Original Article

Equianalgesic Dose Ratios for Opioids: A Critical Review and Proposals for Long-Term Dosing

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Abstract

Clinicians involved in the opioid pharmacotherapy of cancer-related pain should be acquainted with a variety of opioids and be skilled in the selection of doses when the type of opioid or route of administration needs changing. The optimal dose should avoid under-dosing or overdosing, both associated with negative outcomes for the patient. Although equianalgesic dose tables are generally used to determine the new doses in these circumstances, the evidence to support the ratios indicated in these tables largely refers to the context of single dose administration. The applicability of these ratios to the setting of chronic opioid administration has been questioned. A systematic search of published literature from 1966 to September 1999 was conducted to critically appraise the emerging evidence on equianalgesic dose ratios derived from studies of chronic opioid administration. There were six major findings: 1) there exists a general paucity of data related to long-term dosing and studies are heterogeneous in nature; 2) the ratios exhibit extremely wide ranges; 3) methadone is more potent than previously appreciated; 4) the ratios related to methadone are highly correlated with the dose of the previous opioid; 5) the ratio may change according to the direction the opioid switch; and 6) discrepancies exist with respect to both oxycodone and fentanyl. Overall, these findings have important clinical implications for clinicians and warrant consideration in the potential revision of current tables. The complexity of the clinical context in which many switches occur must be recognized and also appreciated in the design of future studies.

J Pain Symptom Manage 2001;22:672–687.

Key Words

Opioid, equianalgesic dose ratios, potency, rotation, switching, chronic pain, opioid toxicity, tolerance

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Accepted for publication: November 7, 2000.

Introduction

Opioids are the mainstay of pharmacological management of moderate to severe cancer pain, and morphine, administered orally, is generally

Published by Elsevier, New York, New York

0885-3924/01/$–see front matter
PII S0885-3924(01)00294-9

considered to be the drug and route of choice respectively.[1] However, it is recognized that the route of administration and the type of opioid must, on occasion, be changed.[2,3] The various reasons for these changes include: dysphagia, the practical inconvenience when large quantities of a particular formulation are required, poor response to a particular opioid,[4] and as an emerging strategy in the management of opioid-related adverse effects, particularly neurotoxicity.[4–9] When switching routes or opioids, the goal is to achieve optimal analgesia and avoid the toxicity associated with overdosing and the inadequate pain control that accompanies under-dosing.

In order to assist physicians in the calculation of doses when switching opioids, guidelines in the form of equianalgesic dose tables are available.[10–14] Recent reports have highlighted deficiencies in these tables.[15,16] Current tables are derived from the results of earlier studies of relative potency ratios using single dose crossover designs.[17–23] These studies, although elegant in design, generally utilized single doses and involved subjects who had limited opioid exposure, both in duration and dose. They did not reflect the clinical realities of chronic opioid administration in the treatment of cancer pain, including switches made in the context of opioid-related neurotoxicity or lack of response to a particular opioid. The extrapolation of the results from these studies to the context of opioid tolerant patients may, therefore, be invalid. Recognizing the limitations of early studies, we conducted a review with the aim of critically appraising the evidence supporting the ratios related to chronic administration and determining limitations in currently quoted ratios.

Methods

For the purpose of this review an "equianalgesic dose ratio" refers to the ratio of the dose of two opioids required to produce the same analgesic effect. In this article, an equianalgesic dose ratio of morphine to hydromorphone of 5:1, for example, indicates that 10 mg of orally administered morphine is equianalgesic to 2 mg of orally administered hydromorphone; in other words, hydromorphone is 5 times more potent than morphine. The literature sometimes refers to the "relative potency ratio." From a pragmatic perspective, this is the inverse of the equianalgesic dose ratio. For example, the "relative potency ratio" of morphine to hydromorphone is 1:5. Preference will be given to the use of the term "equianalgesic dose ratio" (EDR) in this article. The reported EDR in this article will also imply the same route of administration for the opioids being compared, unless otherwise stated. However, some of the studies identified in this review compared relative opioid consumption rather than EDR per se, and inferred an EDR from that comparison in the absence of applying any formal measure of analgesia such as a visual analog score. Other studies refer to the term "relative potency" which can apply to any opioid effect, including analgesia. The "relative potency" between morphine and hydromorphone might therefore be reported as 1:5.

The review was restricted to the equianalgesic dose ratios between morphine and the more commonly utilized "strong" opioids, namely hydromorphone, oxycodone, methadone, and fentanyl. Although the major focus of the review was to compare equianalgesic dose ratios between opioids rather than between routes, literature related to ratios between the more frequently used routes of administration was also evaluated. These included the oral (PO), subcutaneous (SC), intravenous (IV), intramuscular, and rectal routes.

A systematic search of the literature was conducted. The following databases were searched: MEDLINE from 1966 to September 1999; CANCERLIT from 1983 to September 1999; and EMBASE from 1988 to September 1999. The search terms included: *opioid/s, opiate/s, narcotic/s, morphine, hydromorphone, methadone, fentanyl, oxycodone, equianalges*, dose ratio, potency, potency ratio,* and *tables.* A broad free-text search method was utilized and included combinations of these words. The inclusion criteria consisted of retrospective and prospective human studies that employed multiple opioid dosing models rather than single doses. Hand searches of 9 major textbooks addressing opioid therapy and the management of cancer pain were conducted. Meeting abstracts of the International Association for the Study of Pain and the American Society for Clinical Oncology were searched. Abstracts that were later published in full were not included. The reference lists of publications identified by

the database and hand searches were examined for further references.

The following data were extracted from eligible studies: 1) the opioids being compared, 2) the study design, 3) the dosing period or number of doses, 4) the number of subjects in the study, 5) the types of patients (i.e., cancer patients, perioperative patients, non-cancer pain, etc.), 6) the reported dose ratio findings, and 7) adverse effects or complications reported.

Results

Eighteen studies met the inclusion criteria. The limited number of studies and the heterogeneity of patient groups, methods, and clinical settings precluded the conduct of a formal meta-analysis. The relative lack of studies examining ratios related to changes in routes of administration did not allow for a detailed assessment.

Hydromorphone

The studies identifying the equianalgesic dose ratios between hydromorphone and other opioids are presented in Table 1.[24–27] Two of these studies[24,26] originated from the same center but related to different patient groups. Both of these studies involved switches between morphine and hydromorphone. The previous opioid was administered for at least 48 hours before the opioid switch. The time to reach stabilization was a minimum of 24 hours[24] and 48 hours[26] respectively, followed by a 48-hour period of stable dosing. The earlier study[24] involved opioid switches that also involved a change of route of administration, whereas the more recent one[26] involved opioid switches without a change in route of administration. Although the latter study included both oral and subcutaneous routes, there were no switches between routes. No significant difference was found in the EDR between morphine to hydromorphone involving oral to oral and subcutaneous to subcutaneous switches. Both studies revealed marked interindividual variability and no correlation between the previous opioid dose and the relative equianalgesic dose ratio. The morphine to hydromorphone (M:HM) EDR derived from these two studies were 5:1 and 5.3:1 respectively. However, the EDRs (expressed as M:HM) for the HM to M switches were 3.5:1 and 3.7:1, differing significantly from the ratio for M to HM switches ($P = 0.0001$). Lawlor and colleagues calculated a unified overall dose ratio of M:HM of 4.3:1 (3.3–4.8, lower quartiles).

Dunbar et al. studied the consumption of morphine and hydromorphone by patient controlled analgesia for the treatment of bone marrow transplantation-related mucositis.[25] Two different groups of patients over a seven-day period (beginning 7 days after transplantation) were compared. All patients were on an analgesic regimen for at least 4 days prior to the start of the study. There was no randomization of patients to treatment groups. An initial EDR of morphine to hydromorphone of 5:1 was assumed. The mean daily drug use yielded a morphine to hydromorphone dose ratio of 3.55:1. Although patient satisfaction was similar between the two groups, resting pain scores were higher in the hydromorphone group. The investigators noted that although a ratio of 7:1, which is occasionally quoted, would have sufficed in the first 2 days of the study, a ratio of 3:1 was more appropriate by the end of the study (7 days later). They postulate that the difference between short term and longer term administration could be the result of: 1) pharmacokinetic variability inherent in short term studies; 2) opioid metabolite accumulation; or 3) patients developing drug tolerance at different levels.

A recent study by Miller et al. compared the analgesic efficacy and adverse effects of hydromorphone and morphine delivered by continuous SC infusion in 74 patients with cancer-related pain admitted to a palliative care unit.[27] The study incorporated a double-blind, randomized, controlled design and excluded cognitively impaired patients. The most common reason for the switches was the inability to take medications orally. The initial PO to SC EDR used for morphine was 2:1 and the EDR of subcutaneous morphine to hydromorphone as 5:1. Although the study was not specifically designed to establish equianalgesic dose ratios, it was reported that, when using a dose ratio of morphine to hydromorphone of 5:1, the hydromorphone group ($n = 33$) required significantly more opioid rescue doses in the first 24 hours than the morphine group ($n = 41$). Over the course of the study, both groups needed an increase in dose (52% and 63% of patients in the morphine and hydromorphone groups respectively—the difference was not significant). The dose increases were 14% in the hydromorphone group and 17% in the

Table 1

Hydromorphone: Equianalgesic Dose Ratios Between Hydromorphone and Other Opioids

Author	Opioids ('to' denotes direction of switch) (routes)	Design (Study Duration)	*n*	Diagnosis (reasons for switching)	Equianalgesic Dose Ratio	Other Findings and Comments
Bruera et al 1996 [24]	M to HM, HM to M (PO), SC, PR) SC to PO/PR n = 37 SC to PO n = 29 SC to SC n = 23	Retrospective (48 hours of stability after opioid switch required)	M to HM 36 HM to M 12	Cancer (Toxicity [32], escalating dose [4], both toxicity and escalatingdose [5], other [6]	M to HM[a] 5.3:1 (4.9–6.4:1) HM to M[a] 3.6:1 (3.3–5.0:1)	PO: SC EDR of 2:1 used. Complications reported for switches to methadone.
Dunbar et al. 1996 [25]	M & HM PCA (IV to IV)	Prospective, open (7 days)	M 36 HM 21	Bone-marrow transplant mucositis Stable pain	3.5:1[b]	No complications reported. Assumed 5:1 ratio at initiation of study.
Lawlor et al 1997 [26]	M to HM HM to M (SC to SC n = 69) PO to PO n = 22)	Retrospective (48 hours of stability after opioid switch required)	91 switches in 74 consecutive subjects M to HM 44 HM to M 47	Cancer (Opioid toxicity in majority of cases)	M:HM of 5.0:1 (4.2–5.9:1)[a] HM:M (expressed as M:HM) 3.7:1 (2.9–4.5)	Dose ratio not dependent on the dose of the previous opioid. EDR of PO : SC of 2:1 used or adverse effects.
Miller et al 1999 [27]	To M & HM (CI SC to SC)	R, DB, controlled trial (72 hours)	74/133 M 41 HM 33	Palliative patients (87%) had cancer)	EDR of morphine to hydromorphone of 5:1 assumed and PO: SC of 2:1. Patients in HM group required more breakthroughs	Assessed opioid consumption. High attrition. Side effects reported.

M = morphine; HM = hydromorphone; C = subcutaneous route; EDR = Equianalgesic dose ration; PO = oral route; IV = intravenous route; PCA = patient controlled analgesia; CI = continuous infusion; R = randomized; DB = Double Blind; X = Crossover.

[a]Expressed as median (first-third quartiles) in the direction of M to HM.

[b]Mean value.

morphine group ($P = 0.3$). The authors suggest that the morphine to hydromorphone *potency ratio* of 1:5 was too low for almost one-half of the patients (stated otherwise: the morphine to hydromorphone EDR of 5:1 was too high). Twenty-eight percent of patients died before completion of the study. Unfortunately, because of progressive disease, only 8 of the patients who completed the study were capable of recording treatment side effects and complete self-assessments of their pain using visual analogue scales. Pain control and adverse effects were assessed by proxy rating in the remainder of those completing the study. This introduced a potential limitation in the interpretation of the study findings.

Generally, these ratios are consistent with those found in the equianalgesic tables of most current resources offering guidelines on the management of chronic pain. However, it is important to recognize the wide ranges in equianalgesic dose ratios, reflecting the large degree of interindividual variation.

Methadone

The studies exploring the equianalgesic dose ratios between methadone[24,28–30] and other opioids are presented in Table 2. Bruera et al.[24] reported a retrospective study of 65 switches from subcutaneous hydromorphone to oral ($n = 37$) or rectal ($n = 28$) methadone. An overall subcutaneous hydromorphone to oral methadone EDR 1.14:1 was calculated, in turn suggesting a morphine to methadone EDR of 10:1 using an EDR of M:HM of 5:1. Patients were switched because of poor pain control ($n = 24$), opioid-related neurotoxicity ($n = 28$) or both ($n = 15$). After the switch, the EDR was calculated when patients were deemed to be stable. Stability was defined as 48 consecutive hours without an increase in pain intensity, as measured by visual analog scales, and the requirement of 3 or less rescue doses. The protocol used for switching to methadone entailed a gradual elimination of the previous opioid and introduction of methadone over a 3-day period. Stabilization occurred within a range of 1 to 6 days following the switch. There was a positive correlation between the dose of the previous opioid and the calculated EDR. The median EDR of subcutaneous hydromorphone to oral methadone was found to be 1.6:1 in patients who had previously been on more than 330 mg of hydromorphone per day, compared to a median EDR of 0.95:1 in those patients taking less than 330 mg per day. Eight patients were reported to have developed respiratory depression during the switch. This was successfully reversed in all cases.

Two follow-up retrospective studies[28,29] confirmed the association between the equianalgesic dose ratio and the dose of the previous opioid. Ripamonti et al. combined data from two centers and compared dose ratios in patients switched from low ($n = 37$) and high ($n = 51$) doses of previous opioid.[29] To facilitate comparison, opioid doses were standardized to subcutaneous hydromorphone equivalents using a dose ratio of 5:1 for morphine to hydromorphone. The median (range) dose for the high- and low-dose groups were 236 mg (36–1080 mg) and 3 mg (1–60mg) per day, respectively. The median (lower and upper quartiles) EDR of hydromorphone (SC) to methadone (PO) for patients switched from low doses of opioid (i.e., doses equivalent to ≤3 mg of SC hydromorphone) to PO methadone was 0.17:1 (0.14:1–0.25:1), compared to 1.5:1 (1.1:1–2.58:1) for patients switched from higher opioid doses (equivalent to >300 mg of hydromorphone SC). There was a highly positive correlation between the equianalgesic dose ratio and the dose of the previous opioid prior to switching to methadone ($R^2 = 0.19$, $P < 0.0001$). Side effects were not reported.

Although the retrospective study by Lawlor et al.[28] originated from the same center as the one by Bruera et al.,[24] a different cohort of patients was studied. Consecutive switches from PO, SC, or IV morphine to PO methadone in 14 patients were evaluated. Patients were switched from doses ranging from 85 mg to 24027 mg of oral morphine per day (for PO to SC morphine an EDR of 2:1 was used). Six additional switches occurred from methadone to morphine. These were included in the analysis only to determine the overall ratio. This study provided further evidence of methadone's high potency relative to morphine and the presence of a changing EDR as determined by the dose of the previous opioid. The main limitation of this study was the relatively small sample size. Side effects were not reported.

In a prospective study, Ripamonti et al. have provided the most compelling evidence to date confirming that the equianalgesic ratio is not

Table 2
Methadone: Equianalgesic Dose Ratios Between Methadone, Morphine and Other Opioids

Author	Opioids ('to' denotes direction of switch) (routes)	Design (Study Duration)	*n*	Diagnosis (reasons for switching)	Equianalgesic Dose Ratio	Other Findings and Comments
Bruera et al 1996 [24] (See Table 1)	HM to Meth HM (SC) to and from Meth (PO,PR)	Retrospective (48 hours of stability after opioid switch required)	65	Cancer (Opioid neurotoxicity [8], poor response [24], both neurotoxicity and poor response [15], and [2])	Overall: 1.14:1 (0.52–2.04:1)[a] According to dose ranges[c]: ⇒13–300 mg: 0.95:1 (0.2–12.3:1[b] ⇒≥300 mg: 1.6:1 (0.3–14.4:1)[b] ⇒13–2076 mg: 1.14:1 (0.5–2.04:1)[b]	Respiratory depression reported in 8 cases (all reversed). Correlation with previous dose noted. Variability of EDR noted.
Lawlor et al 1998 [28]	M to ME M (IV, PO, SC) to and from Meth (PO, PR)	Retrospective (48 hours of stability after opioid switch required)	20	Cancer (Opioid toxicity, poor response)	Overall: 11.20:1 (5.06–13.24:1)[a] According to dose ranges[c]: ⇒42–12012 mg [d]: 11.4:1 (5.9–16.3)[a] ⇒3–240 mg [d]: 8.2:1 (4.37–11.3)[a]	Correlation with previous dose: r = 0.86. Variability of dose ratios noted. Adverse effects/complications not reported.
Ripamonti et al 1998 [29]	HM to Meth M, Oxy, Cod, Bup (SC/ PO to PO)	Retrospective (48 hours of stability after opioid switch required)	88	Cancer	Overall: 0.51:1 (0.20–1.38)[a,e] According to dose ranges[c]: ⇒ 36–1080 mg: 1.47:1 (0.81–2.47:1)[a] ⇒others 0.25:1 (0.17–0.44:1)[e]	Adverse effects/ complications not reported.
Ripamonti et al 1998 [30]	M to Meth (PO to PO)	Cross-sectional, Prospective (Days to stability after switch. See text)	38	Cancer	Overall: 7.75:1 (5–10:1)[b] According to dose ranges[c]: ⇒30–90 mg: 3.7:1 (2.5–8.8:1)[b] ⇒90–300 mg: 7.75:1 (4–10:1)[b] ⇒300 mg: 12.25:1 (10–14.3:1)[b]	Strong correlation (r = 0.91) between previous opioid dose and EDR. Adverse effects/complications not reported.

M = morphine; HM = hydromorphine; Meth = methadone; Oxy = oxycodone Bu = buprenorphine; SC = subcutaneous route; PO = oral route; IV = intravenous route; PR = rectal route; EDR = equianalgesic dose ratio.
[a]Median dose ratio (1st-3rd quartiles)
[b]Median (range)
[c]Daily dose in mg of the previous opioid (the opioid subjects were on prior to switching to methadone)
[d]Expressed as morphine equivalent subcutaneously (sc)
[e]Doses of initial opioid (M, Oxy, Cod, Bup) were converted to a hydromorphone equivalent

fixed when switching to methadone from other opioids.[30] Thirty-eight cancer patients were included in an open study. For data analysis, the patients were grouped according to the total daily dose of morphine prior to the switch. The equianalgesic dose ratios determined (Table 2) varied according to the previous opioid dose. Wide EDRs (2.5:1 to 14.3:1) were noted in this prospective study. Although pain was assessed, adverse effects or complications were not reported.

Oxycodone

The studies addressing the equianalgesic dose ratios between oxycodone[31–36] and other opioids are presented in Table 3. Kalso and Vainio switched 20 patients with uncontrolled cancer pain who were taking so-called "weak" opioids (and nonsteroidal anti-inflammatory drugs in some cases) to intravenous morphine or oxycodone in an elaborate randomized, double-blinded, crossover design.[31] Patients first titrated themselves pain-free using IV patient-controlled analgesia for 48 hours. After 48 hours they were switched to the PO form of either morphine or oxycodone. In switching to the PO route the researchers assigned their subjects to two different groups, each with 10 subjects (Group 1 and Group 2). In Group 1, the bioavailabilities of morphine and oxycodone were assumed to be 44% and 66% respectively and for Group 2, the bioavailabilities were assumed to be 33% and 50% respectively. It is not clear why the investigators chose these levels of bioavailability, but in their original manuscript they refer to the wide ranges of bioavailability reported in other studies. Following the switch in route, patients were able to adjust their oral doses to improve pain control. This phase lasted 48 hours and was followed by the crossover phase to the alternative opioid. The routine of first establishing pain control with the intravenous formulation of the opioid followed by a switch to the oral form was repeated. In this study, the investigators reported "potency ratios". The median calculated PO to IV potency ratios (giving comparable analgesia) were 0.31:1 for morphine and 0.70:1 for oxycodone. An equianalgesic dose ratio (EDR) of PO oxycodone to PO morphine of 3:4 was noted (giving an inferred morphine to oxycodone EDR of 1.48:1). Patients receiving intravenous oxycodone required approximately 30% more opioid to produce the same alleviation of pain as with intravenous morphine. This gives an inferred IV morphine to IV oxycodone equianalgesic dose ratio of 0.7:1. Wide ranges were noted, particularly during oral administration of the opioids. Morphine caused more nausea than oxycodone and hallucinations (5 cases) occurred only during morphine treatment. There were no other major differences in the side effects between the two opioids. This result was consistent with previous studies by Beaver et al.[17,18]

Glare and Walsh enrolled 24 patients with cancer-related pain[32] in an open, non-randomized study with the aim of primarily assessing the safety and efficacy of oxycodone. The majority of patients (n = 19) were already taking oxycodone, in combination with acetaminophen or aspirin, upon enrollment. Twenty patients completed the study. Fifteen patients required a dose adjustment. The median number of dose adjustments required following the initial switch was 1 (range 0–6) and the median number of days to reach the effective dose were 3 (range, 1–10), indicating relatively stable patients with respect to pain control. Ten patients had occasion to be switched from PO oxycodone to morphine administered orally or parenterally. Limited information is given about these patients and the number of patients switched to PO or parenteral morphine is not indicated in the original paper. Using potency ratios of PO oxycodone to PO morphine of 1:1 and PO oxycodone to parenteral morphine of 3:1, they observed that analgesia was effectively and safely maintained in this small number of subjects.

Silvasti et al. compared the consumption of morphine and oxycodone in two different postoperative patient groups over a 24-hour period.[35] Either morphine or oxycodone were administered in IV boluses using a patient controlled analgesic pump. No difference in pain scores was noted between the two patient groups throughout the 24-hour period. The consumption of morphine and oxycodone was similar in the two groups and the authors concluded that the two opioids were equipotent.

Three recent studies have suggested that oxycodone is relatively more potent than morphine.[33,34,36] All three studies involved cancer patients, two incorporated a double-blind, randomized, crossover design.[33,34] In the study by Heiskanen and Kalso, 45 patients were en-

Table 3
Oxycodone: Equianalgesic Dose Ratios of Oxycodone Relative to Other Opioids

Author	Opioids ('to' denotes direction of switch) (routes)	Design (Study Duration)	*n*	Diagnosis (reasons for switching)	Equianalgesic Dose Ratio[a]	Other Findings and Comments
Kalso and Vainio 1990 [31]	M & Oxy (Oxy IV to Oxy PO M IV to M PO M PO to Oxy PO M IV to Oxy IV Oxy IV to M IV)	R, DB, X (96 hrs ± 96 hrs)	20	Cancer	Oxy IV to Oxy PO 0.7:1 (0.49–0.78:1) M IV to M PO 0.31:1 (0.17–0.35:1) M PO to Oxy PO 1.48:1[b] MIV to Oxy IV 0.7:1 (0.6–0.88:1)	
Glare & Walsh 1993 [32]	Oxy PO to M PO or IV (PO to PO or IV)	Prospective, open, not randomized (at least 5 days)	10 out of 24	Cancer	Oxy PO to M PO 1:1 Oxy PO to M IV 3:1	Designed to assess the efficacy and safety of oxycodone.
Heiskanen & Kalso Pain 1993 [33]	M to Oxy Oxy to M (CR PO to PO)	R, DB, X (48 hrs to stabilize then 3–6days)	27 evaluable out of 45 enrolled	Cancer (Stable pain)	Oxy to M 2:3[c] M to Oxy 4:3[c]	
Bruera et al 1998 [34]	M to Oxy Oxy to M (PO)	R, DB, X (7days)	23 out of 31	Cancer (Stable pain)	M to Oxy 1.5:1 Oxy to M (1–2.3:1)	
Silvasti et al 1998 [35]	Oxy IV (PCA) M IV (PCA)	R, DB, (24 hours)	24 (Oxy IV] 25 (M IV)	Post-operative	M to Oxy 1:1[d]	
Gagnon et al 1999 [36]	M & HM to Oxy (SC)	Retrospective (minimal 24 hours of stability)	19 (8 M to Oxy) (11 HM to Oxy)	Cancer (opioid-related toxicity, poor response)	Overall: M to Oxy 1.4:1 M to **Oxy** 1:1 HM to Oxy 0.4:1	

M = morphine; M = hydromorphine; Oxy = oxycodone; SC = subcutaneous route; PO = oral route; IV = intravenous route; CR = controlled release formulation; PCA = patient controlled analgesia; R = randomized; DB = double-blind; X = crossover.
[a]Ratios expressed in the direction of the switch unless otherwise stated. Ratios are quoted as per original papers - median (and range) where available.
[b]Ratio was inferred from median doses given in the original paper.
[c]Based on consumption.
[d]Expressed as morphine equivalent (morphine to hydromorphone ratio of 5:1 used).

rolled to compare the steady-state pharmacodynamic profiles, safety, and efficacy of controlled-release PO formulations of oxycodone and morphine.[33] Patients were first randomized to receive either oxycodone or morphine in an open-label titration phase. Based partly on the premise that oxycodone has been shown to have a higher and less variable oral bioavailability than morphine,[31,37] an EDR of oxycodone to morphine of 2:3 was selected to guide the initial switches. When a stable daily dose was reached, the double-blind crossover sequence was randomized. Using a double blind approach, patients were administered medication for a minimum of 3 days to ensure that a steady state was reached. Twelve patients were titrated with oxycodone and 15 with morphine. Since there was a difference in the pain scores and the amount of rescue analgesics used between the oxycodone and morphine stable phases, the dosing cannot be considered equianalgesic. Patients receiving oxycodone in the first phase, most of them after oxycodone titration, had better pain control than those receiving oxycodone in the second phase. The oxycodone to morphine total opioid consumption ratio was lower in patients receiving oxycodone first (2:3) as compared to patients receiving oxycodone in the second phase (3:4). The authors speculate that this is likely related to the crossover design and accompanying period effect (they propose that crossover designs should, in the future, include titration to effect with each opioid.). The authors postulate that the relative equianalgesic doses of various opioids are different at the initiation of opioid treatment when compared to longer term dose exposure. There was wide individual variation in both pain control and the incidence of adverse effects. There were trends towards less vomiting and nightmares with oxycodone as compared to morphine.

Gagnon et al. reviewed their program's experience with parenteral oxycodone in a retrospective review.[36] Sixty-three patients with advanced cancer had been switched to oxycodone by SC administration from a variety of other strong opioids. Most of the patients had been switched to oxycodone because of opioid neurotoxicity. A subgroup of 19 patients who were switched from morphine (n = 8) and hydromorphone (n = 11) were selected to determine the EDR between morphine and oxycodone. To facilitate the comparison, patients who received hydromorphone had their doses converted to morphine SC equivalents, using a morphine to hydromorphone EDR of 5:1. The mean ($\pm$SD) and median combined morphine to oxycodone EDR were 1.9:1 $\pm$ 1.5:1 and 1.4:1, respectively. In effect, this translates to 15 mg of morphine SC being equivalent to 10 mg of oxycodone SC. Local skin/site reactions to the oxycodone administration were observed but otherwise no adverse effects were recorded.

Fentanyl

The equianalgesic dose ratios between parenteral fentanyl[38–41] and other opioids are listed in Table 4. All four studies identified are relatively small.[38–41] The only prospective study identified in this group aimed to compare the efficacy and adverse effects between subcutaneously administered fentanyl and morphine, rather than to specifically determine the equianalgesic ratio between the two opioids.[41] Of the 50 hospice patients with cancer-related pain who were approached to take part in this study, 30 participated and 23 completed it. Patients entered in the study were generally stable, lucid and tolerating morphine well. Using a double-blind, randomized, crossover design, patients were switched to morphine or fentanyl using a conversion EDR of morphine 10 mg: fentanyl 150 μg (i.e., a potency ratio of fentanyl to morphine of 66:1).[41] Three days later the opioids were switched. Because of difficulties blinding the breakthrough medication, meperidine (pethidine) was used for rescue doses. This may have affected the interpretation of the results. Patients on fentanyl reported significantly more pain on the second day. Overall, the morphine-first group had a lower dose of opioid throughout the study than those patients who received fentanyl first (most patients were receiving infusion doses equivalent to less than 100 mg of morphine per day). The number of rescue doses was significantly greater in the fentanyl-first group on days 2 and 3 than the morphine-first group. The authors postulate that this may suggest an inadequate ratio for converting PO morphine to SC fentanyl, or it may be that the steady state of SC fentanyl was not reached before PO morphine levels diminished (15 patients had been on PO controlled release formulations of morphine prior to the study). No patients experi-

Table 4
Fentanyl: Relative Analgesic Potency Ratios Between Fentanyl and Morphine

Author	Opioids ('to' denotes direction of switch) (routes)	Design (Study Duration)	*n*	Diagnosis (reasons for switching)	Potency Ratio[a]	Other Findings and Comments
Paix et al 1995 [38]	M to Fent (CSCI) (HM to M) (M to Suf)	Retrospective	9 out of 11	Cancer (Toxicity)	SC Fent to SC M 68:1 (range 15–100:1) (SD ±) 23:1	
Woodhouse A et al 1996 [39]	M, pethidine (meperidine), Fent	Prospective 48 hrs	55 Morphine (19) Fentanyl (18)	Postoperative (variety of indications)	Used EDR of 1 mg M = 0.01 mg Fent Noted that ratio may have been too high since patients receiving fentanyl required significantly more opioid than morphine at 48 hrs.	
Watanabe et al 1998 [40]	M to Fent CSCI HM to Fent CSCI (PO/ SC to CSCI)	Retrospective (24 hours of stability after opioid switch required, no more than 2 rescue doses)	17 out of 22	Cancer (Opioid neurotoxicity poor response	SC Fent to SC M 85.4:1 (65–112.5:1) SC Fent to SC HM 23:1 (10.7–29.7:1)	
Hunt et al 1999 [41]	M to Fent (CSCI to CSCI) Fent to M (CSCI to CSCI)	R, DB, X (6 days)	23	Cancer patients	SC Fent: SC M of 66:1	Meperidine (pethidine) was used for breakthrough analgesia. The authors report that the ratio of 66:1 appeared appropriate.

M = morphine; HM = hydromorphine; Fent = fentanyl; Suf = sufentanyl; CSCI = continuous subcutaneous infusion; SC = subcutaneous route; PO = oral route; R = randomized; DB = double-blind; X = crossover; EDR = equianalgesic dose ratio.
[a]Expressed as mean (range).

enced an obvious withdrawal syndrome when switching to SC fentanyl. Despite these differences, they concluded that the conversion ratio they used of SC morphine 10 mg to SC fentanyl 150 μg is adequate but cautioned that additional breakthrough doses may be required in the days following a substitution of oral morphine to SC fentanyl.

Two retrospective studies report on the equianalgesic dose ratios relative to subcutaneously administered fentanyl by continuous infusion.[38,40] Paix et al. report 11 palliative patients with cancer-related pain who, with the exception of one who was on PO codeine and one switched from morphine administered epidurally, were switched from morphine by continuous SC infusion to fentanyl continuous SC infusions because of significant adverse effects and opioid-related neurotoxicity.[38] They compared the mean daily dose of morphine and fentanyl required to give stable analgesia (stability criteria were not clearly defined in the original article) before and after the change of drugs. The mean (±SD) fentanyl to morphine relative *potency ratio* was 68:1 ± 23:1 (range, 15:1–100:1). Stated in terms of an EDR, this translates to 1 mg of SC morphine being equianalgesic to 15 μg of SC fentanyl. Watanabe et al.[40] reviewed the charts of 22 palliative patients with cancer-related pain who had been switched from a variety of opioids to sc fentanyl by continuous infusion. Five of the 22 patients were switched to fentanyl from transdermal fentanyl (due to poor pain control) and 17 from other opioids (because of opioid-related neurotoxicity). The patients were therefore relatively unstable in terms of pain control and the presence of opioid-related toxicity. In 13 patients who were switched from morphine or hydromorphone and reached dose stability (defined as no dose changes and no more than 2 rescue doses per day for 48 hours), the median relative *potency ratio* of SC fentanyl to SC morphine (n = 4 patients who stabilized) was 85.4:1 (range 65:1–112.5:1). This translates to an EDR of 1 mg of SC morphine being equivalent to 11.8 μg of SC fentanyl. The *relative potency ratio* of SC fentanyl to SC hydromorphone (n = 6) was 23:1 (range 10.7:1–29.7:1). The authors noted a wide range of dose ratios and suggested that a more cautious fentanyl to morphine *potency ratio* of 100:1 may be advisable but acknowledged that the small size of the study was a major limitation.

In a randomized, double-blinded study, 55 postsurgical, opioid-naïve patients were randomized to receive morphine, meperidine (pethidine), or fentanyl intravenously by patient-controlled analgesia.[39] This study did not aim to specifically determine the equianalgesic ratios between the opioids, but compared opioid consumption among the 3 groups. The researchers noted that (when using ratios of 1 mg morphine = 10 mg meperidine/pethidine = 0.01 mg fentanyl) equivalent amounts of opioid were used by the fentanyl and morphine groups at the end of the first day, but the fentanyl group used significantly more than the morphine group by the end of the two-day study period. The authors suggested that this difference was related either to fentanyl having a shorter duration of action than the other opioids (because of its higher metabolic clearance) or that the doses selected were not equipotent. They dismissed the latter reason on the grounds that the demand ratios (the number of successful to total demands made) were similar for each of the drugs.

Discussion

Our systematic review of the literature resulted in a number of both general and specific findings. Based on these findings, we propose a number of revisions in relation to the current equianalgesic tables. Furthermore, we wish to highlight some important methodological issues in relation to future research in this area.

General Findings

There are a surprisingly small number of studies that have assessed opioid equianalgesic dose ratios in the context of chronic pain management and repeated opioid dosing. Those that do exist are heterogeneous in terms of size, subjects, settings, specific aims, and study methods, particularly those relating to the calculation of relative potency ratios. In many of the selected studies, the determination of an equianalgesic dose was often not a primary outcome measure and thus the study design lacked the required elaboration to capture many of the multiple factors known to influence pain intensity and opioid efficacy. Most of the studies involved small sample sizes. Given the interindividual variation in dose ratios, small sample

size is therefore quite a major limitation in the interpretation of study findings. The validity of comparing ratios derived from postoperative surgical patients with those from patients with advanced cancer is also questionable. Unlike most surgical study patients, many patients with advanced cancer have varying degrees of renal impairment, hepatic impairment, differential tolerance to different opioid effects and psychosocial distress. Also, the duration of exposure to opioid and the number of doses varies across studies. Although tolerance is a highly complex and controversial issue,[42] the degree to which it does occur is likely to vary greatly across these studies. Pain is also regarded to be a multidimensional construct.[43] The degree to which the multidimensionality of pain is assessed and addressed across various study settings and studies in similar settings is likely to be highly variable. Heterogeneity therefore exists among these studies in many aspects, a factor that warrants recognition, particularly when one is attempting to compare their findings.

Specific Findings

Wide ranges. Most of the studies report very wide ranges in EDR (see Tables). This reflects the marked observed inter- and intra-individual variability among patients' responses to different opioids. Numerous factors contribute to this variability, including the route of administration, a drug's half-life, bioavailability, drug interactions, the pathophysiology of the pain state, clearance by the liver and/or kidneys, accumulation of opioid metabolites, access to the receptors and binding affinity to the receptors, to mention but a few. Other factors include a patient's prior opioid exposure and the clinical context of the switch, e.g. opioid-related neurotoxicity and confusion.

High potency of methadone. All the studies indicate a higher potency of methadone than is often accepted or indicated in the equianalgesic dose tables of most standard sources. Clearly, an EDR of PO morphine to PO methadone of 1:1 underestimates the potency of methadone when given long-term. An EDR of 3:1 or 4:1 can only be relied upon for patients who are treated with low morphine doses. Although an EDR of 10:1 is likely more appropriate when patients are switched from relatively higher doses of a specific opioid to methadone, it is also recognized that the ratios depend on the dose of the previous opioid (see below).

Ratios depend on the dose of the previous opioid. The assumption that the same relative potency ratio operates irrespective of the level of opioid dose reached prior to an opioid switch is flawed, specifically with respect to methadone. Two relatively large retrospective series[24,29] and a prospective study[30] have demonstrated a significant correlation between the dose of the previous opioid and the dose ratio between methadone and the previous opioid. In the case of a morphine to methadone switch, for example, the higher the morphine dose, the higher the morphine to methadone equianalgesic dose ratio will likely be. This phenomenon has not been well studied in the case of other opioids. Two studies[24,36] failed to identify the phenomenon in the case of switches between morphine and hydromorphone.

Inconsistencies related to oxycodone and parenteral fentanyl. Earlier studies suggested that oxycodone may be either slightly less potent[31] or equipotent to morphine.[32,35] Recent studies suggest that PO oxycodone appears to be 1.5 to 2 times relatively more potent than PO morphine.[33,34,36] Wide ranges in EDR are however reported. Similarly, wide ranges are reported in the limited studies addressing the relative *potency ratio* of parenteral fentanyl relative to other opioids.[38,40,41] The *potency ratios* of SC fentanyl to SC morphine reported are in the order of 68:1 (mean) to 85.4:1 (median):1. The manufacturers suggest a SC fentanyl to SC morphine potency ratio of 100:1.

Possibility of directional inequality of cross tolerance. The equianalgesic dose ratio for a switch from morphine to hydromorphone, for example, is generally considered to be the same as a switch from hydromorphone to morphine, i.e., a single ratio serves bidirectional switching. However, recent studies suggest that ratios may indeed change according to the direction of the switch.[24,26,28,36] The clinical relevance of this is not yet clear. Although it is unlikely to have major impact in switches at lower doses, it is possible that failure to recognize the directional difference in ratio may result in negative consequences when switching at higher doses.

The mechanisms underlying this phenomenon are not clear but could relate to the generation of active metabolites.[26,42]

Proposals for Updating Current Equianalgesic Dose Tables

Equianalgesic dose tables should display prominent footnotes that indicate the following:

1. *Relevancy for long-term dosing.* Some guidelines and textbooks quote ratios that are more applicable to acute pain management. These tables may, for example, indicate hydromorphone to be up to 10 times more potent that morphine.[44] Since the ratios differ depending on whether an opioid is being administered on a one time basis (or only 2 or 3 doses) or multiple (long-term) dosing, tables should indicate clearly what they are intended for—short term administration versus chronic, long term administration.
2. *Equinalgesic dose ratio tables are guidelines.* It is important to emphasize that equianalgesic conversion schema are only meant to act as guidelines. Although current tables can serve as useful guidelines when switching an opioid type or route of administration, they do not recognize the wide variation between individuals. The basis for the observed inter- and intra-individual variability in sensitivity to opioid analgesia and adverse effects is multifactorial, complicated and still poorly understood.[15,42] The relative potency of some opioids may increase with repetitive dosing.[45] The dose, therefore, needs to be individualized and carefully titrated to effect. Despite the variabilities in opioid conversion and responsiveness, the literature does not describe many serious adverse events when switching between morphine, hydromorphone, and oxycodone. However, absence in the literature does not necessarily indicate absence of complications since such events may go unreported. In the case of methadone, serious adverse events have been reported.
3. *Titrate to effect.* See #2 above.
4. *Monitor clinically.* See #2 above. Following a switch, patients should be monitored regularly until stable. This entails monitoring for reported pain intensity in addition to the signs and symptoms of opioid neurotoxicity (e.g., myoclonus, hallucinations, hyperalgesia, cognitive dysfunction), other opioid adverse effects (e.g., somnolence, nausea, and constipation) and acute opioid overdosing. Knowledge of the opioid's elimination half-life may guide the monitoring protocol. Methadone, for example, has a variable, long half-life and complications may only manifest a day or two later. Clinical prudence is, therefore, advised.
5. *Recognition of the lack of complete cross-tolerance between opioids.* The phenomenon of incomplete cross tolerance can lead to greater than anticipated potency in a new opioid, even when from the same general class of opioid analgesic.[42,46] When switching opioids, clinicians should convert the dosage based upon consideration of a range of factors including available equianalgesic dose data, clinical factors, concerns for patient safety, and incomplete cross tolerance. To accommodate these, a further decrease in the predicted equianalgesic dose by a further 30–50% is recommended.
6. *Caution in the setting of renal impairment:* Renal impairment results in the accumulation of certain opioid metabolites, thereby increasing the risk for opioid-related toxicity and potentially altering the relative equianalgesic dose ratio.[8] It is suggested that some opioids such as methadone and fentanyl are free of active metabolites, and their metabolism and elimination are independent of renal function, thereby constituting a lower risk of developing neurotoxicity. However, this premise needs to be studied. Although their metabolites may be analgesically inactive, some caution is advised as they may perhaps exert some central nervous system toxicity. Morphine-3-glucuronide, an analgesically inactive metabolite, is implicated in neurotoxicity.[8]

We suggest that the body of the current equianalgesic tables be updated to reflect the following:

1. *Methadone is more potent than previously accepted.* The higher potency of methadone relative to other opioids and the correlation of the ratio with the dose of the opi-

oid prior to switching have considerable clinical implications and should be represented in updated tables. Foley and Houde comment: "The observed correlation between dose ratio and previous opioid's dose, coupled with the observed wide variation in dose ratio, suggests the need for a highly individualized approach in the process of reaching optimal dose of methadone."[15] An equianalgesic dose ratio of PO morphine to PO methadone of 1:1 in the management of chronic pain is inappropriate, while equianalgesic dose ratios of 3:1 or 4:1 apply only when patients are switched from very low doses of morphine or other opioids to methadone (see #2 below).

2. *The ratios relative to methadone depend on the dose of the previous opioid.* There are some prospective data to provide guidelines.[30] Ripamonti and colleagues suggest the following morphine to methadone equianalgesic dose ratios: i) if the daily oral morphine dose prior to the switch is 30 mg to 90 mg, an EDR of 4:1 should be adequate; ii) if the oral morphine dose is 90 mg to 300 mg per day then an EDR of 8:1 is recommended; and iii) if the dose is greater than 300 mg of oral morphine per day, the EDR should be 12:1 and even higher if the patient is on very high doses prior to the switch.
3. *Oxycodone is more potent than morphine.* An equianalgesic dose ratio of PO morphine to PO oxycodone of 1.5 to 2:1 is recommended as a guideline.
4. *A SC fentanyl to SC morphine potency ratio range of 80–100:1.* This range is likely safe and should suffice as a starting point, with the proviso that patients are monitored and assessed regularly and the dose titrated accordingly.

Methodological Issues and Future Research

Although randomized controlled trials are considered the "gold standard" of evidence, the retrospective nature of some of the studies identified in this review is balanced to some extent in that neither physicians nor patients were aware that the dose ratio was going to be studied at the time of the opioid switch. Nonetheless, both observer and patient bias could have influenced the assessment of pain intensity level and the appearance of adverse effects. In some of the retrospective studies, switching took place because of opioid-related neurotoxicity, the reason many patients undergo switching. Opioid switching in patients with good pain control usually is not necessary, hence a prospective study of opioid switching in such patients may have its own limitations. Furthermore, prospective study of switching versus non-switching in patients with opioid-related toxicity may raise ethical and methodological concerns. However, randomized controlled trials in the context of repeated dosing, and incorporating a crossover feature, may provide useful information. To incorporate a crossover feature in the clinical context of opioid neurotoxicity, anticipatory consent would have to be obtained from the patient (if cognition is intact) or alternatively a proxy (if the patient is incapable of giving consent). Future studies should be designed to specifically clarify equianalgesic dose ratios, rather than use "side data" to infer these ratios.

Conclusion

When switching opioids the goal is to achieve optimal analgesia, hence avoiding the toxicity associated with overdosing and the inadequate pain control that accompanies underdosing. A review of the evidence related to equianalgesic dose and relative potency ratios in the context of multiple opioid dosing reveals that: 1) there exists a general paucity of data and considerable heterogeneity in the nature of the studies; 2) the ratios exhibit extremely wide ranges; 3) methadone is far more potent than previously appreciated; 4) the ratios related to methadone are highly correlated with the dose of the previous opioid; 5) the ratio may change according to the direction the opioid switch; and 6) discrepancies exist with respect to both oxycodone and fentanyl. Overall, these findings have important clinical implications for clinicians and warrant consideration in the potential revision of current tables. The complexity of the clinical context in which many switches occur needs to be recognized and this needs to be appreciated in the design of future studies.

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