

Comparison of The Effects Between Different Opioid Receptors Painkiller

Zhenni Feng ¹, Mingrun Han ², Xiaoyu Liu ^{3,*}, Anyi Sun ⁴

¹ Shanghai Nordanglia Chinese International Schhol, Shanghai, China

²Hengshui No.1 Middle School, Hengshui, China

³Department of Biological Science, Xi'an Jiaotong-Liverpool University, Suzhou, China

⁴Department of Biological Science, Shanghai Jiaotong University, Shanghai, China

* Corresponding Author Email: xiaoyu.liu1902@student.xjtlu.edu.cn

Abstract. In searching for various kinds of painkillers and comparing the pharmaceutical effects of them, morphine and M6G, metadon, sufentanil are the most common and attractive among all the painkillers. The content below would mainly introduce the mechanism of opioid painkillers, which include the receptors and process of how opioids work, and these four drugs in their sources, effective dose, therapeutic effects and side effects. Except the same point of reliving pain, these drugs have different specialties and contraindication, so study them respectively and analogy them in different fields is essential to distinguish them and use them in different situations. Although the data from those literature is very convinced, there are still more studies need to be done to figure out more advanced drugs in the future.

Keywords: Painkillers, Opioid receptors, Morphine.

1. Introduction

In modern society, the treatment of medical conditions is not only a medical issue, but also an extremely broad social issue. Pain is very common in life and varies in severity. Their presence can help people to avoid certain dangers or to recognize information and act as a signal. For example, when humans feel pain in the stomach, they may choose to use some drugs to relieve the pain. One example is cancer. Cancer exists due to many factors, external or internal. There is no denying that cancer is a serious threat to human health and life [1]. The WHO has pointed out that 70% of advanced cancers worldwide can have significant pain, and at least 3.5 million cancer patients suffer from pain every year, only some of whom may receive reasonable and effective pain treatment. In China, only 41% of patients suffering from cancer pain get effective relief, and only 25% of advanced cancer pain gets effective relief. Pain relief for this group of patients requires high-dose, long-term use of narcotic analgesics. Less than 0.2% of patients with long-term cancer pain are suspected to be addicted to treatment. The painkiller is very useful in clinical realm, it can release the tension of patient before the operation and decline the pain of some specific diseases which make people suffer a lot. For many years, physicians have favored the use of opioids [2].

And opioids are a common painkiller and can be used to relieve moderate to severe pain. While the use of this type of medication is effective, it also has many side effects that are difficult to ignore. Examples include addiction, nausea and vomiting, dizziness, and diabetes. Depending on the type, the side effects can also vary slightly. Opioids medication include morphine, methadone, sufentanil, oxycodone, codeine, and dulcolax. The above drugs are used in the course of daily treatment depending on the patient's condition.

For example, sufentanil is an opioid with the strongest analgesic effect among painkillers, and its analgesic intensity is 5~10 times that of Fentanyl. According to the different dosage, there are three methods of Sufentanil intravenous anesthesia: high dose, medium dose and low dose. High dose is 8-50 µg/kg body weight, used for anesthesia in cardiothoracic surgery, neurosurgery, and other complex large operations. Medium dose is 2-8 µg/kg, mainly used for anesthesia of complicated general

surgery. The low dose is 0.1-2 $\mu\text{g}/\text{kg}$, used for induction of general anesthesia or anesthesia for small outpatient operations [3].

The main text will focus on the comparison between morphine and other analgesics. The comparison will be done from different perspectives, such as method of use and dosage, onset of action, analgesic effect, side effects, types of binding receptors, and effects on various systems.

2. Mechanism of Pain production

When the opioid is eaten or injected into people's body, it can be transported to specific parts of brains with the help of blood flow. Due to its fat-soluble and micro-molecular features, it can pass through the membranes, and gets to synapses. It can specifically combine with opioid receptors both on presynaptic and postsynaptic membranes [4].

And the opioid receptors consist of two parts. the receptor and the G protein. And the G protein is divided into G_α , G_β , and G_γ . Once the opioid combines with the receptor, it will cause structure change of the protein, and then result in the separation of the whole, and each part has its function. On the presynaptic membrane, the G_β and G_γ can combine with the calcium channels, and keep them closed, preventing calcium ions flowing in, so it is hard to make vesicles and release neurotransmitters, which is crucial in passing action potential between synapses. When it comes to the postsynaptic membrane, oppositely, they can combine with potassium channels and keep them open, promoting potassium ions to flow out, which causes hyperpolarization of the postsynaptic neuron, making it harder to have depolarization. Both can be great factors constraining the spread of pain action potential [5].

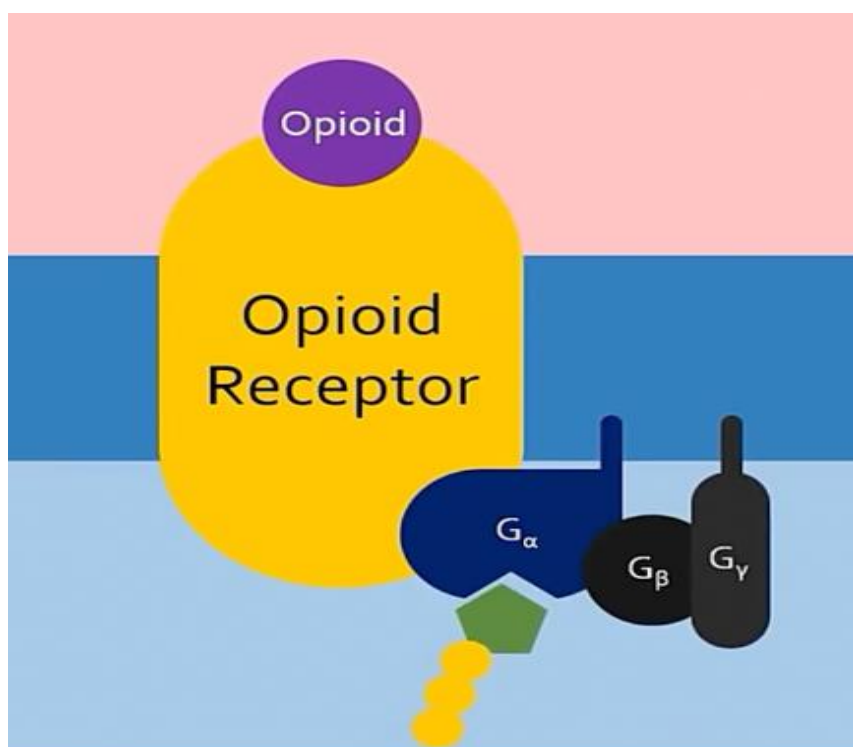


Fig 1. Main mechanism of opioid receptors

There is a natural substance called cAMP in human's cells, which can combine with protein channels, and promote or inhibit the transportation of ions, for instance, it can help calcium ions to flow in, while inhibit Potassium ions from flowing out. It is literally helpful in the spread between synapses. However, the G_α can combine with and paralyze the enzyme called adenyl cyclase, whose function is generating the cAMP. So, it indirectly constrains the spread by inhibiting the generation of cAMP. These are the basic mechanisms of opioid receptors [6].

3. Painkillers

3.1. Morphine

Morphine is extracted from the opium poppy and is a powerful painkiller. It can be taken for both acute pain and chronic pain. For example, mostly used for severe pain caused by trauma, surgery, burns, et cetera. There are several methods used to administer morphine: oral; via inhalation; by injection, such as muscle, intravenously or into the space around the spinal cord; or via rectal suppository. The following four aspects will be introduced: its pharmacological effects, clinical applications, and possible adverse effects [7].

Table 1. Morphine affects parts and the effects of its different aspects of action

	Pharmacological action	Clinical application	Adverse reaction
CNS	Primary agonist opioid μ receptors	1. Pain 2. Pre-anesthetic drugs	1. Respiratory depression 2. Dizziness, nausea, vomiting 3. Continuous medication: tolerance, dependence, addiction 4. Abrupt discontinuation: withdrawal symptoms
Smooth muscle	1. Digestive tract 2. Anti-contractin: reduces uterine tension, frequency and amplitude of contractions. 3. Increases ureteral and bladder sphincter tension	Diarrhea	1. Constipation 2. Induce aggravation of biliary colic
Angiocarpy	1. Dilates resistance vessels and cerebral blood. 2. Reduce the load on the heart.	Cariogenic asthma	Orthostatic hypotension

The first is the effect on the central nervous system, which mainly acts on various parts of this system. For example, the glial region of the spinal cord, the midbrain, the respiratory center of the brainstem, the hormone-producing part of the hypothalamus, and the regulating center. Its clinical application is mainly for pain suppression, but also as a pre-anesthetic drug. In the trial for pain relief in patients with advanced cancer, the mean initial dose was 40 mg/day in 216 patients: the mean maximum dose was 90 mg/day; the mean maintenance dose was 60 mg/day: the mean duration of dosing was 47.5 days, with the regimen reaching 425 days. The actual dose was 30-1050 mg/day. 173 patients were treated in the order of death11: (72% in 124 cases): pain relief after radiotherapy and chemotherapy (12% in 20 cases). The disease progression (coma) can take the drug (19 cases accounted for 11%); adverse reactions (10 cases accounted for 5%); only one patient due to the occurrence of severe respiratory depression, the drug was discontinued after one dose [8].

By using morphine will also cause some possible side effects. Some examples are respiratory depression, dizziness and nausea. The frequency of administration may also produce different effects, the continuous use may lead to tolerance, or even dependence. Drug resistance is the decrease in the strength of the body's response to a drug after repeated use, as evidenced by the gradual increase in the dose and the shortening of the interval between doses. Dependence refers to both physical and mental dependence. There are many possible causes. For example, receptor down-regulation, receptor phosphorylation and decreased sensitivity, inability to bind to the drug due to receptor invagination,

and G-protein decoupling [9]. Abrupt discontinuation can lead to withdrawal reactions. After discontinuing the drug, patients may experience excitement, insomnia, tears, sweating, tremors, vomiting, diarrhea, and even loss of consciousness, all of which can cause great pain. For example, morphine and heroin withdrawal symptoms begin 6 to 10 hours after withdrawal, and are most severe 36 to 48 hours after withdrawal. Alternative therapies can be chosen for the condition, using methadone or dihydroetorphine alone or in combination, with 6 to 7 days of protest for basic detoxification [10].

Drug overdose can also lead to acute intoxication. The specific manifestations are coma and respiratory depression (2 to 2 times/min), pinpoint pupil constriction, decreased blood pressure, decreased body temperature, shock and even respiratory paralysis (the main cause of death). Patients can be given artificial respiration, oxygen and opioid receptor blocking drugs [11].

In addition to the central nervous system, morphine can also be used to act on smooth muscle. It is distributed in the walls of the arterial and venous vessels of the body, the bladder, the uterus, the male and female genital tract, the digestive tract, the respiratory tract, and the eyes. Morphine has an effect on inhibiting peristalsis and the secretion of digestive juices. It can also increase the tension of the ureter and bladder sphincter. Clinical applications can be used for non-bacterial, wasting diarrhea to reduce symptoms. The adverse effects of morphine are constipation and induced colic.

The last application is about cardiovascular. Its pharmacological action is mainly used to dilate resistance vessels and cerebral vessels, and can reduce the load on the heart. This means that morphine can be used to relieve cardiogenic asthma. Dyspnea due to sudden onset of pulmonary edema in acute left heart failure is called cardiogenic asthma. It can be effectively treated with oxygen as well as intravenous morphine. The treatment of this condition is based on the principle of dilating the peripheral blood vessels and reducing the pre and after load of the heart. The adverse effect of this type is caudal upright hypotension [12].

3.2. Morphine-6-glucuronide (M6G)

Morphine-6-glucuronide (M6G) is a major active metabolite of morphine, which has analgesic effects more potent than morphine's.

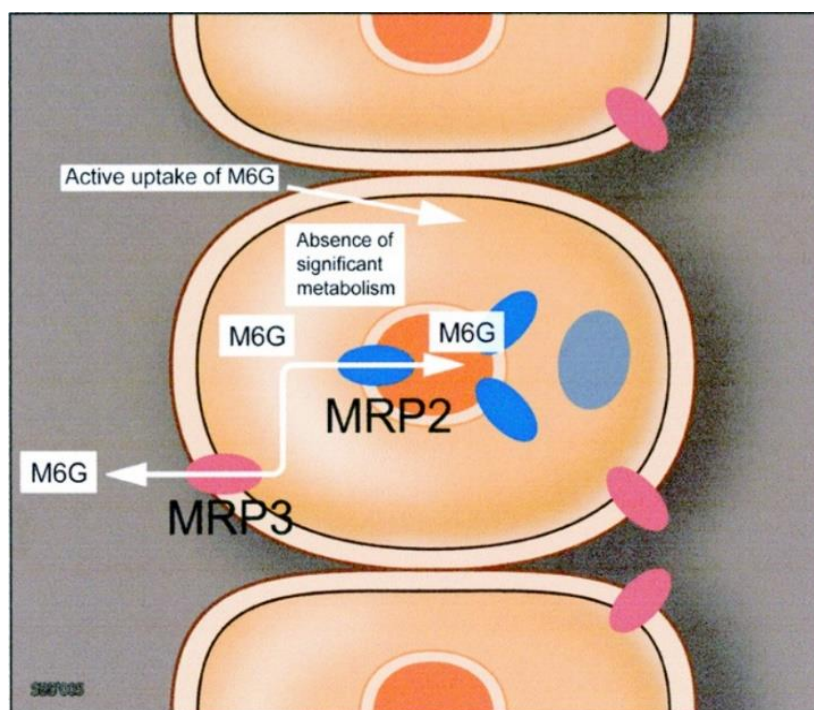


Fig 2. Transport of M6G in hepatocytes. $M6G(\text{substrate}) \rightleftharpoons MRP2 \& MRP3$

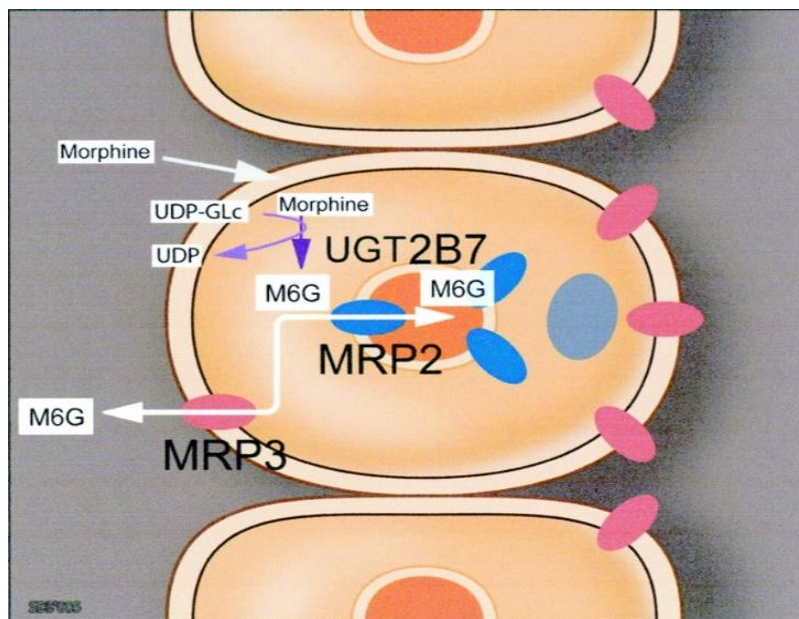


Fig 3. Metabolism and transport of morphine in hepatocytes.

As shown in figures, figure 1 shows the transport of M6G in hepatocytes [13]. M6G is actively pumped from the blood into the liver cell via a yet unknown transporter protein. M6G is not metabolized but is the substrate of efflux transporter proteins, multidrug resistance proteins Mrp3 and Mrp2. Figure 2 shows the metabolism and transport of morphine in hepatocytes. Morphine is metabolized in the hepatocyte to morphine or morphine-3-glucuronide (M3G) and M6G in a reaction catalyzed by UDP glucuronosyl transferase 2B7 (UGT2B7). Both glucuronides are proteins multidrug resistance proteins Mrp3 and Mrp2. In humans, after intravenous M6G infusion, little or no morphine or morphine-3-glucuronide (M3G) is detected in plasma, which suggesting that M6G is not significantly metabolized. M6G is deglucuronidated in the gut and the product morphine molecule is partly taken up by enterocytes. And then enterocytes are able to glucuronidate morphine and transport the resultant glucuronide to the bloodstream. M3G and M6G are cleared by the kidneys and accumulated in the kidney failure [14].

The affection of M6G has been widely accepted as a strong agonist at the μ -receptor. It has been stated that M6G provided approximately 85% of the analgesic effect of morphine. According to data that collected, classified and analyzed by Klimas, R., & Mikus, G. (2014), the compounds of plasma AUC (area under the concentration– time curve) data is used as a distinction measure. Since the different routes of drug administration, mutable dose and diversity research participants, the report data of C_{max} (maximum concentrations), AUC and mean concentrations reveal a large variation. Nevertheless, data are very consistent regardless of the morphine doses used or the pharmacokinetic parameter reported when compute the comparative contributions of morphine and M6G to the whole effect (Table below). Besides, based on AUC data (Table below), the comparative contribution of M6G partly dependent on the route of morphine administration with 96.6%--oral, 85.6%--s.c., 85.4%--i.v., 68.3%--i.m. and 91.3%--rectal administration.

As the data demonstrated in the experiments, when morphine is given i.v. as a single dose, about 80% of the total analgetic contribution is from M6G. 97.6% of the analgetic effect was contributed to M6G when morphine is given orally in renal insufficiency patients. As mentioned before, M3G and M6G are accumulated in the kidney failure, hence, M6G would occur to a higher contribution to analgesic effects after multiple administration of morphine.

3.3. Metadon

Methadone is an opioid receptor agonist. Its pharmacological action is similar to that of morphine, and its analgesic efficacy and duration is comparable to that of morphine. This product can also produce respiratory depression, cough, temperature, pupil contraction, sedative effect is weak, but

repeated administration can still cause obvious sedative effect. It has obvious inhibitory effect on respiratory center, and has obvious pupil contraction effect and smooth muscle excitation effect. It is used for all kinds of pain and severe pain caused by trauma, operation, advanced tumor, etc. It is characterized by effective oral administration, long duration of action to inhibit the withdrawal symptoms of morphine addicts, and still effective after repeated administration. The onset of tolerance and addiction was slow, and the withdrawal symptoms were mild, but the withdrawal was difficult [15].

Regarding the effect of methadone on the central nervous system, the first analgesic effect is manifested by binding to opioid receptors (μ -receptors) in the body's anti-pain system (thalamus, ventricle, periaqueductal gray matter and spinal cord glial area), mimicking the effect of endogenous opioid peptides, improving the pain threshold and reducing the body's perception of pain. The second is sedative and hypnotic effect, which is manifested by inhibiting the upward activation system of

brainstem reticular structure, resulting in sedative effect. Binds to opioid receptors in the limbic system, eliminating emotional responses to pain while improving sleep by reducing pain and emotional responses. About to euphoric effects, its performance is excited brain reward pathway (ventral septal nuclei, the ventral tegmental area) and prefrontal cortex (including μ -receptor, weaken or remove inhibitory gamma-aminobutyric acid (GABA) inhibition of dopamine neurons, neurons make the reward pathway in the brain dopamine neurotransmitter release increased, and the corresponding dopamine receptor, It causes the organism to experience euphoria. The effect of respiratory depression is manifested as reducing the sensitivity of respiratory center to carbon dioxide tension and inhibiting the pontine respiratory regulatory center, resulting in central respiratory depression. We also inquired about the effects of methadone on the immune system, and about plasma proteins, which were shown to increase plasma α_2 and β -globulin, IgM and IgG. You can see lymphocytosis. About allergic reaction, can promote mast cells to release histamine, skin itching, urticaria, rash, skin edema and joint swelling pain; Rare hemorrhagic urticaria.

Intravenous methadone takes effect in about 4 min and binds plasma proteins. The rate is about 60%~90%, which is widely distributed in the whole body tissues and can penetrate the placenta. Barrier and distribution into milk. Methadone is mainly metabolized in the liver as N-demethylation and cyclization reaction, metabolites are inactive, metabolites. The original form of methadone is excreted through feces and urine. Individual pharmacokinetics of methadone. There are large differences, single or repeated administration, pharmacokinetic characteristics are also very. The elimination half-life varies widely (the range is reported to be 15-60 h), the half-life of single administration can exceed 18 h, when repeated administration, Dosage needs to be carefully adjusted. Methadone accumulates in adipose tissue The adina period is related to the fat ratio or the individual patient. Low doses of methadone (5-10mg). The analgesic half-life of 10 mg is shorter than the elimination half-life and may lead to disease. Increased frequency of drug administration and drug accumulation. When given 20 mg or higher. At dose, the half-life was close to the analgesic effect, about 35 h.

3.4. Sufentanil

Sufentanil is one of the Derivatives of Fentanyl. It can combine with μ opioid receptors, and have a quick and effective function in reducing pain. The efficiency of Sufentanil to release pain is 9.3 times higher than Fentanyl, and approximately 2304 times higher than Morphine. And that is because the efficiency of Sufentanil to combine with μ opioid receptors is 7.7 higher than Fentanyl, and Sufentanil have a high selectivity towards μ opioid receptors than δ receptors, so it have a faster and more accurate way to target μ receptors. Besides, the fat-solubility of Sufentanil is twice higher than Fentanyl, which means Sufentanil features faster and more flexible to get through the vascular walls and play its part in brain [16].

The same as Fentanyl, the actuation duration of Sufentanil is relative to the dose injected, but with the same dose people inject, Sufentanil have a quicker time to release pain and return to the original state, which is because the distribution volume and elimination half-life of Sufentanil is both smaller

than Fentanyl. After injection, the time to start work of Morphine, Fentanyl and Sufentanil is 15, 5~9 and 3 min, and in terms of the time to return to the original state, Sufentanil is the fastest as well.

Sufentanil has few effects to human's bodies. Not only does Sufentanil have a high efficiency to reduce pain, Sufentanil also features low in toxic effect and wide in scope of application, because the analgesic effect of Sufentanil can be quickly and effectively antagonized by Propylene Normorphine and Naloxone. As for the effects of Sufentanil to circulatory system, Using Sufentanil can reduce cardiac index, heart rate and myocardial oxygen consumption, but compared with fentanyl, it will make the patient have a more stable vascular circulation state, which can stretch the blood vessels without myocardial inhibition. When it comes to the effect to respiratory system, The respiratory system of the human body will be inhibited when using Sufentanil, which changes when dosage is different. After the injection of Sufentanil, the expansion of the chest wall will become very rigid, so that the breathing resistance will become huge. However, fentanyl will inhibit breathing more, and the recovery time is also longer.

A small amount of Sufentanil is always being injected before the operation for its clinic use, which can relieve the tension and reduce the possibility of inhibiting breathing, in comparison to Fentanyl. The dose of intravenous Sufentanil should be determined according to the specific situation of the patients, such as age, body mass, combined use of other drugs and operation types. The dosage should be reduced for frail and elderly patients as well as those who have used respiratory drugs and those with poor liver, because Sufentanil needs to be metabolized mainly by the liver, and poor liver conditions will damage the body. Patients who have received opioid treatment or have a history of opioid abuse need to use larger agents, because the sensitivity of Sufentanil is much lower than normal people [17].

To sum up, Sufentanil not only has good analgesic effect and high safety, but also has few adverse reactions. It can effectively reduce the pain and shorten the recovery time of the patients. It is worth popularizing in the clinic.

4. Conclusion

The human sensation of pain can help avoid and prevent a certain level of danger, such as cuts, and pain in individual body parts. As the severity of a disease increases (e.g., cancer), the pain sensation also increases. Likewise, pain medication is needed during and after surgery. Even everyday symptoms such as headaches can be relieved by pain medication. Therefore, painkillers are developed and manufactured. Due to the current development in the field of medicine, the variety of analgesics is increasing. The initial morphine extracted from poppy flowers and manufactured to other types such as M6G, sufentanil, methadone and so on. Although all of these drugs are opioids, the actual degree of effect provided by different drugs varies by finding experimental data. The application in the clinical field also needs to be considered in the light of the actual situation before use. Based on the data concluded so far, more versatile and effective painkillers will be developed in the future.

References

- [1] Young, P. J., & De Jong, A. (2021). New Insights into the Comparative Effectiveness of Fentanyl and Morphine Infusions in ICU Patients [J]. *American journal of respiratory and critical care medicine*, 204(11), 1243–1245.
- [2] van Dorp, E. L., Romberg, R., Sarton, E., Bovill, J. G., & Dahan, A. (2006). Morphine-6-glucuronide: morphine's successor for postoperative pain relief [J]. *Anesthesia and analgesia*, 102(6), 1789–1797.
- [3] Nagamatsu, K., Ohno, Y., Ikebuchi, H., Takahashi, A., Terao, T., & Takanaka, A. (1986). Morphine metabolism in isolated rat hepatocytes and its implications for hepatotoxicity [J]. *Biochemical pharmacology*, 35(20), 3543–3548.

- [4] Mitchell T B, White J M, Somogyi A, et al. Switching between Methadone and Morphine for Maintenance Treatment of Opioid Dependence: Impact on Pain Sensitivity and Mood Status [J]. American Journal on Addictions, 2010, 15(4):311-315.
- [5] Dong Xing, Li Chen, Liru Guo, Lantao Wang, Xiaoli Liu. A comparative study of intranasal sufentanil drip versus subcutaneous morphine injection for the treatment of cancer eruption pain [J]. Chinese Journal of Pain Medicine, 2022, 28(02):119-124.
- [6] Yuan Zeng, Guohua Wang, Yong Yang. Comparative study on the efficacy of hydromorphone, sufentanil and morphine in intravenous self-administered analgesia in patients with refractory cancer pain combined with oral difficulties [J]. Chinese General Medicine: 1-9[2022-08-20].
- [7] Tongbao Zhan, Liangshuang Yin, Weiwei Tong, Chunfang Fan, Xiaohong Bai, Jinbo Cheng. Effects of methadone maintenance treatment on attentional bias in heroin-dependent patients [J]. Chinese primary care medicine, 2020, 27(9):1030-1034.
- [8] Guangwei Geng. (2019). An exploration of methadone drug interactions [J]. Electronic Journal of Clinical Medicine Literature.
- [9] Kangyu Morimoto. Pain-related response and nociceptive processing in the central nervous system [J]. Modification by diltiazem, morphine or clonidine.
- [10] Chunyin Wu, Xiaoqing Chai, Shuhua Shu, Min Zhang, Chuanyao Li. Effects of different opioid receptors on hyperactivity and analgesic process induced by hydrocodone hydrochloride in mice [J]. Chinese Journal of Gerontology, 2017, 37(10):2376-2378.
- [11] Artificial intelligence and opioid use: a narrative review medRxiv [J]. Pain Med. Pub Date: 2022-07-25 Seema Gadhia, Georgia C Richards, Tracey Marriott, James Rose.
- [12] Klimas, R., & Mikus, G. (2014). Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucuronide, and morphine-3-glucuronide [J]. British journal of anaesthesia, 113(6), 935–944.
- [13] Hao Pei, Ailin Luo. Pharmacological effects and clinical applications of sufentanil [J]. Pharmacopoeia, 2009, 28(11):1482-1485.
- [14] Qiaoqiao Yan. Pharmacological effects and clinical applications of sufentanil [J]. Health (Academic Edition), 2015, 9(04):138.
- [15] Dongxue Bai, Huifen Zhu. The standardized use of morphine injection [J]. Chinese aesthetic medicine 2010, vol. 19, no. z1, 153 p., ISTIC CA, 2010.
- [16] Zhiji Cai. A comparison of the application of narcotic analgesics in China with the global status quo [J]. Chinese Journal of Clinical Pharmacology. 1993, 9(4):215
- [17] Cunde Wang, Kun Liu, Bo Jiang. Clinical efficacy analysis of morphine controlled-release tablet dose titration in the treatment of cancer pain [J]. Chinese practical medicine, 2002.