

Eric Prommer

Levorphanol: the forgotten opioid

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E. Prommer (✉)
VIP Palliative Care Program,
Greater Los Angeles Healthcare,
Division of Hematology/Oncology,
UCLA School of Medicine,
11301 Wilshire 111-H,
Los Angeles, CA, USA
e-mail: eric.prommer@med.va.gov
Tel.: +1310-478-3711

Abstract Background: Levorphanol (levo-3-hydroxy-N-methylmorphinan) is a strong opioid that is the only available opioid agonist of the morphinan series. Levorphanol was originally synthesized as a pharmacological alternative to morphine more than 40 years ago. It is considered a step-3 opioid by the World Health Organization (WHO) and has a greater potency than morphine. Analgesia produced by levorphanol is mediated via its interactions with μ , δ , and κ opioid receptors. Levorphanol is also an *N*-methyl-D-aspartate (NMDA) receptor antagonist. There is evidence that levorphanol may inhibit uptake of norepinephrine and serotonin.

Similar to morphine, levorphanol undergoes glucuronidation in the liver, and the glucuronidated products are excreted in the kidney. Levorphanol can be given orally, intravenously, and subcutaneously. **Objective:** This article reviews the pharmacodynamics, pharmacology, and clinical efficacy for this often overlooked step-3 opioid. **Conclusion:** The long half-life of the drug increases the potential for drug accumulation. Levorphanol has clinical efficacy in neuropathic pain.

Keywords Pain · Levorphanol · Opioids · NMDA · Glucuronidation

Introduction

Pain is one of the most common and incapacitating symptoms experienced by patients with advanced cancer [1]. Current treatment is based on the concept of an “analgesic ladder” by the World Health Organization (WHO), which involves a stepwise approach to the use of analgesic drugs [2]. Medication potency increases at each step of the WHO ladder, from non-opioid drugs (step 1, e.g., aspirin and nonsteroidal anti-inflammatory), through weak opioids (step 2, e.g., codeine) plus a non-opioid analgesic, to strong opioids (step 3, e.g., morphine) plus a non-opioid analgesic [3]. Step-3 opioids include hydromorphone, oxycodone, oxymorphone, fentanyl, methadone, and levorphanol. Levorphanol was originally synthesized as a pharmacological alternative to morphine more than 40 years ago. It is considered more potent than morphine and has been described as being “similar to methadone” [4]. Little has been written about this opioid,

and it is important that clinicians not forget that this is an option for moderate to strong pain. The purpose of this review is to examine the pharmacokinetics, pharmacodynamics, and clinical uses of levorphanol.

Structure of levorphanol

When compared with morphine, levorphanol lacks an oxygen group and a 6-hydroxyl group (Fig. 1). Otherwise, levorphanol is structurally identical to morphine. The presence of the 3-hydroxyl group on the aromatic ring leads to the formation of a 3-glucuronide product [5]. Uridine diphosphate glucuronosyl transferase (UGT) isoenzyme 2B7 is a UGT isoenzyme of major importance for the glucuronidation of many clinically important opioid compounds in humans. This UGT catalyzes glucuronidation of both the 3-hydroxyl and the 6-hydroxyl position of morphinan derivatives.

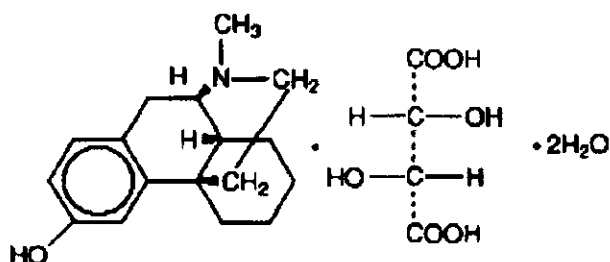


Fig. 1 Structure of levorphanol

Opioid receptor interactions

Levorphanol has strong affinity for μ , δ , and κ opioid receptors, and its interaction with these receptors is stronger than morphine. K_i values (nM) for levorphanol are 0.21 ± 0.02 at the μ -opioid receptor, 4.2 ± 0.6 at the δ -opioid receptor, and 2.3 ± 0.3 at the κ -opioid receptor [6]. Levorphanol is considered a full κ agonist [7]. Levorphanol has high affinity for κ -receptor subtypes, κ_1 and κ_3 with K_i values of these receptors of 8.1 nM and 5.6 nM, respectively [8]. Levorphanol has poor affinity for κ_2 receptors [8]. These receptor interactions may provide the basis of the described unidirectional cross-tolerance with morphine [9]. Laboratory evidence suggests that the primary κ receptor responsible for analgesic activity is the κ_3 receptor [8]. Levorphanol apparently does not cause internalization of the κ -opioid receptor [10].

NMDA receptor interaction

Levorphanol is a noncompetitive NMDA receptor antagonist [11]. In rat forebrain synaptic membranes labeled with [3 H] MK-801, a noncompetitive NMDA receptor antagonist, levorphanol was able to displace [3 H] MK-801 at a high affinity (K_i 0.6 μ M) [11]. Surprisingly, this was similar to ketamine (K_i 0.8 μ M), which is considered a strong NMDA antagonist. Levorphanol is also more potent NMDA antagonist than racemic methadone (DL-methadone) (K_i 6.0 μ M) [11]. Levorphanol has a lower K_i value than dextromethorphan, which is also considered a potent NMDA receptor antagonist [11].

Other receptor activities

Like morphine, levorphanol has anticholinergic effects [12]; like methadone, levorphanol inhibits the uptake of serotonin and norepinephrine [13].

Formulation

Table 1 summarizes the various formulations of levorphanol. It is available in oral and parenteral forms, doses, and concentrations, which are summarized in the Table. The oral form is available as scored tablets.

Compatibility

Levorphanol tartrate is a white crystalline powder, soluble in water and ether but insoluble in chloroform [14]. It has a molecular weight of 443.5 [14]. Levorphanol is compatible with glycopyrrolate, atropine, propofol, and scopolamine [15]. The pH of levorphanol tartrate injection is 4.2 to 4.4. Levorphanol tartrate is stable in light and should be stored at room temperature. Levorphanol tartrate injection has been reported to be physically incompatible with solutions containing aminophylline, ammonium chloride, amobarbital sodium, chlorothiazide sodium, heparin sodium, methicillin sodium, nitrofurantoin sodium, novobiocin sodium, pentobarbital sodium, perphenazine, phenobarbital sodium, phenytoin sodium, secobarbital sodium, sodium bicarbonate, sodium iodide, sulfadiazine sodium, sulfisoxazole diethanolamine, and thiopental sodium [15].

Pharmacology/route of administration

Levorphanol can be administered orally, intravenously, and subcutaneously and intramuscularly. Levorphanol has poor absorption via the sublingual route compared with other opioids such as morphine sulfate (18% absorption), buprenorphine (55%), fentanyl (51%), and methadone (34%) [16]. The pharmacokinetics of levorphanol have been studied in a limited number of cancer patients after IV, IM, and PO administration. Levorphanol is subject to first-pass metabolism to produce a 3-glucuronide metabolite [17]. There are little data on the activity of this metabolite, but problems with sedation and other neuropsychiatric toxicities suggest activity (see Adverse effects). The conjugated metabolite of levorphanol appears rapidly in plasma after all routes of administration and can reach

Table 1 Formulations

Routes	Formulation	Dose/concentration
Oral	Tablets (scored)	1 mg, 2 mg, 3 mg
Parenteral	Ampules	2 mg/ml (1 ml)
		2 mg/ml (10 ml)

concentrations that are fivefold to tenfold higher than the intact drug, especially with chronic dosing at 6-h intervals [17]. Plasma concentrations of levorphanol after chronic administration in patients with cancer also increase with the dosage, but the analgesic effect is not correlated with the plasma concentration of levorphanol [17]. Plasma protein binding at steady state in ten patients averaged $40 \pm 2.6\%$ [17]. Levorphanol enters the cerebrospinal fluid where concentrations of the drug can reach 60 to 70% of the corresponding plasma levels of the drug [17].

Intravenous administration

Onset of analgesia is within 20 min. After IV administration, plasma concentrations of levorphanol decline in a tri-exponential manner with a $t_{1/2}$ of approximately 11 to 16 h and a clearance of 0.78 to 1.1 l/kg/h [17]. Levorphanol is rapidly distributed (<1 h) and redistributed (1 to 2 h) after IV administration and has a steady-state volume of distribution of 10 to 13 l/kg [17]. The duration of analgesia ranges from 6 to 15 h.

SC administration

When given by the subcutaneous route, analgesia occurs within 60–90 min [15]. Duration of analgesia when given by this route ranges from 4 to 15 h. [15].

IM administration

Clinical data suggest that absorption is rapid with onset of effects within 15 to 30 min of administration [15].

Oral administration

Onset of analgesia after oral administration is 10–60 min [17]. Levorphanol is well absorbed after oral administration with peak plasma concentrations occurring approximately 1 h after dosing [17]. The actual bioavailability of levorphanol tablets compared with IM or IV administration is not known. Plasma concentrations of levorphanol increase with dose. High plasma concentrations of levorphanol can be reached in patients on chronic therapy owing to the long half-life of the drug. In a study of 11 cancer patients, Dixon and coworkers have reported plasma concentrations from 5 to 10 ng/ml after a single 2-mg dose and up to 50 to 100 ng/ml after repeated oral doses of 20 to 50 mg/day [17]. The duration of analgesia ranges from 6 to 15 h. With chronic oral dosing, the half-life can be as long as 30 h, indicating that drug accumulation can occur [17].

Biotransformation

Xenobiotics such as opioid drugs are, in general, metabolized and excreted largely as glucuronides by the liver and kidney [5]. Levorphanol is no exception and possesses a hydroxyl group at position 3 on its aryl ring, which is metabolized in the liver to a glucuronide metabolite. This metabolite is excreted in the bile and is ultimately renally excreted. Small amounts of levorphanol are conjugated to sulfates [15]. Little unchanged drug is found in the bile, urine, or feces. There is no evidence of involvement of the cytochrome oxidase enzymes in the metabolism of this drug.

Elimination

Kidney disease

Metabolites of levorphanol are renally excreted. The high volume of distribution and increased protein binding suggest that levorphanol should not be dialyzable. *In the setting of renal disease, the dosing interval should be increased as with any opioid that depends on renal excretion.*

Liver disease

The predominant mode of metabolism is hepatic. Data regarding hepatic extraction and clearances are not available. One would expect bioavailability to vary in pathologic conditions where hepatic blood flow and liver metabolic function are impaired. *In the setting of hepatic insufficiency, it is advisable to consider an increased dosing interval.*

Drug interactions

In vivo drug–drug interaction studies involving levorphanol have not been performed. One advantage of levorphanol is its lack of interaction with the CYP450 system. However, similar to morphine, drugs that affect glucuronidation should be expected to potentiate or decrease the effects of levorphanol. Drugs such as tricyclic antidepressants, phenothiazines, and ranitidine inhibit glucuronidation and can potentiate the effects of levorphanol as they do with morphine. On the other hand, inducers of glucuronidation such as carbamazepine, phenobarbital, phenytoin, and rifampin have the potential to decrease the effect of levorphanol, as they do with morphine. One would expect the concomitant use of central nervous system depressants with levorphanol would result in additive central nervous system effects. *The use of MAO inhibitors and levorphanol is not recommended.*

Adverse effects

Experience and clinical trial work suggest that the type and incidence of adverse effects are those typically seen with strong opioids [14]. The occurrence of adverse effects is dose-related. Like other strong opioids, levorphanol can cause nausea, vomiting, sedation, pruritus, constipation, and biliary spasm [14]. Levorphanol has been shown to cause moderate to marked increases in pressure in the common bile duct when given in analgesic doses. It is not recommended for use in biliary surgery [14]. Levorphanol can cause urinary retention due to its anticholinergic effects. Levorphanol causes histamine release [18]. The incidence of dizziness associated with levorphanol use is approximately 10% [14].

A clinical trial evaluating levorphanol in neuropathic pain demonstrated the occurrence of neuropsychiatric events such as anger, irritability, or mood or personality change in the higher dose group (see below) [19]. Levorphanol has been shown to be teratogenic in mice. There are no adequate or well-controlled studies in pregnant women. Therefore, levorphanol should be used in pregnancy if the risk-benefit ratio is favorable [14]. Animal studies suggest that levorphanol crosses the placenta [14]. It is not known if levorphanol is excreted in breast milk, but it is structurally related to morphine, which is excreted in breast milk [14].

Clinical studies

Neuropathic pain

Levorphanol was studied as a treatment for chronic neuropathic pain [19]. Types of neuropathic pain included peripheral neuropathy, focal nerve injury, postherpetic neuralgia, spinal cord injury with incomplete myelopathy, central pain after stroke or focal brain lesion, or clinically definite multiple sclerosis. Criteria for exclusion included previous opioid therapy exceeding 360 mg of codeine per day (40–60 mg morphine equivalent). Patients were allowed to maintain their non-opioid analgesics.

The most common types of concomitant medications were antidepressants (in 24 patients), nonsteroidal anti-inflammatory drugs (in 24 patients), and anticonvulsants (in 11 patients). Randomization was to either high-strength (0.75 mg) (16 mg max) or low-strength (0.15 mg) (3 mg max) capsules of levorphanol for 8 weeks under double-blind conditions. Intake was titrated by the patient to a maximum of 21 capsules of either strength per day. Dosing schedule was three times daily. Outcome measures included the intensity of pain as recorded in a diary, and included pain relief, quality of life, psychological and cognitive function, number of capsules taken daily, and blood levorphanol levels.

Among the 81 patients evaluated, high-strength levorphanol capsules reduced pain by 36% compared with a 21% reduction in pain in the low-strength group ($P=0.02$). Specifically, the only type of neuropathic pain that did not benefit was central pain after stroke. On average, patients in the high-strength group took 11.9 capsules per day (8.9 mg per day), and patients in the low-strength group took close to the 21 allowed (18.3 capsules per day; 2.7 mg per day). Affective distress and interference with functioning were reduced, and sleep was improved, but there were no differences between the high-strength group and the low-strength group in terms of these variables. *Noncompletion of the study was primarily due to adverse effects of the opioid.*

Opioid-agonist effects measured on the subscales titled "Dry mouth," "Itchy skin," "Sweating," "Sleepy," "Noise," "Carefree," and "Drunk" increased during treatment in both treatment groups. Those in the high-strength group reported significantly greater effects with regard to "Itchy skin," "Sweating," and "Skin clammy." Some adverse effects were reported only by patients in the high-strength group, including anger, irritability, or mood or personality change in six patients, generalized weakness or confusion in five patients, and dizziness or loss of equilibrium in two patients. CNS effects were more consistently seen in the high-dose arm.

Equianalgesic dosing

Levorphanol is four to eight times as potent as morphine [14]. Two milligrams of intramuscular levorphanol tartrate depresses respiration to a degree equivalent to that produced by 10 to 15 mg of intramuscular morphine in man [14]. Levorphanol is approximately five times as potent as oxycodone and methadone by oral and parenteral routes according to published single-dose equianalgesic tables (4).

When converting from oral levorphanol to subcutaneous levorphanol a 2:1 ratio is used [14]. One milligram of levorphanol IV is equivalent to 1 mg subcutaneously [14]. There have been no prospective clinical studies evaluating reliability of the conversion ratios between levorphanol and other opioids as suggested by the equianalgesic table. Because there is incomplete cross-tolerance among opioids, it has been suggested that the total daily dosage of levorphanol be started at *approximately 1/15 to 1/12* of the total daily dosage of oral morphine, with subsequent adjustment of dosage based on the patient's clinical response [14].

As with any drug whose plasma half-life exceeds the duration of analgesia produced, there is risk for drug accumulation. Therefore, time must be allowed for steady state to occur. It is recommended that patients placed on fixed-schedule dosing (round-the-clock) with this drug, care should be taken to allow adequate time after each dose

change (approximately 72 h) for the patient to reach a new steady state before a subsequent dose adjustment to avoid excessive sedation due to drug accumulation [14]. The initial levorphanol dosage should be reduced by 50% in elderly patients and cautiously escalated.

Schedule of administration

Intravenous The usual recommended starting dose for IV administration is up to 1 mg given by slow injection [15]. This may be repeated every 3 to 6 h as needed. Levorphanol also has been given by continuous infusion [20].

Subcutaneous The usual recommended starting dose for SC administration is 1 to 2 mg. This may be repeated every 6 to 8 h as needed. There is no information on its use as a continuous subcutaneous infusion.

Oral The usual recommended starting dose for oral administration is 2 mg. This may be repeated every 6 to 8 h as needed.

Levorphanol for breakthrough pain Current recommendations for the management of breakthrough pain generally favor the selection of a short-acting opioid at a dose proportionate to the total daily dosage [21]. Drugs and routes of administration with a fast onset should be chosen to meet the characteristics of a pain flare, specifically high-intensity pain of short duration. Even drugs such as morphine may not be optimal owing to the time needed to reach peak effect. Levorphanol has been used as a breakthrough medication [20]. The slow onset of action and potential for accumulation offset the benefits of its use for breakthrough pain. At this time, it is advisable to use a short-acting opioid to manage breakthrough pain that occurs during titration with levorphanol [21].

Conclusions

Levorphanol is the only available opioid agonist of the morphinan series. Levorphanol was originally synthesized as a pharmacological alternative to morphine more than 40 years ago. It is considered a step-3 opioid with a greater

Table 2 Pharmacoeconomics: comparison to methadone and morphine

Opioid	Cost per tablet
Levorphanol 2 mg	AWP: *\$1.74
Morphine (sustained release) 15 mg	AWP: *\$ 0.89
Methadone 5 mg	AWP: *\$0.09
Methadone 10 mg	AWP: *\$0.14

AWP average wholesale price (dollars)

potency than morphine. Levorphanol can be administered orally, intravenously, and subcutaneously. Analgesia produced by levorphanol is mediated via its interactions with μ , δ , and κ opioid receptors. Levorphanol is also a NMDA receptor antagonist. Levorphanol has strong affinity for μ , δ , and κ opioid receptors and interacts more effectively with μ , κ , and δ opioid receptors than does morphine. Levorphanol has high affinity for κ receptor subtypes, $\kappa 1$ and $\kappa 3$ with K_i values of these receptors of 8.1 and 5.6 nM, respectively. The pharmacoeconomics of methadone and morphine compared with levorphanol are shown in Table 2.

Levorphanol is subject to first-pass metabolism to produce a 3-glucuronide metabolite. There are little data on the activity of this metabolite, but problems with sedation and other neuropsychiatric toxicities suggest it has activity. The conjugated metabolite of levorphanol appears rapidly in plasma after all routes of administration and can reach concentrations that are fivefold to tenfold higher than the intact drug, especially with chronic dosing. This is especially true for dosing at 6-h intervals. As with any drug whose plasma half-life exceeds the duration of analgesia produced, there is risk for drug accumulation.

Therefore, time must be allowed for steady state to occur. It is recommended that care be taken in patients placed on fixed-schedule dosing (round-the-clock) with this drug to allow adequate time after each dose change (approximately 72 h) for the patient to reach a new steady state before a subsequent dosage adjustment to avoid excessive sedation due to drug accumulation. Because of its NMDA blockade, levorphanol has been shown to be effective in neuropathic pain but has not been compared with other opioids in this regard.

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