse effects.[47-49,51]

The opioid conversion to methadone could be done by an abrupt "stop and go method" in which original opioid is stopped abruptly with replacement by methadone or by a "progressive 3 day switch" in which the original opioid is tapered with incremental escalation of methadone by 1/3rd dose every day over 3 days. The relative equianalgesic ratio of oral morphine to oral methadone has been from 4:1 to 12:1 in various studies and associated with low evidence. Current international guidelines have refrained from providing universal conversion ratio for methadone citing the need for individualized dose conversion from experienced practitioners owing to safety concerns and large inter-individual dose variance reported from several studies.[7,48,50,52-54]

Methadone in paediatric cancer pain

In a study by Madden *et al.* evaluating the attitude, belief and practices of paediatric palliative care physicians reported that majority (77%) prescribed methadone as an oral liquid form to children with advanced cancer and most of the majority (70%) were not favouring loading dose in their practice.[15]

Advantages of methadone in paediatric patients with advanced cancer were its safety and efficacy as a first-choice opioid, availability as a liquid formulation and its infrequent dose requirements. Being a long acting opioid, the initial dose administered was 0.1mg/kg every 12 hours. When used early in the course of cancer pain, pain scores significantly improved on methadone initiation which led to improved insomnia extending into later follow-up visits.[15,16]

Paediatric pain physicians could be reassured with the potential adverse effects of methadone; in the form of propagation of QTc and arrhythmia risk to be low and uncommon (although a baseline electrocardiograph and dyselectrolytemia are recommended by American pain society).[55] Also, the American pain society recommends QTc prolongation greater than 450ms to consider modifying or removing methadone; greater than 500 ms to withhold and discontinue methadone.[43] Paediatric QTc thresholds may be variable among pre-pubertal and adolescent children.[56] No sudden deaths, torsade de pointes, ventricular fibrillation were reported in children receiving methadone for cancer pain.[56]

Most paediatric palliative care providers preferred equianalgesic dosing with dose reduction rather than weight based formulae with methadone switchover whereas preferring weight based formula for methadone dose initiation in opioid naïve children.[16] Although World health organization recommends weight based dosing in methadone loading doses defined by increasing initial frequency, American pain society doesn't recommend loading dose citing safety as primary concern.[43,55] There are no published reports of methadone induced severe dysrhythmia in paediatric pain practice.[15-17,20,56]

Cancer pain in paediatric population is often a combination of nociceptive and neuropathic components which respond effectively to methadone. Although literature evidence of methadone efficacy in pediatric oncology is sparse, there is evidence support for establishing safety and efficacy of methadone in treating pediatric cancer pain especially

when pain becomes refractory to conventional opioids.[17] Methadone is indicated in children needing long term opioid therapy developing opioid tolerance and opioid induced hyperalgesia.[17]

Pharmaco-resistant neuropathic pain may be encountered in pediatric cancer pain practice secondary to chemotherapy related neuronal injury, solid tumour related nerve trapping, post-surgical neuropathic pain and in complex pain associated with end of life care. The first line therapy in the clinical decision algorithm for pediatric neuropathic cancer pain includes gabapentinoids, tricyclic antidepressants and methadone.[18] Very low dose methadone (less than half of the standard starting dose of 0.1mg/kg) has been successfully used in treatment of refractory neuropathic pain induced by vincristine in acute lymphoblastic leukaemia.[19]

Evidence based recommendations for methadone in pediatric cancer pain with further prospective studies should bring it back to the mainstream opioid prescription practice in near future.[16]

Methadone as an anti-cancer treatment

In vitro pro-apoptotic effects and animal model tumour growth-inhibitory chemo-enhancer properties of methadone have gained much attention as a potential anti-neoplastic agent, although evidence based clinical oncology perspective doesn't favour. However, methadone from a clinical point does improve quality of life in patients with cancer pain. Methadone is neither recommended nor justified to be used as an anti-cancer drug and its role as an anti-cancer agent is a misconception.[4,13,57]

Methadone – Establishing safety

Since the turn of the century, opioid related deaths started becoming a health care concern leading to measures taken to curb "opioid crisis". At around the same time, methadone was being implicated in about 1 out of 3 opioid related deaths. Food and drug administration (FDA) adverse event reporting system (FAERS) implicated methadone as the second most common agent in drug related arrhythmia since 2000.[58]

The interpretation needs to be carefully done as several confounders were attached with the methadone related deaths. The varied pharmacological profile with inter-individual variation in clinical end effects with drug interactions, substance abuse and non-prescribed use of methadone were neglected. Methadone prescriptions were not provided by a trained palliative care giver till then. Respiratory depression and arrhythmia leading to sudden death were not investigated in detail as most patients were receiving methadone in end of life care. Associated cardiac failure, use of servo ventilator dependent central respiratory drive in obstructive sleep apnoea patients, ensuring strict alcohol abstinence, antidepressant/anticonvulsant/benzodiazepine sedative co-administration, substance abuse, opioid dependent craving, anti-retroviral treatment, patient selection with prior behavioural risk evaluation, baseline QTc prolongation, counselling with regular monitoring follow-up, structural heart disease, dyselectrolytemia, impaired hepatic metabolism, individualized drug treatment with monitored dose titration were never mentioned.[12,43]

Many guidelines were proposed after 2008 to address methadone safety. Most of them emphasized on prevention of cardiac arrhythmia and association of methadone with QTc prolongation rather than address the real issue. The quality of evidence was extremely limited. This led the American pain society to publish methadone safety guidelines in 2014 in collaboration with heart rhythm society and college on problems of drug dependence which is considered as a benchmark for methadone safety prescription.[43]

It needs to be recognized that methadone is a unique pharmacological drug, which has its own set of safety check to be achieved prior to prescription by an expertise, to initiate and titrate the drug periodically under clinical monitoring limiting the adverse effects.

Methadone in palliative care cancer pain practice: Is it safe to use?

An expert consensus for safe use of methadone in hospice and palliative care was put forth by McPherson *et al*. in 2019.[12] This consensus came in view of safety concerns raised against methadone in terminally ill patients and end of life care leading to disproportionate increase in opioid related deaths.[12] Methadone has been established to be safe when used in opioid naïve patients with careful titration instituted in an ambulatory setting and has equal success in opioid rotation in outpatient setup.[26] Methadone has been established to be safe beyond the hospital setting and has been corroborated by various studies to be safe despite the inherent risk of respiratory depression and the risk of arrhythmia due to QTc prolongation.[14,59-62]

Low dose methadone in end of life care

Low dose oral methadone in addition to the regular opioid has been used as an adjuvant in end of life care patients to treat complex pain. Although better analgesic profile, improved quality of life and opioid dose reduction were achieved, there was an increased risk of sedation and delirium.[4,13,14,21] Also, the very low evidence quality of methadone in end of life care, makes its recommendation in clinical practice inconclusive. Although potentially effective as an adjuvant, it is not substantiated till further evidence arises.[13]

Conclusion

Methadone is unique in its pharmacological properties with varied inter-individual differences and drug interactions. The safety of methadone is well established in cancer pain management. Methadone prescription should be carried out by experienced pain and palliative care providers with careful dose titration and clinical monitoring. Methadone needs to be evaluated in pain specific and cancer specific subtypes. Methadone has the versatility to be utilized in pediatric difficult pain scenario and complex pain management-an enigma in end of life.

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