DOI: https://doi.org/10.17816/RA624003

History and prospects for the use of morphine in clinical practice: a literature review

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ABSTRACT

The authors analyzed various studies on acute and chronic pain syndrome treatment. This review provides brief historical data on the discovery and use of morphine from ancient times to present. Morphine remains one of the most common painkillers worldwide and has a rich history dating back more than 200 years. Its basic properties, pharmacokinetics, pharmacodynamics, and principles of use are discussed. No drug has had such an impact on society as morphine because of its medical use as a pain reliever and its illicit use as a drug of addiction and abuse. This review includes the main modern recommendations for the treatment of acute and chronic pain, particularly from the World Health Organization for the treatment of chronic pain and the Procedure-Specific Postoperative Pain Management (PROSPECT) group for the treatment of postoperative pain in various surgical interventions. The types of opioids and their clinical use are described, and the authors' opinion on the current use of morphine for treating acute and chronic pain syndrome is presented.

Keywords: morphine; history; application.

To cite this article:
Raspopin YuS, Shifman EM, Feoktistova DA. History and prospects for the use of morphine in clinical practice: a literature review. *Regional anesthesia and acute pain management.* 2024;18(1):33–40. DOI: https://doi.org/10.17816/RA624003

Received: 28.11.2023 **Accepted:** 31.01.2024 **Published:** 29.02.2024

DOI: https://doi.org/10.17816/RA624003

История и перспективы применения морфина в клинической практике: обзор литературы

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АННОТАЦИЯ

Проанализированы различные материалы по лечению острого и хронического болевого синдрома. В обзоре представлены краткие исторические данные открытия и использования морфина начиная с древних времен и до настоящих дней. Морфин остаётся одним из самых распространённых обезболивающих средств в мире, имеет богатейшую историю, насчитывающую более 200 лет. Освещены основные свойства препарата, его фармакокинетика и фармакодинамика, принципы применения. Ни один препарат не оказывал такого влияния на общество, как морфин, благодаря его медицинскому применению в качестве обезболивающего препарата, а также по причине незаконного употребления в качестве наркотического средства, вызывающего привыкание и злоупотребление. В обзор включены основные современные рекомендации по лечению острой и хронической боли, в частности рекомендации Всемирной организации здравоохранения по лечению хронической боли и группы PROSPECT (Procedure-Specific Postoperative Pain Management) по лечению послеоперационной боли при различных оперативных вмешательствах. Описаны виды опиоидов и их клиническое применение, озвучено мнение авторов о современном месте морфина в лечении острого и хронического болевого синдрома.

Ключевые слова: морфин; история; применение.

Как цитировать:
Распопин Ю.С., Шифман Е.М., Феоктистова Д.А. История и перспективы применения морфина в клинической практике: обзор литературы // Регионарная анестезия и лечение острой боли. 2024. Т. 18, № 1. С. 33–40. DOI: https://doi.org/10.17816/RA624003

Рукопись получена: 28.11.2023 **Рукопись одобрена:** 31.01.2024 **Опубликована онлайн:** 29.02.2024

BACKGROUND

With a history going back centuries, morphine continues to be one of the most widely used analgesics in the world. The alkaloid morphine was discovered by Friedrich Sertürner in 1803, but the history of opium use goes back more than 1000 years. Few drugs have affected society as much as morphine, due to its use for pain relief and its illicit use leading to addiction and abuse. Worldwide sales and production of opium-derived drugs are increasing each year, making up approximately 900 tons per year [1].

AIM

Our aim was to briefly review the history of morphine use and present a modern view of its place in the treatment of chronic and acute pain syndromes.

SEARCH METHODOLOGY

The databases and electronic libraries PubMed (MedLine), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, eLibrary.ru were searched for the articles published in English and Russian from 1 January 1940 to 15 July 2023. The search query included English and Russian words and phrases such as "morphine" (морфин), "history of morphine" (история морфина), "spinal anesthesia with morphine" (спинальная анестезия морфином), "epidural anesthesia with morphine" (эпидуральная анестезия морфином), "chronic pain, morphine" (хроническая боль, морфин), "acute pain, morphine" (острая боль, морфин). The search identified more than 75 000 articles, focusing on clinical guidelines, systematic reviews, meta-analyses, and historical articles. As a result, 31 papers were reviewed.

DISCUSSION

History of the discovery and use of morphine

The history of discovering morphine and its derivatives goes back several thousand years. They are mentioned in such great writings as those of Homer, Paracelsus, Hippocrates, Theophrastus, etc. Called the "plant of joy," opium was used to treat a variety of conditions in both adults and children, including pain of various origins, restlessness, coughing, bleeding, diarrhea, and even colds. The return of opium to Europe in the early 1500s is associated with the name of the Swiss physician Paracelsus. He popularized the use of *Laudanum*, an alcohol tincture of opium. It was used to treat conditions like weakness, fatigue, insomnia, coughs, diarrhea, and of course pain of various origin [2]. The modern discovery of morphine has been associated with the name of the German pharmacist Friedrich Wilhelm Adam Sertürner. In 1803, Sertürner isolated a crystalline substance from opium and later named it morphine in honor of Morpheus, a Greek god associated with sleep and dreams, because the new substance could induce a dreamlike state [3, 4]. It was the first pure alkaloid isolated from plants [5]. In 1806, the young pharmacist published several papers on a new substance that interested the French chemist Joseph Louis Gay-Lussac, who translated them into French. As a result, Sertürner's research was widely recognized, and the scientist was awarded an honorary doctorate from Jena University [6]. Since then, the alkaloid has been the subject of intense research, with the discovery and study of the opioid receptor system and its effects on the body.

In the mid-1800s, commercial manufacturing of morphine began, and the invention of the syringe and needle made it easier to use. With no other treatment options, doctors regularly recommended morphine for chronic pain and even promoted it as a way to overcome opiate addiction. At the same time, a war broke out between the European countries and China over the right to import opium [7]. Morphine was widely used during the American Civil War in 1861 to treat wounded soldiers who later became addicted to it, often overdosing and dying. In the 1880s, morphine abuse was considered an ethical rather than medical problem. Between 1870 and 1880, the use of morphine more than tripled. At that time, scientists were searching for new forms of painkillers that would not have the negative addictive effects of morphine. In the late 19th century, in 1874, the English chemist Alder Wright created heroin by acetylating morphine with acetic anhydride. For a long time, doctors believed that heroin was a cure for morphine addiction. In fact, it turned out to be more addictive than morphine [8].

Until the 1900s, the use and distribution of opioid drugs was unregulated. Morphine and opium could be used legally without a doctor's prescription. Therefore, governments in many countries started to consider regulations that might reduce drug use. This led to the Pure Food Act of 1906 in the USA. It outlawed counterfeit drugs and required labeling of substances such as morphine. In 1914, the Harrison Narcotics Tax Act was passed to regulate and tax the production, importation, and distribution of opioids. Prescribing physicians and pharmacists were made responsible for dispensing opioids. A few years later, in 1924, a new law prohibited any use of heroin. All these measures significantly reduced morphine and opiate use [9]. In Russia, the first law On Measures Against Opium Smoking was adopted on 7 June 1915.

With the discovery of morphine, scientists tried to understand its mechanism of action. Therefore, one of the first papers [10] to discover opioid receptors dates back to 1971, when A. Goldstein et al. suggested the existence of opioid receptors using levorphanol. In 1973, C.B. Pert

and S.H. Snyder published the first detailed radioisotope study of opioid receptors with 3H-naloxone [11]. A series of studies on new receptors followed. In 1976, W.R. Martin et al. concluded from *in vivo* studies in dogs that there are several types of opioid receptors that could not be immediately distinguished. Only in 1995, some studies identified the first three so-called classical opioid receptors (μ, δ, and χ) and the fourth belonging to a new type of nociceptive receptors, ORL-1. The receptors were named MOR, DOR, KOR, and NOR, respectively. These receptors are linked to a G protein on the membrane surface with which opioids interact as ligands. The main function is pain regulation. Opioid receptors are most prevalent in the brain, but are also found in the spinal cord, gastrointestinal tract, and to a lesser extent in other organs. Acting on μ, δ, and κ receptors can produce an analgesic effect on the body, although the μ-type receptor is considered the most important. In addition, activation of μ-agonists leads to respiratory depression and severe sedation, while stimulation of κ-agonists causes psychiatric disorders [12]. By acting on opioid receptors, morphine and other opioids not only relieve pain but can also increase the rate of growth and division of cells, including malignant ones. They can contribute to a wide range of emotional states, from depression to euphoria, regardless of the actual condition of the person, and can lead to severe mental and physical dependence. In addition, opioids can decrease appetite, inhibit pulmonary ventilation, suppress gastrointestinal motility and cough reflex, etc. [12, 13].

As opiate receptors were better understood, the search and development of synthetic opioids began. Many different derivatives of morphine and other opioid drugs have been discovered. In modern clinical practice, they are widely used to treat painful syndromes [14].

Types of opioids

Two terms, "opiates" and "opioids," are used to distinguish methods of production. Opiates are natural derivatives of poppy plants, such as morphine and codeine. Opioids are all synthetic and natural substances, regardless of their mode of action on opioid receptors, which are known to stimulate or block them. Unfortunately, morphine and its derivatives have many undesirable effects. The most common effects include tolerance, withdrawal, short-term euphoria, and mental and physical dependence in case of long-term use. For this reason, most countries have strict controls on opioids and restrictions on their use [15, 16]. Since 2000, multimodal analgesia has become increasingly popular. Multimodal analgesia improves the quality of postoperative pain management and reduces the total dose of opioids used by using different analgesics, regimens, and routes of administration [17]. Nevertheless, it is not yet possible to completely replace opioid analgesics.

Pharmacodynamics and pharmacokinetics of morphine

Areas of morphine use are related to its pharmacological properties. It is a hydrophilic drug that binds only 20–35% to proteins, mainly albumin [18]. Several forms of morphine are currently manufactured, including suppositories, tablets, capsules (including sustained-release capsules), injection solutions, and oral syrups. The spinal and epidural routes of administration have been widely used, thereby reducing the total drug dose and, correspondingly, the number of side effects [19]. Morphine is rapidly and completely absorbed by any route of administration. In this case, due to its hydrophilicity, the effect starts after 30–40 minutes and lasts up to 5–6 hours. When morphine is administered enterally, it first passes through the liver, where it is highly metabolized. As a result, only about 30% of the drug reaches the systemic circulation and higher doses are required compared to parenteral administration. It is also actively metabolized in other organs, such as the brain and kidneys, where it is broken down into metabolites that are excreted in the urine and bile [20]. More recently, with the availability of sustained-release forms, oral drugs have become increasingly popular. Their effect can last up to 12 hours, reducing the need for more frequent dosing.

Currently, morphine is manufactured in two forms (water-soluble salts), such as morphine sulfate and morphine hydrochloride, which slowly penetrate the blood-brain barrier, the dura mater, and the substance of the brain and spinal cord. This is associated with a relatively late onset of action of the drug (approximately 30–40 minutes), but also with a prolonged analgesic effect which can last up to a day (depending on the route of administration and dose) [13]. The liposomal form of morphine sulfate is of particular interest. This sustained-release form consists of microparticles with lipid membranes containing morphine. This form of morphine provides a relatively rapid and long-lasting effect that can last up to a day, and up to 2 days with epidural administration. At the same time, it is less likely to cause adverse effects such as euphoria, respiratory depression, and gastrointestinal motility depression [21].

Morphine in clinical practice

Although morphine has a history dating back more than two centuries, it remains the drug of choice or the gold standard for the treatment of both acute and chronic pain. Moreover, morphine is a reference drug to which other painkillers are compared.

The analysis of PubMed literature revealed growing interest in the drug, with approximately 70 000 publications starting from 1826. Over the past 30 years, publications have focused on the clinical use of

morphine in various therapeutic areas for the treatment of chronic and acute pain.

Most developed countries, including Russia, use opioids to treat chronic pain, according to World Health Organization guidelines. They are used as the treatment of choice for the management of moderate to severe pain, starting at step 2 of the three-step ladder of analgesia, when non-opioid analgesics are not effective [22]. In this case, oral forms are usually used. The dose depends on parameters such as the patient's age, comorbidities, previous use of the drug and, of course, the patient's satisfaction with pain relief. It has been suggested that parenteral analgesia, including morphine, should be preferred. Switching to oral analgesia should occur within a few days. The effectiveness of early initiation of oral morphine is supported by several publications showing that oral analgesia is comparable to parenteral analgesia and has some advantages. First, it is a technologically simple, non-invasive, and cost-effective method of drug delivery that reduces the burden on the healthcare professional [22–24]. However, different routes of opioid administration are used in the treatment of chronic pain, depending on the situation. For example, intrathecal therapy, with an established safety profile and fewer side effects compared to oral or parenteral analgesics, is an effective treatment option for patients with malignant or benign chronic pain [19]. The 2016 Polyanalgesic Consensus Conference guidelines [25] recommend morphine and ziconotide as first-line therapy for local and diffuse chronic cancer pain and pain of other origin. Basically, these are two drugs that have been approved by the U.S. Food and Drug Administration (FDA) for intrathecal monotherapy in the treatment of chronic pain. A recent systematic review [26] confirmed the effectiveness of intrathecal morphine for the treatment of non-cancer pain. For example, a randomized clinical trial demonstrated the effectiveness of both epidural morphine and hydromorphone for the treatment of hard-to-treat postherpetic neuralgia [27].

Morphine is no less important in the treatment of acute pain syndrome, especially in the analgesia of the early postoperative period. The PROSPECT (Procedure-Specific Postoperative Pain Management) group, established in 2002 by the European Society of Regional Anesthesia and Pain Management and consisting of surgeons and anesthesiologists, provides specific recommendations for the management of postoperative pain in various surgical procedures [23]. These guidelines are based on randomized clinical trials and systematic reviews, have a high evidence base, and cover 20 surgical procedures. Morphine and other opioids are indicated to treat breakthrough pain in most major surgical procedures. It can be used in many regimens including scheduled prescriptions, patient-controlled analgesia and as an adjunct to regional analgesia. It is also used in major invasive abdominal surgery, such as caesarean section, gynecologic surgery, including treatment of malignant neoplasms, liver and spine surgery. Therefore, in obstetrics, where up to 90% of anesthetic cases are spinal, there are many randomized clinical trials, systematic reviews, and meta-analyses showing that intrathecal morphine administration is the preferred method of pain relief in the early postoperative period with a high level of evidence and reliability [28]. This option has significant advantages over systemic opioid administration. The key is to reduce the total dose of opioids to reduce the risk of adverse events without compromising the quality of pain relief [2]. Intrathecal morphine has long remained the gold standard for treating both chronic and acute pain [29–31].

CONCLUSION

The analysis of more than two centuries of morphine use suggests that intrathecal administration is the most effective and relatively safe treatment option for acute and chronic pain. Optimal opioid doses can achieve an adequate pain profile with minimal side effects. Unfortunately, there are no forms of morphine available for subarachnoid administration in Russia today. The manufacturer of morphine hydrochloride solution, the Moscow Endocrine Factory, restricts the intrathecal use of the drug in its instruction for use. Recently, however, epidural administration of morphine has become possible. The Association of Obstetric Anesthesiologists-Resuscitators is working on the possibility of approving the intrathecal route of morphine hydrochloride and producing ampoules with doses adapted to regional methods of analgesia. In response, the Moscow Endocrine Plant plans to conduct a multicenter, open label, randomized clinical trial in five large multidisciplinary hospitals in general surgery patients to confirm the effectiveness and safety of intrathecal use of the drug. The study will last one year and is scheduled to start in November 2023, so it is hoped that intrathecal morphine will be available in Russia by the end of 2024.

ADDITIONAL INFORMATION

Funding source. Not specified.

Competing interests. The authors declare that they have no competing interests.

Author's contribution. Yu.S. Raspopin — analysis of literature data, writing the text of the article; E.M. Shifman — analysis of literature data, writing the text of the article; D.A. Feoktistova — analysis of literature data.

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