Ondansetron: an effective treatment for the withdrawal symptoms of opioids?

"Current medications used to reduce symptoms of opioid withdrawal all possess specific drawbacks that make existing treatments inadequate. Potential for drug abuse, dangerous side effects and barriers to treatment have led to the search for alternative treatment approaches."

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"Only a few hours have passed since using the last injection of morphia, and already the feeling of comfort brought on by the action of the drug is passing off. The patient is overcome by a feeling of uneasiness and listlessness; the feeling of self-consciousness and self-possession is gone, and is replaced by extreme despondency; a slight cough gradually brings on dyspnoea, which is increased by want of sleep and by hallucinations."

– Dr H Kane, *The Hypodermic Injection of Morphia*, 1880 [1].

What is opioid withdrawal?

Opioid withdrawal (OW) is a constellation of symptoms that occur when serum opioid levels abruptly decrease in patients who have developed physical dependence from repeated or chronic opioid exposure. These withdrawal symptoms include CNS activation and sleeplessness, diarrhea, rhinorrhea, piloerection and psychomotor agitation, among others [2]. Managing OW symptoms is the first step in a drug-abstinence treatment program, and is important for obtaining a better treatment outcome [3]. OW symptoms are one set of factors reinforcing ongoing opioid abuse. Aside from its role in opioid abuse, OW complicates the management of opioid medications used for legitimate medical goals [4].

Mechanism of opioid withdrawal

The precise mechanism underlying OW is not completely understood. Chronic activation of opioid receptors leads to upregulation of cAMP signaling pathways through increased activity of adenylyl cyclases (subtypes I and VII), cAMP-dependent protein kinase A and tyrosine hydroxylase [2]. These changes are thought to be a homeostatic response to inhibition of neurons in the locus ceruleus by opioids, which has been shown to be a key brain region involved in OW [2]. The locus ceruleus is a noradrenergic nucleus that regulates stress responses, autonomic nervous system activity and arousal. Tolerance to the inhibitory effects of opioids on the locus ceruleus occurs with chronic opioid administration, and unopposed firing of locus ceruleus neurons and noradrenergic overactivation occur when opioid concentrations fall. However, this explanation does not offer a complete picture of the mechanisms underlying OW. It is evident that other pathways are involved in the expression of withdrawal, since ablation of the locus ceruleus does not alter the expression of naloxone-precipitated or spontaneous OW in animal models [5]. Finally, the mesolimbic dopamine reward system is also implicated in certain withdrawal symptoms. Chronic opioid exposure leads to activation of CREB, causing production of dynorphin that activates κ-receptors in neurons located in the ventral tegmenal area (VTA) and decreases the release of dopamine in the nucleus accumbens. These changes lead to dysphoria and anhedonia, which can present during early phases of withdrawal [2,5,6].

Current methods of treating withdrawal are inadequate

The primary medications used for opioid detoxification and treatment of OW are drugs that bind to opioid receptors, and nonopioid drugs such as the α_2-agonist clonidine. However, these detoxification regimens are inadequate. No current regime completely and safely eliminates withdrawal symptoms.

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Clonidine

Clonidine decreases the release of norepinephrine by acting on presynaptic noradrenergic receptors, and is commonly used in clinical practice to treat hypertension. It has been used since the 1980s to treat the autonomic symptoms caused by noradrenergic hyperactivity associated with withdrawal [7,8]. However, the overall efficacy of clonidine is only moderate in reducing withdrawal symptoms, and is less effective than opioid agonists at relieving anxiety, sleeplessness, muscle aches and craving associated with OW. Clonidine is also associated with severe side-effects such as hypotension and sedation that limit its use to medically supervised environments [9].

Methadone

Drugs that bind to opioid receptors are also used to treat OW during the detoxification process. Methadone is often used as a substitute for heroin, and strongly reduces withdrawal symptoms [10]. However, opioid agonists like methadone, which is very potent and long-acting, are difficult to use by nonexperts, are associated with potentially severe side effects and abuse, and are subject to US Drug Enforcement Administration schedule II restrictions. Methadone is difficult to titrate rapidly and safely for the relief of withdrawal symptoms, and it is difficult to use for rapid detoxification outside of a medically monitored environment.

Buprenorphine

Buprenorphine is a newer drug used for opioid detoxification. It is a partial μ-opioid agonist and κ-receptor antagonist that has been found to be more effective than clonidine and about as effective as methadone when used for opioid detoxification [11]. However, physicians must meet certain qualifications and be granted a special waiver to prescribe buprenorphine for treatment of opioid dependency. The institution of buprenorphine therapy can also exacerbate withdrawal symptoms, especially if large doses of longer acting opioids have been used by the patient. Compliance with and adherence to outpatient therapy has also been identified as an area in which improvement is needed [12].

Better opioid withdrawal treatments are needed

Current medications used to reduce symptoms of OW all possess specific drawbacks that make existing treatments inadequate. Potential for drug abuse, dangerous side effects and barriers to treatment have led to the search for alternative treatment approaches. The ideal agent to reduce symptoms of OW should involve a nonopioid, nonaddicting medication to minimize the potential for abuse. It should prevent the development of physical dependence and/or treat the symptoms of acute withdrawal with a wide therapeutic window and low side-effect profile, and should be available in a wide variety of formulations (e.g., intravenous, oral). This type of medication would improve access to effective treatment, particularly in non-monitored outpatient settings, and could radically improve treatment of opioid dependence. A treatment that could prevent the development of OW may also ameliorate other problems associated with physical dependence, such as analgesic tolerance and opioid-induced hyperalgesia. We believe drugs that target the 5HT3 receptor may fulfill these criteria.

A new approach: 5HT3 receptor antagonist drugs

Recent evidence from our laboratories, employing pharmacogenetic haplotype-based computational mapping, have linked the 5HT3 receptor to physical dependence and OW [13]. These agents offer several advantages, including a very benign side-effect profile, several available forms of administration and little potential for abuse.

Physiology of the 5HT3 receptor

The 5HT3 receptor is a ligand-gated cation channel found on neurons in the central and peripheral nervous systems, other cell types such as mononuclear cells and intestinal enterochromaffin cells. These receptors modulate neurotransmitter and neuropeptide release of dopamine, GABA, substance P, cholecystokinin, acetylcholine and even serotonin itself. In the CNS, 5HT3 receptors are found primarily on GABAergic neurons in the area postrema, nucleus tractus solitarii, nucleus dorsalis nervi vagi, nucleus caudatus, nucleus accumbens, amygdala, hippocampus, entorhinal cortex, frontal cortex, cingulated cortex and dorsal horn ganglia [12]. These locations suggest involvement with the vomiting reflex, pain processing and control of anxiety [14].

Despite the diverse location and action of 5HT3 receptors in the CNS and periphery, blockade of 5HT3 receptors in animal experiments does not change normal behavior. The only changes noted in healthy human volunteers were occasional constipation and clinically insignificant changes in

cardiac conduction patterns without evidence of CNS effects. There are several 5HT3 receptor antagonists already on the market and approved by the US FDA. The 5HT3 receptor antagonist ondansetron has been available in the US market since FDA approval was granted in 1991, and is a well-tolerated drug with few side effects.

Evidence for 5HT3 modulation of opioid withdrawal

Several lines of evidence point to the role of 5HT3 receptor antagonists in reducing OW. In addition to pharmacogenetic evidence, our work in animal models has shown that the 5HT3 receptor antagonist ondansetron treats and prevents OW in mice in a dose-dependent manner [13]. Morphine-induced physical dependence is also associated with decreased 5HT3 protein expression and downregulation of *Htr3a* gene expression in brainstem nuclei associated with opioid dependence in mice [13]. Additional data from our laboratories in a series of translational studies shows that the 5HT3 receptor antagonist ondansetron can significantly decrease objective measures of OW by up to 76% in humans [13]. We have since conducted an additional study confirming the efficacy of another 5HT3 antagonist, palanosetron, in decreasing objective measures of OW, implicating a drug class effect (unpublished data).

Although data are far less clear and compelling, 5HT3 receptor antagonists have also been considered for the treatment of addiction [15,16]. Some of the laboratory evidence supporting these considerations includes observations that 5HT3 receptors modulate the mesolimbic dopamine reward system, implicated in reinforcing effects of drugs of abuse [17]. Other animal studies implicate 5HT3 receptors in addiction and withdrawal as well. *Htr3a*-deficient mice display diminished sensitization to cocaine [18]. Ondansetron reduces the conditioned place preference induced by morphine in rodents, which is a measure of the use-reinforcing properties of addictive drugs [19].

Significance & future perspective

Ondansetron and other 5HT3 antagonists offer exciting new treatment options for OW. Strong preclinical evidence in animals and early translational studies in humans from our group support our hypothesis that 5HT3 receptor antagonists are effective in treating many OW signs and symptoms [13]. Other studies from the medical literature provide evidence that supports the biological plausibility of our hypothesis. The implications of the finding that 5HT3 receptor antagonists reduce OW are substantial. It will have a dramatic impact on our ability to treat opioid abuse by offering an effective, easily delivered, low-cost method to detoxify patients from opioid therapy with low side effects and potential for abuse.

> *"Ondansetron and other 5HT3 antagonists offer exciting new treatment options for opioid withdrawal."*

However, despite these promises, much more work must be done. Our findings, while novel, need to be confirmed in larger high-quality translational studies and clinical trials. The precise molecular mechanisms and pathways by which 5HT3 receptor antagonists modulate OW require further elucidation; molecular and MRI imaging may assist this work. The ability for 5HT3 receptor antagonists to prevent multiple domains of physical dependence, including opioid tolerance and hyperalgesia, if co-administered with opioid therapy, is an intriguing theory that is derived from our findings. Finally, combination of 5HT3 receptor antagonists with other agents to treat withdrawal may lead to even more efficacious treatments for this troublesome medical problem.

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