History of Anesthesia

In the arms of Morpheus: the development of morphine for postoperative pain relief

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Purpose: To analyse the historical development of morphine for postoperative analgesia and how this development was shaped by the evolution of anesthetic techniques.

Methods: After a systematic review of the literature, information was gathered from primary sources.

Principal Findings: In ancient medicine, some plant derivatives were used to alleviate pain including: alcohol, cannabis, mandrake, and opium. Over the past two centuries, opium and its derivatives have become the most widely used analgesics for severe pain. Before the development of general anesthesia, surgery was only performed out of extreme necessity. It is probable that an analgesic such as opium would have been given following surgery although its use may not have been recorded. The first description of postoperative opium was by James Moore in 1784. Morphine was isolated from opium by Friedrich Serturner in 1805. However, it was not until the development of the hypodermic needle and syringe nearly 50 yr later that the use of morphine became widespread. Over the last century, various delivery systems for morphine have been developed including subarachanoid and epidural injection, and more recently patient-controlled intravenous, epidural and intranasal analgesia. In addition, many new opioids have been synthesized.

Conclusion: Since its isolation from opium almost 200 yr ago, morphine remains the most widely used analgesic and the standard against which all new opioids for postoperative pain relief are compared.

Objectif : Décrire le développement historique de la morphine comme analgésique postopératoire et montrer comment il a été façonné par l'évolution des techniques anesthésiques.

Méthode : On a d'abord passé systématiquement en revue la documentation pertinente, puis rassemblé les informations des principales sources.

Constatations principales : La médecine ancienne utilisait certains dérivés de plantes pour soulager la douleur: l'alcool, le cannabis, la mandragore et l'opium. Au cours des deux derniers siècles, l'opium et ses dérivés sont devenus les analgésiques les plus utilisés contre la douleur vive. Avant l'avènement de l'anesthésie générale, l'intervention chirurgicale n'était réalisée qu'en cas d'extrême nécessité. Il est probable qu'un analgésique comme l'opium ait été administré à la suite d'une opération sans qu'on en consigne l'emploi. La première description de l'utilisation postopératoire d'opium revient à James Moore en 1784. La morphine a été isolée de l'opium par Friedrich Serturner en 1805. Cependant, son usage ne s'est répandu qu'avec l'arrivée, 50 ans plus tard, de l'aiguille hypodermique et de la seringue. Pendant le siècle dernier, on a mis au point différents systèmes d'administration de la morphine, y compris l'injection sous-arachnoïdienne et péridurale et, plus récemment, l'analgésie intraveineuse, péridurale et intranasale contrôlée par le patient. De plus, nombre de nouveaux opioïdes ont été synthétisés.

Conclusion : Depuis que la morphine a été isolée de l'opium, il y a près de 200 ans, elle demeure l'analgésique le plus utilisé et une norme de comparaison pour tout nouvel opioïde utilisé pour soulager la douleur postopératoire.

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PAIN is an integral part of life and, as such, attempts to relieve pain must be as old as human-kind. Some of the earliest pharmacological methods of pain relief included the plant derivatives: alcohol, cannabis, mandrake, and opium.[1] These analgesics were used for surgical analgesia as long as 2500 yr ago. For example, in the ancient Indian work the Sushruta Samhita, written perhaps as early as 400 BC, it was advised that alcohol be used before surgery to produce insensibility to pain.[2] Dioscorides (Circa 54-58 AD), a Greek physician and surgeon, recommended patients should take mandrake mixed with wine before limb amputation: "For such as cannot sleep, or are grievously pained, and upon whom being cut, or cauterized they wish to make a not-feeling pain".[3] Celsus (AD 14-37) in *De Medicina* suggests the use of opium before surgery.[4] In the Middle Ages, Theodoric, a 13th century monk and physician, described the *spongia somnifera*, a mixture of several narcotic substances including, opium, mandrake, henbane, mulberry, lettuce and hemlock, all boiled within a sponge, which was then sniffed to provide anesthesia for surgery.[5]

Despite the widespread use of these compounds for surgery there were no concomitant descriptions of their application for pain relief after surgery, although it seems logical they would have been so employed. Only opium and related compounds are still used as analgesics. The evolution of opium and its derivative morphine for postoperative pain relief will be reviewed.

Opium

Opium has been known for millennia to relieve pain and its use for surgical analgesia has been recorded for several centuries as noted above. However, its use as an agent for postoperative pain relief has only been described since the late 18th century, although it may have previously been used for this purpose but not recorded. Over the past two centuries, opium and its derivatives have emerged as the most effective analgesics for postoperative pain relief.

Oral administration

Laudanum, or tincture of opium, was a mixture of opium, alcohol, and various other ingredients. It was often given in whiskey or rum and became a widely used agent to prepare patients for surgery until the discovery of effective anesthesia. There were many recipes for laudanum, the most famous being that of Thomas Sydenham (1624-89). Sydenham's recipe, given in his work on dysentery in 1669, contained 1 pound sherry wine, 2 ounces opium, 1 ounce saffron, 1 ounce powder of cinnamon, and 1 ounce powder of cloves.[6] Sydenham's laudanum was used in Europe and North America into the early 20th century. Several other opioid preparations were popular in the 18th and 19th centuries. "Black-drop", otherwise known as Lancaster or Quaker's Black Drop, contained opium, verjuice, nutmeg, saffron and yeast, and was reputedly three times stronger than laudanum. Paregoric was a weaker preparation, named after the Greek word for "soothing" or "consoling" and included opium, honey, licorice root, camphor, aniseed and wine. Dover's powder, first developed by the English physician and buccaneer Thomas Dover (1660-1742), contained opium, salt peter, tartar, licorice and ipecacuanha.[7] Dover claimed, "In two or three hours at furthest the patient will be free from pain". In addition to producing his opium-containing "sweating powder", Thomas Dover was the second captain aboard the privateer *Duke* that rescued Alexander Selkirk (Robinson Crusoe) from one of the Juan Fernández islands in 1709.

The first record of postoperative analgesia was the use of opium in 1784 by the Glasgow-born London surgeon James Moore (1763-1834). He clearly realized the limitations of opium for surgical anesthesia, but praised its postoperative benefits when he wrote: "Opium...is highly expedient to abate the smarting of the wound after the operation is over, and to induce sleep; but the strongest dose we dare venture to give has little or no effect in mitigating the suffering of the patient during the operation".[8] In the same year, Moore also devised an appliance for compression of nerves producing numbness in a limb before surgery, presumably by neuropraxia.[8]

Five years later, the Scottish surgeon, Benjamin Bell (1749-1806) also found opium compounds to be good postoperative analgesics: "In general they prove most useful when given immediately after, when they very commonly alleviate that pungent soreness of which patients at this time usually complain; and by continuing to give them in adequate doses from time to time, we are often enabled to keep the patient easy and comfortable....[9]

Analgesia following laparotomy was first described by Ephraim McDowell (1771-1830) in May of 1816. McDowell gave "...a wine glass full of cherry bounce, and thirty drops of laudanum..." to a woman following laparotomy and surgical removal of a six pound ovarian tumour, following which she recovered uneventfully.[10] Of the five cases of laparotomy and ovariotomy in his two reports, this was the only one in which McDowell recorded using postoperative analgesia.[10,11]

Rectal administration

The first reference to postoperative opium using the rectal route of administration was by Shoemaker in 1891. In his *Materia Medica and Therapeutics* he recommended a rectal opium suppository which "...quiets the nervous system after operations upon the female pelvis...".[12]

Morphine

The isolation of morphine from crude opium was one of the most important discoveries of nineteenth century medicine. In the early 1800s Friedrich Serturner (1783-1841), a pharmacist's apprentice in Germany, was working on isolating the active principle of opium. Serturner's first discovery in 1805, was a new acid, "mekonsaure" or "mohnsaure", present in opium.[13] However, trials on dogs revealed that mekonsaure was inactive. He then reported finding a water-insoluble crystalline substance which had an "almost alkaline-like character"; he called this the "principium somniferum".[14] Animal experiments proved this was indeed an active principle of opium. Serturner later named the active ingredient of opium "morphium" after the Greek god of dreams.[15] In 1817 Serturner published another paper which, unlike his previous publications, received widespread attention.[16] In a French translation of Serturner's work, Gay-Lussac added an editorial in which he suggested the name morphine rather than morphium.[17]

From the time of its discovery by Serturner, morphine was manufactured and used in an oral form, morphine acetate, which was a difficult and expensive salt to prepare. In 1831, William Gregory, an Edinburgh physician and chemist, discovered a cheap method of isolating and purifying morphine salts.[18] However, there was no financial or clinical advantage in the use of morphine over paregoric and laudanum. These traditional media for delivering opium alkaloids orally were of similar cost and efficacy, and already established in the medical and public eye. It was not until the development of the hypodermic needle and syringe in the 1850s that the use of morphine became widespread.

Parenteral administration

Intravenous injection preceded subcutaneous administration by almost two centuries. Sir Christopher Wren (1632-1723), the English architect who designed St. Paul's Cathedral, was the first to inject liquid into a vein. Working with the celebrated chemist Robert Boyle in 1659, Wren injected an infusion of opium into a vein on the hind leg of a dog using a goose quill as the needle and an animal bladder as the syringe. He noticed that "the opium...did within a short time stupify, though not kill the dog".[19]

The first subcutaneous placement of morphine was described in 1836 by the French physician GV Lafargue. His "inoculation" method involved introducing a morphine paste under the epidermis by means of a vaccination lancet.[20] Lafargue intended his inoculation method to have local effect but he speculated that systemic effect might be possible. To satisfy his curiosity he inoculated himself 13 times in the forearm and soon became overwhelmed by a sensation of extreme somnolence.[21] Unfortunately Lafargue was so preoccupied with his intention to create a local effect that he failed to recognize the significance of the systemic action of morphine even though he experienced it himself.

In 1845, the Irish surgeon Francis Rynd (1801-1861) became the first to introduce a fluid subcutaneously. In order to treat a patient with trigeminal neuralgia, Rynd developed a special instrument which could inject a morphine solution beneath the skin: "On the 3rd of June a solution of fifteen grains of acetate of morphia, dissolved in one drachm of creosote, was introduced to the supra-orbital nerve, and along the course of the temporal, malar, and buccal nerves, by four punctures of an instrument made for the purpose."[22] No description of the instrument was given - the predecessor of the modern hypodermic syringe - until his 1861 publication which described it as a retractable trocar and cannula that allowed fluid to enter the tissues by gravity alone.[23]

In 1853, the subcutaneous route of drug administration using a syringe and hollow needle was introduced by Alexander Wood of Edinburgh (1817-1884). Wood did not invent the syringe and hollow needle but modified a design already manufactured by a local chemist - a "Mr. Ferguson of Giltspur Street, London".[24] Wood's intention was to produce a local effect by injecting morphine directly into the painful area. However, when he checked on his first patient the morning following a subcutaneous morphine injection he was "a little annoyed to find she had never wakened; the breathing also was somewhat deep, and she was roused with difficulty".[24] Obviously Wood noticed the systemic effects of the morphine injection on his patient, but he maintained that its local analgesic effects were of primary importance.

The systemic action of a subcutaneous opioid injection was first fully understood in 1858 by the London surgeon, Charles Hunter. He published one paper on October 16, 1858 in the *Medical Times Gazette* advocating Wood's technique of morphine injection.[25] Two weeks later he published another paper in the

same journal, reporting that the injection of morphine at a site remote from the painful area produced equal pain relief. Hunter concluded "The idea that the relief results from localisation of the remedy in the painful part is erroneous—equal relief being afforded in either case".[26] This was the beginning of a heated debate between Hunter and Wood, which was carried out through correspondence in the *British Medical Journal* and *Lancet*. Wood claimed the local effects of morphine injected subcutaneously were of primary importance, whereas Hunter claimed the systemic effects were paramount. Part of their debate also included an argument over the name for the technique. Hunter coined the term "hypodermical" in 1863, but Wood insisted that Hunter's "hypodermical" was identical to his own "subcutaneous" injection.[27,28] Although both words refer to the same technique, the difference apparently lay in the purpose of the injection - local *vs* systemic. In the end, the Medical and Chirurgical Society of London appointed a special committee to settle the question of whether systemic or local effects of morphine injection were of primary importance. After two years the results were published and unanimously favoured Hunter.[29] To some extent Wood has been vindicated by the discovery of peripheral opioid receptors.[30,31]

The first recorded use of subcutaneous morphine for postoperative pain-relief was in 1863 by James Paget (1814-1899). Paget gave 1/3 grain (20 mg) morphine by subcutaneous injection after a leg amputation under chloroform anesthesia, "...with the view of inducing freedom from pain, and some refreshing sleep after a return to consciousness."[32] According to the report, this practice "... had been in use for some time at the Middlesex Hospital, and has afforded much comfort and ease, especially after many of the more important and painful operations". Paget recommended 1/4 to ½ grain (15-30 mg), "...according to circumstances."[32]

Although intravenous, subcutaneous and intramuscular routes of administration remain important methods of postoperative pain relief, great advances have been made with the introduction of regional techniques such as spinal and epidural injection.

Neuraxial administration

The New York neurologist, Leonard Corning (1855-1923) described the first use of spinal anesthesia in 1885.[33] He injected a cocaine solution into the space between the eleventh and twelfth thoracic vertebre in a man with "spinal weakness and seminal incontinence" and achieved decreased sensation and impaired reflexes in the lower extremities.[33] It has been argued that Corning unintentionally produced epidural rather than spinal anesthesia since no cerebrospinal fluid was reported to have been recovered in his syringes.[34] Corning speculated his method might be used as an alternative to general anesthesia. His idea came to fruition 14 yr later in the hands of the German surgeon August Bier (1861-1949) who described six cases in which "cocainization of the spinal cord" was performed for surgery on the lower extremities.[35] All of his patients experienced post-anesthetic headache, nausea and vomiting. In the time-honored manner of the day, Bier and his assistant also attempted spinal injections of cocaine on each other, as recorded in this paper. They both developed severe headaches, and a number of cuts, bruises and burns were acquired while testing the efficacy of analgesia.[35]

One year later, Rudolph Matas (1860-1957), a vascular surgeon from New Orleans, was probably the first to inject an opioid by the spinal route. Matas often used a saline solution, containing both cocaine and morphine, for his spinal injections. The addition of morphine was intended to prolong the effect of cocaine as well as to provide sedation.[36] Another early record of spinal injection of morphine comes from the annual report of the Dundee Royal Infirmary for 1909-10. In a list of 35 spinal anesthetics given that year, nine contained morphine combined with hyoscine and atropine. Although not specified in the report, the injections were probably given for pain relief and this may be the first deliberate use of spinal morphine for postoperative analgesia.[37]

Spinal opioid injections seemed to fall out of favour after these few anecdotal reports in the early 1900s. However, interest resumed after the biochemical demonstration, in 1973, of opioid receptors in the brain[38,39] and then in 1977 in the spinal cord.[40,41] In 1976, before the discovery of spinal cord opioid receptors, Yaksh and Rudy administered various opioids including morphine into the spinal subarachnoid space in rats.[42] They noted that the opioids produced an action (blocked spinal reflexes and decreased response to painful stimuli) limited to the spinal cord and speculated these opioids caused a direct action on pain transmission in the substantia gelatinosa.[42] The following year Snyder discovered that opioids exert their action through selective opioid receptors located in both the brain (especially in the limbic system and periaqueductal gray area of the brainstem) and spinal cord (particularly localized in the substantia gelatinosa), thus implying that opioid analgesia can be mediated in both regions.[40,41]

This demonstration of opioid receptors in the spinal cord led to the reintroduction of spinal opioid injection

for clinical use. The next recorded use of spinal opioid injection in humans appears in the literature in 1978 when Wang used spinal morphine injections for relief of cancer pain. He also speculated that the technique might be useful for postoperative analgesia.[43]

A similar reintroduction of the use of epidural morphine occurred following the discovery of the opioid receptors in the spinal cord. In 1901, a new method of regional anesthesia was described in France by Jean Sicard (1872-1929)[44] and one week later in the same journal by Fernard Cathelin (1873-1945).[45] Both investigators described injection into the epidural fat surrounding the spinal cord dura. Sicard named the technique "extradural injection by the sacrococcygeal route" whereas Cathelin named the method "epidural injection by the sacral canal". Cathelin was the first to use the technique for surgery in four patients undergoing inguinal hernia repair. Unfortunately, a reduced but not complete loss of sensation was achieved in these operations. He also speculated that epidural injection might be a useful technique for pain relief in: rectal cancer, hemorrhoidal fissures and, an obstetrical indication, "accouchement douloureux". Almost 80 yr were to pass before opioids were injected into the epidural space for pain relief by Behar and colleagues in 1979.[46] Following this report, the use of epidural opioids for postoperative pain relief quickly gained acceptance and several publications in the early 1980s confirmed its efficacy.[47–49] Ultimately, it was the discovery of opioid receptors in the spinal cord that led to the effective treatment of postoperative pain by neuraxial administration without profound sedative effects.

Submucosal administration

Submucosal routes of administration have also been used with success in the delivery of opioids postoperatively. These include transnasal, transmucosal, and sublingual administration. For example, transnasal and transmucosal opioids have been used for pre-induction of anesthesia in children[50,51] and have the potential for postoperative use. Sublingual buprenorphine has been used postoperatively with good analgesic success on both a scheduled and patient-demand basis.[52]

Transdermal administration

The transdermal delivery of opioids has also gained recent popularity for both palliative care and postoperative pain control. In particular, the transdermal fentanyl patch has been used since the late 1980s for postoperative analgesia.[53]

Intra-articular administration

Recently, opioids have been found to exert analgesic effects by acting at peripheral sites, particularly where there is inflammation. In 1991, Stein and colleagues were the first to describe that morphine injected intra-articularly in the knee joint following arthroscopy considerably reduced postoperative pain.[30] The analgesic effect of the morphine was shown to be mediated by a local action and not by CNS redistribution. Since this study, numerous randomized controlled trials have been done to assess reduction of postoperative pain following injection of opioid into the knee. A systematic review of 36 of these randomized controlled trials concluded that intra-articular morphine may be effective in reducing postoperative pain following knee surgery.[54]

Other opioid delivery systems currently under investigation and with the potential for postoperative pain control include the pulmonary route of administration using a powder form of morphine or fentanyl.

Patient controlled analgesia

One currently popular method of pain control, patient controlled analgesia (PCA), was first proposed by the Boston dentist William Morton (1819-1868) for use in labour.[55] Morton first suggested "self-serve" anesthesia in 1847 by allowing the woman in labour to hold an ether sponge to her face when she felt pain. He wrote: "...it is best, in most cases in this stage of labour, to allow her to hold the sponge herself, and apply it to her mouth when she feels a pain coming on." This was the forerunner of patient-controlled inhalation analgesia with nitrous oxide and oxygen mixtures, popular in the 1940s-70s.

The first use of intravenous opioids with patient controlled analgesia was also in obstetrics. In a 1969 lecture, James S. Scott, from the University of Leeds in England, reported the use of "self-service" intravenous analgesic administration in his obstetric practice over the preceding five years.[56] This was offered to any woman who had experienced inadequate analgesia in her first labour. She could be given control of her own pain relief through a specially designed apparatus with a spring, which the woman compressed when she needed pain relief, allowing meperidine to be delivered through the intravenous infusion. The first postoperative use of PCA with an opioid was described by Sechzer in 1967.[57] Postoperative patients pressed an analgesic-demand button which alerted the nurse to give a small amount of intravenous morphine or meperidine until the pain was controlled. Sechzer concluded that this "analgesic-demand method was ...an excellent system for treatment for postoperative pain".[57]

Since intravenous PCA was introduced by Scott, new delivery systems have been developed using the

same concept of patient control over dosing. Patient-controlled epidural analgesia (PCEA) with either an opioid or a combination of opioid and local anesthetic is used both in obstetrics, and for postoperative analgesia.[58–60] Preferred opioids for PCEA include synthetic compounds such as fentanyl, sufentanil, and alfentanil because, as opposed to morphine, they have high lipophilicity and thus a rapid onset of action. Subcutaneous PCA using morphine has also been reported in the literature as an effective method for postoperative pain control.[61] Patient-controlled intranasal analgesia (PCINA) using meperidine or fentanyl, but not morphine, is a recent development which has been used in palliative care[62] as well as for postoperative pain management.[62,63]

Conclusion

Nearly 5000 yr after opium was first cultivated and isolated by the Sumerians, opium and its derivatives remain the best analgesics. Since the isolation of morphine from opium almost 200 yr ago many different delivery systems have been used for its administration. Basic research demonstrated the existence of opioid receptors in 1973, opening new avenues for the use of morphine in pain relief. Although many new pain-relieving compounds have been developed in the twentieth century, morphine remains the standard by which all new analgesic preparations are judged. For those who practise surgery and are responsible for postoperative pain relief the sentiments of Thomas Sydenham, extolling the virtues of opium more than three centuries ago, remain relevant: "None of us would be calloused enough to practise our profession without it".

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