Introduction to cancer pain

Pain is recognized as an important but neglected public health issue. About 80% of patients with advanced cancer suffer from pain as the major symptom. In about 60% of these, the pain is moderate to severe in intensity. The World Health Organization (WHO) recommends the use of strong opioids for management of moderate to severe cancer pain. The European Association of Palliative Care (EAPC) recommends morphine as the first-line strong opioid for these patients. Response to morphine varies significantly between patients and even within the same patient at different stages of the illness trajectory. Finding a morphine dose that provides adequate analgesia with tolerable side-effects can be difficult. While most cancer patients tolerate morphine well, about 10-30% of patients do not and suffer from inadequate analgesia, intolerable side-effects or a combination of both. The EAPC Research Network gathered evidence-based clinical practice recommendations on interventions to manage the side-effects of oral opioids, including dose reduction of the systemic opioids, symptomatic management of the side-effect and changing the route of administration. If all fails, opioid switching, the therapeutic strategy of switching one opioid for another, may be the only option for symptomatic relief. There is evidence to support the therapeutic maneuver of opioid switching in clinical practice, although the evidence is largely anecdotal or based on observational and uncontrolled studies. Opioid switching is not without intrinsic problems. Given the wide conversion ratios reported in literature, we risk under- or over-dosing. It is recommended that opioid switching should not be a mere mathematical calculation, but form part of a more comprehensive assessment of pain, side-effects, comorbid diseases, and concomitant drugs. Good cancer pain control remains a high priority for doctors and treatment should be highly individualized.

Abstract

Pain is one of the most common and often most feared symptom in cancer patients. Effective management of cancer pain remains a high priority and is an ongoing challenge in both the oncological and palliative care settings. The World Health Organization (WHO) recommends the use of strong opioids for management of moderate to severe cancer pain. The European Association of Palliative Care (EAPC) recommends morphine as the first-line strong opioid for these patients. Response to morphine varies significantly between patients and even within the same patient at different stages of the illness trajectory. Finding a morphine dose that provides adequate analgesia with tolerable side-effects can be difficult. While most cancer patients tolerate morphine well, about 10-30% of patients do not and suffer from inadequate analgesia, intolerable side-effects or a combination of both. The EAPC Research Network gathered evidence-based clinical practice recommendations on interventions to manage the side-effects of oral opioids, including dose reduction of the systemic opioids, symptomatic management of the side-effect and changing the route of administration. If all fails, opioid switching, the therapeutic strategy of switching one opioid for another, may be the only option for symptomatic relief. There is evidence to support the therapeutic maneuver of opioid switching in clinical practice, although the evidence is largely anecdotal or based on observational and uncontrolled studies. Opioid switching is not without intrinsic problems. Given the wide conversion ratios reported in literature, we risk under- or over-dosing. It is recommended that opioid switching should not be a mere mathematical calculation, but form part of a more comprehensive assessment of pain, side-effects, comorbid diseases, and concomitant drugs. Good cancer pain control remains a high priority for doctors and treatment should be highly individualized.
The practice of opioid switching and the available alternative opioids used vary widely between different centers, depending on local experience and the available alternatives to morphine. For simplicity purposes, the term “opioid switching” will be used in the remaining of this article to represent the clinical practice of substituting one strong opioid for another. Opioid switching is gaining popularity as a therapeutic strategy. It has become established practice in pain management in helping to achieve a more favorable analgesia vs. side-effect profile.

**Incidence of opioid switching**

In a review article published in 2008, the incidence of opioid switching from retrospective trials ranged from 20 to 44%. Trials on opioid switching mainly focus on the positive results, and the condition for switching is not described in detail or standardized. In two recent prospective studies published in 2006 and 2009, 25% and 34.2% of cancer patients respectively required opioid switching after using their own local guidelines or protocols on pain management.

**Indications for opioid switching**

In a more recent prospective study published in 2009, the indications of opioid switching in 118 cancer patients in an acute palliative unit were evaluated. The reasons for switching in these 118 patients included uncontrolled pain in 15.2%, side-effects in 28.8% and combination of both uncontrolled pain and side-effects in 50.8%.

**Opioid switching: What does evidence say?**

Some studies on opioid switching have shown an improvement in the side-effect profile, especially with improvements in relation to side-effects related to the central nervous system and the gastrointestinal system. Whether there is a true difference among opioids in relation to the side-effect profile is subject to considerable debate. Some argue that the overall reduction in the morphine equivalent daily doses (MEDD), due to incomplete cross-tolerance, may have caused reduced opioid-related side-effects rather than actual differences between opioids at the same equianalgesic doses. Large, randomized, controlled trials have not been performed to directly compare opioids, and smaller individual trials are underpowered to demonstrate superiority of one opioid over another.

Some studies have reported factors associated with increased need for opioid-switching including terminal stages of cancer and longer length of stay. In a retrospective analysis including 273 cancer patients amongst whom 103 patients (37.7%) required opioid switching, an increased incidence of opioid switching was found to be associated with terminal stages of cancer. In another retrospective analysis including 191 terminal cancer patients, 80 patients (41.9%) of whom required opioid switching, a longer length of stay in a palliative care unit was found to be associated with an increased incidence of opioid switching.

The Cochrane review in 2004 identified 52 reports on opioid switching to improve pain relief and drug tolerability. This review included 23 case reports, 15 retrospective studies or audits, and 14 prospective uncontrolled studies. No randomized controlled trials on opioid switching were identified. All 52 reports, except one study, showed favorable outcomes in improving pain control and/or reducing opioid-related side-effects. Although the evidence supporting opioid switching is largely anecdotal, or based on observational and uncontrolled studies, the reviewers concluded that for patients with inadequate pain relief and intolerable opioid-related side-effects, a switch to an alternate opioid may be the only option for symptom relief.

Another systematic and critical review on opioid switching published in 2006 included 31 reports. This review reported that opioid switching resulted in clinical improvement in more than 50% of patients with chronic pain with poor response to one opioid. However, this data is also based on open studies and small case series.

**Interindividual variation & role of pharmacogenetics**

The concept that different individuals respond to morphine differently is not a new one. In the 1950s, Lasagna & Beecher reported a 65% “success rate” with morphine in an experimental pain model. Opioid switching is based on incomplete cross-tolerance and differences in pharmacokinetic and pharmacodynamic properties which account for inter-individual variation in response to opioids. Recent research in pharmacogenetics, based on animal and human models, has highlighted the
importance of a genetic influence on morphine responsiveness\textsuperscript{7}. Research has identified differences in $\mu$-opioid receptor densities, variations of the gene coding for this receptor and differences in the process of receptor renewal. Genetic differences in factors affecting drug transportation and metabolism have also been identified.

**Intrinsic limitations with opioid-switching**

Despite the growing popularity of opioid switching as a therapeutic strategy in pain management, opioid switching is not without problems. The problems with opioid switching are related to:

1. Opioid availability. Opioid-switching is limited by the availability of alternate opioids, or availability of a particular preparation \textsuperscript{1}. 
2. Problems with conversion tables. In switching from one opioid to another, equianalgesic conversion tables are used to guide the dose conversion. However, there are intrinsic problems with equianalgesic dose conversion tables. Many available conversion tables were calculated in opioid-naïve patients. Some conversion data were derived from single-dose studies or studies not originally designed to evaluate equianalgesic dosing \textsuperscript{9}. This can result in under- or over-dosing. Furthermore, there is no one universally adopted conversion table. Different conversion ratios exist and often do not take into account for age, organ failure or polypharmacy, all of which may warrant adjusted doses \textsuperscript{1}. In some situations e.g. methadone to fentanyl, conversion tables do not exist. Opioid switching also has demonstrated directionality; that is a reciprocal ratio cannot be used for reverse switching.

**Recommendations**

Since opioid switching is not without intrinsic problems, it is recommended that clinicians thoroughly consider measures to control side-effects, re-evaluate the cancer pain, and consider use of adjuvant analgesic or non-pharmacological measures of pain control, before putting off a considerably effective therapy.

If opioid switching is the only available option, some authors emphasize that opioid switching should not be a mere mathematical calculation \textsuperscript{16} They recommend that opioid switching should form part of a more comprehensive evaluation of pain, side-effect intensity, comorbidities and concomitant drugs. Therefore it is recommend that the process of reaching an optimal dose after opioid-switching should be highly individualized, particularly when patients are switched from high doses of opioids, given the wide variation of conversion ratios given in literature.

**Summary**

Opioid switching is a therapeutic intervention to help improve analgesia and side-effect profile. Existing equianalgesic conversion tables serve as a guide only. Given the wide variation of conversion ratios in literature, in reaching an optimal dose after opioid-switching, each case needs to be individualized.

**References**