Special Editorial

Methadone is Now Available in India: Is the Long Battle Over?

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Abstract

Context: Morphine and fentanyl had so far been the only available opioids in India in step three of the World Health Organization analgesic ladder. Especially for those not tolerating morphine and particularly for those developing neurotoxicity, an inexpensive alternative was essential. Many years of advocacy by palliative care activists have resulted in methadone being now available for sale in India for pain management. However, the characteristic pharmacokinetics and pharmacodynamics of methadone raise potential issues of safety. **Aims:** This study aimed to recommend the essential steps for ensuring availability of methadone for improved pain relief in India, while at the same time ensuring safe use. **Conclusions:** Two steps are suggested. Firstly, the palliative care community in India must launch an educational program on methadone freely available to all potential prescribers of this medicine. Secondly, we must advocate with drug controllers of states and union territories for making methadone available only through recognized medical institutions and for ensuring that indiscriminate sale through pharmacies is avoided.

Keywords: Access to essential medicines, India, methadone, opioid access, World Health Organization analgesic ladder

Introduction

There is an ethical question that what conflict could the introduction of any new medicine bring up between beneficence and non-maleficence. By introducing new medicine, how much of benefit are our patients are likely to get? How much harm are we likely to do? That some harm could happen is almost inevitable. Medical science accepts it as the "double effect"– that if the benefits vastly outweigh the harmful effects, we accept it.

Palliative care activists in India have grappled with this question for more than 20 years. The draconian Narcotic Drugs and Psychotropic Substances (NDPS) Act of 1985[1] had unfortunately reduced the consumption of medical morphine in the country from 716 kg in 1985 to a mere 18 kg by 1997.[2] The 716 kg itself was of course a minuscule what was needed for a country with one-sixth of the world's population. It is estimated that, if everyone who needed opioid medicines for pain relief got it, India would need about 36,500 kg of morphine every year.[3] The reduction from 716 kg to 18 kg, as can be expected, was associated with a significant worsening of the pain burden.

In addition, there was an unmeasured risk that came up with the use of more harmful alternatives. Medical practitioners who generally tend to go by evidence-based medicine in most medical matters, blindly adopted pentazocine as an alternative, not only for pain relief, but even for people with acute myocardial infarction in coronary care units. Pentazocine, in addition to being too short acting and having a significant incidence of dysphoria, increases heart rate and blood pressure significantly.[4] The direct consequence of this on people with myocardial infarction would be immediate worsening of ischemia, proportionate to the increase in heart rate and blood pressure. Of course, this was never documented and we have no evidence, but we know it for a fact that many deaths occurred from this indirect consequence of the NDPS Act.

Following advocacy by palliative care activists, and following a Delhi High Court decision in response to a public interest litigation filed by Ghooi and Ghooi,[5] the Central Government asked all state governments to amend their NDPS rules following a model was given. Continued advocacy by palliative care activists resulted in amendment of the rules in several states and implementation of the amendment by a few.

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Except for those palliative care physicians who were trained in a Western country, most others in India learned to use opioids, particularly with its oral administration, over the subsequent years.

Their experience also brought to light the inadequacy of morphine as an opioid in a large number of patients. Indeed, available literature tells us that only about three-fourths of cancer pains respond well to the use of simple application of the World Health Organization's three-step analgesic ladder,[6] with emphasis on the use of oral morphine. The other one-fourth do not get satisfactory relief.[7,8]

One of the reasons for the inefficacy could simply be the nature of pain. Some pains, like some colics or some headaches, could even be worsened by morphine. Many others, particularly with neuropathic pain, would have inadequate relief. Typically, there could be some relief with the initiation of morphine, but as the dose increases, patients get neurotoxicity in the form of unpleasant dreams or myoclonus and often delirium, especially in patients with renal impairment and in the elderly. The reason for such poor sensitivity to opioids in some pains is partially explained by the pharmacokinetics of morphine. Morphine is metabolized to several metabolites including morphine-6-glucuronide (M6G), which is believed to be pharmacologically active and to contribute to pain relief, M3G, and others including normorphine.

It is suspected that at least one of these metabolites is a contributor to neurotoxicity.[9] The natural question that arises is, if we switch over to an opioid that does not produce those metabolites, can such neurotoxicity be avoided?

It was indeed shown that switching from morphine to another opioid could well control some pains which morphine did not. Hence, such "opioid-switch"– switching over from one opioid to another – has now become a standard practice in many patients with pain who poorly responded to morphine.

The problem peculiar to India was that the few institutions that have access to morphine typically do not have a viable alternative. It is true that fentanyl in various formulations has been available, but because of its poor performance in titration of the dose and because of the cost, it was an impractical alternative for many patients. In fact, not infrequently, it added more financial burden and suffering to patients because they had to sell their possessions or borrow money from loan sharks to buy the medicine only to find that the resources later dry up and the person who got the benefit of pain relief was plunged back in a sea of pain.

It is in this background that palliative care activists in India sought an inexpensive opioid that could be used for switching from morphine. We learned to our surprise that, indeed methadone was being manufactured in India for export to other countries, it had just not been approved for sale in India. We debated whether we should try to get it approved for pain management in the country. How ready were we? We wondered whether methadone with its pharmacokinetic and pharmacodynamic differences from morphine could endanger patients if it were widely available. Nevertheless, we hoped that we could get it approved for sale and advocate, to limit its use by those tertiary or secondary care institutions which could take the trouble to study the medicine in depth. Of course, over time, more doctors could become familiar with it and it could become more freely available.

Doctors dealing with addiction medicine were more efficient than palliative care activists in their advocacy for methadone. They eventually got it approved for opioid agonist therapy in patients with dependence. Our efforts to get it approved for pain management made slow progress, and finally in 2016, we heard that the approval did come through and methadone was approved for sale for pain management in India.

We understand that the formulation of methadone available in India is a mixture of R and S racemic 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. Thus, it could be significantly effective both in nociceptive and neuropathic pain and could be effective to treat central sensitization, reduce tolerance, and act as an opioid-induced hyperalgesia. A huge number of patients in India who denied pain relief could benefit.

However, a few challenges await us. We know that sometimes opioids such as morphine and transdermal fentanyl are used inappropriately by doctors who have had no learning or experience with such opioids, but wish to relieve the pain and use inappropriate dose to the detriment of the patient. If such use of methadone occurred without adequate empowerment, and if doctors prescribed methadone just as they used morphine, the danger of accumulation is frightening. In view of its pharmacokinetic and pharmacodynamic features and particularly in view of the "methadone deaths" that we hear about from the West, it is essential that we develop a system to ensure the use of methadone is effective and safe.

Therefore, the potential solution appears to be twofold:

1. We need to promote pain education with emphasis use of opioids in general, so that doctors have easy access to such instruction and use opioids safely.
2. We also need to work with state drug controllers and educate them about the positives and negative aspects of methadone and advocate for limiting its use to "Recognized Medical Institutions" including safe storage and dispensing, specially in the early stage.

If we achieve both, we could gain a significant reduction in the burden of health-related suffering in our country. If we fail, we would be contributing to a serious danger. Therefore, we cannot afford to fail. We have no choice but to work hard at both the above courses of action.

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Conflicts of interest

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