

Breaking the Barrier: Challenges of Methadone Use – An Introductory Observation

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Abstract

Background: Palliative care physicians in India have achieved access to methadone for pain relief in cancer patients. Despite being an effective drug in terms of analgesia, there are a number of reasons why this opioid medication is not as much as popular as morphine. We identified and tried to overcome a few such barriers in treating cancer pain with methadone. **Methods:** The clinical information of ten adult cancer patients (six males and four females), who voluntarily received methadone for their severe pain in the month of August 2019 were analysed retrospectively. We converted morphine to methadone in all ten patients under the supervision of an experienced practitioner. **Results:** During the methadone therapy, eight out of ten patients who were given methadone exclusively for their pain had adequate pain relief initially. The barriers identified included difficult titration methods due to distinct pharmacology, patient selection, clinical inertia, communication and co-ordination among physicians, communication among patient and physician, and patient and caregivers, and vigilant monitoring. **Conclusion:** Methadone is still finding its place in India for cancer pain management. As the drug is new to Indian practitioners, we have to overcome these barriers and facilitate its judicious use in cancer pain management.

Keywords: Methadone, pain management, palliative care

INTRODUCTION

In cancer pain management, only three-fourths of pain responds to the World Health Organization (WHO) three-step analgesic ladder,^[1] implying that a large number of patients require oral morphine at some point of their disease trajectory. The other one-fourth gets inadequate relief.^[2,3] In India, morphine and fentanyl had so far been the only available opioids in step three of WHO analgesic ladder. Some pains such as neuropathic pain have inadequate pain relief with morphine. Furthermore, as the dose of morphine increases, patients suffer from neurotoxicity, especially those with renal and hepatic impairment.^[4]

Switching of opioids, or opioid rotation, has now been a standard practice in many patients with pain that responds poorly to morphine. The problem in India is that many institutions do not have any other alternative to morphine. Fentanyl is available in various formulations but due to its cost, it is impractical for many patients. The palliative care activists in India sought an inexpensive and a practical alternative opioid to morphine. It is a matter of surprise indeed that methadone was being manufactured in India for export to other countries,

but it was not approved for sale in India. Many years of advocacy and efforts by activists have resulted in methadone being now available for sale in India for the purpose of pain management.^[5]

Methadone available in India is a racemic mixture of R and S forms. The R form is a mu and delta agonist. S methadone is an N-methyl-D-aspartate antagonist and an epinephrine and serotonin reuptake inhibitor. These properties of methadone justify its use in both neuropathic and nociceptive pain and could be effective to treat central sensitization. Methadone has no ceiling effect and is long acting. It has been in use in for patients with opioid use disorder and has been found to cause fewer withdrawal effects. It is inexpensive and has a broad spectrum of action.^[6]

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The pharmacokinetics and pharmacodynamics of methadone are different from morphine and fentanyl. Effective training is necessary for Indian doctors to use methadone safely. The physicians need to learn the opioid drugs and conversions, understand the interactions and dose modification, and train the family and caregivers. A trained physician can initiate, monitor, follow-up, and document it with the assistance of well-instructed family caregiver. It is also essential that the potential risks and benefits are discussed with families/patients, and concurrent drugs that prolong the QT interval are avoided.^[7]

After appropriate training, we prescribed methadone to ten patients in 1 month posting in the palliative care unit and retrospectively analyzed our findings and identified a few barriers. We hereby report our initial experience of methadone use in patients with their presenting symptoms, their pain score on presentation and at discharge, their daily morphine dose, converted methadone dose, satisfaction level on morphine and methadone and their current status.

METHODS

Patient information

The clinical information of 10 cancer patients (6 males and 4 females; age 22–69, average of 43.5 years old), who voluntarily received methadone for their severe pain in the month of August 2019 at palliative care unit, Dr. B. R. A. Institute Rotary Cancer Hospital, AIIMS, New Delhi were retrospectively analyzed. The inclusion criteria were patients diagnosed with cancer, with severe unrelieved cancer pain numerical rate scale (NRS >7 even after more than 1 month of continuing oral morphine dosage with good compliance). The exclusion criteria^[8] were concurrent pentazocine, nalbuphine, butorphanol administration (may precipitate withdrawal symptoms), concurrent monoamine oxidase inhibitor therapy, respiratory depression, severe liver disease, patients with mild, intermittent, or short duration pain that can be managed with other pain medications, prolonged QTc >500 ms for males and >470 ms for females and electrolyte disturbances.

Treatment

We carefully performed conversion of morphine to methadone in all ten patients with the supervision of an experienced physician. We have oral methadone in form of syrup with a concentration of 5 mg/ml available in our hospital supply. We used a syringe for accurate dosing for patients. All adjuvants were prescribed without any change in the dosages. All patients were prescribed laxatives with opioids as it is a routine practice of our department.

Dose conversion

- Step 1: We determined the oral morphine daily dose (OMDD) which include the baseline and breakthrough morphine medications
- Step 2: The OMDD is noted, and then, we used appropriate conversion ratio to know daily methadone requirement in each patient [Table 1]

Table 1: Methadone conversion ratio

OMDD (mg)	Conversion ratio (morphine: Methadone)
<30	2:1
30-99	4:1
100-299	8:1
300-499	12:1
500-999	15:1
1000-1200	20:1
>1200	Consult

OMDD: Oral morphine daily dose

- Step 3: We reduced the calculated methadone dose to further 30% to account for the incomplete-cross tolerance.

Opioid switch^[8]

We used two different methods of morphine to methadone switch.

Three-step switch method/stepped approach [Table 2]

- Day 1: We reduce original OMDD by 1 / 3, added 1 / 3 as calculated methadone dose, and used morphine for rescue
- Day 2: We reduced the existing OMDD analgesic by 2 / 3, and added 2 / 3 of calculated methadone dose in three divided doses, and used morphine for rescue
- Day 3: We gave total dose of methadone calculated in three divided doses and used morphine as rescue analgesic.

Rapid switch method [Table 3]

We determined dose of methadone from OMDD using same steps as in stepped titration method). We stopped morphine immediately and administered methadone in three divided dose in 24 h.

Morphine immediate release dose (1 / 6th of OMDD) was given as rescue analgesia. We observed patient in ward for atleast 3 days and adjusted dose as appropriate.

Maintenance dose

Once patients are on a stable methadone dose, the dose was adjusted if required by increments of 20% every week and not earlier.

Breakthrough dose

We prescribed tablet morphine immediate release for breakthrough pain (one sixth of OMDD).

Monitoring

We admitted patient in our ward for at least 3 days and continuously monitored patients for sedation, lethargy, and respiratory depression. After discharge, we did a close follow-up of patients by the telephone. We assessed patients after 1 week of discharge from palliative care unit in pain clinic of our department with recent electrocardiogram (ECG) and electrolyte reports.

RESULTS

Here, we summarized the details of ten patients where we have used methadone for the purpose of opioid switch

Table 2: Stepped titration method

Patient number	1	2	3	4	5	6
Patient demographics	41 years/male	48 years/male	47 years/male	22 years/female	39 years/female	42 years/female
Presenting symptoms	Pain chest back, pelvis	Pain Right shoulder and upper limb	Pain Right thigh radiating to limbs	Pain lower back radiating to bilateral limbs	Pain chest	Pain lower back radiating to left lower limb
Primary cancer	Ca lung	Ca lung	Leiomyosarcoma right thigh	Metastatic ewings sarcoma	Metastatic chondrosarcoma	Ca rectum
NRS on presentation	10/10	6/10	7/10	10/10	8/10	10/10
OMDD	360 mg oral morphine	90 mg oral morphine	240 mg oral morphine	240 mg oral morphine	120 mg oral morphine	360 mg oral morphine
Converted methadone dose	(12:1) 30 mg oral methadone	(4:1) 22.5 mg oral methadone	(8:1) 30 mg oral methadone	(8:1) 30 mg oral methadone	(8:1) 15 mg oral methadone	(12:1) 30 mg oral methadone
Methadone dose given to patient after ~30 % reduction	22.5 mg	15 mg	22.5 mg	22.5 mg	12.5 mg	22.5 mg
NRS at discharge	2/10	3/10	3/10	2/10	2/10	The patient discontinued methadone due to severe intractable pain.
Satisfaction level on morphine	3/10	6/10	5/10	4/10	1/10	Satisfaction level with morphine was 3/10 and that with methadone was 2/10. Later on patient was given a trial of intrathecal morphine which showed excellent results. So, she was considered for intrathecal implant and was planned for the same. At present patient is having a NRS-2/10 on intrathecal implant with morphine
Satisfaction level on methadone	9/10	8/10	6/10	8/10	9/10	
Current status	Continuing on the same oral dose of methadone since last 2 months	Methadone dose was increased to 22.5 mg over next two weeks. Now continuing with same dose since 2.5 months	Methadone dose was increased to 30 mg over next week. Now continuing with same dose for 2.5 months	Continuing on the same oral dose of methadone for last 2 months	Continuing on the same oral dose of methadone since last 2 months	

NRS: Numerical Rating Scale, CT: Computed tomography, OMDD: Oral morphine daily dose

[Tables 2 and 3]. Five patients got adequate pain relief (NRS <4) after methadone switch and they are continuing on same dose of methadone they are titrated on. In three patients, methadone dose increased over subsequent weeks, and now they have adequate pain relief. In one patient due to severe pain and patient request, an intrathecal implant procedure was performed, she had adequate pain relief after the procedure and she is doing well on intrathecal implant with morphine. In one patient, NRS was decreased from eight to five on 2nd day of methadone switch, after discussing computed tomography scans, ganglion impar block was performed successfully. Methadone was again titrated on 120 mg OMDD. At present, the patient is having pain relief on 10 mg oral methadone per day for 2 months.

No significant side-effects were observed in any of the ten patients.

DISCUSSION

When introducing new medicine, how much of benefit or harm we are likely to do to our patients? In the mid-1940s, methadone was introduced as an analgesic but due to its side-effect profile soon lost favor.^[9] It was re-emerged in the 1980s due to its better understanding of pharmacokinetics and pharmacodynamics. Oral methadone was included as

an analgesic in the 20th edition, WHO model list of essential medicines in 2017.^[10]

In India, methadone was introduced for opioid dependence treatment as substitution therapy in the year 2012.^[11] It became commercially available in 2014 for pain management.^[12] In 2015, methadone was listed as an “Essential Narcotic drug” by the Government of India for medical and scientific use under the modified National Drug and Psychotropic Substances Act 2015.^[13]

Methadone should be used in cancer pain undisputedly and risks due to inappropriate use rather than benefits should not compromise its use as an alternative to morphine in management of cancer pain.^[14] It may have role in cancer pain if other opioids are not tolerated keeping the issues of dose titration in consideration.^[7]

Various methods of dose conversion from morphine to methadone have been described. In nonurgent setting the preferred method of methadone conversion is the “start low, go slow” method. The “Marley Makin” model demands titration to methadone over 5 days. On day 6, the total daily dose of methadone is calculated as an average of days 4 and 5 methadone requirement. This is a very resource intensive method and not suitable in a public hospital setting.^[15] In the “German method,” there is no notion of fixed or

Table 3: Rapid titration method

Patient number	7	8	9	10
Patient demographics	69 years/male	47 years/female	40 years/male	40 years/male
Presenting symptoms	Pain right side of the face radiating to the ear and neck	Pain lower back and abdomen	Pain lower back and radiating to bilateral limbs	Pain perineal region
Primary cancer	Ca right tonsil	Ca cervix	STS thigh with skeletal metastasis	Ca anal canal
NRS on presentation	10/10	8/10	9/10	8/10
OMDD	180 mg	300 mg	180 mg	240 mg
Converted methadone dose	(8:1) 22.5 mg oral methadone	(12:1) 25 mg oral methadone	(8:1) 22.5 mg oral methadone	(8:1) 30 mg oral methadone
Methadone dose given to patient after ~30 % reduction	15 mg	22.5 mg	15 mg	22.5 mg
NRS at discharge	2/10	1/10	2/10	NRS decreased to 5/10 after 2 days.
Satisfaction level on morphine	5/10	3/10	2/10	After discussion of CT scans, the patient was found to be an ideal candidate for ganglion impar block.
Satisfaction level on methadone	8/10	9/10	8/10	The patient was given ganglion impar block which was successful.
Current status	Methadone dose was increased to 22.5 mg over next 2 weeks Now continuing with same dose for 2.5 months	Continuing on same oral dose of methadone for last 2.5 months	Continuing on same oral dose of methadone for last 2.5 months	Methadone was again titrated on 120 mg OMDD. At present, the patient is having pain relief on 10 mg oral methadone per day for 2 months

NRS: Numerical rating scale, CT: Computed tomography, OMDD: Oral morphine daily dose, STS: Soft tissue sarcoma

adapted conversion ratios and methadone is started at a dose of 5 mg every 4 hourly without considering previous morphine dose.^[16,17] The “Edmonton method” uses a 10:1 morphine to methadone dose conversion done over 3 days.^[18] Our stepped titration.

Method is an adaptation of the Edmonton method, and it takes into account that morphine to methadone conversion is not a linear process.^[19] This method has been quoted in various literature.^[8,20] The expert consensus white paper published in 2019 describes safe and appropriate use of methadone in palliative care setting.^[21] The method of conversion in opioid tolerant patients suggested in this paper, although based on expert consensus and published literature is yet to be verified by a large sample randomized clinical trial.

There are various advantages of methadone use in the treatment of cancer pain [Figure 1]. Despite all these advantages, few barriers were recognized during the period of methadone introduction in our palliative care unit [Figure 2].

We believe that clinical inertia is a major reason why methadone is not as popular as morphine. Despite its introduction as an economically commercial available drug since 2014 the pain physicians are unwilling to embrace, it due to its need for cautious use. The necessity for baseline ECG further makes its use cumbersome. A similar initial growth curve was seen with morphine, but its ease of use has made morphine a very popular opioid without much effort.

The main finding of our study is that, dealing with all barriers under normal clinical conditions, and taking into consideration, a new opioid with different pharmacodynamics and pharmacokinetics, rotation to oral methadone in a palliative care unit appears to be safe and efficacious during at-least

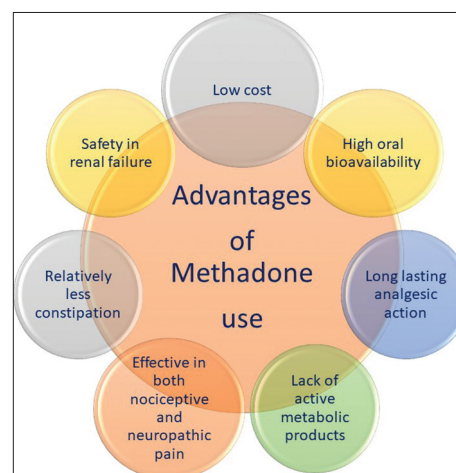


Figure 1: Advantages of methadone use in cancer pain management

2 months after opioid switch. Moreover, its use is yet to gain the general acceptance as can be seen by its limited utilization in a tertiary care hospital of India. The suitability of its use in the rest of the country is even more challenging.

Our study describes the initial experience of methadone use in Indian scenario, given that most studies of methadone rotation published to date have no data from India. In this retrospective study, it is worth noting that the findings we report are generally in agreement with the results published for methadone use earlier.^[22,23]

CONCLUSION

Methadone prescription is still in process of finding its place in India for cancer pain management. As the drug is new to Indian

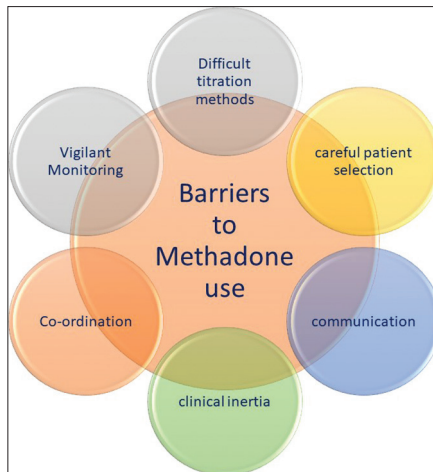


Figure 2: Barriers to methadone use in cancer pain management

practitioners, we must understand all common barriers in its use and must be very vigilant in prescribing methadone. All pain physicians should be educated about this wonder analgesic and to integrate the workshops on safe use of methadone with that of palliative care sessions.

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Conflicts of interest

There are no conflicts of interest.

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