

Acute Pain and Opioids: Through the Ages

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Opioids have been used for the management of pain for many hundreds of years. However, most of our understanding of the science of how these drugs work and how they are best used in the acute pain setting is very recent.

HISTORY OF THE USE OF OPIOIDS IN PAIN MANAGEMENT

Up until the 19th century

Opium has been used, at least for its psychological effects, for centuries. Sumerians, who lived over 5000 years ago in what is now modern day Iraq, called it the 'joy plant'. In the 8th century BC their direct descendants, the Assyrian-Babylonians, were aware of its analgesic effects as well as its sedative and hypnotic properties.¹ Hippocrates was known to have prescribed the drug but it would seem that he used it mainly for 'diseases of women'.²

The earliest written reference describing the use of opium as an analgesic is thought to have come from Theophrastus, a pupil of Plato and Aristotle.^{1, 2} Often called the founder of Greek botany, Theophrastus wrote a large number of treatises on botany in the 3rd century BC. Two of his writings, *De plantis* and *De causis plantarum*, were translated into Latin and include a description of the properties of opium and its medical uses, including its use as an analgesic.

Pre-modern physicians seemed to have a good idea of the effects of opium and based their knowledge on the experiences of others. However, in the absence of evidence, did they always use the drug appropriately? The practices of physicians around the time of Hippocrates were examined by Pioreschi and colleagues in 1998.³ To assess the effectiveness of historical drug administration practices they used what they called the efficacy quotient, or EQ. Their formula was based on the number of times a drug was used 'correctly' – i.e. correctly in the modern sense according to known physiological effects – and the number of times it was used incorrectly. As examples, a physiologically appropriate use for opium would include its administration for joint pain and headache, even though opioids may not be thought of as appropriate first-line treatment for these in today's clinical setting: inappropriate use of opium included its prescription to dry up a runny nose.

An EQ of 1 would indicate that the drug was used as often for appropriate conditions as for inappropriate ones. When these authors examined 150 uses of opium outlined in the *Hippocratic Corpus*, they calculated an EQ of 1.08 and concluded that Hippocratic physicians used the drug in a fairly indiscriminate way, even though they knew of its physiological effects – i.e. analgesia, somnolence, constipation and mood alteration.³

That said, it is highly possible that they could do exactly the same calculations on the way opioids are sometimes used today – not always in the right dose and not always for the appropriate reasons – and they could conclude that opioids are sometimes still used in indiscriminate ways and without evidence of benefit. For example, some patients today are prescribed huge doses of opioid for management of their chronic noncancer pain even though opioid use may not be appropriate and even though this practice may result in opioid-induced hyperalgesia.⁴

There were very few changes in the ways in which opium was used for pain relief over the next few hundred years. Up until the start of the 14th century, opioids could be prescribed by physicians who had trained in University medical schools, surgeons (generally lay people and considered to be of inferior status), medical practitioners (also lay people) and apothecaries; later, French kings restricted the prescribing of opioids – and laxatives – to physicians only.⁵

One scholar, Roger Bacon, who lived in Paris at this time (he died in 1294), believed there were two main problems with physicians when it came the use of opium. He said '(They are ignorant) of the relation of the quantity of noxious drugs and the body, nor is the method of giving them known, nor what quantity for which condition or age'.⁵ He was quite correct, but these deficiencies in knowledge would not start to be addressed until some 700 years later.

Despite opium being in common use from that time on for the treatment of pain, and for the treatment of numerous other ailments, even basic forms of investigation into the use of this drug did not start until the 17th century – the time when there were a great many advances in a number of scientific disciplines.

Although Sir Christopher Wren is best known as an architect (for example, for St Paul's Cathedral and the many other buildings he designed after the Great Fire of London), he began his career after training as a mathematician and physicist and at one stage was a professor of astronomy.⁶ By the age of 17 he had invented, among other things, a pneumatic engine, a weather clock or barometer, and a new language for the hearing impaired. In 1662, he joined other mathematicians, scientists and scholars to form the Royal Society of London for Promoting Natural Knowledge, under a charter granted by Charles II.⁶

As outlined by Gibson,⁶ Wren, in 1656, became the first person to describe the intravenous injection of a number of substances including wine, ale and a variety of drugs. With the help of the famous physicist, Robert Boyle, he did this using a goose quill and pig's bladder, and one of the drugs he injected was opium. Details of his experiments were only published many years later, in 1665, in the first volume of the *Philosophical Transactions of the Royal Society*. Included in the notes is a description of the technique used to inject opium and crocus metallorum (an antimony sulphate preparation used at the time as an emetic) into dogs 'by making ligatures on the veins and then opening them on the side towards the heart, and by putting into them slender syringes or quills, fastened to bladders containing the matter to be injected whence the larger vessels that carry the blood are most easy to be taken hold of'.

Wren also noted that the opium was 'soon circulated into the brain, and did within a short time stupefy but did not kill the dog'. He suggested the technique could be used for anaesthesia, but as his study was to examine the feasibility of injecting fluids intravenously, he did not emphasise it or pursue it. Wren also experimented with canine blood transfusions and worked with Thomas Willis, of cerebral artery Circle of Willis fame, as well as Robert Boyle.

Towards the end of the 18th century and the first part of the 19th century, some exciting discoveries were made in the field of pharmacology. Not least of these was the isolation of morphine from opium by Sertürner in 1803/1804. He coined the name morphium (later changed to morphine), after Morpheus, the Greek God of dreams. Another 50 years on, the administration and efficacy of morphine was greatly improved by the introduction of the hypodermic needle and syringe. These were developed by Wood based on a design already manufactured by a Mr Ferguson – a local London chemist.⁷

The history of the parenteral administration of morphine has been summarised by Hamilton and Baskett.⁷ Wood was the first to inject morphine subcutaneously (SC), intending to produce a local analgesic effect in a painful area. Apparently he was somewhat annoyed, when he checked the next morning, to find the patient was unconscious. He had noticed the systemic effects but still believed that pain relief resulted from morphine's local effects. It took a London surgeon, Charles Hunter, to realise that it did not matter where the SC morphine was injected, the result was pain relief. Following the ensuing prolonged and often acrimonious discussion between the two in letters to the *Lancet* and the *British Medical Journal*, a committee of the local Medical and Surgical Society (now the Royal Society of Medicine) was formed to settle the argument; it concluded that the systemic effects of an injection of morphine were of most importance.

Oral opium was first used for postoperative pain relief by London surgeon James Moore in 1784; the first report of SC morphine injections (using a syringe) for postoperative analgesia was by James Paget in 1863 – he suggested 15-30 mg doses, huge in comparison to doses used today.⁷ There were also case reports of the use of intrathecal morphine as early as 1901.^{1, 8} Records showing other early use come from the Dundee Royal Infirmary in the UK: in the period 1909-1910, apparently 35 spinal anaesthetics were given in one year: 9 contained morphine,

presumably given for postoperative pain relief.⁷ This technique seemed to fall out of favour relatively quickly. It might have had something to do with the very large doses (e.g. 10 mg) used then compared with the doses used today.

The 1930s to 1950s

Up until this time the use of morphine for pain relief was widespread, but there was still no good evidence about the optimal dose, how best it might be given, how effective it might be in different circumstances or how they worked. That is, the concerns that Roger Bacon had expressed in the 13th century, had not yet been addressed.

In the early 1930s, there was increasing interest in basic research relating to pain relief. For example, an analgesia program was established at the National Academy of Sciences in the US (the precursor of the NIH), for the purpose of investigating the chemistry and pharmacology of analgesics and then testing them in laboratory animals followed by tests on humans in the clinical setting.⁹ They decided to start their program by looking at the alkaloids of opium. By the end of the first 10 years of the program they could relate the molecular structure of opioids to pharmacological activity – both of the standard drugs, morphine and codeine, as well as novel opioid compounds. They recognised that alterations in chemical structure could often result in predictable changes in pharmacological effect and had also synthesised new opioids such as oxycodone, methadone and pentazocine.⁹

The 1950s

The 1950s were also marked by significant innovations – this time in research methodology – innovations that would help significantly in the understanding of opioids. These included the mouse hot-plate method that would complement the tail-flick procedure developed in 1942, two procedures that have become standard tools for assessment of the antinociceptive effects of opioids in rodents.¹ The coaxial stimulated guinea pig ileum preparation was also developed in 1955 – a preparation later used in the discovery of the presence of enkephalins in animal tissues in 1974.¹ The 1950s also saw the introduction of the double-blind study, which greatly contributed to the reduction of experimenter and patient bias, especially in drug evaluation trials.¹

From the advances that were made in stereochemistry and knowledge about drug molecules and composition during this time, it was also becoming apparent that some drugs, like opioids, probably worked by interacting with receptors.

But 100 years after morphine was first given by SC injection, and many thousands of years after it was first used for pain relief, albeit as a component of opium, no one had tried to establish the best dose to give.

In 1954, one such study was performed by Lasagna and Beecher.¹⁰ They compared doses of 10 mg and 15 mg of morphine per 70 kg body weight, injected subcutaneously. As the larger dose had the higher incidence of side effects they declared that 10 mg was the optimal dose. The idea of the study was good – the conclusion not so. This idea of fixed doses or fixed doses per kilogram body weight unfortunately persisted for years. Also, unfortunately, these authors cautioned against flexibility in dosing because of the possibility of dangerous side effects, and warned against higher doses because of the risks of dependence.

The 1960s

Basic research into opioids advanced very rapidly at this time. Large scale studies on the mechanisms of dependence were made possible by the development of animal models of opioid dependence.¹ The opioid antagonist naloxone was also synthesised – a drug that would prove not only to be invaluable in the clinical setting, but would later be used by Snyder and Pert to identify opioid receptors in the brain.¹¹

In addition, very basic forms of patient-controlled analgesia (PCA) had been introduced for the relief of postoperative¹² and labour pain.¹³

The 1970s

The very big advances in the knowledge of how opioids worked came in the 1970s. Firstly in 1973, was the demonstration by Snyder and Pert, using tritium labelled naloxone, of opioid receptors in the brain.¹¹ This was followed by the identification of endogenous opioids in 1975.¹⁴ In the same year Laurie Mather's group published the first of a series of papers on the pharmacokinetics and pharmacodynamics of opioids administered by different routes.^{15, 16} It was

somewhat amazing, that up until this time, there was not a proper scientific basis for these common clinical methods of opioid administration.

In 1976, Yaksh and Rudy¹⁷ showed that morphine injected into the subarachnoid space in a variety of animals resulted in pain relief that was dose-dependent and reversible with naloxone. Just a year after this, Snyder^{18, 19} and others were able to show that opioids exerted their action through selective opioid receptors located in both the brain (especially in the limbic system and periaqueductal gray area of the brainstem) and the spinal cord (particularly in the substantia gelatinosa) – that is, that pain relief from opioids could be mediated at both sites.

The demonstration of opioid receptors in the spinal cord was followed within a very short time by reports on the clinical use of spinal²⁰ and epidural opioids.²¹

OPIOIDS AND ACUTE PAIN MANAGEMENT - THE 1980'S ONWARDS

Newer acute pain management techniques and Acute Pain Services

In the 1980s the use of epidural morphine for postoperative analgesia became commonplace. At this time, PCA, first developed by Sechzer²² in the early 1970s, also started to become part of routine (usually postoperative) pain management rather than primarily confined to experimental settings. In large part, the introduction of Acute Pain Services (APSs) in the late 1980s²³ helped the use of newer techniques such as these to become widespread.

By the 1990s, opioids had been given by virtually every route imaginable in attempts to treat acute pain. Not just intravenously and spinally, but intranasally, transmucosally, by intra-articular injection and inhaled.

Has the patient benefited?

Have these recent advances helped patients to become more comfortable?

Recent meta-analyses have shown the PCA results in better analgesia than opioids given by intramuscular (IM) injection – but only slightly.²⁴ The results of these meta-analyses were a little unexpected but could reflect two things. Firstly, in an experimental setting, it may be that the IM opioids were given truly on demand and therefore would be expected to be relatively effective. The other reason could be that in most studies, the size of the bolus dose of morphine delivered by the PCA machine is limited, often to just 1 mg. By limiting the inherent flexibility of the technique and giving all patients access only to a fixed bolus dose, the potential effectiveness of the technique is also restricted. PCA should not be used as a 'one size fits all' method of pain relief.²⁵

Epidural analgesia, on the other hand, consistently results in significantly better pain relief compared with IM opioid analgesia – whether opioids and local anaesthetics are used alone or in combination.²⁴ It has been difficult to show better patient outcomes following the use of epidural analgesia for acute pain. However, such evidence as does exist points to the need to include local anaesthetics in the solution used if better outcomes are to be achieved. With this combination, improvements in postoperative respiratory, cardiac and bowel function have been reported.²⁴

Another look at opioid doses

Suggestions for the optimal dose of an opioid had changed little from the days of Lasagna and Beecher. However, results of early APS audits suggested that the doses of both epidural²⁶ and parenteral²⁷ opioids were better based on the age of the patient than their weight. Audit results of PCA use also showed that there was a huge interpatient variation in the dose of opioid required to achieve analgesia²⁷ and that rather than cautioning against flexibility in dosing because of the possibility of dangerous side effects, and warning against higher doses because of the risks of dependence, as was suggested by Lasagne and Beecher,²⁷ better pain relief would not be obtained unless a wide variation in doses was tolerated and pain relief titrated to the individual patient.

The magnitude of this variation in opioid dose as patient age increases is much greater than can be accounted for by the age-related changes in physiology that are seen in older patients. While there are alterations in renal and hepatic function and cardiac output, which will in turn alter drug pharmacokinetics, it appears to be a primarily pharmacodynamic phenomenon.²⁸

This had been demonstrated in a study by Scott and Stanski.²⁹ They looked at both the pharmacokinetic and pharmacodynamic components of (anaesthetised) patient responses to alfentanil and fentanyl infusions. The doses given were those required to produce the same EEG

stage. They found that there were no age-related changes in pharmacokinetics but that the amount of opioid to produce this EEG effect decreased as patient age increased. In fact, there was a 50% decrease in dose required, or a 50% increase in brain sensitivity to opioids, from age 20 to 89.

The reasons behind these changes are not yet clear. However, it is known that in rats, ageing is associated with reductions in opioid receptor density and increases in opioid receptor affinity. In general, there are also age-related changes in synthesis, axonal transport, uptake and receptor binding of many neurotransmitter systems.²⁸

At the other end of the lifespan, age also appears to be the most important factor determining opioid requirements. Marked changes are seen in the dose requirements and responses to opioids in premature and term neonates and infants. In the laboratory, rat pups are much more sensitive to the effects of morphine than older rats. This probably results from a number of factors, including developmental changes in the opioid receptor (including expression, distribution and function) and changes in the way the developing nervous system processes pain.³⁰ Pain processing in the immature peripheral and CNS is very different from the mature one.

In the clinical setting, neonates and infants also seem to be more sensitive to morphine given for postoperative pain³⁰. In older children, average PCA morphine requirements also change with age.³¹

RECENT ADVANCES

New ways to administer opioids continue to emerge. One of the more recent is the development of an extended-release epidural morphine preparation that, once injected, can provide pain relief for up to 48hr.³² Another new technique is iontophoretic fentanyl PCA.^{33, 34} This system uses a small electric current to speed transfer of drug across the skin. In the case of fentanyl, it means that peak blood concentrations may be seen within minutes or so, compared with many hours when traditional transdermal fentanyl delivery systems are used.

Extended-release epidural morphine

An advantage of the extended-release epidural morphine preparation is that only a single dose is needed, which means that epidural catheters are not - possibly of benefit in patients prescribed thromboprophylactic heparin in the postoperative period. However, administration of a single dose also means that there is no opportunity for individual patient titration. There also appears to be a high reported incidence of respiratory depression, but this may be an inaccurate estimate as it would seem that many investigators still define respiratory depression as a decrease in respiratory rate, when this is known to a less reliable indicator than increasing sedation.²⁴ The preparation it is intended for lumbar administration only and combination with local anaesthetics is not advised. As noted above, where there is evidence of better patient outcome after epidural analgesia, local anaesthetics seem to be an important component of the solution used.

Iontophoretic fentanyl PCA

This system delivers a preprogrammed bolus dose when activated - as does the commonly used IV PCA system, but no IV lines are required. However, the size of the bolus dose is fixed and therefore it may not provide the flexibility of dosing that is needed in the acute pain setting. With IV PCA bolus doses, the size of the bolus dose can be readily altered - with this new system it can not.

It has been shown to be as effective as 'standard' IV PCA morphine.³³ This means that the comparative studies limited the size of the IV PCA morphine bolus dose to 1 mg. It is known that for PCA to be more effective, the bolus dose often needs to be greater than this - and also sometimes smaller. IV PCA is not a one size fits all technique.²⁵

WHERE TO NOW?

Although opioids have been used to treat pain for thousands of years, problems with their use remain. Because of the enormous interpatient variation in dose requirements, effective pain relief will still require titration of opioid dose, regardless of route, for each patient. There will still be issues relating to the side effects that can result from opioid administration as well as problems related to the development of tolerance and opioid-induced hyperalgesia.

Will there be better opioids - maybe opioid agonists with high selectivity for different receptor types? Will there be better ways to treat side effects? Or will improved analgesia with opioids

result from combination with other drugs that can modulate opioid receptor mediated effects such as ketamine, naloxone, CCK antagonist³⁵ or maybe a newer drug such as F13640, a 5HT-1A receptor agonist?³⁶

Only time will tell whether any of these advances will be as clinically significant as those made over the previous 3-4 decades.

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