Treatment of Refractory Cancer Pain with Methadone

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ABSTRACT

One-third of cancer patients currently experience cancer-related pain, significantly affecting their quality of life. Since the introduction of the World Health Organization (WHO)'s analgesic ladder, pain management has become increasingly standardised, facilitating more effective treatment strategies. Methadone, classified as a step 3 opioid analgesic on the WHO ladder, is primarily utilised for managing refractory cancer pain. This article explored the advantages and disadvantages of methadone in the context of refractory cancer pain, focusing on its metabolism and pharmacokinetic properties. In conclusion, methadone demonstrates significant advantages in pain relief for cancer patients. With ongoing research into its metabolic mechanisms and dosing strategies, methadone has the potential to become a safer and more widely used opioid in the treatment of refractory cancer pain in the future.

Key Words: *Methadone, Refractory cancer pain, Metabolism.*

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Refractory cancer pain (RCP), which does not respond to standard opioids and/or combination analgesic therapies, affects approximately 10-20% of patients, particularly those with an advanced stage of cancer. In such cases, high-dose opioid therapy often proves ineffective, and patients may experience adverse reactions associated with high opioid doses. Methadone is commonly used in the treatment of RCP, yielding benefits in both analgesia and the reduction of adverse reactions.

Methadone, possessing a diphenylheptane structure, structurally differs from other opioid agonists, which mostly have a phenyl-piperidine structure. Methadone has a chiral centre and therefore two enantiomers: R (-)-methadone ((R)-MTD) and S (+)-methadone ((S)-MTD). Both mono-prescription tablets exhibit unique pharmacokinetic properties and well-defined pharmacological effects. (R)-MTD is a potent mu-opioid receptor (MOR) agonist that binds tightly to mu-opioid receptors in the body and mimics a variety of opioids naturally produced by the body, including endogenous opioid peptides such as endorphins and enkephalins.

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The therapeutic effect of (R)-MTD binding to MOR is facilitated through the modulation and release of additional neurotransmitters, including substance P, dopamine, noradrenaline, and acetylcholine. The effects of this interaction can reduce and eliminate medicine cravings, induce anaesthesia, analgesia, and sedation, while alleviating nausea, antitussive properties, vomiting, constipation, hypotension, mild bradycardia, and withdrawal symptoms and signs associated with tolerance and dependency.[1]

Methadone hydrochloride available in market is a racemic mixture of two stereoisomers: (R)-MTD and its enantiomer, (S)-MTD. These two stereoisomers exhibit different pharmacological profiles. The (R)-MTD exerts most of the opioid effects of the racemate, because its binding affinity and analgesic potency are 30 to 50 times higher than those of (S)-MTD.[2] In addition to functioning primarily as an opioid receptor agonist, methadone demonstrates a certain degree of attraction to κ- and δ-opioid receptors as well.[3] Methadone has demonstrated incomplete cross-tolerance with other μ-opioid receptor agonist analgesics, making it an essential treatment option for patients with RCP. Furthermore, it blocks non-aminergic reuptake in the periaqueductal grey region of the brain and inhibits presynaptic N-Methyl-D-aspartate (NMDA) receptors.[4] By antagonising NMDA receptors in the central nervous system, methadone alleviates pain and promotes recovery, while also regulating the propagation of painful stimuli, thereby reducing hyperalgesia and the progression of opioid tolerance.[5] Neuropathic pain states may parallel the development of morphine tolerance through similar activation of NMDA receptors and associated intracellular events, suggesting that methadone may be particularly effective for treating neuropathic pain. By antagonising NMDA receptors in the central nervous system,

the specific action of (S)-MTD on MOR-Gal counteracts the rewarding and dopamine- releasing effects of the (R)-MTD isomer.[2] Research indicates that methadone should be prioritised as a first-line opioid option for the management of cancer-related neuropathic pain (CRNP) in scenarios where conventional non-opioid therapies or other opioids demonstrate inadequate efficacy or tolerability.[6] Moreover, methadone's endocytosis further mitigates the development of tolerance, positioning it as a more suitable option for chronic pain management compared to other opioids. Its lower activation of the dopaminergic system results in a reduced potential for addiction.[7,8] For patients with RCP who require high-dose opioid analgesia, methadone emerges as an excellent choice.

On the other hand, the human ether-a-go-go-related gene (*hERG*), also known as *KCNH2*, encodes specific potassium channels in heart tissue. These potassium channels are commonly referred to as hERG channels in scientific literature (also known as Kv11.1 channels). Methadone induces cardiotoxicity by blocking voltage-gated potassium channels encoded by hERG, which prolongs the QT interval on the electrocardiogram and increases the risk of ventricular tachycardia.[9] A systematic analysis suggests that repeated use of methadone seems to result in methadone accumulation, ultimately increasing sensitivity to QTc prolongation. In addition, studies have shown a clear, dose-dependent, and consistent correlation between methadone and hERG channel inhibition as well as QTc interval prolongation.[10] Furthermore, the analgesic and respiratory depressive effects of opioid medicines are both mediated through the activation of MOR, which are ubiquitous throughout the body, including in the central nervous system and the peripheral nervous system.[11] Methadone buildup can lead to sedation, respiratory depression, and even death. Importantly, the peak respiratory depressive effect of methadone typically occurs later and lasts longer than its peak analgesic effect, especially during the early stages of treatment.

Methadone is mostly metabolised in the liver, predominantly through N-demethylation into the pharmacologically inactive 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine (EDDP), followed by conversion to 2-ethyl-5-methyl-3 and 3-diphenylpyrroline (EMDP).[12] Recent studies have identified cytochrome P450 (CYP) enzymes as critical players in this metabolic process, with CYP2B6 emerging as the primary catalyst for clinical methadone metabolism, clearance, stereoselective distribution, and medicine interactions — superseding the previously believed role of CYP3A4. The polymorphism of CYP2B6 significantly alters methadone metabolism and clearance rates, thereby impacting plasma concentrations. Individuals carrying the CYP2B6*6 allele tend to have higher methadone plasma concentrations, whereas those with the CYP2B6*4 allele exhibit lower levels. This genetic variability partly explains the differences observed in individual responses to methadone treatment.[13] This highlights the importance of considering individual genetic variations when prescribing methadone, as homozygous carriers of CYP2B6*6 may require special attention and dose adjustments to ensure the safety and effectiveness of the medication.[14]

Furthermore, medicines such as ketamine, isoflurane, citalopram, and various psychotropic medications serve as substrates for CYP2B6 and may impact methadone metabolism. Interactions between methadone and these drugs can lead to increased plasma levels, thereby elevating the risk of potential adverse effects, including respiratory depression and QT interval prolongation.[14]

Methadone and its metabolites are primarily excreted *via* the kidneys. Importantly, methadone does not accumulate in cases of renal failure, making it a viable analgesic option for patients with renal insufficiency.[15]

(S)-MTD, as a novel N-Methyl-D-aspartate receptor (NMDAR) channel blocker, is currently making significant strides in the treatment of depression. Clinical trials have shown that (S)-MTD may have rapid and sustained antidepressant effects in patients with an inadequate response to antidepressant therapy.[16] Given that depressive symptoms often occur in patients with cancer pain, the antidepressant effect of methadone is undoubtedly an added bonus.

Methadone is currently a commonly used medicine for RCP. The prolonged half-life of methadone can cause elevated therapeutic levels in certain individuals, potentially resulting in severe, detrimental, and even fatal side effects. Elevated methadone levels can cause respiratory depression and severe arrhythmias. However, individual variation in pharmacokinetics, combined with methadone prolonged half-life, can lead to accumulation and side effects such as QT interval prolongation. With proper monitoring of baseline electrocardiograms and careful management of potential medicine interactions, methadone can be used safely in clinical settings.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

XZ: Conceptualisation and writing of the original draft.
QW: Formal analysis, validation, writing, review, and editing.
WZ: Writing, review, editing, and funding acquisition.
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