

Advances in the use of opioids in treating neuropathic cancer pain

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ABSTRACT

Neuropathic cancer pain has been challenging for both physicians and patients. As opioids' positive analgesic effect has been confirmed by some randomized studies in recent years, they are gradually becoming a first line option for the treatment of neuropathic cancer pain. Researches and trials in this field mainly concentrate on the pathogenesis of the pain and the metabolism, excretion and potential analgesic mechanisms of different opioids. Selective use of opioids, which has a dual mechanism of action, may be helpful in controlling neuropathic cancer pain. This review summarizes the different properties and usages of a variety of opioids.

KEY WORDS

Cancer pain; assessment; treatment; traditional Chinese medicine

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Introduction

Malignant neuropathic pain (MNP) is a common type of cancer related pain. García de Paredes *et al.* reported their multi-center epidemiological investigation on MNP (1). The study investigated 8,615 cancer patients to identify the incidence of NP, of which 2,567 patients (30%) had pain and 33% were clinically diagnosed with neuropathic pain. The data showed that MNP was a common type of pain in cancer patients.

MNP has been a big challenge in cancer pain management. The efficacy of opioids observed was controversial, and some studies have even shown that opioids are not effective in treating MNP. However, with advances in both pre-clinical and clinical studies in recent years, the definite effect of this agent in the treatment of neuropathic pain has gradually been confirmed. To inform the clinical treatment of MNP, this review summarizes the different properties and usages of a variety of opioids as follows.

Morphine

In 1804, a German pharmacist, Friedrich Sertürner, first isolated an alkaloid from the natural opium. Due to its hypnotic effects, it took the name "morphine" from the Greek god of dreams Morpheus. In 1827, morphine was first introduced into clinical settings for the treatment of pain. During an 80-year history of clinical application, morphine has already become the most representative analgesic in the strong opioid family, and also the drug of choice recommended in the World Health Organization three-step analgesic ladder in treating severe cancer pain.

In 2005, *New England Journal of Medicine* published a Canadian investigation on the analgesic effect of morphine on neuropathic pain (2), a most furiously scrutinized study in recent years about morphine in such treatment. The primary endpoint of this randomized, double-blind, active placebo-controlled, four-way crossover study was the average pain intensity at the maximum tolerated dose, and the secondary endpoint included the impact of pain on physical functionality and mental state of patients, drug side effects, maximum tolerated dose and quality of life. 57 patients with neuropathic pain were enrolled, including 35 cases of diabetic peripheral neuropathic pain and 22 cases of posttherapeutic neuralgia. Subjects underwent 5-week treatment courses with each of the following regimen in random order: active placebo (lorazepam), gabapentin, morphine and the combination of gabapentin and morphine. The dose reached the maximum tolerated level by week 3, maintained over week 4 and tapered in the first four days in week 5, followed by withdrawal in the last three days. Forty-one patients completed the 20-week

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clinical trial.

This study showed that administration of morphine alone and combined morphine and gabapentin treatment both relieved pain effectively. Compared to baseline, the average pain intensity significantly decreased from 5.72 to 3.70 after morphine monotherapy. The average pain intensities were 4.49, 4.15 and 3.06 in patients receiving placebo, gabapentin monotherapy, and combined morphine and gabapentin therapy respectively. Compared with the placebo group, both the morphine group and the morphine plus gabapentin group were associated with significantly decreased pain intensity. Although the reduction was most remarkable in the latter, there was no significant difference between the two morphine-containing treatments ($P=0.04$). On the other hand, this difference was considerably significant when comparing with the gabapentin monotherapy group ($P=0.001$). Surprisingly, no difference in the analgesic effect was found between active placebo and gabapentin, a long-term first-line option for neuropathic pain. Meanwhile, despite lower dosage of each agent, the combined regimen was likely to have constipation and dry mouth more frequently than gabapentin and morphine alone respectively.

The study not only reconfirmed the objective effect of morphine in the treatment of neuropathic pain but also revealed its critical role in improving mood, limited mobility, sleep and quality of life.

Some investigators have carried out studies on combination therapy with focus on the pathogenesis of neuropathic pain. Maria Osikowicz *et al.* (3) compared the effects of morphine combined with antagonists of varying subtypes of glutamate receptors in animal models of chronic constriction injury of sciatic nerve, finding that combined therapy was more effective in relieving hyperalgesia and allodynia in mice. Attention has also been paid to the effect of morphine combined with minocycline on neuropathic pain (4). The investigators believed that as a semi-synthetic tetracycline, minocycline obviously enhanced the analgesic effect of morphine by inhibiting the function of glial cells in the central nervous system and significantly suppressing their proliferation after the occurrence of neuropathic pain. It reduced not only central sensitization but also morphine tolerance in animal models of neuralgia.

Nociceptive pain is very common in patients with malignancies when complicated with neuropathic pain, making it difficult to implement a clinical trial on MNP based on the similar mechanism to objectively determine the effect of the analgesics. Nonetheless, in view of those results and the particular role of opioids in managing cancer-related pain, more and more oncologists and palliative therapists have attached importance to the application of opioids as the first-line option

for MNP, in combination with other drugs to meet individual needs when necessary. This may be the ideal solution at present.

Oxycodone

Oxycodone is a semi-synthetic opioid developed by Germany in 1916, with the first clinical application reported in 1917. In recent years, oxycodone is being more commonly prescribed. According to the 2009 data of the International Narcotics Control Board, the global sales of oxycodone has rapidly increased to 75.2 tons in 2007 from 11.5 tons in 1998, with the U.S. population consuming up to 82% of the total volume. This country also ranked first in per capita cost of oxycodone around the world, followed by Canada, Denmark, Australia and Norway.

Oxycodone is a pure agonist opioid whose therapeutic action for MNP treatment has been confirmed by numerous studies. Compared with other opioids, oxycodone is remarkably advantageous in the treatment of neuropathic pain -- both single-agent and combination therapy has shown satisfying analgesic effect. In a one-month study on the analgesic efficacy of oxycodone among 366 neuralgic patients (at an average age of 62.6 years; 61.2% being male), Spanish investigators found that pain relief was achieved in 50.4% subjects (1). In a multi-center, prospective, open, long-term clinical trial on oxycodone hydrochloride treatment of neuropathic pain after spinal cord injury, Barrera-Chacon JM *et al.* (5) combined the therapy with anticonvulsant for 83% of the 54 patients (94.74%) on whom the therapeutic efficacy was evaluable. The results showed a sharp decrease in the average VAS score of patients administered with oxycodone compared with their former treatment (7.1 ± 1.3 vs. 4.3 ± 1.7 , $P < 0.001$).

Some studies have also found that oxycodone in combination with other analgesics may improve neuropathic pain. Gatti A *et al.* (6) observed that oxycodone/acetaminophen relieved neuropathic pain effectively. In a prospective study, Li Xiaomei *et al.* (7) observed the efficacy of controlled-release oxycodone monotherapy or combined with gabapentin in treating MNP. 63 patients with moderate to severe MNP were enrolled and accepted a one week controlled-release oxycodone monotherapy initially, and then their pain intensity was re-evaluated. 62.7% had a significant pain release and their pain intensity decreased to mild or no pain. To patients whose pain intensity was still moderate to severe, gabapentin were added as coanalgesics from the beginning of the second week. Satisfactory pain relief was also observed in this group of patients. Oxycodone/Oxycodone.

Oxycodone has widely drawn the attention of investigators due to its advantages in the treatment of neuropathic pain. Australian researchers have shown in an animal-based study



on the opioid receptor affinity of oxycodone that, unlike morphine, oxycodone exerts analgesic effect mainly by κ receptor agitation. A subsequent study further clarified that the κ -2b-opioid receptor subtype was the major receptor excited by oxycodone. However, this study also caused controversy as some investigators still believed that oxycodone acted in a similar way as morphine, primarily by binding μ -receptor (8).

Recent advances in the understanding of its analgesic mechanism in the treatment of neuropathic pain revealed that oxycodone serves as different types of opioid receptor agonists for a variety of conditions. While κ -receptors are primarily excited in the mouse model of diabetes, μ -receptors are mainly excited by oxycodone in non-diabetic models to trigger analgesic effects binding with μ 1-receptors (9,10). The benefits of oxycodone in neuropathic pain treatment may also be associated with the selective agitation of κ -receptors. Sung B, *et al.* (11) found in a mouse model of neuropathic pain that mechanical hyperalgesia was associated with increased expression of κ -receptor mRNA in dorsal root ganglia. It could be inferred that oxycodone might exert its analgesic effect through the agitation of κ -receptors.

Fentanyl

There are few up-to-date pre-clinical or clinical data of fentanyl for the treatment of NP, particularly randomized controlled results.

Studies on the clinical efficacy of fentanyl for NP can be divided into two categories. One is to evaluate or observe the efficacy of immediate-release fentanyl in relieving breakthrough pain in chronic NP patients with opioid tolerance. This is also the main direction of studies on fentanyl therapy for NP. In a multi-center, randomized, double-blind, placebo-controlled open-label study, Simpson DM *et al.* (12) enrolled persistent chronic NP patients, including those with diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), neuropathic pain after nerve injury and complex regional pain syndrome (CRPS), to determine the analgesic effect of immediate-release fentanyl lozenge for episodes of breakthrough pain. Of the 79 participants in the randomized double-blind phase, 77 completed the entire treatment. Compared with placebo, immediate-release fentanyl lozenges demonstrated a quick analgesic effect and maintained for 2 hours. As a result, four-fold fewer patients needed extra drugs compared with the placebo group. Adverse effects were observed in 63% patients, mainly including nausea (13%), dizziness (13%), lethargy (10%) and vomiting (5%). Karanikolas M *et al.* (13) conducted a small prospective study to evaluate the effect of intravenously administered fentanyl in 16 cases of perioperative NP patients, which also revealed effective

alleviation of pain.

Few studies have focused on the clinical efficacy of transdermal fentanyl therapy in the treatment of MNP. One of the most representative studies was conducted by Agarwal S *et al.* (14). This prospective open-label study enrolled 53 patients with chronic NP, of which 25 cases had peripheral neuropathic pain, 19 had complex regional pain syndrome (CRPS) and nine had undergone amputation. Forty subjects completed the 16-week observation. The results showed that transdermal fentanyl therapy significantly reduced pain in those patients, as 57% (30/53) of them had pain relief greater than 30% and 37.4% reported improved quality of life.

Methadone

In the late 1930s, German chemists first synthesized methadone to safeguard against potential shortage of opiate raw materials in the face of World War II. Its name, Dolophine, was derived from the Latin word "do-lor," meaning free of pain. The drug was introduced into the U.S. soon after the end of the Second World War (1947) and widely used for treatment of narcotic withdrawal and pain. In recent years, the efficacy of methadone in the treatment of neuropathic pain are widely studied and recognized.

Methadone is a diphenylmethane, and a racemic mixture of its L- and D-isomers is used for medical purposes. Having a 50-fold stronger analgesic effect than the D-isomers, the L-isomers are almost the only source of power for methadone. As a pure opioid agonist, methadone binds mainly to μ -opioid receptors, and may also act as an NMDA receptor antagonist to inhibit pain sensitization by blocking the excitement of NMDA receptors. Hence, it is effective in reducing MNP sensitization.

Methadone is characterized by a long elimination half-life of about 72 hours; bioavailability as high as 90%; and single-dose analgesic effect sustainable for 4-8 hours. Unlike other opioids, this fat-soluble, highly protein bound (about 87-90%) substance is mainly metabolized by the P450 enzyme in the liver into inactive pyrroline and pyrrolidine, so there is no accumulation of toxic metabolites. Since a small portion of the original chemical is excreted from the bile, its metabolism relies strongly on liver function, eliminating the risk of accumulated toxicity for patients with renal failure.

Despite its double-action mechanism and low price, methadone is not widely used in the management of cancer-related pain. The reason may due to its reputation for the effect on narcotic withdrawal, as well as a long half-life and great individual differences in metabolism, particularly among the vulnerable elderly and children (15). Currently, this drug is often prescribed by experienced pain specialists or palliative care



specialists.

Immediate-release tapentadol

Nucynta is co-developed by Grünenthal and Johnson & Johnson. On January 23, 2008, Johnson & Johnson filed a new drug application with the FDA, which was approved on November 21. On February 17, 2009, U.S. Drug Enforcement Administration (DEA) proposed that the drug be included in the list of class II controlled substances. However, based on the findings of pre-clinical animal studies (lower risk of tolerance and drug abuse than morphine), Johnson & Johnson attempted to apply for inclusion in the list of class III controlled substances. That brought on long consultation and communication and resulted in the delay of market entry, though the drug was eventually listed as a class II controlled substance on June 22, 2009 by EDA. On June 23, 2009, the drug entered the U.S. market with approvals from both FDA and EDA. On August 10, 2010, it passed the EU Decentralised Procedure and was approved for application in the 26 member countries of EU, with both sustained-release and oral liquid being available.

Tapentadol is the first novel centrally acting analgesic approved by the U.S. FDA in the last 25 years. With a dual mode of action, it not only activates μ receptors but also acts as an $\alpha 2$ -norepinephrine receptor antagonist to inhibit norepinephrine reuptake. Despite similar chemical structure to tramadol, it has a stronger analgesic effect, but slightly weaker than morphine. Currently, tapentadol is approved by the U.S. FDA for the treatment of moderate to severe acute pain. However, since norepinephrine reuptake inhibitors are often prescribed in combination with opioids to enhance the analgesic effect for chronic malignant pain and neuropathic pain, the dual mechanism of action will empower this analgesic with ample prospects in this field.

Levorphanol

Levorphanol is another strong opioid analgesic with a dual mode of action, often used in the management of severe pain. First successfully developed in Germany, 1948, it is the levorotatory stereoisomer of morphinan and a pure opioid agonist. It has affinity to μ , κ , and δ opioid receptors, but lacks complete cross-tolerance with morphine. Relevant basic studies were described as early as 1971. Levorphanol acts similarly to morphine but with a 4- to 8-fold potent. An oral dosage of 4 mg is equivalent to about 30 mg of oral morphine, while intravenous administration has a 2-fold efficacy. With a longer half-life and duration of action (4-15 hours) than other commonly seen opioids, levorphanol

is often used for managing chronic non-cancer pain and cancer-related pain. As an opioid receptor agonist, this substance plays the same role as methadone and ketamine to block central sensitization by competitively binding to NMDA receptors against excitatory amino acids. It is getting more attention due to its role as a serotonin–norepinephrine reuptake inhibitor by interacting with σ -receptors. Tritium has been used as a radioactive marker of morphinan in studies to locate opioid receptors in the human nervous system.

In 2003, a randomized controlled study on the effect of levorphanol on peripheral and central neuropathic pain was published on the New England Journal of Medicine by Michael C, *et al.* (16) from the University of California School of Medicine, which enrolled 81 eligible subjects to randomly receive high-dose and low-dose oral levorphanol for 11 weeks (3 weeks for titration, 4 weeks for maintenance, and 4 weeks for readjustment). The average dose was 2.7 mg/d for the low-dose group and 8.9 mg/d for the high-dose group. As a result, pain alleviation was much better in the high-dose group. The study received universal praise as soon as it was published. Some researchers believed that the clinical application of this substance should be reevaluated on the level of the dual mechanism of action, and some even considered the drug as a "long-forgotten" solution for NP. Lately, an increasing number of clinical trials on this drug have confirmed its effect in treating neuropathic pain.

Tramadol

Tramadol is a weak synthetic opioid developed by Grünenthal GmbH in 1962. As a weak opioid to treat moderate cancer pain according to the WHO 3-step ladder, it shows no obvious selective affinity to μ , κ and δ receptors. Its active metabolite, O-desmethyiltramadol, has much stronger affinity to the μ receptor than tramadol and is thereby the most essential active component. Tramadol inhibits both uplink and downlink transmission of pain by activating opioid receptors in the upward chain or suppressing the activation of opioid receptors in the downlink, respectively. The latter is achieved by activating the two descending inhibitory pathways: the nerve fibers projected from the periaqueductal gray to the spinal cord that release neurotransmitter 5-HT; and those projected from the locus coeruleus to the spinal cord that release norepinephrine. The two types of fibers indirectly inhibit the upstream conduction system through synaptic connections with inhibitory neurons in the spinal cord, thus achieving analgesic effects.

In view of the double mode of action, tramadol has been increasingly used in recent years for treatment of neuropathic pain and has shown some remarkable results. Therefore, the



Guide for Neuropathic Pain Therapy published in the 2010 edition of the European Federation of Neurological Societies (EFNS) has adopted Class A evidence from randomized clinical trials to list tramadol as a first-line analgesic along with tricyclic antidepressants, pregabalin and gabapentin.

Few clinical trials have used tramadol for the treatment of MNP. In a prospective clinical study on malignant neuropathic pain, Mishra S *et al.* (17) enrolled 818 patients for a 6-month observation. The results showed significant pain relief in all of the treatment groups: tramadol, codeine, morphine and amitriptyline, gabapentin or dexamethasone combination.

In summary, the analgesic efficacy of opioids in treating NP and MNP has been confirmed by a number of well-designed clinical trials. Given their rich variety and formulation, different pharmacological characteristics and mechanisms, more prospective randomized studies are especially required to further verify their different therapeutic effects and provide more powerful evidence to guide our clinical practice. Compared with chronic non-malignant neuropathic pain, MNP is relatively complicated and always combined with nociceptive pain. So, it's difficult to conduct a strictly designed RCT study. It may be sensible to carefully refer to the results in non-cancer NP.

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