

Dezocine: A Totally Different Opioid

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Introduction

“At such times I have certainly felt it a great responsibility to say that pain, which I know is an evil, is less injurious than morphia (morphine), which may be an evil. Here experience is needed. Does morphia tend to encourage the very pain it pretends to relieve?”(Albutt 1870) [1].

“When dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperesthesia, neuralgia and irritability become manifest” (Rossbach 1880) [2,3].

The dangers of opioid overuse have been known for at least 150 years, yet in 2021 we are in the midst of an opioid epidemic with addiction and overdose deaths at a crisis level worldwide, especially in the US. Opioids like morphine were used cautiously for severe pain by most physicians until a massive change in attitude occurred in the late 1980s. The idea was spread, through aggressive marketing, that opioids like oxycodone could be administered safely for long term use in moderate to severe pain. This notion proved to be false and is credited for playing a major role in creating the massive opioid crisis we now face. As a result of this crisis, the perception of the general public now is that all opioids are bad and should be avoided at all costs.

What Are Opiates, Opioids?

Opiates and opioids are chemicals that bind to opioid receptors. Even though the terms are technically different as described below, the terms opiates and opioids are most often used interchangeably. Opioid receptors are everywhere in the body, especially in the brain, and are involved in most bodily functions. The most common use of opiates and opioids is for treatment of severe pain. The use of opiates to treat pain goes back to at least 3400 BC with the Sumarians cultivating the poppy plant, and in 1803 the analgesic component of the poppy, morphine, was isolated by Friedrich Serturmer in Germany [4].

Opiates are chemical compounds that are extracted or refined from natural plant matter (poppy sap and fibers) such as opium, morphine, codeine and heroin. Opioids

are chemical compounds that generally are not derived from natural plant matter. Most opioids are synthesized *in vitro* and include dextromethorphan (NyQuil, Robitussin, TheraFlu, Vicks), dextropropoxyphene (Darvocet-N, Darvon), loperamide (Imodium), hydrocodone (Vicodin), oxycodone (Oxycontin, Percocet), oxymorphone (Opana), meperidine (Demerol), methadone (Dolophine), fentanyl (Ultiva, Sublimaze, Duragesic patch), carfentanyl (Wildnil, for veterinary use).

Opiate Receptors

Opioid receptors are a group of transmembrane inhibitory G protein-coupled receptors with endogenous opioid peptides as their natural ligands. They mediate the response to most hormones, neurotransmitters, drugs, and are involved in almost all bodily functions including sensory perception. The endogenous opioid system consists of three families of opioid peptides, the beta-endorphins, enkephalins, and dynorphins, that interact with three identified subtypes of opioid receptors, the mu (MOR), delta (DOR) and kappa (KOR) opioid receptors respectively. These endogenous peptides are transcribed from cellular DNA and translated by cellular mechanisms as precursor peptides. These precursor peptides are stored in cellular vesicles, released by a variety of specific stimuli and are then cleaved by specific peptidases to interact in an exquisitely complex and balanced fashion with their respective receptors. It should come as no surprise that when we interfere with the fine-tuned natural balance of the endogenous opioid system by administering non-endogenous opiates or man-made opioids that many unexpected and adverse responses occur.

Agonists, Antagonists, Partial Agonists

An agonist is a compound that binds to a receptor on the cell surface and results in a biological action by the receptor. This action can be a specific ion channel opening as is the case in ion channel receptors, or in the case of opioid receptors the specific ligand binding results in a sequence of intracellular reactions leading to a complex cellular response. An agonist can be a full agonist, causing a maximum intracellular response, or a partial agonist, causing a less than maximal intracellular

response. An antagonist is a compound that binds to a specific receptor and blocks the receptor from being activated by an agonist. As with agonists, an antagonist can be a full antagonist which completely blocks the specific intracellular reaction, or a partial antagonist, which partially blocks the specific intracellular reactions that are linked to specific receptor binding. Drugs like morphine, oxycodone, heroin and fentanyl are full MOR receptor agonists. The drug naloxone (Narcan) is an example of a MOR receptor antagonist which is administered to block the respiratory depression effects of MOR receptor agonists in an emergency overdose situation.

Biased Signaling

As well as all the intricate specific interactions a compound can have with a receptor that have been touched on so far, there is an additional level of binding specificity found in certain families of receptors including the opioid receptors, that being biased signaling. In the case of opioid receptors, ligand binding can activate one or both of two intracellular biochemical pathways. One pathway involves the so called G-protein signaling pathway and the other involves the so called beta-arrestin signaling pathway. Although an over-simplification, it is generally thought that G-protein coupled receptor signaling is associated with MOR receptor agonist analgesic properties, while respiratory depression, addiction and other undesirable side effects are thought to be mediated through beta-arrestin signaling pathways.

Not All Opioids Are the Same

With the exquisitely complex interactions that opioids have with opioid receptors that have been discovered so far, it should be very apparent that not all opioids are the same. Compounds like morphine, heroin, oxycodone, fentanyl, methadone and codeine are full MOR receptor agonists and along with their pain alleviating properties, they also demonstrate severe respiratory depression, sedation, constipation and addiction effects. The search for safer potent analgesics, as well as treatments for opioid use disorder (OUD) is critical to address the current opioid crisis and to prevent a re-occurrence.

Dezocine

Dezocine is an opioid analgesic that was patented by American Home Products (Wyeth) in 1978 and was approved by the US FDA in 1986 with the name Dalgan [5]. It was more potent than morphine with regards to analgesia [6], but displayed a greatly reduced level of undesirable side effects such as respiratory depression and addiction. It was used as a post-operative analgesic until its distribution was discontinued in the US in 2011 for reasons that were never made public. The reasons may have been related to the aggressive

marketing of other opioid compounds like oxycodone and oxycontin that occurred during that time following the now infamous statements that chronic use of opioid analgesics for non-malignant pain was safe [7]. With the frenzied marketing and prescribing of oral opioids like oxycontin there was no major demand for another opioid medication like dezocine, which was available only as an injectable solution for intravenous or intramuscular administration and which was relatively expensive to produce. This and the rising awareness of a growing crisis with prescription opioid addiction, and the expiration of patent protection, may have contributed to the corporate decisions to discontinue distribution of dezocine in the US.

While the use of dezocine in the US ended, it is still commonly used in China for perioperative moderate to severe pain and makes up over 45% of the opioid analgesic market in China [8]. Dezocine is not a scheduled medication as classified by the World Health Organization, and no addiction has been reported [5]. Dezocine is primarily used in China for perioperative pain, but its use is expanding into other areas of pain, including cancer pain. A meta-analysis of published work demonstrated that dezocine was as effective as morphine for cancer pain, but dezocine had less than half of the adverse responses that morphine displayed [9].

Dezocine is a partial MOR and a partial KOR agonist [5,10,11]. Being only a partial MOR agonist may explain its greatly reduced respiratory depression effects and its apparent lack of addiction. There is no direct information on whether dezocine is a biased ligand at the MOR or KOR opioid receptor, but there is indirect evidence based on similarities with other compounds that dezocine is most likely a G-protein coupled receptor biased ligand [5]. With years of use and hundreds of thousands of patients treated with dezocine in the US from 1986 until 2011, and up to the present in China, there are no reports of dezocine addiction or abuse in the literature. A Pubmed (<https://pubmed.ncbi.nlm.nih.gov/>) search of the literature using the search terms 'dezocine addiction' and 'dezocine abuse' reveal only 6 and 11 citations respectively, none of which speak of actual addiction or abuse of dezocine in humans. A Pubmed search using the term 'dezocine overdose' returned no citations.

A landmark study by Liu demonstrated that dezocine, along with its MOR and KOR opioid receptor activity, also has norepinephrine and serotonin reuptake inhibitor activity [12]. This is highly significant since serotonin reuptake inhibitors are a mainstay of depression therapy and, as a result, this discovery has opened inquiry into the effects of dezocine on depression. It was found that dezocine reduces depression as well as pain in the perioperative period [13]. It has been

found to be effective in animal models of depression by nature by nature of its KOR opioid receptor agonist and its serotonin reuptake inhibitor activities [14]. Dezocine has been found to be an effective analgesic in an animal model of neuropathic pain [15]. This is also highly significant since neuropathic pain has been extremely difficult to treat, with currently used opioids being generally ineffective. Serotonin and norepinephrine reuptake inhibitors have been recommended as first line treatments for neuropathic pain [16].

With regards to the ongoing opioid crisis, the current strategies of opioid replacement with methadone or buprenorphine have not been extremely effective. Both drugs have significant respiratory depression and abuse effects themselves. Dezocine has been shown to alleviate rapid morphine withdrawal symptoms in an animal model of opioid use disorder (OUD) [17]. Dezocine may offer a better alternative than methadone or buprenorphine for treatment of OUD because of its superior qualities that include lack of addiction and reduced lethality. This concept has led to a current patent for development of dezocine to treat OUD and other opioid receptor associated diseases [18].

One hurdle to expanded use of dezocine has been that it is currently only available as an acidic solution for intravenous or intramuscular injection. Attempts at oral dosing have been hindered due to formulation issues and a large oral first pass metabolism. The search for alternate routes of administration has included an intranasal approach [18]. Dezocine is a very hydrophobic small molecule (mw = 245.4, log P = 3.23) and as such is an excellent candidate for intranasal administration due to its ability to freely diffuse across membranes. An intranasal route also avoids the problem of oral first pass metabolism.

Conclusion

A solution to the problems of effective pain control, addictive and lethal opioid analgesics and the OUD that is fueling the opioid crisis may be right under our nose in the form of dezocine.

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