Strong opioids for cancer pain

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The past decade has seen much research on the mechanisms by which opioids promote analgesia. The challenge for clinicians involved in the management of chronic cancer pain is now to translate the knowledge that has emerged from basic science and animal models into safe and effective treatment strategies, not only for patients in hospitals and hospices but also for patients at home. This is all the more important because of the new directions being taken in the use of strong-opioid alternatives to morphine, where much practice is based upon personal experience rather than rigorous clinical evidence[1]. In this paper I outline the role of morphine in the management of cancer pain and discuss the role of strong-opioid alternatives.

As yet, no drug has shown sufficient advantages to supersede oral morphine as the strong opioid of first choice in chronic cancer pain. Three elements are critical to achieving an acceptable balance between side-effects and analgesia—thorough clinical assessment, careful dose titration and the use of laxatives. Most patients can be kept on a stable dose of morphine for weeks or months[2]. If requirements increase, this is usually because nociceptive input has increased with progression of the disease, and this calls for a rigorous reassessment of the pain syndrome[3].

SAFETY AND TOLERABILITY OF CHRONIC THERAPY WITH MORPHINE

The side-effects of chronic morphine therapy range from nausea and constipation to mild cognitive impairment, somnolence, myoclonus and hallucinations. Respiratory depression is an effect to which tolerance develops rapidly, allowing use in chronic cancer pain without serious respiratory risk. Constipation is mediated via enteric as well as spinal and possibly supraspinal opioid receptors[4] and tolerance to this side-effect does not seem to develop—hence the almost universal need for laxatives. In most cases the cognitive impairment and dizziness that occurs within a few days of beginning therapy or increasing the dose is self-limiting. O'Neill *et al.*[5], examining the effects of repeated oral doses of morphine, found that patients receiving small doses actually showed enhanced performance in some measures of cognitive function, and in cancer patients receiving long-term morphine treatment Vainio *et al.*[6] detected only a slight and selective effect on functions related to driving.

Somnolence and a constellation of signs and symptoms referred to by some workers as opioid-induced neurotoxicity (delirium, hallucinations, multifocal myoclonus)[7] can limit the dose during chronic therapy. The collective symptoms of opioid-induced neurotoxicity, which are not reversed by naloxone[8], seem to be mediated by at present unidentified non-opioid receptors[9].

Risk factors associated with the development of opioid-induced neurotoxicity include inappropriately rapid escalation of dose, advanced age of the patient, renal impairment, poor hydration and the concomitant use of other psychoactive drugs[10]. There are also case reports describing the rare phenomenon of morphine or diamorphine induced hyperalgesia and allodynia, which has occurred when the opioid dose was increased despite signs of opioid-induced neurotoxicity[11].

MORPHINE METABOLITES

Morphine is metabolized predominantly in the liver, by glucuronidation. The major metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Because the glucuronides are water-soluble and excreted in urine, there is an increased risk of side-effects in patients with renal impairment.

In laboratory animals M3G has no analgesic action; but, despite lacking affinity for opioid receptors, it is many times more potent than morphine in eliciting opioid-induced neurotoxicity[12]. M6G, on the other hand, displays high affinity for the μ opioid receptor and its antinociceptive activity is greater than that of morphine in laboratory animals[13]. Recently, genetically modified mice lacking one or other opioid receptor have been produced. Morphine had no analgesic activity in mice lacking the μ opioid receptor, whereas M6G and diamorphine were potentially antinociceptive[14]. These findings suggest that, in addition to working via the μ opioid receptor, M6G acts at a receptor separate from that which mediates morphine analgesia. This is unlikely to be a δ or κ opioid receptor since the antinociception is not blocked by the relevant selective antagonists[15].

In a study of 109 cancer patients no correlation was shown between myoclonus and cognitive dysfunction and plasma concentrations of morphine and M6G[16]. On the

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other hand, three case series have suggested that high concentrations of M3G in plasma and a high ratio of M3G to M6G in cerebrospinal fluid are important factors in the development of opioid-induced neurotoxicity in patients receiving chronic morphine therapy[16–18]. Some workers have speculated that M3G might antagonize the action of morphine, but this seems unlikely. An electrophysiological study in rats demonstrated that M3G did not possess any significant antinociceptive effect[19] and in a series of 39 cancer patients no correlation was found between high M3G concentration and poor analgesia. None of the patients in this series, however, displayed signs or symptoms of opioid-induced neurotoxicity[20].

MORPHINE 'POORLY RESPONSIVE' PAIN

The World Health Organization, in its approach to cancer pain management, advocates the use of strong opioids not as single agents but in combination with non-opioids, usually non-steroidal anti-inflammatory drugs and appropriate adjuvant analgesics. This strategy should offer good or moderate relief of pain in about 80% of cancer patients. Morphine has no ceiling dose and requirements vary considerably between individual patients. A 'poor response' to morphine—i.e. inadequate analgesia—is best viewed as a consequence of dose-limiting side-effects. Neuropathic pain and movement-related pain are disproportionately represented amongst patients whose pain responds poorly to morphine[21].

Neuropathic pain

Neuropathic pain arises from dysfunction of the peripheral or central nervous system and is typically experienced in an area of altered sensation. The examining clinician may be able to elicit pain by means of a stimulus that does not normally cause pain (allodynia), or identify an exaggerated response to a normally painful stimulus (hyperalgesia). In a series of 595 cancer patients referred to a pain service based in an anaesthesia department, 213 (36%) had pain with a neuropathic component[22].

Neuropathic pain states are maintained by complex mechanisms involving altered peripheral activity, central excitatory or inhibitory activity and sympathetic nervous system activity[23]. Another factor is disruption of nerve fibres, which can reduce opioid sensitivity through loss of opioid receptors[24].

In animal models that simulate peripheral nerve damage, a wide variety of neuropeptides and their receptors are affected. Most notable is cholecystokinin (CCK), which may have a critical role in modulating response to opioid therapy[25]. CCK receptors are intimately linked to μ opioid receptors and, when CCK binds to its receptor, changes are induced that lessen the response to μ opioid agonists such as morphine[26]. High levels of CCK are associated with a decline in opioid effectiveness; conversely, opioid sensitivity is increased by the use of CCK antagonists[27]. In animal models, CCK receptors appear to be upregulated in neuropathic pain, and this could further contribute to the poor response to morphine[28].

There is increasing evidence that neuropathic pain states involve prolonged activation of the *N*-methyl-D-aspartate (NMDA) receptor, leading to increased neuronal activity or 'wind-up'[23]. In this state of hypersensitization, mechanical and thermal stimuli are amplified, with development of hyperalgesia. Activation of the NMDA receptor has also been implicated in the development of tolerance to morphine, and a likely site of action for both hyperalgesia and morphine tolerance is the dorsal horn of the spinal cord[29]. Serotonin and noradrenaline dampen incoming pain impulses in descending inhibitory pathways[30] but become deactivated following reuptake at nerve terminals; drugs that inhibit this reuptake, such as amitriptyline, have proved effective in the management of neuropathic pain.

Some commentators have suggested that neuropathic pain should be regarded as inherently insensitive to opioids[31]. Others argue that opioid responsiveness in neuropathic pain should be regarded as relative, as a consequence of a shift in the dose response curve to the right, though recognizing that in practice, dose-limiting side-effects prohibit escalation to a level sufficient to produce effective analgesia[21].

STRONG-OPIOID ALTERNATIVES TO MORPHINE

When cancer pain responds poorly to morphine despite appropriate adjuvant analgesia, the patient and his or her pain syndrome must be carefully reassessed. One strategy is to use lower doses of morphine (or diamorphine) via the epidural or intrathecal route. If this is impracticable or undesirable an alternative is to use an alternative strong opioid, to provide a better balance between side-effects and analgesia. In the UK the number of alternative strong opioids licensed for management of chronic cancer pain has expanded rapidly. These drugs are now available in immediate-release and sustained-release preparations as well as novel delivery systems.

Oxycodone, used widely in the US, is now licensed in the UK. In controlled trials including patients with cancer, oxycodone was at least as effective an analgesic as controlled-release morphine[31]. There have been reports of a lower incidence of delirium with oxycodone[32]. Vomiting is less frequent than with morphine, constipation more so[33].

Transdermal fentanyl is a popular alternative to morphine and is particularly useful if the oral route is not possible. An open randomized cross-over study compared

transdermal fentanyl with sustained-release oral morphine in 202 cancer patients. In this study fentanyl was associated with less constipation and daytime drowsiness than morphine but greater sleep disturbance and shorter sleep duration[34]. Oral transmucosal fentanyl citrate, a novel preparation resembling a lollipop, may have a place in the treatment of breakthrough and incident pain in cancer patients. The onset of action is rapid. Dose titration is required, however, since there is no clear relation between the total daily dose of the long-acting opioid the patient is taking and the dose of transmucosal fentanyl needed to manage breakthrough pain[35].

Galer[36] reported success, in a series of patients with morphine 'poorly responsive' pain, after switches from morphine to hydromorphone, levorphanol or methadone. The benefit of such switches would depend on incomplete cross-tolerance between the drugs, with cross-tolerance to the analgesic effect less than cross-tolerance to the side-effects. Bruera *et al.*[37] examined this phenomenon in cancer patients by studying 48 switches between morphine and hydromorphone and 65 switches from hydromorphone to methadone. The dose ratio for morphine/hydromorphone did not change over a wide range of doses, and they saw this as evidence for complete cross-tolerance between these two opioids. But the hydromorphone/methadone ratios were higher in those patients receiving large hydromorphone doses, and this they took to be evidence of incomplete cross-tolerance between hydromorphone and methadone.

When a patient has toxic effects from morphine, should an alternative strong opioid then be tried? The rationale for this controversial proposal is that opioid toxicity associated with the accumulation of active metabolites should be relieved by a switch to an opioid free of such metabolites—e.g. oxycodone, fentanyl or methadone[38]. Some centres suggest that as many as 41% of patients require a switch to an alternative opioid, whilst others quote a figure close to 2%. Consensus amongst UK palliative care physicians is that a diagnosis of opioid toxicity necessitates careful evaluation, being one of the many potential causes of similar symptoms and signs in patients with advanced cancer. In a retrospective review of 138 referrals to a hospital-based palliative care team, opioid toxicity was identified as being a major contributing factor in 13 out of 57 patients loosely categorized as 'confused'. Symptoms resolved in 11 of these 13 patients with a reduction in opioid dose rather than a switch to an alternative strong opioid[39].

OPIOID ACTIVITY AT NON-OPIOID RECEPTORS

Opioids act by binding to and activating μ, δ and κ opioid receptors. Morphine has a high affinity for the μ receptor with at least 50 times less affinity for the δ receptor and negligible affinity for the κ receptor[40]. Some opioids are distinct from morphine in having additional activity, acting as non-competitive NMDA receptor antagonists and inhibitors of monoamine reuptake. Dextromethorphan, methadone and levorphanol seem the most promiscuous of these opioids with affinity for the NMDA receptor in the low μmol range (similar to that of ketamine) and an ability to inhibit the reuptake of noradrenaline and serotonin in some cases at nmol concentrations. NMDA receptor antagonists can block the hypersensitivity seen in neuropathic pain, potentiating the analgesic action of morphine[41] and attenuating the development of morphine tolerance. Serotonin and noradrenaline reuptake inhibitors act in synergy with morphine to promote analgesia[42] and, interestingly, most of the opioids that display activity at the NMDA receptor also inhibit the reuptake of these monoamines.

In animal models, methadone reduces pain behaviour provoked by stimuli mimicking neuropathic pain, and attenuates the development of tolerance—although electrophysiological studies have suggested that this is primarily an effect mediated via opioid receptors[43]. As yet, reports of the efficacy of methadone in the management of cancer-related neuropathic pain are anecdotal, but clinical trials are in progress.

Dextromethorphan, however, in combination with morphine (Morphidex) enhanced analgesia in a double-blind study[44], although when used as a single agent it did not show any analgesic activity[45].

This striking synergy between NMDA receptor antagonists and μ opioid agonists is seen with the subcutaneous coadministration of ketamine (a potent NMDA receptor antagonist) and diamorphine—a strategy that has been reported highly effective in many cases of otherwise intractable cancer pain[46]. There is also a good case for assessing more closely the utility of opioids such as methadone or levorphanol, particularly when cancer pain is associated with hyperalgesia, allodynia or the rapid development of tolerance to morphine.

Levorphanol, obtainable in the USA and Scandinavia, is no longer available in the UK. Unfortunately methadone, with its long and variable half-life, requires careful dose titration during the initial switch to avoid toxicity. Long-term follow-up has also shown an appreciable incidence of side-effects, with nearly half of 54 cancer patients reporting excessive drowsiness[47].

CONCLUSION

Whilst the under-use of opioid drugs undoubtedly leads to unnecessary suffering[48], clinicians are faced with a bewildering number of strong opioids to choose from. Carefully designed studies are needed to clarify the role of

strong-opioid alternatives to morphine. Meanwhile, oral morphine remains the strong opioid of first choice for management of chronic cancer pain.

Note

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