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REVIEW ARTICLE

Mellar P. Davis
Declan Walsh

Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration

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M.P. Davis (✉) · D. Walsh
Harry R. Horvitz Center for Palliative Medicine, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA
E-mail: davism6@ccf.org
Phone: +1-216-4454622
Fax: +1-216-4449464

Abstract Methadone, a synthetic opioid, has unique pharmacodynamics and pharmacokinetics, which contribute to its unique ability to relieve pain unresponsive to other potent opiates and its unique dosing and drug interactions. Several guidelines of administration have been established. Physicians who are involved in pain management should have a fundamental understanding of methadone's unique properties.

Keywords Methadone · *N*-methyl-*d*-asparate receptor · Morphine · Pharmacokinetics · Pharmacodynamics

Introduction

Pain is a common experience in patients with advanced cancer. Approximately 80% of cancer patients experience moderate to severe pain in the advanced stages of their illness [1]. The World Health Organization (WHO) has recommended a step-by-step approach to the management of chronic pain, based upon the intensity of pain [2]. Strong opioids are considered the agents of choice for moderate to severe pain. Opioids have no ceiling effect, and the doses required vary considerably among patients [2]. A subset of 20% of patients will have pain that is poorly responsive to morphine, and these will account for 70% of the total prescribed opiate doses. A second subset of patients will develop dose-limiting toxicities as morphine doses are escalated. The dose-limiting toxicities include the neuropsychiatric manifestations of myoclonus, hallucinations, delirium, and sedation and gastrointestinal side effects, such as intractable nausea with vomiting or gastroparesis [2]. An alternative Mu agonist is required in these circumstances. Methadone is an attractive alternative opioid as a second-line analgesic. Not only is it the least expensive of the highly potent Mu agonists, but it is well absorbed orally and rectally [3, 4]. Methadone is both a long- and a short-acting analgesic and controls pain when it is unresponsive to other Mu agonists, such as fentanyl, hydromorphone and oxycodone [5, 6, 7]. Methadone, unlike morphine, lacks neuroactive metabolites, which accumulate in renal failure [3, 8, 9, 10]. Methadone has two nonopiate analgesic receptor activities: the prevention of monoamine reuptake in the periaqueductal gray and presynaptic inhibition of *N*-methyl-*d*-asparate (NMDA) receptors [11, 12, 13, 14]. The drawbacks to the use of methadone include its association with addiction therapy and its unique pharmacokinetics.

Pharmacodynamics of methadone

Methadone is a unique analgesic with a broad spectrum of receptor affinities. The Mu opioid receptor is traditionally viewed as the main mediator of analgesia and responsible for some of the opioid side effects. The central hyperalgesia and neurotoxicity appear to be

related to morphine metabolites such as morphine-3-glucoronide or normorphine [15]. Nociceptive transmission in chronic pain is associated with the loss of Mu receptors in presynaptic c-fiber terminals and generation of depolarization via cholecystokinin-B receptors and NMDA receptors [16]. Such imbalance of receptors produces a central state of hypersensitivity, reduces opioid analgesia and promotes morphine tolerance [16]. A combination of an Mu agonist and an NMDA antagonist produces an additive analgesic response while limiting opioid tolerance [17]. Delta and kappa opiate receptor activation also produces analgesia [18, 19]. Finally, the downward modulation of pain transpires via the descending tracts of the periaquaductal gray (PAG) and is mediated by the monoamines, serotonin and norephinephrine [20]. The prevention of reuptake in the PAG, classically associated with tricyclic antidepressants, improves pain control, particularly in the case of neuropathic pain. Morphine, unlike methadone, has little antagonism for NMDA receptors and does not inhibit re-uptake of monoamines. Methadone has similar potency to morphine for Mu receptors. However its efficacy with chronic dosing is greater [21, 22, 23, 24, 25]. Methadone's affinity for the delta receptor is greater than morphine's [18, 19]. Methadone binds to the NMDA receptor to the same degree as does ketamine [11, 14, 26, 27]. The *R*-isomer of methadone has opioid receptor affinity, and the *S*- and *R*-isomers have comparable NMDA receptor antagonism. The *S*-isomer of methadone is a potent inhibitor of 5-hydroxytryptamine and norephinephrine uptake [28]. Methadone's re-uptake of monoamine inhibitor activity does not correlate with its Mu receptor affinities. The superiority of methadone over morphine in terms of efficacy can be understood as a product of Mu receptor agonist, 5-hydroxytryptamine and norephinephrine re-uptake blockade and NMDA receptor antagonism. The delta receptor agonist activity of methadone leads to desensitization of this receptor and may also account for the reduction of opioid tolerance associated with methadone [19, 20].

Pharmacokinetics and routes of administration

Methadone is a synthetic opioid whose structure is quite different from that of morphine. It is available as a hydrochloride powder and can be administered by mouth, per rectum and parenterally [3, 4, 6, 19, 29, 30]. Methadone is entirely absorbed by the gastrointestinal tract. However there is some metabolism of methadone in the gut wall [8, 9]. Methadone is partially metabolized in the intestinal wall by CYP3A4 [31, 32, 33]. The oral bioavailability is 80%, with a range of 41–99%, which is three-fold the bioavailability of oral morphine. The oral bioavailable co-efficient of variation is 15%, as against 50% for oral morphine. Methadone binds to alpha 1-acid glycoprotein in plasma [8, 9, 10, 34]. Only 11% of methadone remains unbound [35]. Methadone is *N*-demethylated by liver microsomes [36]. Methadone has a rapid and extensive initial distribution phase, which occurs within 2–3 h, and a prolonged elimination phase lasting for 15–60 h [8, 9, 10, 37, 38, 39].

Unlike morphine, which is glucuronidated, methadone is metabolized by the type I cytochrome P450 group of enzymes. The cytochrome P450 group consists of 12 families with >40% identical gene content and 30 active subfamilies with >55% identical gene content. The designation of each includes the prefix CYP with a number (i.e. 1, 2, 3 etc) indicating the enzyme family; a capital letter designates its subfamily, and a number represents the individual enzyme [40]. The CYP1, CYP2, CYP3 enzyme family is responsible for many drug biotransformations and most of the P450 content of the liver [40]. The main enzyme mediating *N*-demethylation of methadone is CYP3A4, with lesser involvement of CYP1A2 and CYP2D6. Most of methadone's drug interactions are related to inducers or inhibitors of CYP3A4 [40, 41]. The clearance of methadone is increased by chronic dosing due to auto-induction of CYP3A4 [40, 41, 42, 43]. The acute primary half-life is 14.3 h and the acute secondary half-life is 54.8 h, which with chronic dosing produces a single exponential half-life of 22.2 h due to auto-induction of metabolism [8, 9, 10]. CYP2D6 preferentially metabolizes (*R*)-methadone CYP1A2 and CYP3A4 metabolize both enantiamers. CYP3A4 expression varies up to 30-fold [28]. CYP1A2 and CYP3A4 can be induced or inhibited by several different medications. A genetic polymorphism exists for CYP2D6 [28, 40]. The polymorphism of CYP2D6 ranges from poor to very rapid metabolism, and, combined, the inter-individual variability of activity of CYP1A2 and CYP3A4 accounts for the large inter-individual variations in methadone pharmacology [28, 40].

Urinary and fecal excretion of methadone and *N*-demethylated metabolites increase from 22.2% in acute to 62% in chronic phase dosing [21]. The urinary metabolite-to-methadone ratio triples with chronic dosing. Sixty percent of methadone is eliminated by nonrenal routes. Renal excretion is pH dependent. Low urinary pH levels increase renal clearance three-fold and decrease the major metabolite-to-methadone ratio [44]. However, methadone does not accumulate in renal failure [44]. Methadone is poorly removed by hemodialysis [45]. Methadone concentrations in gastric juice are 25- to 200-fold that measured simultaneously in the blood. As much as 2% of the administered dose can be recovered in gastric juice in an 8-h period. With chronic use salivary concentrations may be ten-fold those measured simultaneously in the blood [46].

Methadone does appear in breast milk, with a mean ratio of milk to plasma level of 0.44. The infant's exposure based upon the average milk intake would be 2.79% of maternal doses [47]. Methadone's metabolism is altered during pregnancy [48, 49]. Pregnant patients have a statistically greater elimination constant and a reduced half-life of methadone. The apparent increased clearance is also associated with reduced oral bioavailability. Methadone does cross the placenta, and most neonates born to mothers on methadone maintenance will suffer from withdrawal if untreated.

Routes of administration other than oral routes

Rectal administration of methadone can produce rapid relief of pain owing to rapid absorption, which is usually complete within 30 min [4, 29, 30]. The pharmacokinetics is similar to that after oral dosing, demonstrating a rapid and extensive distribution phase and a slow elimination phase. The dose ratio for the rectal to the oral route is 1:1, whereas for intravenous or subcutaneous administration the dose is half of the oral dose [6, 39, 50, 51]. Intravenous methadone produces a 23% higher concentration-to-dose ratio than oral dosing owing to the shunting of metabolism from the gut wall via CYP3A4 and avoidance in liver first-pass effects. Subcutaneous methadone was initially associated with an adverse subcutaneous reaction, but toxicity is uniformly manageable by frequent site rotation and the use of either dexamethasone or hyaluronidase and by diluting the methadone to lower concentrations in solution [39, 50, 51, 52].

Epidural methadone has been used postoperatively for patient-controlled analgesia [53, 54]. The mean quantities of methadone required to produce analgesia were 10.3 mg for the first 12 h postoperatively, 6 mg for the second 12 h, and 7.7 mg for the second day. Plasma concentrations gradually accumulate owing to rapid vascular uptake. The systemic activity contributes to analgesia. Continuous epidural methadone has been used for cancer pain, with an initial dosage of 4 mg of 0.1% solution of methadone three times a day, gradually increasing to 8 mg four times a day [53, 54]. Good pain control was obtained in 80% of patients. No comparison between parenteral, oral and epidural route was available. There is very little advantage to the epidural route of administration owing to rapid absorption and accumulation of serum levels.

Methadone interactions

Most drug interactions with methadone involve inducers or inhibitors of the cytochrome P450 system, as previously mentioned [42, 43]. Methadone is extensively metabolized by three enzymes (i.e., CYP1A2, CYP3A4, and CYP2D6), and genetic polymorphism exists for CYP2D6, with both CYP1A2 and CYP3A4 activity inducible by various agents [28]. For instance, CYP1A2 can be induced by cigarette smoke and CYP3A4 is inhibited by rifampicin [28, 55]. Hence, the metabolism of methadone is genetically and environmentally determined and can be greatly influenced by medications whose effect is related to cytochrome enzyme activity.

Tricyclic antidepressants

Tricyclic antidepressants are metabolized by several cytochrome enzymes [56]. However; CYP2D6 is the principal cytochrome isoenzyme. Competitive inhibition of CYP2D6 stems from co-administration of desipramine and methadone. Desipramine plasma levels increase when administered with methadone [42, 43, 57].

Antiviral agents

The antiretroviral agent zidovudine interacts with methadone. Zidovudine's metabolism is inhibited and clearance is delayed. The area under the curve (AUC) of plasma concentrations of zidovudine is increased by oral methadone 43%. Zidovudine (AZT) is metabolized predominantly by a type II reaction producing an AZT-glucoronide. Acute oral methadone treatment increases the AUC of oral AZT by 41–43% and that of intravenous AZT by 19%. Initial methadone dosing reduces the clearance of oral AZT by 21% and that of intravenous AZT by 19%. With chronic methadone dosing there is an increase of 29% in the AUC for oral AZT and of 41% in the AUC for intravenous AZT, and an overall decrease in clearance by 26% in clearance for AZT given by either the oral or the intravenous route. When compared with administration without methadone [57], these effects are a result of reduced production of AZT-glucoronide and reduced renal clearance of AZT [57]. When AZT is combined with oral methadone, AZT doses may have to be reduced. On the other hand the non-nucleoside analogue nevirapine induces CYP3A4 and, when co-administered with methadone, leads to reduced plasma levels and reduced analgesia [58, 59]. Ritonavir induces CYP3A4 and decreases methadone plasma levels, precipitating a withdrawal syndrome [60].

Serotonin-selective re-uptake inhibitors

The serotonin-selective re-uptake inhibitors (SSRI) influence the activity of several cytochrome enzymes

[61, 62, 63]. The CYP1A2 activity is inhibited in declining order of potency by: fluvoxamine, paroxetine, sertraline, fluoxetine, norfluoxetine and nafozadone. Venlafoxine has very little inhibitory activity. Paroxetine and fluoxetine are potent inhibitors of CYP2D6, and fluvoxamine has less inhibitory activity. Finally, nefazodone, fluvoxamine, norfluoxetine, paroxetine, desmethyl sertraline, fluoxetine and sertraline are inhibitors of CYP3A4, listed in declining order of potency. Venlafoxine does not appear to inhibit CYP3A4. Both fluvoxamine and fluoxetine have increased serum methadone levels when co-administered with methadone. SSRI agents co-administered will boost methadone serum levels in rapid metabolizers (i.e. CYP2D6) and have produced toxicity and respiratory arrest when added to a methadone maintenance program [61, 62]. Venlafaxine has least potential for drug interaction.

Antifungal medications

Ketoconazole and fluconazole are potent inhibitors of CYP3A4. The administration of fluconazole 200 mg per day increases the AUC of methadone by 35% and the mean peak and serum levels by 27% and 48%, respectively. Overall, methadone clearance is reduced by 28% when fluconazole is co-administered [64]. It seems likely that ketoconazole, a more potent inhibitor CYP3A4, would also interact with methadone.

Classic antiseizure medications

The classic antiseizure medications carbamazepine, phenobarbitol and phenytoin are inducers of CYP3A4. Phenytoin lowers blood levels of methadone by 50% after 3–4 days of co-administration. Phenobarbitol and carbamazepine increase methadone metabolism, precipitating withdrawal symptoms [42, 43]. Valproic acid and gabapentin do not interact pharmcokinetically with methadone [42, 43].

Carbamazepine is metabolized by CYP3A4. Carbamazepine induces its own metabolism in a time-dependent fashion. Owing to auto-induction of metabolism via CYP3A4, the half-life of carbamazepine decreases with time. Methadone's metabolism is accelerated when it is co-administered with carbamazepine as a result of the induction of CYP3A4 by carbamazepine and auto-induction of CYP3A4 by methadone [42, 43].

Neuroleptics

Resperidone is a new anti-psychotic with a high affinity for the serotonin, $5HT_{2A}$, receptor and the dopamine (D_2, D_3, D_4) and adrenergic (alpha-1 and alpha-2) receptors. Resperidone is extensively metabolized by the liver via the type I reactions. Co-administration of resperidone and methadone can precipitate an opiate withdrawal reaction [65].

Alcohol and cigarettes

Chronic alcohol ingestion increases methadone metabolism and reduces serum levels, while acute alcohol increases the AUC and may accentuate methadone toxicity [66]. Cigarette smoking induces CYP1A2 and reduces methadone levels [28].

Antituberculosis agents

Rifampicin is commonly used to treat tuberculosis, which occurs frequently in the AIDS population. Rifampicin induces cytochrome CYP3A4. Initiation of rifampicin therapy during maintenance methadone therapy can precipitate an opioid withdrawal reaction [55, 67].

Antibiotics

Fusidic acid is an active antibacterial agent used to treat gram-positive infections [68]. Chronic dosing activates the cytochrome enzyme system and accelerates antipyrine metabolism [69]. Patients receiving stable doses of methadone who are subsequently treated with fusidic acid will have signs of methadone underdosage.

Benzodiazepines

Benzodiazepines and methadone have additive toxicity and their co-administration accentuates the respiratory depression and sedation associated with both agents [42, 70]. Three cases of fatal drug overdose have been reported as a result of co-administration of methadone and alprazolam. The postmortem blood concentrations of methadone were in the lower ranges or below the concentrations previously identified with methadone overdose fatalities [69].

Delta-9-tetrahydrocannabional

Interesting experimental information is available indicating synergistic antinociceptive effects when various Mu opioids are combined with low doses of delta-9-tetrahydrocannabional. In the tail-flick test rodent pain model the analgesia of methadone is enhanced four-

fold and that of its derivative 1-alpha-acetyl-methadol three-fold when they are combined with small doses of delta-9-tetrahydrocannabinol. This combination has not been tested in cancer patients [71].

Nonsteroidal anti-inflammatory medications

The combination of ibuprofen and methadone has been used for chronic pain. Administration of both agents together increases analgesia without increasing side effects [72]. Also, when regular doses of diclofenac have been added to patient-controlled analgesia with methadone a relevant opioid-sparing effect has been observed [73].

Helpful hints on combining methadone with other medications

Polypharmacy is common in advanced cancer patients, increasing the risk of drug interactions. Opioids are frequently combined with co-analgesics for the purpose of either accentuating analgesia or reducing side effects. Methadone is no exception (Table 1). When methadone is combined with other agents for the purpose of treating neuropathic pain, either valproic acid or gabepentin should be used rather than the classic antiseizure medication. Tricyclic antidepressants can be used with caution, but levels need to be monitored because of delayed clearance of tricyclic antidepressants. If antidepressants of the SSRI class are also used: venlafoxine has the fewest potential drug interactions. Methylphenidate would be a good alternative. Patients with AIDS frequently have tuberculosis and are taking several antiviral agents. Rifampicin, ritonavir and nevirapine precipitate methadone withdrawal symptoms, and higher doses of methadone may be necessary. Zidovudine doses need to be adjusted downward and monitored. Fluconazole will increase methadone plasma levels, and care must be taken when both are administered together. Finally, frequent use of benzodiazepines to calm anxiety or induce sleep should be avoided because of their potential effects of respiratory depression and sedation.

Table 1 Interactions of methadone with other drugs

Medications whose serum levels are increased by methadone	Desipramine Zidovudine
Medications associated with reduced methadone clearance	Acute ethanol ingestion Fluconazole Fluoxetine Fluvoxamine Ketoconazole
Medications associated with increased methadone clearance	Carbamazepine Chronic alcohol ingestion Fusidic acid Nevirapine Phenobarbital Phenytoin Resperidone Rifampicin Ritnavir
Medication associated with synergistic toxicity	Benzodiazepines
Medication associated with synergistic analgesia	Dronabinol Ibuprofen

Side effects of methadone

Several common side effects are associated with methadone and occur with other Mu agonists. Nausea, vomiting, dizziness, clouding of consciousness and pruritus may be anticipated. These occur in a minority of patients. Methadone is less constipating and fewer laxatives are required to prevent constipation [74]. Hallucinations are rarely associated with methadone [75, 76]. A retrospective review identified only 4 patients with methadone-related hallucinations among 3,000 adults admitted to an inpatient substance abuse service. An isolated pediatric patient has also been reported as having hallucinations while receiving methadone [75, 76]. Myoclonus is common with opioid medications; however, methadone has not been included in recent reviews [77]. We have described a patient with mild myoclonus associated with parenteral methadone. Urticarial reactions have been associated with intravenous administration [78].

Methylnaltrexone, a quaternary opioid receptor antagonist, does not cross the blood–brain barrier or reverse methadone analgesia. Intravenous methylnaltrexone can reverse methadone-induced constipation within 1–2 days and improve the oral–cecal transit time by selectively blocking the Mu receptors in the gastrointestinal tract [78, 79, 80].

Methadone is less sedating than morphine. The highly lipophilic nature of methadone produces less nausea. Methadone accumulates rapidly within the central vomiting center owing to its lipophilic properties, whereas opioids at this level are antiemetic. Symptoms of opioid withdrawal can be seen when patients are rotated from high levels of morphine to methadone, because of methadone's comparatively high potency and efficacy. Less well-known side effects attributable to methadone also include antidiureses and exacerbation of asthma [3]. Approximately 6–16% of patients discontinue methadone due to toxicity [3]. Particular situations for which methadone should be used with caution include pain in the elderly, because of delayed clearances, psychogenic pain, and intolerance of low doses of opioids. Methadone is safe in chronic renal failure and stable liver disease [3]. Contraindications

include allergies to methadone or its preservatives, respiratory depression, severe chronic obstruction lung disease, acute asthma and concurrent administration of monoamine oxidase inhibitors [3].

Maintenance methadone programs have so far involved a significant death rate related to diverted methadone, and frequently to co-ingestion with other, illicit, medications. As in the case of co-administration of benzodiazepines and methadone, fatalities can occur at relatively modest doses [81, 82, 83, 84, 85].

Once a patient is settled with stable doses of methadone driving is not precluded. There is a slight reduction in performance skill during medication with methadone. Individuals should not drive when doses are being adjusted upward [86, 87].

Equi-analgesic dose ratios

Methadone's efficacy increases with chronic dosing compared with that of morphine. This is due in part to its long elimination phase and prolonged half-life and in part to the nonopioid analgesic receptor activity (i.e., the NMDA inhibition and the monoamine reuptake inhibition) as previously described. The dose ratio of methadone to morphine is inversely proportional to the daily morphine dose administered. Older equi-analgesic tables suggested a dose ratio of 1:1 between oral methadone and oral morphine and between the two agents with parenteral dosing. These tables failed to take into account the unique pharmacokinetics and pharmacodynamics of methadone. Other equi-analgesic tables indicated an oral morphine-to-methadone ratio of 4:1, and 2.7:1 for the parenteral route [87, 88]. In a prospective study the median daily oral morphine dose was 145 mg and after rotation to methadone the median equi-analgesic dose of methadone was 21 mg a day. The dose ratio of morphine to methadone was 2.5:1 at lower doses of morphine and 14.3:1 at daily morphine doses of >300 mg. The median dose ratio of morphine to methadone is 7.75:1. The average number of doses needed per day to maintain analgesia is 2.4, which means a dosing interval of 8–12 h, as is usual for maintenance of analgesia [88, 89]. Methadone should be administered more frequently in the first 48 h in order to establish analgesia. Forty-eight hours will be required to establish steady state blood levels.

The subcutaneous hydromorphone-to-oral methadone ratio proposed is 1:6–1:10. However, clinical experience with methadone demonstrates that a lower dose of methadone is needed than expected on the basis of equi-analgesic tables. A retrospective experience of rotation from subcutaneous hydromorphone to oral methadone suggests that equi-analgesic doses are near unity. A rotation over 3 days with overlap established steady state analgesia in 3–6 days. The ratio of subcutaneous hydromorphone to oral or rectal methadone is 1.14:1 [90, 91]. The subcutaneous hydromorphone-to-oral methadone ratio was 2.2:1, and an equi-analgesic ratio of 1.2:1 was found for subcutaneous hydromorphone to rectal methadone [90, 91]. This is due to reduced first-pass hepatic clearance of methadone when it is given per rectum. The parenteral hydromorphone-to-methadone ratio for both oral and rectal methadone combined is 1.6:1 for hydromorphone doses greater than 330 mg per day s.c. and 0.95:1 at hydromorphone doses of less than 330 mg per day [90, 91].

Several protocols of methadone administration have been published. Protocols of methadone dosing involve either self-administration of oral methadone at fixed doses and flexible (as needed) intervals or, alternatively, administration of equi-analgesic doses calculated on the basis of the total daily dose of oral morphine equivalents, divided into thirds and given at fixed 8-h intervals [5, 89].

As with other analgesic studies, the use of visual analogue pain relief scales is not comparable to serial visual pain intensity scales for the purpose of quantifying the analgesia achieved with methadone over time [92].

Pharmacoeconomics

Patients receiving high doses of opioids or parenteral opioids on a long-term basis incur a very large pharmacy cost. This can be particularly detrimental to hospice programs, which are under capitative reimbursement. Analgesic expenditures may exceed the per diem allowance. The cost of methadone is one-tenth the cost of other opioids, and it is particularly attractive as an alternative to sustained-release morphine, fentanyl, parenteral hydromorphone, or sustained-release oxycodone. Methadone can decrease the cost of pain management to less than one-tenth that with these other medications. The total cost of equivalent pain relief in Canadian dollars is $110 per month for oral methadone, $105 per month for rectal methadone and $3,450 for parenteral hydromorphone [29, 30]. Methadone is an ideal agent for use in developing countries, whose budgets for health care are extremely limited.

Methadone for relief of cancer pain

Indications for methadone include moderate to severe cancer pain, nociceptive pain, neuropathic or mixed nociceptive, and failure to respond to morphine or development of toxicity with morphine [3, 93, 94, 95].

Other indications are the need for cost-effective analgesia in patients requiring enormous doses of opioids, requirement for analgesia in patients with renal failure, chronic nonmalignant pain, and pain in patients with a history of drug abuse [3]. Methadone is an excellent agent for the treatment of pain in patients with complete or partial bowel obstruction and can be taken on an "as needed" basis [96]. This is due to its milder gastrointestinal side effects and the lesser risk of precipitating complete bowel obstruction.

Methadone is more than a Mu agonist. The lack of cross tolerance allows for early rotation to methadone when cancer pain fails to respond to morphine and toxicity such as myoclonus, confusion, hallucinations, nausea and vomiting develop. In a study with doses of methadone fixed (at 10 mg) but taken at intervals selected by the patient (i.e. "ad libitum") during the loading phase, 12 of 15 patients obtained excellent analgesia. The mean daily dose was 44 mg during the first day and dropped to 22 mg at the end of the dose-adjustment week. Treatment periods varied from 8 to 270 days, and analgesia was maintained throughout [97].

In another study, patients with cancer pain who had failed to respond to increasing doses of opioids or were experiencing intolerable side effects used methadone doses of 10% of the previous morphine-equivalent dose up to a maximum of 40 mg of methadone as a single dose every 3 h on an "as required" basis for analgesia. When daily requirements were stable, the total methadone dose taken within 24 h was divided into two regular doses. The median morphine equi-analgesic dose per day was 480 mg for 33 patients prior to titration. Pain was neuropathic in 11, nociceptive in 3, and mixed in 19. Stable methadone doses were achieved in 3 days for 29 of 33 patients. The median daily dose of methadone was 80 mg. Twenty-six (78%) had a good response and 4 (12%) were withdrawn, 3 due to a terminal state making it impossible to participate in the trial and 1 because of failure to respond. Methadone dose alterations were necessary in 15 (45%) [7].

A cross-sectional prospective study was carried out in 24 patients who experienced substantial side effects limiting morphine titration [98]. Methadone was initiated at 20% of the daily morphine dose. The total daily methadone dose needed was calculated and this dose divided into three and given 8-hourly. Allowance was made for one additional breakthrough dose. A significant decrease in pain intensity occurred within 24 h. Stable methadone doses were achieved within 3 days. Nineteen of the 24 patients were successfully rotated to methadone, and 5 required alternative treatment. Drowsiness was the main reason for rotation to methadone. Most patients had an improvement in the adverse side effects previously experienced. Drowsiness and confusion improved. Except for dry mouth, gastrointestinal symptoms substantially improved. Equi-analgesic doses were related to the morphine dose at the time of rotation. Patients with a mean morphine dose of 59 mg daily required a mean methadone daily dose of 20 mg by day 3, and patients with a mean morphine dose of >200 mg prior to rotation required a mean daily methadone dose of 45 mg by day 3. The mean maximal methadone dose was 32 mg for the entire group at the time of death, which occurred within a mean of 48 days [98].

Methadone has been used in United Kingdom hospices since the Pain Relief Foundation's recommendation in 1993 [5]. The protocol (Table 2) contains "ad libitum" dosing at 3-h intervals using 10% of the daily oral morphine equivalent. The starting maximum single methadone dose was limited to 30 mg. Of the 146 patients observed, the mean age was 55.8 years and the mean daily dose of morphine or diamorphine was 750 mg. Patients unable to take oral methadone could be converted to subcutaneous methadone by reducing the oral methadone dose in half and diluting the methadone solution and adding hyaluronidase. The utilization of these guidelines produced a consistently good results without toxicity problems and no deaths attributable to methadone. The as needed dosing scheme was key to preventing overdose [5].

The largest single retrospective experience of methadone analgesia for moderate to severe cancer pain is from Milan Italy (Table 3) [89]. One hundred and ninety-six patients were treated at 8-h intervals. Evaluations were made at baseline and 7, 15, 30, 45, 60 and 90 days after initiation of methadone analgesia. A Palliative Index, the Karnosky Performance Status, pain intensity, insomnia, drowsiness, confusion, dry mouth, nausea and vomiting, constipation and dyspnea were evaluated, as well as mean daily dose and reasons for withdrawal from study. The opioid-naïve patients were started on 3 mg every 8 h. Patients receiving <60 mg of morphine were treated with 5 mg of methadone every 8 h. Patients receiving 70–90 mg

Table 2 Guidelines for methadone administration in the United Kingdom [5]

Step 1	Stop morphine (or other opioids)
Step 2	Give fixed doses of methadone at one-tenth of the 24-h oral morphine dose when the 24-h dose is <300 mg (oral)
Step 3	When the 24-h morphine dose is >300 mg (oral) the fixed methadone dose should be 30 mg
Step 4	The fixed dose is taken as needed but not more frequently than every 3 h
Step 5	On day 6, add the total dose of methadone administered in the last 48 h, divide by 4 and give at 12-h intervals
Step 6	If additional doses are needed after day 6 adjust the doses as for sustained-release morphine

Table 3 Guidelines for methadone administration in Milan

Step 1	Stop morphine (or other opioids)
Step 2	Give methadone at fixed intervals: every 8 h
Step 3	If the total morphine or equivalent dose per day is <90 mg (oral) a methadone dose ratio of 1:4 (methadone to morphine) is used. The methadone dose is divided by 3 and delivered every 8 h
Step 4	If the morphine dose per day is between 90 and 300 mg (oral) a dose ratio of 1:8 (methadone to morphine) is used; the total methadone dose is divided by 3 and given at 8-h intervals
Step 5	If the total daily dose of morphine is >300 mg/day (oral) a ratio of 1:12 (methadone to morphine) is used. The total daily methadone dose is divided by 3 and given at 8-h intervals
Step 6	Patients maintained on an 8-h schedule of methadone may have 10% of the daily methadone dose for breakthrough pain

started with a methadone dose of one-quarter of the total daily morphine dose, which was divided into three doses given at 8-h intervals. The methadone-to-morphine dose ratio was 1:6 when the daily morphine dose exceeded 100 mg. The median age was 59 years, and 61.7% of patients were male. The median Karnofsky Performance Status was 60. Nearly one-third of patients had head and neck cancer. The majority of patients were rotated for reasons of poor pain control. Significant analgesia was obtained and had a positive influence on the Palliative Index. Only 11% withdrew due to analgesic inefficacy. Intolerable side effects occurred in 6.6%. Most patients required less than 20 mg per day. No life-threatening toxicity such as respiratory depression, coma or serious side effects such as hallucinations were observed. No deaths occurred as a result of methadone or treatment [89].

Conclusion

Methadone is a unique analgesic, being a Mu receptor agonist, an NMDA receptor antagonist, and a monoamine re-uptake inhibitor. It is characterized by a prolonged elimination phase and auto-induction of its own metabolism. Methadone's pharmacokinetics are unique and differ from those of other opioids. Predictable drug interactions based upon the cytochrome system have been reported. Drug interactions are more numerous than with morphine. The use of methadone as a second-line analgesic in the treatment of pain associated with advanced cancer is compelling. Guidelines for the use of methadone have been published.

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