Levorphanol: Rewinding an Old, Bygone Multimodal Opioid Analgesic!

Sir,

Levorphanol is a synthetic opioid racemic mixture "levo-3-hydroxy-N-methylmorphinan," which was developed in the 1940s as an opioid agonist [Figure 1]. It was approved for use in the United States in the year 1953. It is also referred to as "The Forgotten Opioid" as levorphanol is neither prescribed nor known to many physicians.[1] As per the WHO, levorphanol is a step 3 opioid and is considered eight times potent than

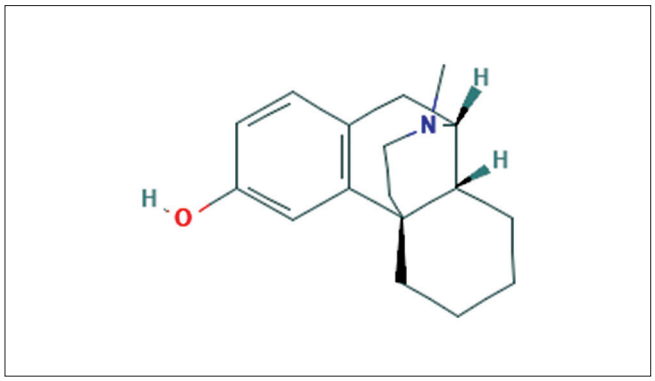

Figure 1: Chemical structure of levorphanol. (Figure source: National Center for Biotechnology Information. PubChem Compound Database; CID = 5359272, https://pubchem.ncbi.nlm.nih.gov/compound/5359272: accessed January 26, 2019)

morphine (2 mg levorphanol is equivalent to 15 mg morphine). Along with mu-receptor agonist properties, levorphanol has delta, kappa1, and kappa 3 receptor agonist properties. It is an N-methyl-D-aspartate (NMDA) receptor antagonist and also inhibits reuptake of norepinephrine and serotonin.

Pharmacologically, levorphanol appears similar to methadone. Pham *et al*. compared the basic and clinical pharmacology of methadone with levorphanol and found that levorphanol is more potent as an NMDA antagonist, has a greater affinity toward delta and kappa opioid receptors, has a shorter plasma half-life (11–16 h) with a longer duration of action (up to 11 h), and has no significant CYP450 interactions or risks of serious QTc prolongation.[2] Levorphanol bypasses first-pass metabolism in the liver as cytochrome enzymes have no role in its metabolism; therefore this does not lead to serious drug interactions such as methadone. It undergoes Phase II metabolism by glucuronidation to an active metabolite levorphanol-3-glucuronide which is excreted by kidneys. Therefore, in renal insufficiency/failure, it can accumulate and can lead to adverse events.

The issues with methadone are its unpredictable pharmacokinetics and pharmacodynamics and QTc prolongation, leading to life-threatening arrhythmias. Methadone is a racemic mixture of R-and S-enantiomers which is extensively metabolized by several isoforms of cytochrome 450 (CYP450) enzymes. Unpredictable genetic polymorphisms affect metabolism, clearance, and susceptibility to drug interaction, which leads to inadequate analgesia, respiratory depression, opioid withdrawal syndromes, drug accumulation, and toxicity.[3] Moreover, methadone does not have any significant effect on delta and kappa opioid receptors.

Reddy *et al*. felt that due to its multimodal mechanism of action, levorphanol is a drug which has been useful in treating chronic pain conditions such as phantom limb pain which is otherwise difficult to treat pharmacologically with regular medications.[4] Thus, levorphanol can be used in several chronic pain conditions such as cancer pain, chronic neuropathic pain, postherpetic neuralgia, spinal cord injury, central poststroke pain, fibromyalgia, and multiple sclerosis. It can be used orally, intramuscularly, and subcutaneously. Sublingual absorption is inconsistent and not recommended.[5] The recommended dosing is orally 6 mg/day in 3–4 divided doses, 1 mg every 6–8 h intravenously, and 1–2 mg subcutaneously/intramuscularly every 6–8 h. It has been used safely in elderly patients as well.[6] Due to its long half-life, the drug can get accumulated after prolonged use, especially in patients with compromised renal function.

In conclusion, levorphanol appears to be a potent, broad-spectrum analgesic with a better safety profile due to its predictive pharmacokinetics without the need of any monitoring. It can be used in patients who are suffering with chronic pain of any etiology who have not benefitted with morphine, antidepressants, gabapentinoids, and other miscellaneous group of drugs.

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Conflicts of interest

There are no conflicts of interest.

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