

## Opioids in pain management

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**Opioids are our most powerful analgesics, but politics, prejudice, and our continuing ignorance still impede optimum prescribing. Just over 100 years ago, opium poppies were still grown on the Cambridgeshire fens in the UK to provide oblivion for the working man and his family, but the brewing lobby argued on thin evidence that their potions were less dangerous. The restriction of opioid availability to protect society and the individual continues in many countries. In this review I focus on chronic and cancer pain, but many of the principles apply in acute pain. The justification for this focus is that patients with chronic pain may suffer longer and unnecessarily if we prescribe and legislate badly.**

### Dose titration and differences between clinical and laboratory pharmacology

The clinical use of opioids shows a difference between their clinical pharmacology and their laboratory pharmacology. What happens when opioids are given to someone in pain is different from what happens when they are given to someone not in pain. The respiratory depression that results from the acute use of opioids is seen in studies of volunteers who are not in pain. But respiratory depression is kept to a minimum when appropriate regular doses of opioid are given to patients with chronic pain. Patients maintained on oral morphine without respiratory depression who then receive successful nerve blocks must have their morphine dose reduced. Failure to reduce the dose will result in respiratory depression.<sup>1,2</sup> One explanation is that the respiratory centre receives nociceptive input<sup>3</sup> which counterbalances the respiratory depressant potential of the opioid. Absence of this pain input, for example because of a successful nerve block, leaves the respiratory depressant effect of the opioid unopposed.

The clinical message is that opioids need to be titrated against pain. Excessive doses, doses greater than needed to relieve pain, or doses given when there is no pain, will cause respiratory depression. However, concern about respiratory depression should not inhibit the appropriate use of opioids—ie, to provide analgesia when the pain is deemed to be opioid sensitive. A postoperative patient who complains of pain when the previous dose has had time to be absorbed needs more drug. The titration, size of doses, timing of doses, and use of escape doses has to be well organised.<sup>4</sup>

The difference in opioid pharmacology between individuals with and without pain also applies to addiction. The drug-seeking behaviour synonymous with drug addiction does not occur in patients after pain relief with opioids in childbirth, operations, or after myocardial infarction.<sup>5</sup> Drug addicts are not in pain. The political message is that the medical use of opioids does not create drug addicts, and restrictions on this medical use hurt patients.

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### Common opioids

Morphine  
Diamorphine (UK)  
Pethidine/meperidine  
Methadone  
Hydromorphone  
Oxycodone  
Fentanyl (lollipop/transdermal)  
Buprenorphine

### Clinical issues

Unresolved issues in clinical opioid use include the choice of opioid (panel), tolerance, pain sensitivity to opioids, and whether to change the drug or change the route of administration when things go badly. Cloning of opioid receptors has revealed many receptor subtypes, doubtless with more to come. The irony is that, because clinically we titrate opioids to effect, we cannot logically expect to see much difference in efficacy between opioids. This expectation is based on the assumption that all types of pain respond equally well to all opioids. This assumption may be wrong, particularly if differences in receptor selectivity between opioids can be exploited to manage different types of pain. However, there is no available clinical evidence of such differential efficacy. Similarly, although in some patients a change of opioids (at the same level of analgesia) can reduce adverse effects, we have no data on which to make policy.

### Choice of opioid

Morphine is the standard opioid against which others are judged. Beliefs that other drugs act faster, last longer, or have a better balance between effect and adverse effect for a particular patient often have little empirical credibility. Political decisions limit medical availability and hence choice of opioids in many countries. Particular agonists and mixed agonist-antagonists may be the only permissible opioids in some countries, because of perceived lower dependence liability. Partial agonists may not relieve severe pain if the ceiling to their effect occurs at low doses.

### Efficacy differences: speed of onset and duration of effect

There is little difference between different opioids in speed of onset and duration of effect; faster onset and longer effect are achieved by changing the route of administration

or formulation. Fast onset of effect is not a critical factor if the patient is receiving continual analgesics for chronic pain, but may be relevant in patients taking the drug on an as-needed basis for acute or chronic pain. With the intravenous route, there is little difference in onset time (2 min) between different opioids. With intramuscular injection, the more lipophilic the drug, the faster the onset time (20 min). Normal-release oral formulations take 1 h to work, whereas sustained-release formulations may take 2–4 h.<sup>6</sup> Fast-onset, fast-offset opioids would be highly desirable in childbirth or for chronic movement-related pain. Sustained-release oral formulations, subcutaneous or intravenous infusions, or spinal injections are used to achieve duration of effect of longer than 4–6 h.

### Toxic and active metabolites and differences in adverse effects

Pethidine has a toxic metabolite, norpethidine.<sup>7</sup> Norpethidine causes tremor, twitching, agitation, and convulsions, and these effects increase with multiple dosing and in the presence of impaired renal function. Since use of pethidine is not associated with any specific advantage, it is a poor choice if multiple doses are needed.

Morphine has an active metabolite, morphine-6-glucuronide (M6G), which is a major metabolite in man and is more potent than morphine. Intrathecal M6G is 10–20 times more potent than morphine,<sup>8</sup> and it may also contribute to the analgesic effect of morphine by its action through a different receptor subtype.<sup>9</sup>

Unexpected degree and duration of effect of M6G can occur in patients with severely impaired renal function given morphine or derivatives in whom there is a cumulation of M6G.<sup>10</sup> The glucuronidation of morphine is not affected significantly in cirrhosis,<sup>11</sup> but in precoma states, the kinetics<sup>12</sup> and dynamics<sup>13</sup> of morphine metabolism are altered.

Difficulties arise with morphine only if a fixed-dose schedule is used without taking account of renal function, or without adequate titration against pain intensity. Drug doses should be decreased substantially if creatinine clearance is less than 30 mL/min per 1.73 m<sup>2</sup>. With less severe renal dysfunction, careful titration is needed, but it should always be remembered that renal function deteriorates with older age.

### Adverse effects

Any opioid that produced fewer adverse effects than morphine, at a dose which provided the same degree of analgesia, would be an improvement. For most clinically important adverse effects, there are no comparative data at equianalgesic doses to allow recommendation of any of the alternatives. The key factor is equianalgesic dosing. If the adverse effect is mediated via opioid receptors, then similar effects should occur at equianalgesic doses of different opioids that act through the same receptors. A common claim is that a drug has fewer adverse effects than morphine, but only because the comparison was made at a much less effective dose than the morphine dose. Some idea of the adverse effects that may be expected within 6 weeks on oral morphine comes from a randomised study by Moulin and colleagues<sup>14</sup>—13 of 46 chronic non-cancer patients had dose-limiting adverse effects, 18 reported nausea, 17 dizziness, and 19 constipation.

Differences in the rate of adverse effects between opioids are apparent in randomised single-dose postoperative

studies of dysphoria; Houde<sup>15</sup> reported a rate of 20% with pentazocine and butorphanol versus 3% with other opioids. Rigorous 3-day multiple-dose comparison of oxycodone and morphine at equianalgesic doses also showed differences in the rate of adverse effects in a few patients.<sup>16</sup> If the adverse effect is mediated by opioid receptors, then these differences may be explained by differences in receptor binding; if such events are not mediated via opioid receptors then some other explanation must be sought.

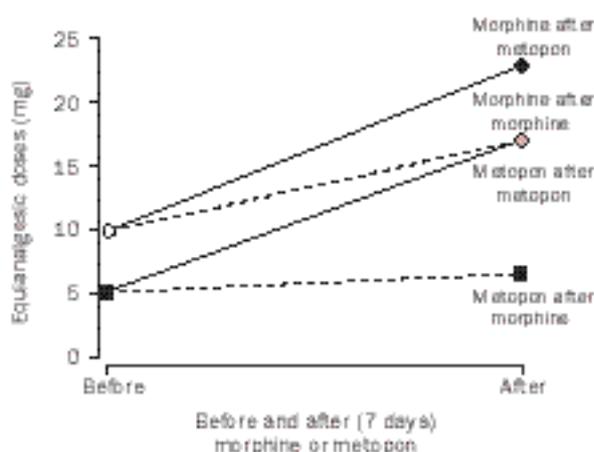
Constipation is a side-effect of all opioids, and is opioid-receptor mediated with both central and peripheral mechanisms; tolerance to this effect develops slowly if at all. Moulin and colleagues<sup>14</sup> reported that about 40% of patients on oral morphine were constipated. This proportion may be increased among patients with severe illness. Claims that other opioids cause less constipation than oral morphine are open to the challenge that the comparison was not made at equianalgesic doses.

The extent to which nausea and vomiting are mediated by opioid receptors is arguable. Some of the effect may come from stimulation of opioid receptors at the chemoreceptor trigger zone in the medulla. If the effect is receptor-related, equianalgesic doses of different opioids would be expected to produce the same amount of nausea. For most patients tolerance develops quickly, but some patients have nausea with all opioids at effective doses. Pain itself can also cause nausea.<sup>16</sup> Moulin and colleagues<sup>14</sup> showed that 40% of patients on oral morphine may have nausea. Kalso and Vainio's comparison<sup>17</sup> of morphine and oxycodone showed that there may be differences between individual patients with different opioids.

Pethidine is said to be the opioid of choice for biliary colic because its atropine-like effect will counteract the opioid action on smooth muscle. Topical atropine, however, does not relax a contracted gall bladder and there is no good evidence to suggest that pethidine has any clinically significant advantage at equianalgesic doses over other opioids for biliary or renal colic. The interaction between pethidine and inhibitors of monoamine oxidase is another reason why pethidine is not the first choice of opioid for the management of severe chronic pain.

### Tolerance

Tolerance is the need for a higher dose (or increased plasma concentration) to achieve the same pharmacological effect. Clinicians argue that the need for a greater dose is driven by worsening disease rather than by pharmacological tolerance, and cite the fact that many patients are maintained satisfactorily on the same oral morphine dose for months. It is ingenuous to argue that opioid tolerance does not occur in man. Two classic experiments showed chronic tolerance when patients' analgesic response to a test dose was measured before and after chronic dosing.<sup>18,19</sup> Houde and colleagues<sup>18</sup> found that in ten patients challenged with a single dose of morphine, before and after 2 weeks of regular morphine injections, the response to the second challenge was less than to the first. Houde<sup>19</sup> also showed that in 13 patients challenged with single doses of morphine or metopon (no longer in use), before and after 1 week of regular injections of either drug, the dose-response curve was again shifted to the right after the regular injections; to complicate matters, this change was greater for the drug that was given repeatedly after the first challenge (figure). The two studies show tolerance, less effect from the same dose after repeated



#### Dose required to achieve same degree of pain relief when rechallenged after 1 week of chronic dosing

13 patients had a controlled relative potency assay to compare morphine and metopon after 1 week of regular dosing with either drug. Reproduced with permission from Houde.<sup>18</sup>

injections, and, because the slopes of the four lines in the figure differ, incomplete cross-tolerance is evident from the second study.

The pragmatic issues are whether the escalation of dose that some patients require, and which produces different adverse effects, can be avoided by changing opioid or route of administration, or by blocking tolerance.

#### Oral morphine: success and failure

In patients with chronic pain opioids are usually given by mouth. The dose is calculated by titration over a few days, and then the drug is given regularly, without waiting for the pain to come back. The initial reactions of nausea or dizziness commonly abate. If constipation is likely laxatives are given. If a patient's pain starts to increase the dose is increased. Audits of cancer pain report that the use of analgesics according to the WHO ladder can relieve pain for 80% of patients;<sup>20</sup> for most of the 80% the relief will be good, for a few patients it will be only moderate.

Oral opioids will "fail" in patients who are unable to swallow, and then the route of administration needs to be changed to sublingual, transdermal, or suppository. In patients who are able to swallow, oral morphine can fail because of intolerable or unmanageable adverse effects, opioid-insensitive pain, and movement-related pain. These situations present particular clinical difficulties for diagnosis and management, and the controversy between proponents of change of drug or change of route of administration but same drug is unresolved.

Intolerable or unmanageable adverse effects due to opioid action via opioid receptors will not be improved by changing to an equianalgesic dose of a different opioid that acts on the same receptors. For this approach to work would require different dose-response curve slopes for the effect and adverse effects for different opioids, and we have limited evidence for such differences. The case reports of changing opioid to reduce the adverse effects and maintain analgesia commonly describe complex cases that defy simple interpretation, but Kalso and Vainio's randomised study<sup>17</sup> indicates that there may be exploitable differences. In that double-blind crossover study, morphine and oxycodone hydrochloride were given to 20 patients with severe cancer pain and equal analgesia was achieved with morphine and oxycodone, but morphine caused more nausea than oxycodone and hallucinations occurred only

with morphine.<sup>17</sup> Whether changing the route of administration (same drug) can improve the balance between efficacy and adverse effect is unclear. The necessary evidence would come from a randomised comparison of oral and injected dosing with the same drug.<sup>17</sup>

#### Opioid-insensitive pain

Chronic cancer pain and non-cancer pain are not always relieved by opioids. Opioid-insensitive pain can be defined as pain that does not respond progressively to increasing opioid dose. The most common causes of this type of pain are nerve compression and nerve destruction. Controversy has arisen about whether the opioid insensitivity is absolute or relative; if it is relative (dose-response curve shifted to the right) then giving greater doses would produce analgesia. The academic answer is that the insensitivity is usually relative, but increasing the opioid dose provokes intolerable or unmanageable adverse effects. A working rule is that if the pain is in a numb area—as a marker for a damaged nervous system—we should be less confident that opioids will work, except at doses that give troublesome adverse effects, and our threshold for considering other strategies (change of route or drug) should be lower. We have no simple way to test for opioid sensitivity other than time-consuming titration.

The usual pharmacological solutions for neuropathic pain include oral antidepressants, anticonvulsants, and local anaesthetics,<sup>21</sup> with spinal infusions of local anaesthetic and opioid mixtures as the last resort. There is still no quality evidence that changing from oral morphine to another oral opioid, methadone, or ketabemidone, with different opioid-receptor binding profiles, makes a difference. Differences in opioid sensitivity need to be assessed in efficacy comparisons of changing opioid or route of administration in chronic pain. The same drug by a different route must act on the same receptors. The issue is whether changing the route allows for a dose increase and effective analgesia without an increase in adverse effects.

#### Movement-related pain

Movement-related pain is difficult to manage. The doses of oral opioid required to control movement-related pain may be excessive when the pain stops (no movement). Two audits show that pain on movement is a major problem for half of those whose pain is controlled at rest.<sup>22,23</sup> Fast-onset, fast-offset opioids administered by injection might improve management of pain on movement.

#### Changing drug (opioid rotation) or changing route of administration

Oral morphine is the standard oral opioid, but the clinical dilemma is what should be done when oral morphine does not work—should the oral opioid or the route of administration be changed? There is limited quality evidence to guide the clinician. Physicians who can change the route of administration do so, while those who cannot change the drug. Until we have more hard evidence that there is genuine advantage in changing the drug, such as a differential rate of adverse effects or evidence from a randomised comparison of the two strategies, this question remains unresolved. Kalso and colleagues' small randomised study<sup>24</sup> showed that changing from oral morphine to subcutaneous or epidural morphine improved

pain relief and reduced adverse effects. Until there is a well-controlled randomised trial of adequate size, we can all continue with our beliefs unchallenged. My vote is to change route of administration not drug, but I am in the privileged position of being able to do this.

This dilemma also raises other issues. When changing drugs and not route of administration, comparisons must be made at equianalgesic doses. By contrast, when changing route of administration and not drug, the dose of the drug must be adjusted, particularly between oral and parenteral routes if the opioid undergoes extensive first-pass metabolism. Endless argument can result. For morphine, the effect of a single injected dose was six times that of a single oral dose.<sup>25</sup> In the multiple-dose context of chronic pain, ratios of two to one or three to one are used successfully. The active metabolite may contribute more to the analgesic effect with repeated doses than with a single dose.<sup>10</sup> Moreover, the basis on which such decisions are made constantly changes. The original spinal (generic for intrathecal and extradural) opioid question was whether spinal opioid alone was better than simpler injection routes. Randomised comparison of subcutaneous and epidural morphine showed little difference between the two routes in efficacy and adverse effects.<sup>24</sup> Currently it is the use of spinal combinations of local anaesthetic and opioid that promises the greatest clinical benefit.

Continuous spinal infusions of a combination of local anaesthetic and opioid exploit the synergy between local anaesthetic and opioid.<sup>26,27</sup> Low doses of both components can provide analgesia with little loss of mobility. Although there are many randomised trials of these combinations in postoperative pain, there are few in chronic pain.<sup>28</sup> Such spinal infusions can succeed in neuropathic and movement-related pain when oral opioid has failed, and the addition of clonidine may provide additional benefit in neuropathic pain.<sup>29</sup> Technical debate continues over the relative advantages of epidural versus intrathecal and high-cost implant versus simple percutaneous catheters and external syringe drivers. In my experience, the epidural with external syringe driver works well.

### Opioids in non-cancer pain

In 1999, opioids are used for cancer pain, but we still argue over the use of opioids in non-cancer pain. Medical proponents of opioid use in non-cancer pain argue that when there is no other effective remedy and opioids are effective then they should be used. Some oppose this view on the basis of harm to the individual, and yet there is no evidence that long-term opioid use creates irreversible physical change. Lurking behind such opposition is the view that increased opioid availability is bad for society. The issue of opioids in non-cancer pain cannot, however, be properly addressed by such polarised positions. A bedridden patient with multiple sclerosis and opioid-sensitive pain has to be seen in a different light from a 25-year-old with back pain. The danger is that legislation that denies opioid access to the latter also forbids it to the former. Common sense dictates that not all patients with non-cancer pain should be treated with opioids. However, that small number of patients for whom opioids are the only effective remedy have the right to receive effective relief, as do their doctors to prescribe such relief for them.

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