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An update on analgesics

I. Power*

Royal Infirmary, University of Edinburgh—Anaesthesia, Critical Care and Pain Medicine, 51 Little France Crescent, Edinburgh EH16 4SA, UK
* E-mail: ian.power@ed.ac.uk

Editor's key points

- Development of new analgesics is a slow process, categorized in terms of improving pain relief and reducing side-effects.
- Tapentadol represents an interesting new molecule that activates opioid receptors and inhibits norepinephrine uptake.
- Modulation of endogenous pain-controlling systems is a further interesting development.

Summary. Recent introduction of new analgesics into the clinic is best described as a slow process with activity classified into two main areas: improving analgesic efficacy/potency and reducing side-effect profile. This review article describes some of the recent advances with an emphasis on use in the acute setting. In this respect, opioids continue to be the mainstay (but not the only) analgesic and there have been important improvements in their clinical effect profile. For example, tapentadol has been introduced as a mixed opioid and norepinephrine uptake inhibitor which, unlike tramadol, does not require metabolic activation and does not suffer from isomer-dependent pharmacodynamics. Opioid antagonists have received much attention recently either used alone, methylnaltrexone (s.c) or alvimopan (p.o), or in combination, Targinact (oxycodone/naloxone), and appear to be effective in reducing opioid side-effects such as those in the gastrointestinal tract. Other agents where there has been recent development include the use of gabapentin, methylxanthines, and local anaesthetics. An interesting area of translation of basic research is in the inhibition of breakdown of endogenous opioids with opiorphin, targeting of the endocannabinoid system, and the use of ampakines to obtund opioid-induced side-effects. It is clear that there is still much work to be done, but the need for highly efficacious analgesics with good side-effect profile remains.

Keywords: acute pain; analgesia; pharmacology

This article was written as part of Professor Jennifer Hunter's Festschrift entitled 'Anaesthesia and Critical Care in the 21st Century: The First Decade' which will be held in May 2011. I was asked to present an update on analgesics, mainly those used in the 'acute' setting that would give some idea of the advances we have made in alleviating pain after surgery or trauma. My consideration of this was rapidly fashioned by various articles published in the recent past, indicating that for the acute setting, progress in terms of the introduction of new drugs has been incredibly slow. Woolf[1] in an article about overcoming obstacles to developing new analgesics states that 'despite substantial financial investment by the pharmaceutical industry over several decades, there has been little progress in developing new efficacious and safe analgesics'. Woolf then indicates that this is leading some pharmaceutical companies to consider withdrawing from the acute pain relief market, and that the problem might be a lack of understanding of pain itself. Certainly, there does seem to be a lack of understanding of how to design studies to investigate acute pain relief. This is clearly shown by a recent article entitled 'Getting the pain you expect'.[2] The problem seems to be our design of studies in many ways, which allows us to accept placebos, 'nocebos' (that is, negative outcomes, see Tracey[2]), and reappraisal effects in humans. Our clinical studies tend to neglect these and to set them aside and Quessy[3] has addressed this issue in an article entitled 'Where are the new analgesics?'

and suggests an alternative approach to early phase analgesic trials using a multivariate input model. Certainly, trial design does seem to be a large part of the problem, but also the issue is that in addressing pain, we must also address safety and efficacy. This was very well demonstrated by the attempts to improve upon the safety profile of non-steroidal anti-inflammatory drugs where by selectively changing the action of drug molecules, the enzyme affected was influenced. The result was that efficacy was improved, but safety markedly affected, so that some of the drugs were withdrawn because of unexpected cardiovascular side-effects.[4]

As a result, senior researchers are now asking the question 'what is this thing called pain?'[1] There is no doubt that when we deal with pain after surgery or trauma, we are dealing with the various classifications proposed by Woolf which include nociceptive: associated with the detection of potentially tissue damaging stimuli; inflammatory: tissue damage; and pathological: damage to the nervous system (neuropathic).

Part of the problem with pain after surgery is that consent renders the patient open to accepting nociceptive damage and anaesthesia, while greatly minimizing and allowing invasive surgery has very little effect on the nociceptive process. Also, after surgery and trauma, these classifications become somewhat blurred as neuropathic pain can appear immediately after a surgical process. In looking for new analgesics

that work in the acute setting, there is a problem of having to address many types of pain simultaneously, using the same compounds. We are indeed a long way from Tracey's postulation of making postoperative pain 'pleasant'.[2] However, Tracey's idea of arranging more suitable studies may well render an individualized approach to the problem of pain possible and produce safer and more effective analgesics.

Analgesia for acute pain relief still tends to be drawn from the traditional opiates, aspirin and the non-steroidal drugs, paracetamol, and local anaesthetics. The opiates were in wide use as a natural product, and, for example, in the 15th century, 'the Soporific sponge' was mentioned where opium is mixed with various herbal products and then dried, so that the sponge could be warmed later and used for pain relief. 'Opium' was used widely in the 19th century and indeed quoted in the family doctor as 'the best medicine we possess'. In 1803, Serturner assimilated crystals from opium and named them 'morphine' after the Greek God of dreams, Morpheus. Morphine was delivered on the point of a lancet and washed into the wound, injections not yet being available. This moved on until Stein and colleagues[5] realized that opioids were part of the physiology of the inflammatory, painful process and suggested that where tissue damage occurred, local anti-inflammatory analgesic opioids were released to aid the repair process.

Opioids have continued to be the mainstay of our armamentarium against pain based on new formulations, mixed preparations, novel norepinephrine inhibitors, and the use of opioid antagonists to address the thorny issue of opioid-related gut side-effects.[6–16] Each of the evidence-based guidelines that exist about the relief of acute pain address the efficacy and safety in different ways, but the aim has been to improve on the efficacy of drugs like morphine and reduce its drastic side-effects, including nausea, gastrointestinal effects, and acute loss of the patent airway and hence hypoxia. Aspirin was introduced as an attempt to improve upon the palatability profile of the older sodium salicylate and the non-steroidals resulted from that in due time. Paracetamol was made available by an entirely different chemical process, but this routine drug taken by all of us seems to be one of the best analgesics that work from cradle to grave, although smitten by the dire side-effect of liver impairment upon overdose. New drugs such as tramadol and now tapentadol make use of the endogenous pain-modulating pathway that occurs in response to tissue damage, giving the pharmacological site of action for most of our presently used drugs.[17] Opioids work at various sites of the pain pathway but are of course inherent to the modulation of pain physiologically. Non-steroidal anti-inflammatory drugs work at the site of tissue damage and in the central nervous system. The descending pathways from the brain down to the lower sensory pathways for pain depend on various substances, including enkephalins, endorphins, and norepinephrine that have been used for the production of analgesics. The introduction of tapentadol is an example of this.[6–9] Therefore, attempts need to be made to improve efficacy and reduce side-effects in an

individualized fashion. It may be that increased understanding of the genetic role of our pain physiology might allow us to do this and produce individualized approaches to tissue damage and pain, but again we are someway from that at present. One new possibility is the introduction of 'epigenetics in pain and analgesia', which might allow a personalized, individualized approach to pain and tissue damage.[18]

The aim should be to stop viewing morphine, for example, as a two-faced God, Janus, that produces powerful analgesia that is blighted by common, serious, and sometimes life-threatening adverse effects.[19]

New opioid formulations

Perhaps, the most successful introduction of different opioid preparations has been the use of older drugs in new delivery systems. Transdermal patches delivering opioids directly through the skin have enabled the use of low-dose individualized therapy that can be utilized to improve analgesia while reducing side-effects. Transdermal fentanyl and buprenorphine patches are now almost routine parts of our therapy for acute pain, although very much in the setting where the patient's response to opioids has been well identified. Other areas where morphine has been provided in a distinct and different way include the use of sustained-release epidural morphine 'Depodur'. This preparation may be a useful analgesic, in that it provides morphine-sustained relief in microcapsules given epidurally producing 'a single-dose extended-release epidural morphine'. Various publications have reported on the efficacy and potential side-effects of using extended release therapy epidural morphine.[20–22] Nausea, vomiting, and oversedation can occur, and the patient must be monitored closely, especially if inadvertent spinal administration occurs.[23]

Another preparation that has been introduced to try to improve upon the safety of morphine is its renally eliminated metabolite morphine-6-glucuronide that is more potent than the parent drug but offers an extended duration of action.[24–26]

Both these preparations of extended-release epidural morphine and morphine-6-glucuronide offer perhaps improved efficacy in some situations but do not prevent the life-threatening effects of opioids.

Methadone

Methadone is a synthetic analogue of morphine that was used extensively in the past for pain relief. However, variable pharmacokinetics can make dose adjustment difficult in the acute situation. It does have the advantage of having a long duration of action and in one recent study, it was found that for patients having complex spine surgery, a single dose of methadone (0.2 mg kg^{-1}) before surgical incision reduced postoperative pain scores, and thus reduced opioid requirements. There was no increase in opioid-related side-effects and the authors concluded that 'preoperative treatment with a single dose of methadone improves postoperative

pain control for patients undergoing complex spine surgery'.[27]

Paracetamol

Multimodal analgesia is now routinely used for pain relief during surgery, but a recent study suggested that an anti-emetic routinely given in theatre could interfere with the action of paracetamol, via the central serotonergic mechanism. However, a more recent study has found that a similar anti-sickness drug, ondansetron, does not block paracetamol-induced analgesia in an animal model.[28] The use of i.v. paracetamol has become widespread for post-operative pain relief, and the evidence for this was recently supported by a study in children that found after adenotonsillectomy that i.v. paracetamol was associated with similar analgesic properties and early recovery to that of tramadol.[29]

Tapentadol

We have utilized the dual effect of opioids in pain relief physiology for sometime with the introduction into clinical practice of tramadol, where the two isomers of the drug act as an opioid agonist and as a reuptake inhibitor of norepinephrine and 5-HT. Hence, it produced analgesia by affecting the nociceptive process and also boosting the central modulation of pain.[17] [30] This dual effect has some considerable benefits, but the difficulty with tramadol was that it was an atypical racemic opioid, inhibition norepinephrine reuptake depended upon one isomer, inhibition of 5-HT uptake on the other, and the active metabolite depended on tramadol being metabolized in the first place, so that, for example, a weak μ-opioid receptor (MOP) agonist was produced. Unfortunately, tramadol is metabolized by P4502D6 and some 5–15% of the population are poor metabolizers.[9] Tapentadol has recently been introduced into clinical practice; it is a non-racemic molecule that is a moderate MOP agonist and only effects the uptake of norepinephrine into nerve endings.[6–9] [31] No metabolic activation is required for analgesia and there are no active metabolites. Tapentadol itself is presently prepared as tablets and has been approved by the FDA for moderate to severe pain, and the potency is said to be somewhere between morphine and tramadol. Tapentadol therefore boosts the endogenous opiate effect of 'morphine' and enhances the descending modulatory pain system. It does not appear to cause the confusional states sometimes associated with tramadol. In various studies, tapentadol has been found to be effective even for severe postoperative pain.[6] There is every possibility that tapentadol may improve upon the analgesic safety of morphine and tramadol while reducing the incidence of side-effects, if used appropriately.

Dual oxcarbazepine and COX inhibitors

The problem of postoperative neuropathic pain is common and can be difficult to treat. Attention is turning to any pharmacological interaction between drugs routinely given at the time of surgery and pain produced by tissue damage as in orthopaedic surgery. In one study, the authors described a pharmacological interaction between the anti-epileptic oxcarbazepine and two COX inhibitors in a rat model of inflammatory hyper analgesia.[32]

Catecholamine-O-methyltransferase polymorphisms

It does seem that some polymorphisms [including catecholamine-O-methyltransferase (COMT)] are related to postoperative pain intensity. In a recent study, the authors carried out a prospective observational clinical trial in patients having third molar extraction. Seven patients had persistent pain and the proportion that had the rare forms of COMT polymorphisms were associated with increased postoperative pain. From this early report, it seems that COMT polymorphisms can be associated with the clinically meaningful outcome of pain after elective surgery.[33]

Gabapentin

In a number of studies, the uses of anti-convulsants such as gabapentin have demonstrated an improvement in analgesic efficacy. In one recent study, gabapentin has been shown to be useful for preventing and treating acute pain after a Caesarean section; however, maternal sedation was much higher in the patients given gabapentin.[34]

Methylxanthines

Clinical studies have demonstrated adjuvant analgesia, and some intrinsic analgesia, in the treatment of headache, but not postoperative pain. Caffeine clearly exhibits complex effects on pain transmission; knowledge of such effects is important for understanding adjuvant analgesia and considering situations in which dietary caffeine intake may have an impact on analgesic regimens.[35]

Ropivacaine and neuropathic pain

Local anaesthetics can alleviate some types of neuropathic pain, and part of this effect may be related to sensitization of the antinociceptive pain pathways that occur in the neuropathic pain state, and spinal glial cells have been shown to play some part in this. In an animal model, epidural ropivacaine was shown to have such effects on glial cells, so that the analgesia was much more prolonged than the local anaesthetic effect itself. In this study, the authors suggested that this might represent a new approach for glial cell inhibition and for neuropathic pain treatment.[36]

Fentanyl

Fentanyl is now available by injection, skin patch, and by transmucosal absorption. In addition, fentanyl has been developed in a nasal formulation that allows for very rapid nasal mist pain relief. For fentanyl, this does seem to be true, and so a rapid onset of fentanyl given nasally may well be available to supplement background analgesia.[37]

Opioid antagonists

It is interesting to consider that opioid antagonists are now being used to improve pain relief, rather than reverse excessive sedation or respiratory depression. In the search for a better balance between efficacy and safety (and regulatory authorities inspect the latter before the former), attempts have been made to use the known opioid antagonists that we have to reduce those side-effects, especially sedation and respiratory depression. A result of this is that formulations have been prepared that contain naloxone in a tablet for oral ingestion that also contains oxycodone. Other opoid antagonists have also been used and one of these is methylnaltrexone, which does not pass the blood–brain barrier. A third peripherally active MOP antagonist is alvimopan, designed to reside in the periphery.

Naloxone and oxycodone

A preparation has now been established that includes substantial amounts of naloxone together with oxycodone, both in prolonged release forms. When taken by mouth, the naloxone is metabolized in the liver, so that peripheral antagonism of opioids exists in the gut, but that after metabolism, little naloxone passes into the central nervous system. Hence the peripheral action of the naloxone when given with oxycodone is established. Such preparations were designed to reduce the challenge of 'opioid-induced constipation in chronic pain management'. The name of the drug containing naloxone and oxycodone, both extended the least preparations, is Targinact (manufacturer Mundipharma) and the dose of naloxone is substantial across the range, for example, the dose that contains 40 mg of extended-release oxycodone contains 20 mg of naloxone. The aim is to prevent the gastrointestinal side-effects of opioids and various studies have demonstrated that this does work, with little effect on analgesia.[38] [39] In this sense, this oral naloxone and opioid preparation is aimed at dealing with the problem of opioid-induced bowel dysfunction, which we may well have taken for granted when we only had opioid agonists to administer.

Concurrently, another opioid antagonist was approved for opioid-induced bowel dysfunction, methylnaltrexone (Relistor, Wyeth; s.c. dose: 150 mg kg^{-1}, given once a day).[16] [40] The dose of methylnaltrexone given is for opioid-induced constipation in advanced wasting illness, as with carcinoma.[12] When studied in this way, the treatment did not appear to affect central analgesia or precipitate opioid withdrawal. The finding that opioid withdrawal was not precipitated has led to a revaluation of the effects and side-effects of opioids.

Alvimopan was the third peripherally active opioid antagonist introduced to the market in the past few years. This was a capsule (12 mg) given by mouth just before surgery and then another 12 mg dose given twice daily for up to 7 days, with a maximum dose of 15 capsules. This preparation was designed to address the problem of bowel effects after intestinal surgery and the use of opioids.

Bowel recovery time ranged from 10 to 26 h shorter for patients who were given alvimopan ('Entereg'). Recent trials of alvimopan tend to confirm that opioid-induced bowel dysfunction is common, and that alvimopan may be of benefit in this circumstance.[13] [41] [42]

Alvimopan was designed to act as a peripherally active MOP antagonist. The identification of this molecule and the observations in a wide group of patients has led authors to comment on the new insight into opioid effects offered by these peripherally acting MOP. Clinical and laboratory studies performed during the development of these drugs have indicated that peripheral opioid receptors mediate other effects, including decreased gastric emptying, nausea and vomiting, and urinary retention. It is of some surprise that the use of these peripherally active opioid receptor antagonists influences the various side-effects listed, but it is more surprising that drugs such as alvimopan have demonstrated new insights into opioid effects.[10] It seems that 'laboratory investigations with these compounds suggest that opioids affect fundamental cellular processes through mechanisms that were previously unknown. These mechanisms include modifications of human immune deficiency virus penetration, tumour angiogenesis, vascular permeability and bacterial virulence', for such reasons, it seems that peripheral opioid receptors have effects that are evident in clinical medicine far out with the practice of anaesthetics. It may be that some of these agents will be used for treatment of the severely ill, irrespective of the need for any analgesia or sedation.[10]

Opiorphin

An alternative technique to providing analgesia is to prevent the breakdown of endogenous opioids by endopeptidases, and using such a preparation, the potency and duration of action of 'opiorphin' has been assessed with reference to morphine in an animal model. The authors found that opiorphin elicits minimum adverse morphine-associated effects, produces a comparable analgesic potency but seems to be devoid of abuse liability or gut effect. Such work could lead to a powerful class of physiological type analgesics.[43] [44]

The endocannabinoid system

The endocannabinoid system is a signalling cascade consisting of CB_1 and CB_2 receptors, and enzymes for the synthesis and degradation of endogenous ligands for these receptors. Endocannabinoids are involved in many metabolic processes, have been implicated in the transition from acute to chronic pain, and in animal models, in the process of the resolution of postoperative pain.[45–47] Cannabinoids have been studied as acute pain relievers for postoperative pain when given in an oral form with some evidence of activity.[48] The main research activity at present lies in assessing the endocannabinoid system as a means of modulating chronic, neuropathic pain.[49]

Ibudilast

Ibudilast, an inhibitor of glial activation and cyclic nucleotide phosphodiesterases, has shown potential in the treatment of neuropathic pain and opioid withdrawal. In a recent animal study, it was found to be effective in restoring, but not in preventing, morphine tolerance. In that study, the authors found that the mechanism of ibudilast effects needs to be better understood before it could be considered for clinical use.[50]

Antagonism of opioid-induced ventilatory depression by ampakines

While naloxone is being utilized to prevent mainly gastrointestinal side-effects associated with opioids, ampakines may be used to minimize opioid-induced ventilatory depression. Oertel and colleagues[51] found that when ampakines were given, alfentanil decreased respiratory frequency by much less than when a placebo was given. In contrast, the ampakine did not affect alfentanil-induced analgesia in electrical- or heat-based experimental models of pain. Such results support the use of ampakines as selective antidotes in humans to reduce the respiratory effects of opioids, but without affecting analgesia.[51]

Conclusion

Advances in therapy of pain have been slow, but better trial design will address this producing, it is hoped, safer, and more effective drugs in the near future.

Conflict of interest

None declared.

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