HOT SPOT

By S. Lawrence Librach MD,CCFP,FCFP, W. Gifford Jones Professor Pain Control & Palliative Care University of Toronto, Director, Cancer Pain Clinic, Toronto Sunnybrook Regional Cancer Centre, Toronto, Ontario

Methadone for cancer pain: An analgesic with a difference

Background

Methadone is a synthetic opioid first synthesized as an analgesic in Germany in the Second World War as an alternative to morphine, which was in short supply. For years in North America, it has been used as a drug for maintenance and withdrawal therapy for opioid addicts. In recent years, there has been a resurgence of interest in its use as an analgesic. Methadone has somewhat unique pharmacodynamic and pharmacokinetic properties that make it a preferred drug in some pains. It also has the advantage of being relatively inexpensive compared to other opioid formulations.

Key aspects of the pharmacology of methadone

- Consists of a racemic mixture of D and L isomers.
- The L-isomer is considerably more potent for analgesia.
- The D-isomer is less of an analgesic, but it does have properties that make it antitussive. This isomer also has an antagonistic effect on the NMDA receptor that has a role to play in neuropathic pain.
- Methadone acts at both mu and delta opiate receptors to produce analgesia.
- Methadone is completely absorbed through the gastrointestinal mucosa, but some partial metabolism occurs within the gut wall making bioavailability about 80%, considerably better than morphine or hydromorphone.
- More highly protein bound than morphine.
- Methadone has no active neurotoxic metabolites, unlike morphine and hydromorphone.
- Methadone is metabolized in the liver, not by glucuronidation, but by the cytochrome P450 group of enzymes which explains some of the interaction seen with methadone and not with other opioids.
- 60% of methadone is eliminated through non-renal routes, mainly the fecal route.
- Urine pH will impact excretion: pH > 6, renal clearance 4% of methadone, pH < 6, renal clearance 30% of methadone.
- Liver or renal disease does not significantly impact the pharmacokinetics of methadone.
- Methadone is very lipophilic.
- It is rapidly distributed in tissues and released slowly from extravascular sites resulting in slow elimination and a prolonged half-life.
- Methadone produces analgesic activity within about an hour after oral administration. Initially, the duration of action is four to six hours much like other potent opioids. However, with chronic dosing, the drug will accumulate and, if administration continues every four to six hours, significant toxicity can occur.
- The half-life of methadone can vary widely from a few hours to more than 100 hours.
- Like other potent opioids, there is wide variability from patient to patient in the pharmacokinetics of methadone.

Routes of administration

- In Canada, only the oral form of methadone is available as available as tablets (1mg, 5mg, 10mg, 25mg), as a solution (10mg/ml), or as a powder that can be reconstituted in liquid form in a variety of concentrations.
- Parenteral methadone can be made from the powder, but subcutaneous administration can be associated with local reactions.
- Rectal administration of methadone can be very effective thanks to the highly lipophilic nature of the drug.

Drug or agents	Interaction effects
Antidepressants	
Tricyclic antidepressants	↑ levels of tricyclics
SSRI drugs	↑ methadone levels
Antivirals	
Zidovudine (AZT)	↑ zidovudine levels
Ritonavir	↓ methadone levels
Antifungals	
Ketoconazole	↑ methadone levels
Fluconazole	↑ methadone levels
Anticonvulsants	
Phenytoin	↓ methadone levels
Carbamazepine	↓ methadone levels
Gabapentin	no effect
Phenobarbital	↓ methadone levels
Antibiotics	
Rifampin	↓ methadone levels
Ciprofloxacin	↑ methadone levels
Clarithromycin	↑ methadone levels
Erythromycin	↑ methadone levels
Isoniazid	↑ methadone levels
Benzodiazepines	Accentuates the respiratory depression and sedation
Neuroleptics	
Risperidone	↓ methadone levels
Cardiac drugs	
Quinidine	↑ methadone levels
Verapamil	↑ methadone levels
Spironolactone	↓ methadone levels
Gastrointestinal agents	
Cimetidine	↑ methadone levels
Somatostatin	↓ methadone levels
Other agents	
Cannabinoids	Accentuates analgesia (animal studies)
Grapefruit juice	↑ methadone levels
Acute alcohol ingestion	↑ methadone levels
Chronic alcohol ingestion	↓ methadone levels
Smoking	↓ methadone levels

HOT SPOT

Methadone for cancer pain: An analgesic with a difference

Supported by an education grant from Pharmascience

Methadone interactions

Because of the involvement of the cytochrome P450 enzyme pathway in metabolizing methadone, drugs and other agents that impact that pathway will therefore affect the metabolism and therefore the pharmacokinetics of methadone.

Side effects of methadone

Methadone has a similar spectrum of side effects to other potent opioids, but there are some differences in prevalence of these side effects. Side effects seem to be less, perhaps related to the highly lipophilic nature of the drug:

- Constipation and nausea seem to be less
- Sedation seems to be less
- Hallucinations are rare
- Myoclonus is less frequent.

One of the rare, but potentially dangerous side effects of methadone is QT interval prolongation and Torsades de Pointes. This usually occurs with high doses of methadone, but drug interactions as described above that increase methadone concentrations may contribute to this.

Obviously, the most dangerous side effect is respiratory depression that was seen much more commonly when the opioid equivalency of single dose methadone was used to calculate chronic dosing.

Dose equivalency of methadone and morphine

Initially, methadone equivalency as expressed in opioid equivalency tables was that 8 mg of methadone was equivalent to 10 mg of morphine. For the pharmacokinetic reasons expressed above, clinicians quickly discovered that, with chronic dosing, methadone was 10 to 20 times more potent than morphine.

When to consider methadone for analgesia

1. Severe complex or neuropathic pain that is not responding to other opioids and adjuvants.
2. Suspicion of opioid tolerance as evidenced by very high doses of opioids.
3. Severe and intractable opioid side effects.
4. Renal impairment or significant liver impairment.

When NOT to consider methadone for analgesia

1. A prescriber who is inexperienced in using opioids and methadone.
2. Limited follow-up of patients or limited accessibility of the prescriber.
3. Non-compliant patients.
4. Drug abuse.

Methadone should only be prescribed by a physician who is aware of its pharmacokinetic and pharmacodynamic properties and who has experience in its use.

If you are not experienced in using methadone, enlist the help of a pain expert.

Methadone dosing

1. Individualize and titrate: patients on low-dose opioid may require a ratio of 1:5, on high-dose 1:20 (methadone/morphine equivalent).
2. 1:10 is most common starting.
3. 1:20 is appropriate starting ratio for elderly patients.
4. For patients on high-dose opioids, greater than 1000 mg morphine equivalent/day 50 mg methadone is upper limit per dose at inception of therapy.
5. Begin dosing at eight-hour intervals.

Morphine to methadone conversion

There are a number of methods for converting from an opioid to methadone. On an outpatient basis, I would recommend:

Day 1	Start 5 to 10 mg methadone every eight hours.** Decrease the other opioid by 1/3. Wait three days to judge initial stabilization. Use other opioid for breakthrough
Day 4	Depending on response, increase methadone by 10 mg each dose. Decrease the other opioid further by 1/3. Allow 5 to 10 mg methadone q4-6h PRN for breakthrough
Day 7	Depending on response, increase the methadone. Stop the other opioid. Use methadone for breakthrough.

***Methadone can be administered q12h

Patients should be cautioned to report increasing sedation immediately to their physician.

Methadone licence

In Canada, a methadone "licence", actually an "exemption", is required to prescribe methadone for analgesia under the Controlled Drugs and Substances Act. An application must be made to the Office of Controlled Substances and an application form for exemption must be completed. The letter of application must state that the physician has had some education or experience in using methadone and that a physician mentor with experience in using methadone is available. Support from the provincial medical licensing body may be required.

The website is: **www.hc-sc.gc.ca/hecs-sesc/ocs/health/methadone.htm**

References are available. Contact Dr. Librach by e-mail at **larry.librach@utoronto.ca**.