Commentary
Is Levorphanol a Better Option than Methadone?

Abstract

Background. Methadone has been a stalwart pharmacologic option for the management of opioid drug dependence for many years. It substitutes for opioid agonists and possesses certain pharmacokinetic properties that confer characteristics preferable to those of other opioids for this application. Methadone is likewise used as an option for the treatment of pain, particularly chronic pain. It has a spectrum of pharmacodynamic activity, including contributions from non-opioid components, that translates to its specific clinical attributes as an analgesic. Unfortunately, basic science studies and accumulated clinical experience with methadone have revealed some undesirable, and even worrisome, features, including issues of safety. The benefit/risk ratio of methadone might be acceptable if there was no better alternative, but neither its pharmacokinetic nor pharmacodynamic properties are unique to methadone.

Objective. We review the basic and clinical pharmacology of methadone and suggest that levorphanol should receive attention as a possible alternative.

Conclusion. Unlike methadone, levorphanol is a more potent NMDA antagonist, possesses a higher affinity for DOR and KOR, has a shorter plasma half-life yet longer duration of action, has no CYP450 interactions or QTc prolongation risk, can be a viable option in the elderly, palliative care, and SCI patients, requires little to no need for co-administration of adjuvant analgesics, and has potentially a lower risk of drug-related Emergency Department visits compared to other opioids.

Key Words. methadone; benefit/risk ratio; levorphanol; drug-dependence; analgesia; opioid.
analgesia above and beyond other opioids, including methadone, has not been elucidated. Interestingly, however, antinociceptive potency against MOR-binding affinity yields a good correlation for the opioids examined, including methadone, but levorphanol is significantly more potent than its MOR binding affinity would imply [8]—suggesting a significant contribution of one or more additional mechanisms of analgesic action. Perhaps the biggest difference between the analgesic pharmacology of methadone and levorphanol is that methadone-induced antinociception involves the opening of ATP-sensitive K⁺ channels, whereas levorphanol-induced antinociception, similar to fentanyl, does not [17].

Also in contrast to methadone, levorphanol does not require CYP 450 metabolism. Levorphanol does, however, undergo phase II metabolism to a 3-glucuronide product that is renally eliminated, which is similar to the phase II metabolic step of other dehydroxylated phenanthrene opioids such as hydrocodone, hydromorphone, oxycodone, and oxymorphone. Another advantage is that it is not a known substrate of P-glycoprotein (P-gp) [15,18]. Perhaps most importantly, levorphanol has not been associated with a risk of QTc prolongation. Other notable characteristics differentiating levorphanol from methadone include: a shorter half-life (11–16 hours compared with 8–60 hours, or even higher, with methadone) [19,20]; more predictable pharmacokinetics, including metabolism and elimination, and lack of arrhythmogenic activity [21]. Recently, several groups have further expanded the structure–activity relationship of levorphanol-related compounds. For example, substitution of the N-methyl in levorphanol yielded compounds having high affinity at MOR and KOR, and further changes at the third position yielded morphinans with notably high affinity for KOR (e.g., <0.05 nM) [10,22]. Incorporation of an indole or aminothiazole fragment to the hexyl ring in levorphanol yielded compounds having enhanced binding to DOR (e.g., <0.5 nM) [23]. Modified ketolevorphanols have been synthesized and tested for opioid receptor-binding affinity and functional activity on the electrically stimulated contractions of mouse ileum. Both agonists and antagonists with potent KOR activity were identified [24]. A comparison summary of methadone and levorphanol is given in Table 2.

**Methadone: Clinical History and Attributes**

Methadone was discovered in Germany during the latter stages of World War II (there are varying stories about its history), either as an alternative to morphine (prompted by the shortage of opium), or through the development of spasmylic agents [25]. Eli Lilly marketed the drug in the United States. Its potential for beneficial use in the treatment of opioid dependence was subsequently recognized, and by 1950, the US Public Health Service hospitals established the use of methadone for the treatment of opioid dependence, spawning the now prevalent methadone-clinics [2,26].

Methadone has several characteristics that also make it an attractive analgesic agent in the management of chronic pain. It possesses good oral bioavailability,
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<th>Levorphanol</th>
<th>Methadone</th>
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<tr>
<td><strong>Pharmacology</strong></td>
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<tr>
<td>Opioid agonist activity</td>
<td>(\mu, \delta, \kappa_1, \kappa_3)</td>
<td>(\mu)</td>
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<tr>
<td>NE reuptake inhibition</td>
<td>Weak</td>
<td>Weak</td>
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<tr>
<td>NMDA inhibition</td>
<td>Strong</td>
<td>Weak</td>
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<tr>
<td><strong>Pharmacokinetics</strong></td>
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<tr>
<td>Bioavailability, Oral</td>
<td>Unknown</td>
<td>35–100%</td>
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<tr>
<td>Duration of action</td>
<td>6–15 hours</td>
<td>4–8 hours</td>
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<tr>
<td>Half-life</td>
<td>11–16 hours</td>
<td>15–60 hours</td>
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<tr>
<td>Metabolic pathway</td>
<td>Phase II glucuronidation to levorphanol-3-glucuronide</td>
<td>3A4-, 2B6-, 2C19-mediated N-demethylation to EDDP</td>
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<tr>
<td>Opioid chemistry</td>
<td>Dehydroxylated phenanthrene</td>
<td>Diphenylheptane</td>
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<tr>
<td><strong>Dosing</strong></td>
<td></td>
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<tr>
<td>Oral MED of 30 mg/day</td>
<td>4 mg</td>
<td>7.5 mg</td>
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<td>Suggested starting dose</td>
<td>1 mg (1/2 × 2-mg tablet) PO 3 or 4 times daily (maximum daily starting dose, 4 mg); titrate up by up to 25% weekly, i.e., if starting at 1 mg PO 4 times daily in the first week, increase to 1 mg PO 5 times daily at second week</td>
<td>2.5 mg (1/2 × 5-mg tablet) PO three times daily (maximum daily starting dose, 7.5 mg); titrate up by up to 25% weekly, i.e., if starting at 2.5 mg PO 3 times daily first week, increase to 2.5 mg PO 4 or 5 times daily at second week (note: as the dose increases, percentage of upward titration decreases due to complex pharmacokinetics)</td>
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<td>opioid naive patients</td>
<td></td>
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<tr>
<td><strong>Routine monitoring</strong></td>
<td>N/A</td>
<td>QTC (ECG performed at least annually or as clinically indicated)</td>
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MOR, DOR, KOR = \(\mu, \delta, \kappa\) opioid receptor type, respectively; EDDP = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene; NE = norepinephrine; NMDA = N-methyl-D-aspartate; MED = morphine-equivalent dose; ECG = electrocardiogram

Refs. [15,19,20]
Methadone’s potential to cause QTc prolongation in the clinical setting has been reported in randomized and cohort studies [30,31], mainly during its use for addiction management. In overdose, methadone prolongs the QTc interval; fatal overdose is associated with cardiac arrhythmias and sudden death [32,33] and the United States FDA requires a black-box warning in the methadone product labeling (since 2006). In vitro findings are consistent with an effect of methadone on the QTc interval (no animal studies of methadone’s QT effects could be found). The question of QTc prolongation caused by methadone has recently been reviewed [5] and is summarized below:

- Methadone significantly inhibits hERG (the human Ether-à-go-go-related gene, KCNH2, that codes for $K_{r}^{11.1}$, the alpha subunit of a K+ channel).
- Methadone has high arrhythmicogenic potential at serum levels comparable to those attained when used for the treatment of opioid dependence.
- The S-(+)-isomer of methadone (RS) is a more potent inhibitor of $I_{Kr}$ (delayed-rectifier potassium current) than is the R-(−) isomer.
- There is a dose–response relationship between QTc changes and methadone serum levels (more serious proarrhythmic responses correlate with higher doses and lower metabolism of the drug).
- Certain populations appear to be at greater risk, including females, those with cardiac congenital channel abnormalities, hypokalemia, or low magnesium.

Some authors consider the observed QTc interval changes to be clinically unimportant [30], but others recommend switching to safer alternatives [30,31,34,35]. Several studies reviewed by Wilcock and Beattie [36] have reported occurrences of QTc prolongation in methadone-treated chronic pain patients, but suggest that electrocardiogram (ECG) monitoring is a reasonable and sufficient safety-monitoring measure. There are suggestions that QT screening be done prior to, or during, methadone use [37,38]. Aside from these resources, one cannot ignore the potential for additive QTc widen-

Significant and unpredictable variability in genetic polymorphisms affecting metabolism, clearance, and drug interaction susceptibility [1] may lead to inadequate analgesia, supra-analgesia, possible opiate withdrawal, or even drug accumulation and toxicity [39]. Methadone is a racemic mixture of $R$- and $S$-enantiomers that is extensively metabolized by several CYP isoenzymes primarily through CYP3A4 and CYP2B6 with CYP2D6 and CYP2C19 having minimal roles responsible for hepatic metabolism in humans [40,41]. $R$-methadone exhibits the desired opioid agonist analgesic properties and is primarily metabolized by CYP3A4 while $S$-methadone is associated with adverse effects such as QTc prolongation and is preferentially metabolized by CYP2B6 [40]. Clinical drug-interaction studies by Kharasch et al. [42–44] suggest that CYP2B6 induction or inhibition consequently affects methadone plasma concentrations, metabolism, and clearance. Thus, genetic polymorphisms in which there is poor CYP2B6 metabolism may result in increased risk for cardiotoxicity.

Levorphanol: Clinical History and Attributes

Levorphanol was first marketed in the 1950s under the trade name Levo-Dromoran [21] and was indicated for the management of moderate to severe pain [20]. Although clinically not used in the treatment of opioid dependence, levorphanol’s similar pharmacokinetic properties could theoretically replace methadone for the same indication. Levorphanol demonstrates good absorption through intramuscular, subcutaneous, and oral administration, but is poorly absorbed through the sublingual route [18,45]. Levorphanol has been studied in a wide array of neuropathic pain syndromes, including peripheral neuropathy, postherpetic neuralgia, spinal cord injury, central post stroke pain, and multiple sclerosis [46]. Possessing mechanisms, in addition to, opioid receptor agonist properties, levorphanol may have particular utility in the management of neuropathic pain [16]. Indeed, the major published clinical practice guidelines for the treatment of neuropathic pain, (American Diabetes Association, American Academy of Neurology, National Comprehensive Cancer Network, Canadian Pain Society [CPS], European Federation of Neurological Societies [EFNS], National Institute for Health and Care Excellence) acknowledge the use of opioids, and the CPS, EFNS, and French Society of Physical Medicine and Rehabilitation (SOFMER) have reviewed the evidence and recognized levorphanol as a potential opioid analgesic option. A controlled study of neuropathic pain that included spinal cord injury (SCI) patients compared the efficacy of levorphanol at low doses (2.7 mg/day) vs high doses (8.9 mg/day) [47]. Both doses showed efficacy, but demonstrated superior analgesic outcomes at the higher dose levels [47,48].

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displays a novel spectrum of pharmacologic action, including agonist and antagonist activity, respectively, at MOR and NMDA-R, NE reuptake inhibition. It has high potency, no active metabolite, slow onset to withdrawal syndrome [3], and can be administered rectally as an alternative to intravenous and oral dosing in palliative care patients unable to ingest oral medication [9,26,27]. The typical starting analgesic dose of methadone is 5–10 mg [28] daily in divided doses, which is one-half or less of the typical addiction treatment dose [29]. However, variable pharmacokinetics and analgesic response, necessity for slow dosage titrations, phase I drug interactions, risk for QTc prolongation, and variable opioid-dosing conversions [2,3,15] result in a tricky benefit/risk ratio, requiring artful prescribing even for the most experienced clinicians. Several sources suggest that titrated methadone escalations should not occur for at least 7– to 10-day intervals because of the variable half-life and metabolic polymorphisms [2,3].
Levorphanol exhibits several advantages over methadone that can be useful in the elderly, palliative care, and SCI patients [15, 21, 48, 49]. Methadone is used as a second-line agent for treating pain in patients at the end of life that is refractory to other opioids, as it can prolong the time to development of opioid tolerance, an advantage that is attributed to its NMDA-receptor blockade and shared with levorphanol [3, 47, 50]. Levorphanol could be considered as a first-line analgesic for cancer pain, neuropathic pain, and as a breakthrough agent although dose escalations, according to some authors should be restricted to no sooner than every 48 hours [50]. An 8-year observational case series of palliative care pain patients with severe chronic noncancer pain (including fibromyalgia and spinal stenosis) treated with methadone or levorphanol reported similar overall response rates of 75% and 70%, respectively. The study noted that the patients on levorphanol did not require adjuvant analgesics and had no QTc issues [49]. Conversion difficulties from other opioids to methadone have been widely reported, but this was not observed when converting to levorphanol [49]. However, not without its own faults, levorphanol possesses some clinical disadvantages with the lack of data, higher cost compared with methadone, and limited commercial availability.

Safety and Mortality Risk

In general, chronic use of opioid therapy remains a high risk, but from a public safety standpoint, levorphanol has a cleaner track record in comparison to methadone. Methadone prescribing for pain increased significantly between 1999 and 2009, and the rate of fatal overdoses during this period was fivefold higher than other opioids [6]. A study comparing the risk of out-of-hospital death in patients receiving methadone found that patients had a 46% increased risk of death during the follow-up period which supported against its as a first-line choice for the management of chronic pain [51]. In the Substance Abuse and Mental Health Services Administration (SAMHSA) Drug Abuse Warning Network (DAWN) report, between 2004 and 2011 methadone was the third most identified opioid (behind oxycodone and hydrocodone), but there was no mention of levorphanol attributed to drug-related Emergency Department visits [52]. However, the underreported utilization of levorphanol undoubtedly reflects its reputation as the “forgotten opioid.”

Conclusion

Methadone occupies an important place in the history of pharmacologic treatment of opioid dependence. However, its broader use for analgesia has renewed heightened concerns about its highly variable clinical pharmacokinetic and metabolic characteristics, and its prolongation of the QTc interval. Unlike methadone, levorphanol is a more potent NMDA antagonist, possesses a higher affinity for DOR and KOR, has a shorter more predictable plasma half-life yet longer duration of action, has no CYP450 interactions or QTc prolongation risk, can be a viable option in the elderly, palliative care, and SCI patients, requires a lesser need for coadministration of adjuvant analgesics, and has potentially a lower risk of drug-related Emergency Department visits. Therefore, it might be time to ask the question: is levorphanol, a better alternative to methadone?

Acknowledgments

Dr. Pham was the primary researcher and writer for all sections of the paper including figures and tables. Dr. Raffa’s contribution centered on the pharmacology and pharmacodynamics. Dr. Fudin was the clinical subject matter expert and primary editor.

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