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Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review

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Abstract
In this paper we describe the results of a systematic search of the literature on conversion ratios during opioid switching. This is part of a project of the European Palliative Care Research Collaboration to update the European Association for Palliative Care recommendations for the use of opioid analgesics in the treatment of cancer pain. Studies were eligible for inclusion if they involved adult patients with chronic cancer pain, contained data on opioid conversion ratios, were prospective and were written in English. Thirty-one studies were identified and included. The majority of the studies had methodological flaws and were not designed to explore or demonstrate equianalgesic dose data. However, the data allow some recommendations to be made that could be helpful to clinicians for whom there are few reliable experimental data on which to base dosing guidelines. Switching to transdermal fentanyl (TDfe) or buprenorphine (TDbu) is an option for patients with stable, controlled pain. Reliable and consistent studies show a ratio of 100 : 1 between oral morphine (ORmo) and TDfe. A ratio of 75 : 1 between ORmo and TDbu may be appropriate, but the supporting evidence here is much less robust. Data are relatively consistent to support a conversion ratio between ORmo and oral oxycodone (ORox) of 5 : 1. Despite some limitations, there is evidence to support the use of an approximate conversion ratio of ORmo:ORox of 1.5 : 1. The conversion between ORox and oral hydromorphone (ORhy) is estimated to be 1 : 4. When switching from different opioids to methadone the conversion ratio is highly variable, ranging from 5 : 1 to 10 : 1 and much higher in some studies. The derived ratios are influenced by several factors, including the reasons for switching and previous opioid doses. An individual treatment decision and strict monitoring is recommended for patients considered at risk.

Keywords
Neoplasm, pain, opioids, conversion ratio, switching rotation

Introduction
Most patients respond favourably to opioid therapy, which is the mainstay of treatment for moderate to severe cancer pain. However, in some patients, the response may be complicated by adverse effects severe enough to compromise benefit or, in other patients, poor analgesia despite increasing doses of opioids.1,2 Opioid substitution has been found to produce an improvement in the opioid response.3–5 The rationale behind opioid substitution is incomplete cross-tolerance between step 3 opioids when used to treat moderate to severe pain in cancer patients.6,7

The equianalgesic dose of an opioid is the dose that produces equivalent analgesia to the reference compound. Knowledge of this dose is required when changing from one opioid to another. This happens in practice for two reasons. The first is when a patient chooses to receive his opioid by a different, more convenient route. A patient stabilized on oral morphine (ORmo), for example, may prefer to change to a
transdermal preparation because it is more convenient to use. This is a very different situation to what usually applies in so-called ‘opioid rotation’. Here the patient is unable to achieve adequate analgesia without disabling adverse effects and may be switched to treatment with another opioid, with the aim of improving the balance between analgesia and adverse effects rather than maintaining the same level of analgesia. Therefore, when one opioid is substituted for another, it is necessary to find a workable conversion ratio between them, which needs to be safe on the one hand, and at the same time effective, particularly if patients are suffering badly, as often happens when a switch is planned. Data on this subject are sparse and often unclear. Inconsistencies in the reporting of conversion ratios make it difficult to interpret results. 8

The original opioid equianalgesic tables were produced on the basis of acute repeated crossover administration (‘so-called relative potency assays’) and need to be re-evaluated in the scenario of chronic opioid administration and ‘opioid rotation’. 9,10 Many aspects of the factors influencing conversion dose ratios between different opioids remain unresolved.

We have undertaken a systematic review of the existing data on conversion ratios during opioid switching as part of the European Palliative Care Research Collaboration (EPCRC) project to update the European Association for Palliative Care (EAPC) recommendations for the use of opioid analgesics in the treatment of cancer pain. 11,12

Methods

A systematic literature search of MedLine, Embase and the Cochrane Central Register of Controlled Trials electronic databases was carried out from each database set-up date to 31 December 2009; text words and MeSH/EMTREE terms have been used as described in Table 1, which reports the search strategy employed for MedLine. Appropriately revised equivalent strategies were developed for Embase and the Cochrane Central Register of Controlled Trials. A hand search of the reference lists of identified papers was also performed. In addition to this search, systematic reviews on oxycodone, morphine, hydromorphone, fentanyl, methadone and buprenorphine, which are part of the same EPCRC project, 11-14 were used to select the studies with a crossover double-blind design comparing different opioids and reporting data on conversion ratios.

Studies were included if they were prospective, performed in adult patients with chronic cancer pain, written in English and contained data about conversion ratios between opioids. Only oral and transdermal administration were considered. Comparative-parallel group studies were excluded. Because of the expected paucity of studies available, no other limits regarding study design were adopted. However, case series with less than 10 patients for each opioid sequence were excluded from the analysis.

Papers were conveniently grouped for specific opioid sequences. For each eligible study, quality of evidence formulated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system 15 and conversion ratios were reported.

The initial search yielded 832 records (332 from Medline, 478 from Embase and 22 from the Cochrane Register of Controlled Trial Databases; Figure 1). Abstracts were read by the authors and 25 were selected for full text examination. 16-40 One of them reported unclear information about fentanyl dosing and the data could not be used in this review. 31

Five additional records 41-45 were retrieved from the concurrent 11-14 systematic reviews and two 46,47 by hand searching. In total, 31 studies were considered for examination of the evidence.

Results

Transdermal buprenorphine and other opioids

Only three studies involving transdermal buprenorphine (TDbu) met the inclusion criteria. One was a prospective cohort study, 16 and two were ‘n of 1’ studies 17,18 (Table 2). In the study by Aurilio et al., 16 16 patients switched from transdermal therapeutic system (TTS) fentanyl to buprenorphine and 16 from TDbu to transdermal fentanyl (TDFe) because of insufficient analgesia associated with side effects. The final conversion ratios were quite different depending on the direction of switching and patient selection, and dose-finding methodology seemed too weak to permit meaningful conclusions. Two ‘n of 1’ studies performed in a small group of patients with stable controlled pain suggest that 0.8 mg of TDbu is equianalgesic to 60 mg of

Table 1. Search strategy applied to Medline database

<table>
<thead>
<tr>
<th>#5</th>
<th>#1 AND #2 AND #3 AND #4 Limits: English, Publication Date to 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>#4</td>
<td>Pain</td>
</tr>
<tr>
<td>#3</td>
<td>neoplasm OR cancer OR tumor OR tumour</td>
</tr>
<tr>
<td>#2</td>
<td>Opioid</td>
</tr>
<tr>
<td>#1</td>
<td>conversion OR equipotency OR rotation OR switch OR substitution OR equianalg OR (dose ratio)</td>
</tr>
</tbody>
</table>
ORmo (ratio 1:75) or 0.6 mg of TDfe (ratio 1.3:1), at different dosage levels (see Table 2).

Hydromorphone and other opioids (excluding methadone)

Five studies of hydromorphone were selected²³–²⁷,⁴⁵ (Table 3). Data on switching to methadone were grouped separately (see below). Only one was a randomized controlled crossover study comparing oral oxycodeone (ORox) and oral hydromorphone (ORhy).²³ Methodology, sample size, study design and performance were of high quality. In this study, the mean final daily doses needed to obtain similar analgesia and comparable side effects were 124 mg (±22 SD) of morphine and 30 mg (±6 SD) of ORhy leading to a ratio of 4:13 (95% CI = 3.76–4.55).

Three studies²⁴–²⁶ presented consecutive case series of patients with chronic malignant and non-malignant pain switched from different opioids to ORhy extended release preparations. In the study by Wallace et al.,²⁵ 248 patients were switched to ORhy for convenience and 85 completed the study. An initial conversion ratio between ORmo equivalent dose and ORhy of 1:5 was used and the ORhy dose was subsequently increased in 23% of patients. Opioid doses used before switching were not reported. Another similar series of cases²⁴ included 73 patients with cancer pain, expected to be stable as to opioid requirements, who were switched from different opioids to ORhy with a ratio of 5:1 between ORhy and the previous morphine-equivalent dose. Data are not available specifically for cancer patients, but in general 20% of patients needed no titration after switching to ORhy, while all the other patients required between one and three titration steps. At stable dosing, cancer pain patients required a mean of 47.9 mg (±51.2 SD) of ORhy compared with a baseline pre-switch dose of 166 mg morphine equivalents/day. In another case series, an initial dose ratio of 8:1 was used to convert from a daily morphine-equivalent dose calculated for many different opioids. From one of the study’s figures it can be calculated that the initial morphine-equivalent dose was about 160 mg and 54% of cases needed to have the initial ORhy dose increased after switching. At stable dosing after titration the final daily ORhy dose was 37.2 mg (±23 SD).

Figure 1. Flow diagram.
In all three studies an improvement of pain control was obtained after switching to ORhy after the stable dose was reached with titration.

The last study reported on 50 patients with poor pain control and/or significant side effects when treated with different opioids. Their initial morphine-equivalent dose was 108.9 mg (±115.8 SD). Of this dose, 60% was converted into ORhy using a 1:5 ratio. The final ORhy dose was 27 mg (±23 SD). Most patients reported an improvement in pain and/or side effects.

**Fentanyl and other opioids (excluding methadone)**

Six studies were examined. One of them reported unclear information about fentanyl dosing and data could not be used in this review. Most of the patients included in the five studies reported in Table 4 were switched from ORmo to TDfe. Only one study specifically aimed at identifying a dose of TDfe equivalent to a previous dose of ORmo (immediate release), which was titrated to obtain stable analgesia. In this study the initial TDfe dose found with a 1:100 ratio versus ORmo had to be increased in 58% of cases and a regression analysis demonstrated a mean ratio between ORmo and TDfe doses of 70:1.

The other studies included small samples of patients, with pain not well controlled and gave sparse information about titration after switching. In some studies the direction of opioid change seemed to affect the dose ratio (Table 4).

**Oxycodone and morphine**

Four randomized, controlled, double-blind, crossover studies (RCTs) and two uncontrolled cohort studies reported data on conversion ratios between ORmo and ORox (Table 5). The RCTs aimed at comparing oxycodone and morphine under stable analgesic conditions and patients were stabilized in a study/entry phase using either immediate release morphine, modified release oxycodone ORox and morphine intravenous patient-controlled analgesia (IV PCA) infusion. Different mean daily doses were compared for ORox depending on study: 93 mg, 148 mg, an approximate value of 40 mg, 145 mg, 193 mg, an approximate value of 75 mg. Details of patients’ previous overall exposure to opioids was not clearly available. In the study by Brue et al., a careful evaluation of the final dose ratio showed a 1.5:1 ratio between ORmo and ORox equivalent doses with 25–50th percentile ratios ranging from 1.25 and 1.5 (maximum = 2.3, minimum = 1). These ratios are consistent with the other RCT results. In the uncontrolled consecutive series patients were switched to ORox.
Table 3. Studies regarding conversion ratios in switching between hydromorphone and other opioids, excluding methadone

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients accrued (completed)</th>
<th>Design</th>
<th>Sequences</th>
<th>Notes</th>
<th>Initial–final ratio</th>
<th>Pre-switch morphine equiv dose mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagen and Babul</td>
<td>44 (31)</td>
<td>Controlled, randomized, double-blind cross over</td>
<td>ORox–ORhy crossover</td>
<td>Comparable pain relief and side effects with ORox and ORhy</td>
<td>4 : 1</td>
<td>Oxy 180 +/- 33 Hy 120 +/- 20*a</td>
</tr>
<tr>
<td>Moriarty et al.</td>
<td>100 (NA)</td>
<td>RCT cross over double blind</td>
<td>Oral morphine–ORhy</td>
<td>ORmo:ORhy = 7.5 : 1</td>
<td>NA</td>
<td>NA b</td>
</tr>
<tr>
<td>Palangio et al.</td>
<td>73 (56)</td>
<td>Uncontrolled, prospective cohort</td>
<td>Opioids–ORhy</td>
<td>Stabilized with different opioids</td>
<td>5 : 1 (in morphine equivalents) Final ratio 3.13 (in morphine equivalents)</td>
<td>166.4</td>
</tr>
<tr>
<td>Wallace et al.</td>
<td>148 (85)</td>
<td>Uncontrolled, prospective cohort</td>
<td>Opioids–ORhy</td>
<td>Stabilized with different opioids</td>
<td>Initial 5 : 1 in morphine equivalents 27% required upward titration</td>
<td>&gt;= 45</td>
</tr>
<tr>
<td>Weinstein et al.</td>
<td>344 (239)</td>
<td>Uncontrolled, prospective cohort</td>
<td>Opioids–ORhy</td>
<td>Stabilized with different opioids</td>
<td>8 : 1 (in morphine equivalents) 54% required upward titration</td>
<td>&gt;= 90</td>
</tr>
<tr>
<td>Wirz et al.</td>
<td>50 (50)</td>
<td>Uncontrolled, prospective cohort</td>
<td>Opioids–ORhy</td>
<td>PPC and/or AE</td>
<td>5 : 1 (in morphine equivalents) 3.9 (in morphine equivalents)</td>
<td>108.9 +/- 115.8</td>
</tr>
</tbody>
</table>

ORhy: oral hydromorphone, ORox: oral oxycodone, ORmo: oral morphine, SC: subcutaneous, TDfe: transdermal fentanyl, PPC: poor pain control, AE: adverse effects, RCT: randomized controlled trial

Pre-switch morphine-equivalent doses are described as a mean, unless differently reported.

*a In a crossover design the initial dose of each drug is titrated and randomly assigned to patients beginning on ORhy or on ORox

b Not available. Original article not retrievable.
### Table 4. Studies regarding conversion ratios in switching between transdermal fentanyl and other opioids

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Design</th>
<th>Sequences</th>
<th>Notes</th>
<th>Initial–final ratio</th>
<th>Pre-switch morphine equiv dose g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donner et al. 28 1996</td>
<td>98 (38 completed)</td>
<td>Uncontrolled, prospective cohort</td>
<td>ORmo–TDfe</td>
<td>Immediate release oral morphine titrated to stable pain relief</td>
<td>100:1 70:1 58% of patients require upward titration</td>
<td>138.6</td>
</tr>
<tr>
<td>McNamara 29 2002</td>
<td>21 (19 completed)</td>
<td>Uncontrolled, prospective cohort</td>
<td>ORmo–TDfe</td>
<td>AE</td>
<td>150:1 unreported, 11 patients required upward titration</td>
<td>&gt;1/2 60</td>
</tr>
<tr>
<td>Mystakidou et al. 47 2003</td>
<td>312</td>
<td>Uncontrolled, non-randomized, prospective cohort</td>
<td>ORmo–TDfe</td>
<td>PPC, convenience, not clearly stated</td>
<td>100:1 Upward titration required in the first week</td>
<td>122.1 ±/− 60</td>
</tr>
<tr>
<td>Mercadante et al. 18 2009</td>
<td>15</td>
<td>Uncontrolled, non-randomized, prospective cohort</td>
<td>TDfe–ORmo</td>
<td>PPC and/or AE</td>
<td>1 : 100 1 : 189</td>
<td>240</td>
</tr>
<tr>
<td>Mercadante et al. 22 2009</td>
<td>11</td>
<td>Uncontrolled, non-randomized, prospective cohort</td>
<td>ORmo–TDfe</td>
<td>PPC and/or AE</td>
<td>100:1 98:1</td>
<td>245</td>
</tr>
</tbody>
</table>

ORmo: oral morphine, TDfe: transdermal fentanyl, OP: other opioids, PPC: poor pain control, AE: adverse effects.
Pre-switch morphine-equivalent doses are described as a mean, unless differently reported.

### Table 5. Studies regarding conversion ratios in switching between oral morphine and oxycodone

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (completing the study)</th>
<th>Design</th>
<th>Sequences</th>
<th>Notes</th>
<th>Initial–final ratio Morphine/oxycodone and doses</th>
<th>Pre-switch morphine equiv dose mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalso and Vainio 40 1990</td>
<td>20</td>
<td>Randomized double-blind crossover</td>
<td>Crossover</td>
<td>Stabilized on IV</td>
<td>1 : 1.48 1 : 1.3–1 : 1.4 depending on direction</td>
<td>NA²</td>
</tr>
<tr>
<td>Heiskanen and Kalso 42 1997</td>
<td>45 (27)</td>
<td>Randomized double-blind, crossover</td>
<td>Crossover</td>
<td>Stabilized</td>
<td>1.5 3 : 2–4 : 3 depending on direction</td>
<td>NA²</td>
</tr>
<tr>
<td>Bruera et al. 41 1998</td>
<td>32 (23)</td>
<td>Randomized double-blind, crossover</td>
<td>Cross over</td>
<td>Stabilized</td>
<td>1.5:1 1 : 5 : 1</td>
<td>NA²</td>
</tr>
<tr>
<td>Lauretti et al. 44 2003</td>
<td>26 (22)</td>
<td>Randomized double-blind, crossover</td>
<td>Cross over</td>
<td>1.8–1</td>
<td></td>
<td>NA³</td>
</tr>
<tr>
<td>Riley et al. 31 2006</td>
<td>48 (41)</td>
<td>Uncontrolled, prospective cohort</td>
<td>ORmo–ORox</td>
<td>PPC and/or AE</td>
<td>2 : 1 unreported</td>
<td>70 (15–540)</td>
</tr>
<tr>
<td>Narabayashi et al. 32 2008</td>
<td>27 (25)</td>
<td>Uncontrolled, prospective cohort</td>
<td>ORmo–ORox</td>
<td>PPC and/or AE</td>
<td>1.5:1 Upward titration required final dose approximated 1 : 1 ratio</td>
<td>44 ±/− 33.8</td>
</tr>
</tbody>
</table>

Pre-switch morphine-equivalent doses are described as a mean, unless differently reported.

²NA: not available. Study design implied titration before randomization (see text).
because of poor pain relief and side effects. In the first study, only the initial 2:1 ratio is given and 74% of patients are reported to have been successfully switched. In the second one, a 1.5:1 (ORmo:ORox) ratio is used, but patients needed a subsequent ORox increase leading to a higher morphine-equivalent dose when stabilized on ORox.

**Switching to methadone**

A significant number of studies focused on switching from different opioids to methadone, usually in patients using ORmo or a variety of opioids converted into an ORmo-equivalent dose. A subset of cases was selected as they reported data on direct conversion from TDfe to oral methadone (ORme). All the studies had serious limitations, important inconsistencies, imprecise or sparse data and none used a method specifically designed to evaluate actual equivalent methadone doses under controlled conditions (Table 6).

**From oral morphine (or oral morphine equivalents) to methadone**

Different practices have been documented regarding switching to methadone. The influence of previous opioid dosing, reason for switching, routes of administration and final ratios after achieving clinical stabilization were variable. Sometimes, when conservative ratios were used, the dose of methadone needed to be increased after switching. In other cases when a fixed 5 to 1 ratio was used, the dose of methadone had to be reduced subsequently in some patients. In most studies a relationship between the opioid dose exposure in terms of the size of the doses used and the final ratio to methadone dose was observed. Patients using higher opioid doses needed lower doses of methadone (Table 6). A review article attempted a meta-analysis of the dose ratio employed, comparing final doses of ORme with ORmo-equivalent doses and found a median ratio of 8.25:1 with increasing ratios associated with higher morphine-equivalent doses before switching.

**Sequence fentanyl–methadone**

Four studies prospectively reported data on switching from TDfe to ORme. All studies were prospective, uncontrolled case series. Overall 72 patients with poor pain relief and adverse effects were involved. The studies had serious limitations. However, these studies, regardless of the protocol, showed similar results. From an initial ratio of 1:20, a final ratio of about 1:17 was achieved. The final ratio was not related to the previous TDfe doses (Table 7).

**Discussion**

Knowledge of the approximate equianalgesic doses of opioids is necessary when changing from one to another. The change may be made because certain opioids may be more convenient for patients as their circumstances change, or it may happen during opioid switching. The concept of changing opioids, particularly as part of an ‘opioid switch’ manoeuvre, remains a challenge because there is a lack of evidence to support the dose conversions used in clinical practice. It is evident that these situations are completely different and conversion ratios have to be adapted in an individual way, according to previous opioid dosages, rapidity of opioid escalation, reason to switch (only adverse effects with controlled pain or convenience) and type of opioid chosen for substitution. For example, while uncontrolled pain may require higher doses of the second opioid, uncontrolled pain associated with states of hyperalgesia produced by rapidly escalating doses of opioids may be at risk of overdosage of the second opioid.

Thus, the choice of a conversion ratio between opioids during switching should not be a mere mathematical calculation, but part of a more comprehensive assessment of opioid therapy, evaluating the underlying clinical situation, pain and adverse effect intensity, comorbidity and concomitant drugs, and excluding any possible pharmacokinetic factor that could limit the effectiveness of certain drugs. More prudent approaches must be applied in less intensively monitored environments, particularly when patients are switched from high doses of opioids to methadone. This group of patients should be referred to specialized centres. On the other hand, the calculated dose of the new regimen is often reduced by 25–50% or initiation of therapy is delayed, and then dose changes may take many days before achieving a status of symptom optimization. This implies a risk of undertreatment in a suffering patient who is experiencing rapid changes in his or her clinical condition.

Thus, the initial conversion ratio should be ideally chosen according to the best evidence gathered from existing studies, where it was possible to retrieve a final conversion ratio after an appropriate balance between analgesia and adverse effects is achieved, while considering the setting of care, the intensive monitoring facilities and possible risks of unintentional overdose. Subsequent dose adjustment and continuous assessment should be carefully considered.

**Buprenorphine and other opioids**

The use of buprenorphine in association with other opioids, for example during opioid switching, has been of
## Table 6.

Studies regarding conversion ratios in switching between opioids and methadone. The equivalence ratio is always refers to daily oral morphine-equivalent dose

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Design</th>
<th>Sequences</th>
<th>Notes</th>
<th>Initial–final ratio</th>
<th>Pre-switch morphine equiv dose mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Conno et al. 1996</td>
<td>36</td>
<td>Uncontrolled, prospective</td>
<td>Opioids–ORme</td>
<td>Convenience</td>
<td>4:1–6:1 depending on dose 4:1</td>
<td>60</td>
</tr>
<tr>
<td>Ripamonti et al. 1998</td>
<td>49 (38)</td>
<td>Uncontrolled, prospective</td>
<td>ORmo–ORme</td>
<td>AE (10), PPC (6), convenience (21)</td>
<td>Inversely proportional to mo doses 7.5:1</td>
<td>145 (median)</td>
</tr>
<tr>
<td>Scholes et al. 1999</td>
<td>33</td>
<td>Uncontrolled, prospective</td>
<td>OP–ORme</td>
<td>PPC (26) and AE (7)</td>
<td>10:1 as needed 6:1</td>
<td>480 (median)</td>
</tr>
<tr>
<td>Mercadante et al. 1999</td>
<td>24</td>
<td>Uncontrolled, prospective</td>
<td>ORmo–ORme</td>
<td>PPC and AE</td>
<td>5:1 4.8:1 Inversely proportional to ORmo dose</td>
<td>125</td>
</tr>
<tr>
<td>Mercadante et al. 2001</td>
<td>52</td>
<td>Uncontrolled, prospective</td>
<td>ORmo–ORme</td>
<td>PPC and AE</td>
<td>Inversely proportional to ORmo doses 5:1</td>
<td>NA</td>
</tr>
<tr>
<td>Mercadante et al. 2003</td>
<td>10</td>
<td>Uncontrolled, prospective</td>
<td>ORmo–ORme</td>
<td>PPC and/or AE</td>
<td>5:1 6.4:1</td>
<td>317</td>
</tr>
<tr>
<td>Tse et al. 2003</td>
<td>37 (27)</td>
<td>Uncontrolled, prospective</td>
<td>ORmo–ORme</td>
<td>PPC and/or AE</td>
<td>12:1 as needed 6:1</td>
<td>120 (median)</td>
</tr>
<tr>
<td>Benitez-Rosario et al. 2009</td>
<td>54</td>
<td>Uncontrolled, prospective</td>
<td>Opioids–ORme</td>
<td>PPC and/or AE</td>
<td>5–10:1 (depending on the cause of switching) 5:1 high variability from 2:1 to 15:1</td>
<td>220 (median)</td>
</tr>
<tr>
<td>Leppert 2009</td>
<td>21</td>
<td>Uncontrolled prospective</td>
<td>Opioids–ORme</td>
<td>PPC prevalently</td>
<td>Inversely proportional to OP doses No ratio reported (but 2.5 fold increase of methadone dose)</td>
<td>NA</td>
</tr>
<tr>
<td>Mercadante et al. 2009</td>
<td>20</td>
<td>Uncontrolled, prospective</td>
<td>ORmo–ORme</td>
<td>PPC and/or AE</td>
<td>5:1 7:1</td>
<td>389</td>
</tr>
</tbody>
</table>


Pre-switch morphine-equivalent doses are described as a mean, unless differently reported.
concern, because of the possible clinical antagonist effect, reducing analgesia or inducing withdrawal symptoms, as buprenorphine is known to be a partial μ-agonist and to have a slow receptor dissociation that could potentially impede in vivo the full effectiveness of the opioid added. Limited experience has shown that at usual clinical doses TDbu does not produce clinical negative interactions during opioid switching.17,18

Switching to transdermal drugs is usually recommended for patients with stable conditions requiring relatively low doses. There is some evidence that 0.8 mg of TDbu (35 μg/h) is equivalent to 60 mg of ORmo and 0.6 mg (25 μg/h) of TDf. A small number of patients in two ‘n’ of 1’ studies were switched in conditions of stability and at different dosages, maintaining the same expected equivalent doses.17,18 The limited experience suggests caution should be exercised in patients with opioid exposure higher than 240 mg ORmo equivalent.

Hydromorphone and other opioids (excluding methadone)

Opioids with similar pharmacokinetic characteristics seem to maintain the expected conversion ratios with hydromorphone. Most studies, despite severe limitations, suggest a ratio of ORhy:ORmo of approximately 1 : 5, and 1 : 4 with ORox. There is a weak recommendation to use a conversion ratio for ORmo:ORhy of 5 : 1.

Fentanyl and other opioids

More reliable studies suggest a ORmo:TDfe ratio of 100 : 1 in both directions,22,28,47 which is different from the initial recommendation of the manufacturers (150 : 1).51 This ratio seems to avoid or reduce the risk of under or overdosing.

Oxycodone and other opioids

Despite limitations, there is some evidence to support the recommendation to use a conversion ratio of ORmo:ORox of 1.5 : 1.

Methadone and other opioids (excluding fentanyl)

The most controversial drug for opioid switching is methadone. Regardless of the possible different receptor profile, the drug is known to accumulate with repetitive dosing. In all studies on opioid switching, methadone has been found to be much more potent than was suggested by single-dose studies. Early studies established a correlation between the previous doses of morphine-like drugs (namely morphine and hydromorphone) and a conversion ratio to methadone.4,34,32,53
However, the conversion ratio is highly variable, ranging between 5:1 and 10:1 in most studies, and depends on several factors, including the reasons for switching. Patients with stable well-controlled pain who are switched specifically for convenience to a simpler drug regimen should start with a ratio of 5:1. Other than the conversion ratio, the route and method of switching is of paramount importance. While a PCA method with minimal methadone doses for background analgesia may be safer, it also may take much longer to achieve the appropriate balance between analgesia and adverse effects. Patients receiving high doses of opioids switched for adverse effects may particularly benefit from switching to methadone at relatively low doses, using a high conversion ratio. At the same time, patients with uncontrolled pain potentially may need higher doses of methadone and low conversion ratios. However, emerging evidence regarding opioid-induced hyperalgesia in patients who had received rapidly escalating doses of opioids has shown that just discontinuing the offending drug may improve analgesia and opioid requirement may become surprisingly low. Moreover, renal insufficiency, liver dysfunction or particular drug interactions may change the potency and effects of the previous, as well as the second, opioid of the sequence. These effects have not been clarified in the context of opioid switching.

Based on existing studies, the conversion ratio may vary widely and change as a function of the previous dose exposure and recent opioid escalation, as well as due to the presence of major organ dysfunction. Some of the indications for switching, for example uncontrolled pain, could influence the final conversion ratio, while the role of age remains to be clarified.

In patients with apparent opioid-induced hyperalgesia no calculation is predictable, and only careful clinical judgement and strict monitoring may serve as a guide to appropriately adjust the doses of the second opioid. Thus, the way to proceed for switching opioids to methadone also depends on the context and facilities of the clinical units equipped to carefully monitor patients. Treatment must be carefully tailored to the individual patient.

**Sequence fentanyl–methadone**

A certain consistency among the studies in terms of a conversion ratio between TDfe and ORme has been found. From an initial ratio of 1:20, a final ratio of about 1:17 was achieved in four open-label prospective studies. In contrast from what was observed with morphine and hydromorphone, the final conversion ratio was not related to the previous TDfe doses.

**Conclusion**

When changing from one opioid to another the required equianalgesic dose will be influenced by the context in which the change is made. There are two main scenarios:

a. changing to an alternative opioid for reasons of convenience or preference;

b. ‘switching’ or ‘rotating’ to an alternative opioid because of uncontrolled pain in the presence of intolerable adverse effects.

Every patient needs to be individually and carefully assessed. On the basis of the evidence, no specific generalizable recommendations can be made. However, conversion ratios between ORhy, ORmo, ORox and TDfe are supported by the available evidence. Opioid conversion to methadone needs very careful consideration as described. In all cases clinicians must be prepared to titrate the dose to the specific individual patient’s need.

Given the particular context in which opioid switching is commonly performed, that is difficult situations that are clinically unrepeatable, it is difficult to test opioid switching in a randomized controlled blinded trial. Retrospective and open-label prospective cohort studies have been performed in different settings, reporting variable influences of modalities, protocols of switching, opportunity of monitoring and doses of previous opioids. On the basis of information provided by existing prospective studies, conversion ratios between hydromorphone, morphine and oxycodone, or transdermal drugs, seem to be relatively predictable when using low doses of the previous opioid.

Opioid switching to methadone requires more expertise with a conversion ratio that is highly individual. Most experts recommend a reduction in the calculated analgesic dose, whatever the sequence chosen, although this has never been substantiated in clinical trials. Re-evaluation steps are recommended to adjust opioid doses subsequently.

Randomized studies are needed to provide definitive recommendations based on more solid evidence. Large and homogeneous groups divided by reason to switch, level of tolerance and type of opioid sequence may provide sufficient data for guiding physicians in decision making to improve the potential of opioid switching, which remains a therapeutic option of indisputable value.

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Conflict of interest statement
None declared.

References


