Recent advances in opioid therapy

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Recent advances in opioid therapy regarding routes of delivery, long-acting preparations, and sequential trials are described. Specifically, the advantages and disadvantages of transdermal therapeutic system fentanyl, transmucosal fentanyl citrate, Kapanol (sustained-release morphine) and individual variability in the responses to different opioids are discussed in detail. Pain and the fear of pain are perhaps the greatest source of suffering. It is common sense to accept that many diseases still cannot be cured, yet the accompanying suffering real. Hence relief is very important. Very few medications surpass opioids in terms of their therapeutic efficacy, ease of application, and lack of organic toxicity. The question is not whether opioids are effective but how to use them rationally. Many patients fail to have adequate analgesia, simply because doctors under-prescribe opioids as a result of lack of knowledge about their optimal usage.

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Three areas in the recent advances of opioid therapy are discussed—routes of delivery, long-acting preparations, and sequential trials.

Routes of delivery

The oral administration of opioids is generally preferred. Apart from the avoidance of painful injections, this route is simple, convenient, and provides stable serum opioid levels. In patients without the option of oral dosing, sublingual administration of an injectable formulation such as pethidine or methadone has been a useful approach.[1] The introduction of transdermal therapeutic system fentanyl (TTS-fentanyl) provides a more convenient delivery than the sublingual route and is even simpler to use than the oral route, needing a simple skin patch.

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In 1989, TTS-fentanyl was introduced in the United States and became available in Hong Kong in 1994. While in the United States it is supplied at four different dosages (25, 50, 75, and 100 μg/hr), in Hong Kong only the 25 μg/hr dose is presently available. It produces consistent and acceptable analgesia. Clinical study has suggested that when TTS-fentanyl is compared to oral morphine (R Patt, personal communication), patients tend to demonstrate more satisfaction and report fewer side effects such as constipation, nausea, and vomiting. The transdermal therapeutic system converts fentanyl from a drug with a relatively short half-life to one with prolonged action. The result is a long latency of effect (average 14 hours) and a similarly long duration of effect after its removal.[2] This reliable delivery and absorption via intact skin leads to steady serum concentrations that are sustained for 72 hours.[3] Hence, the recommended dosing interval is usually 72 hours. It is our experience, however, that in some patients, 60 hourly or even 48 hourly applications are necessary for effective pain relief. Although the recommended maximum dose is 400 μg/hr, doses up to 1200 μg/hr have been used safely and effectively (R Patt, personal communication).

The long duration of TTS-fentanyl action makes it particularly useful in patients with poor compliance, since they do not have to take it frequently. In addition, it does not require the gastrointestinal tract for

absorption. Nausea, vomiting, intestinal obstruction, and other causes of malabsorption are indications for its application. As with all opioids, TTS-fentanyl has abuse potential, but it is not popular with street drug addicts who are generally looking for an instant high. In a society where many patients automatically link morphine with addiction, TTS-fentanyl may be a more acceptable opioid analgesic. On the other hand, long onset of action and long duration of effect after removal can be a disadvantage. These properties make TTS-fentanyl unsuitable for the rapid titration for severe, unstable pain. As a result, it is generally used when other opioids are not well absorbed such as with vomiting.

When TTS-fentanyl is to replace another opioid, it is necessary to follow a conversion formula. We find that the conversion formula provided by the manufacturer is conservative. If it was followed strictly, there would be the likelihood of undertreatment. Whenever it is necessary to convert from an oral opioid to TTS-fentanyl, our practice has been to start intravenous patient-controlled analgesia (PCA) with morphine. Then the patch is applied to the skin at the recommended dose. The PCA serves two purposes; in addition to covering the latent period of TTS-fentanyl, the consumption of morphine also indicates whether or not an additional dosage is needed.

The acceptance of TTS-fentanyl by patients in Hong Kong has been good, possibly because plasters have been a form of traditional Chinese medicine. Despite Hong Kong's subtropical climate, the adhesiveness of the patch has not been a problem. This may be because Asians are generally less hairy than Westerners, or because patients at this stage of disease are not physically active.

One limitation of TTS-fentanyl is the lack of an ideal alternative short-acting opioid to manage breakthrough pain. Pharmacologically, the rescue drug should be identical to that being administered on a continuous basis. With the long latency and long action of TTS-fentanyl, using it as a rescue drug is not practical.

The recently introduced transmucosal fentanyl citrate (Fentanyl Oralet), which has a rapid onset of action (approximately 30 minutes) and a comparatively short duration of effect (approximately four hours) may compensate for this short-coming.[4] This is the lozenge dosage form of fentanyl that has been marketed in the United States since 1994 as a pre-operative anxiolytic. Three different dosages are available: 200, 300, and 400 μg. The recommended dosages are 5 to 15 μg/kg. The patient sucks the lozenge for approximately 10 minutes. Advantages of the mucosal route include decreased hepatic first-pass metabolism and improved patient comfort. A preliminary study found that in 30 children aged two to eight years requiring skin laceration repair, doctors suturing the wound rated the children's sedation and pain control as good or excellent in 83% of patients.[5] The side effects were those expected of any potent opioid. A larger evaluation study is now under way to determine whether transmucosal fentanyl citrate provides analgesia sufficient to facilitate placement of invasive monitoring lines and its suitability for chronic and cancer pain conditions. If the clinical efficacy of its analgesia versus side effects is proven, transmucosal fentanyl citrate could be used to manage breakthrough pain for patients using TTS-fentanyl. The drug is not yet available in Hong Kong.

Long-acting preparations

Controlled-release morphine (MST Continus) was first introduced in the United Kingdom in 1981. In contrast to conventional morphine, which lasts for approximately four hours, it enables a dosing schedule of up to 12 hours. This long duration of action significantly enhances medication compliance and facilitates uninterrupted night-time sleep.[6] However, pharmacokinetic profiles show relatively large inter-patient fluctuations in plasma concentrations with identical doses. Approximately one-third of patients on MST Continus require 8-hourly dosing, instead of the recommended 12-hourly dosing for effective analgesia.[7]

Kapanol is a new sustained-release formulation of polymer-coated morphine sulphate pellets in a gelatine capsule, designed for administration every 12 to 24 hours. This is twice the duration of MST Continus and one-third that of TTS-fentanyl. It has been shown that Kapanol, when given every 12 to 24 hours, controls pain as well as MST Continus given every 12 hours. Clinically, there were no significant differences between Kapanol and MST Continus in terms of pain intensity and side effects.[8] MST Continus releases proportionally more morphine than Kapanol in the first four hours. Hence, the onset of analgesic effect for Kapanol is significantly later than MST Continus, which is 90 minutes.

Breakthrough pain can result in a vicious cycle. Considering that 29% of the breakthrough pain related to the fixed opioid dose occurred at the end of the dosing interval in one study,[9] drugs that provide prolonged, steady serum levels of analgesics should result in less

breakthrough pain. Although Kapanol, given 24-hourly, has a superior sustained-release steady state profile compared with 12-hourly MST Continus, it does not result in less breakthrough pain. Of interest is the finding that the correlation of serum morphine concentrations with pain scores is also not as good as expected.[10] Further investigations will be needed in the area relating to pain scores and serum concentrations.

MST Continus represents an important advance over conventional oral morphine. The prolonged action allows patients to maintain greater freedom, independence, mobility, and control. Kapanol may have an even greater impact on the patient's quality of life. Based on the global assessment score on 152 patients, more patients and clinicians favour Kapanol over MST Continus.[11] Kapanol is not presently available in Hong Kong.

The pellets in capsule preparations will permit Kapanol to be used effectively, even in some patients with nausea and vomiting. It is rare for patients to be totally unable to swallow, but if this is the case, transdermal, parenteral, or rectal administration can be considered. However, if the systemic route is unsatisfactory, it is necessary to consider other routes such as the spinal delivery of opioids. This technique uses only about 1% to 20% of the dosage of opioid needed for the systemic route. Proportionally larger dosage escalation is possible, because treatment begins with a low dose. Of the other opioids available, hydromorphine is also effective intraspinally and is five times as potent as morphine.[12]

Sequential trials

Although the opioids all exert their analgesic effects via similar receptors, failure to obtain pain relief may sometimes be not a matter of route but the choice of drugs. There is considerable individual variability regarding analgesia and side effects. Pharmacologically comparable drugs such as morphine and methadone may produce a different intensity of side effects at any given level of analgesia. This variability demonstrates the need for sequential therapeutic trials to identify the most suitable opioid for a patient.

The underlying mechanisms for such variability are not known, although genetic factors are likely important determinants. The impact of these factors has been demonstrated in animal studies, which have revealed striking differences in sensitivity by more than 110-fold in different mouse strains.[13] In humans, the issue is more complicated. While it has been demonstrated in one study that Chinese patients require less pethidine than do Caucasians for control of post-operative pain,[14] another study based on the requirements of morphine by PCA revealed no such differences.[15] At issue are the cultural concepts, variable metabolisms, and constitutional susceptibilities to side effects. To date, there is no conclusive evidence to support the statement that Chinese need less medication for pain relief. It is important to emphasise individual differences rather than ethnic differences to avoid undertreatment.

The effective dosage for opioids in providing pain relief is determined either when the analgesia is adequate or when the side effects are intolerable. If an opioid has been associated with dose-limiting side effects, a trial of an alternate opioid should be considered. In a prospective survey of 100 consecutive in-patients treated by the Pain Service at the Memorial Sloan-Kettering Cancer Center in the United States, 44 patients required trials of two or more opioid drugs and 20 required trials of three or more opioids to optimise the balance between analgesia and side effects.[4] The existence of different degrees of incomplete cross-tolerance to various receptor-mediated opioids may explain the utility of these sequential trials.[16] We request clinicians working in the Pain Management Service in our hospital to be familiar with at least three commonly used opioids and have the ability to calculate appropriate doses using equianalgesic data.

Using different opioids in the same patient may increase the chance of drug dependence. But addiction should not be a primary consideration in sequential trials. If the patient is in severe pain, opioids will most likely be needed. If the cause of pain is effectively eliminated and the patient shows withdrawal syndrome, detoxification can be carried out. The opioid abstinence syndrome can be avoided by withdrawal of the opioid on a schedule that provides half the prior daily dose for each of the first two days and then reduces the daily dose by 25% every two days thereafter, until the total dose (in morphine equivalents) is 30 mg/day. The drug may be discontinued after two days on the 30 mg/day dose (American Pain Society, 1992). Transdermal clonidine, 0.1 to 0.2 mg/day or oral clonidine, 0.075 mg three times daily, may reduce anxiety, tachycardia, and other autonomic symptoms associated with opioid withdrawal.

In conclusion, our knowledge regarding opioid usage has increased a great deal recently and this offers more possibilities for clinical use. But opioids are only part of pharmacotherapy and it should always be em-

phasised that pain is multi-dimensional and pharmacotherapy is only part of the multidisciplinary approach to the treatment of pain.

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