Original Article

Opioid Equianalgesic Tables: Are They All Equally Dangerous?

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Abstract
Pain is one of the most common symptoms in cancer patients. Opioids are widely prescribed for this and other purposes. Properly used, they are safe, but they have serious and potentially lethal side effects. Successful use of opioids to manage cancer pain requires adequate knowledge about opioid pharmacology and equianalgesia for the purpose of both drug rotation and route conversion. The aim of this study was to demonstrate variations in equianalgesic ratios, as quoted in equianalgesic tables and various educational materials widely available to practicing physicians. We surveyed commercially available educational materials in package inserts, teaching materials provided by pharmaceutical companies, and the Physicians' Desk Reference for equianalgesic tables of commonly used opioids. We found inconsistent and variable equianalgesic ratios recommended for both opioid rotation and conversion. Multiple factors like inter- and intraindividual differences in opioid pharmacology may influence the accuracy of dose calculations, as does the heterogeneity of study design used to derive equianalgesic ratios. Equianalgesic tables should only serve as a general guideline to estimate equivalent opioid doses. Clinical judgment should be used and individual patient characteristics considered when applying any table. Professional organizations and regulators should establish a rotation and conversion consensus concerning opioid equianalgesic ratios. Systematic research on equianalgesic opioid dose calculation is recommended to avoid adverse public health consequences of incorrect or inappropriate dosing. Current information in equianalgesic tables is confusing for physicians, and dangerous to the public. J Pain Symptom Manage 2009;38:409−417. © 2009 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Opioids, analgesics, cancer pain, dosing, equianalgesia

Introduction

Pain is present in 50% of those with advanced cancer, and in more than 80% of the terminally ill. It is the most feared and distressing symptom of advanced disease and requires appropriate assessment and prompt control.[1−3] Opioids are the mainstay of cancer

pain treatment. Most patients achieve pain relief with appropriate opioid dosing through the use of published guidelines.[4,5] Over the last decade, opioid use in the United States has more than doubled, according to the International Narcotics Control Board of the United Nations. Use of opioids requires knowledge of opioid pharmacology, opioid rotation (switching drugs), and opioid conversion (changing routes of administration).

Unlike other medications, opioids have neither a ceiling effect nor uniform therapeutic plasma levels. Consequently, individual titration to a clinically effective analgesic dose is an accepted practice. Titration, however, often is limited by opioid-induced side effects, commonly neurological or gastrointestinal toxicity. In a patient with incomplete pain control or troublesome side effects, opioid rotation or route conversion, or both, may be necessary.[6] There are now many opioids and opioid formulations to choose from during this process. The application of inappropriate relative milligram potency ratios during opioid rotation or conversion may have several serious adverse consequences, including poor pain control, excessive side effects, and death from respiratory depression because of incorrect dosing.[7−9]

Physicians often consult the so-called equianalgesic table before opioid rotation or conversion to determine a new safe starting dose appropriate for adequate pain control. We have noted in clinical practice that various published tables of this type have different equivalence ratios. This raised questions about the accuracy of current recommendations, and their safety and efficacy in clinical practice.

We surveyed commercially available and educational materials for equianalgesic tables in package inserts, the Physicians' Desk Reference (PDR), teaching items provided by pharmaceutical companies, and on Internet web sites. Our primary objective was to examine the variations in equianalgesic ratios, as quoted in equianalgesic tables and various educational materials. In addition, we planned to assess the extent of such variations, and the degree of inconsistency. We present the results of our survey and also briefly discuss possible explanations for the differences observed, and pitfalls in the use of these tables.

Methods

We searched the available equianalgesic tables using package inserts of commercially available, widely prescribed opioid formulations; for example: Duragesic (Janssen Pharmaceutica, Titusville, NJ), Dilaudid® (Abbott Labs, North Chicago, IL), Demerol® (Sanofi-Aventis U.S. LLC, Bridgewater, NJ), Dolphine® (Roxane Labs, Inc., Columbus, OH), Oramorph SR® (Roxane Labs, Inc., Columbus, OH), recommendations from the PDR (Thomson PDR©; retrieved from http://www.pdr.net), product information sections, and available teaching materials provided by pharmaceutical companies intended to guide physician opioid prescribing. We also sought online resources designed to assist in opioid rotation and conversion. We collated the information and summarized it in three groups: 1) ratios available from various pharmaceutical companies; 2) data from the PDR; 3) data from the Internet.

Results

Opioid Route Conversion

Table 1 lists the equianalgesic tables from package inserts and teaching materials for rotation and conversion of various commercially available opioid products. Table 2 summarizes equianalgesic dosing recommendations derived from the PDR for conversion and rotation of commonly used opioids. Some equianalgesic tables and equivalent ratios were occasionally based on 24-hour opioid requirements. Table 3 illustrates equianalgesic tables for rotation and conversion available online.

We found major variability in the route conversion ratios for commonly used opioids (Fig. 1). The conversion ratios of oral to parenteral morphine ranged from 3:1 to 2:1 (Tables 1 and 3) to 6:1 (Table 2). Those for oral to parenteral hydromorphone varied from 2:1 (Table 1) to 5:1 (Tables 2 and 3). Oral to parenteral methadone ratios varied from 2:1 (Table 1) to 10:1 and 4:1 (Table 3).

Opioid Drug Rotation

The tables also varied in the recommended equivalence ratios for opioid rotation (Fig. 2). The parenteral methadone to parenteral morphine equianalgesic ratio varied from

Table 1
Equianalgesic Doses from Conversion Guides and Drug Inserts

Product	Pharmaceutical Company	Source of Equianalgesic Dosing	Oral Equianalgesic Dose to Oral Morphine	Parenteral Equianalgesic Dose to Parenteral Morphine	Equianalgesic Dose of Oral to Parenteral Route
Oxycodone		Package insert (Purdue)	20:30 30:30[b] 20:40[c]	10:15[a]	30:15[a]
Duragesic® Transdermal	Janssen	Package insert	25:60−134 mg/24 hours	25:10-22 mg/24 hours	—
Dilaudid®	Abbott Labs	Package insert	6.5−7.5:40−60	1.3−2:10	4:2 mg
Meperidine		Dilaudid® package insert	300−400:40−60	75−100:10	4:1 —
Dolphine® HCl	Roxane Labs, Inc.	Package insert			2:1 mg
Levorphanol		American Pain Society	4:30 (acute) 1:30 (chronic)	2:10 (acute) 1:10 (chronic)	4:2 (acute) 1:1 (chronic)
Levorphanol		Dilaudid® package insert	4:40−60	1:5	
Morphine		Alberta Hospice Palliative Care Resource Manual second edition (2001)[d]			2:1
Oramorph SR®	Roxane Labs, Inc.	Package insert	—	—	3:1 mg

[a]Duragesic® (Janssen) package insert.
[b]IASP Clinical Updates, Vol. 1, issue 2, July 1993, available at: http://www.iasp-pain.org/AM/AMTemplate.cfm?Section=Home&CONTENTID=7586&TEMPLATE=/CM/ContentDisplay.cfm. Accessed 2008.
[c]Palliative Medicine Handbook by Ian N Back. Available at: http://book.pallcare.info/. Accessed 2008.
[d]Alberta Hospice Palliative Care Resource Manual. Available at: http://www.palliative.org/PC/Clinicalinfo/ACB%20PC%20resource%20manual.pdf. Accessed 2008.

Table 2
Equianalgesic Ratios from the Physicians' Desk Reference

Product	Source of Equianalgesic Dosing	Equianalgesic Dose of PO:Parenteral (mg)	Equianalgesic Dose to 10 mg of IM Morphine (mg)
Morphine sulfate	PDR® Electronic Library	40−60:10[a]	—
Meperidine	PDR® Electronic Library	300−400:75−100[a]	—
Hydromorphone HCl	PDR® Electronic Library	6.5−7.5:1.3−2[a]	1.3[c]
Methadone HCl	PDR® Electronic Library	10−20:10[a]	10[c]
Morphine	PDR® Electronic Library	60:10[b]	—
Hydromorphone	PDR® Electronic Library	7.5:1.5[b]	—
Methadone	PDR® Electronic Library	20:10[b]	—
Codeine	PDR® Electronic Library	200:130[b]	—
Oxycodone	PDR® Electronic Library	30:15[b]	—

PO = oral; IM = intramuscular; SC = subcutaneous.
[a]Tables from hydromorphone HCl product information section, parenteral = IM/SC.
[b]Tables from fentanyl transdermal product information section, parenteral = IM.
[c]Tables from hydromorphone HCl injection product information section, IM/SC route.

1:10−6.7:10 (Table 3) to 1:1 (Tables 1 and 2), a 10-fold difference. The oral meperidine to oral morphine ratios ranged from 6:1 (Table 1) to 10:1 (Table 3), based on 24-hour requirements. Modified-release oxycodone to modified-release morphine ratios ranged from 1:1 to 1:2 (Table 1). Similar variations were found in the ratios between oral morphine and hydromorphone (40−60:6.5−7.5 to 10:2.5 [Tables 1 and 3]). Also, ratios between transdermal fentanyl and both oral and parenteral morphine were wide (Table 1: 25 μg:60 mg to 25 μg:134 mg oral morphine and 25 μg:10 mg to 25 μg:22 mg parenteral morphine).

Discussion

When pain is not relieved adequately by an opioid at a given dose, and limiting side effects supervene, treatment with the same opioid by an alternative route (conversion) or a different opioid by the same route (rotation) is recommended.[10] In our experience and that of others, route conversion and opioid rotation are necessary in advanced cancer illness in up to 40% of patients.[11,12] This practice may have adverse consequences, however, and problems related to incorrect dosing. Multiple considerations (Table 4) should be addressed before both rotation and conversion to avoid errors in applying any equianalgesic table (even those which are accurate). Errors are best avoided by: 1) knowledge of opioid pharmacology, 2) awareness of the limits of equianalgesic tables, 3) application of conversion/rotation guidelines, and 4) tailoring opioid use to individual patient characteristics and response.

The equianalgesic dose is defined as that dose at which two opioids (at steady-state) provide approximately the same pain relief. In the research setting, this is usually standardized to 10 mg of parenteral morphine.[7] Although no

Table 3
Online Opioid Analgesic Converter (www.globalrph.com/narcoticonv.htm)

Product	Equianalgesic Parenteral Dose to 10 mg Parenteral Morphine[a] (mg)	Equianalgesic Oral Dose to 10 mg Oral Morphine[a] (mg)	Equianalgesic Oral Dose to Parenteral Dose[a] (mg)
Morphine	10	10	10:3.3
Fentanyl	0.10	—	—
Meperidine	75	100	10:2.5
Hydromorphone	1.50	2.5	10:2
Methadone	2.0	6.7[b]	10:1[b]
		1[c]	10:2.5[c]
Codeine	120	66.7	10:6
Oxycodone	—	6.7	—

[a]Equianalgesic doses represent the total daily dose requirement.
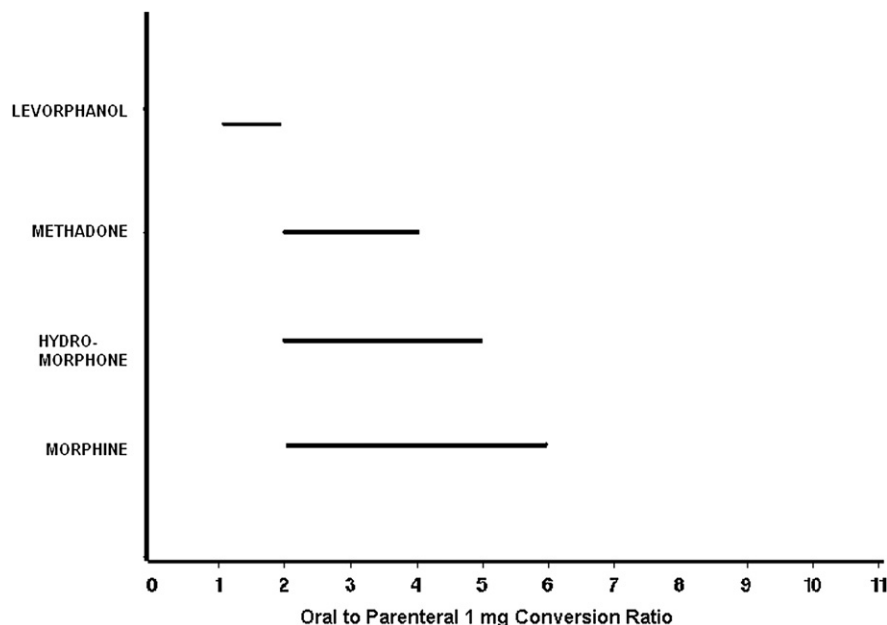[b]Acute short-term dosing.
[c]Chronic dosing.

Fig. 1. Equianalgesic ranges for opioid route conversion.

equianalgesic table can fully address all clinical factors that influence opioid pharmacology or exceptional clinical scenarios, they can certainly contribute to confusion because of variation in the ways equianalgesic doses are illustrated, published, and applied.

Equianalgesic tables are derived largely from single-dose studies, expert opinion, and studies in noncancer patients. Cancer pain studies are inherently difficult to conduct. A parallel study design does not account for interpatient variability (e.g., age, gender, extent of disease, previous opioid experience, psychological factors, and so on). Stratification and randomization may correct for variability, but reduce the pool of potential study subjects. Although a crossover design will reduce the required sample size and also lessen the effects of interpatient (but not intrapatient) variability on study outcomes, carry-over analgesia in 2×2 crossover designs may mask differences in efficacy or toxicity (especially with longer-acting opioids, such as methadone). In the palliative medicine cancer population, any study will be
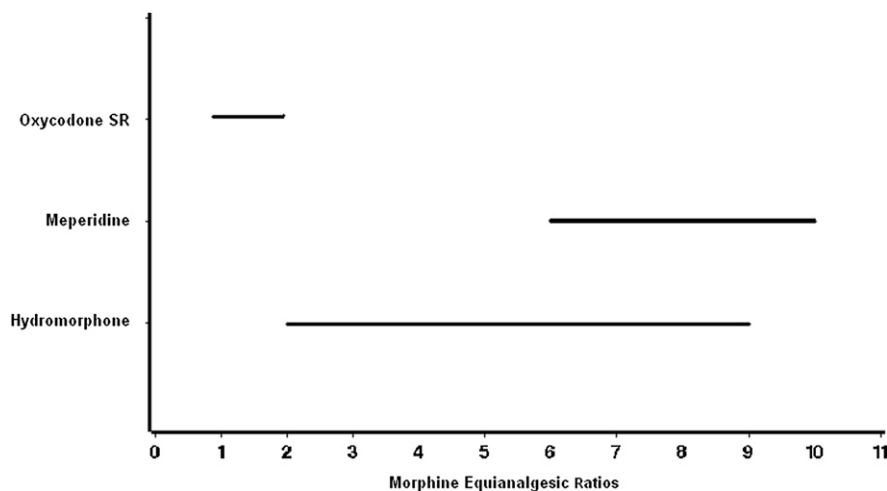

Fig. 2. Equianalgesic dose ratio ranges for opioid rotation to morphine.

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Table 4
Issues to Consider before Opioid Rotation or Route Conversion

1. What are the indications for rotation/conversion?
2. Was the opioid given enough time to judge its efficacy before rotation?
3. What are the alternatives to opioid rotation?
4. Can the goals of rotation be best achieved by using a different route of administration (conversion) rather than different opioid?
5. Are there any factors that would interfere or change the equianalgesic dose?
6. Can equianalgesia change with dose?
7. Is the rotation taking place between opioids with different half-lives?
8. Is the equianalgesic dose safe?
9. Is the pain syndrome responsive to the new opioid?
10. Has the patient been treated with opioids for a short period of time or chronically?

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Table 5
Problems and Pitfalls in Equianalgesic Tables

1. Failure to standardize a reference opioid
2. Failure to address bidirectional differences in equianalgesia for certain opioids
3. Inclusion of wide range of doses in the equianalgesic comparison
4. Use of equianalgesic tables as references for other tables
5. Equianalgesia between short- and long-acting opioids not at steady-state
6. Equianalgesia between opioid formulations and opioid/adjuvant combinations
7. Use of equianalgesia determined by single-dose studies or acute pain
8. Equianalgesic doses in organ failure
9. Use of computations instead of clinical trial to determine equianalgesic ratios

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adversely affected by high dropout rates and variation in pain from disease progression. Even with sound methodology and adequate patient number, other factors, such as drug tolerance and hypersensitivity, are impossible to totally eliminate.

Evidence of the dangers of inconsistent equianalgesic ratios is sparse. This is because opioid clinical trials are often performed in highly selected patients, rarely blinded, seldom powered to adequately detect adverse events, and usually conducted by pain specialists familiar with proper opioid-dosing strategies. In addition, trials with the sole purpose of detecting potentially fatal or serious side effects would be marred by ethical concerns. Recent evidence suggests that opioid-related deaths are increasing exponentially.[13] This is inadequately explained by a rise in drug abuse, and more

closely correlated with an increase in the number of opioid prescriptions.[13] Although these trends cannot be proved to relate to opioid rotation or conversion, they underscore the potentially lethal effects of opioids when incorrectly or inappropriately dosed. This is given credence by a trial that compared methadone and diamorphine in cancer patients, which was prematurely terminated because of higher mortality in the methadone group.[14] Potentially lethal opioid side effects during rotation have been identified in a number of reports.[15–17] In one study of 50 patients with severe cancer pain, six developed respiratory depression on methadone after rotation from hydromorphone.[15] In a case report, a patient developed respiratory depression after rotation from hydromorphone.[16] In another report, one patient on modified-release morphine developed respiratory depression when rotated to transdermal fentanyl.[17] Lethal complications appear

Table 6
Clinical Guidelines for Opioid Route Conversion and Rotation

1. Rotation secondary to toxicity requires a dose 30%–50% lower than the equivalent dose of the second opioid because of incomplete analgesic cross-tolerance.[22]
2. Rotation secondary to uncontrolled pain requires equianalgesic doses.[23]
3. Thirty percent on opioids need an alternative route,[24] as in severe nausea or mucositis.
4. Before rotation because of toxicity, consider treating side effects, lowering opioid dose (if pain is controlled), and use of adjuvant analgesics.[25]
5. Consider pharmacokinetic change with age, comorbid conditions, gender, interacting medications, and organ failure in starting or titrating opioids.
6. Opioids that are partial agonists have less analgesia per dose increment at higher doses than full agonists or opioids with high intrinsic efficacy (e.g., methadone);[26,27] therefore, equianalgesic ratios will change with dose.
7. Rotation between short- and long-acting opioids must be done carefully to avoid withdrawal or overdosing.[28]
8. Rotation in the setting of organ dysfunction is potentially disastrous despite the recommended doses from equianalgesic tables.[29,30]
9. Opioids may worsen intestinal colic. Dexamethasone, glycopyrrolate, or octreotide are better for such pains.[31]
10. Opioid-induced toxicity takes time to resolve. Persistent toxicity after rotation may be because of slow clearance of the first opioid and not the new opioid.
11. Rotating to a new opioid before reaching steady-state of the first opioid is pharmacologically meaningless.

uncommon when opioids are used by pain specialists. The literature concerning opioid-related mortality or potentially lethal complications in clinical practice are disproportionably sparse relative to the volume of opioids now prescribed.

Current equianalgesic tables, therefore, pose several problems:

1. Morphine is the widely accepted prototype opioid analgesic, but some equianalgesic tables confusingly used opioids other than morphine as the reference point.
2. Variable equivalence ranges, within or between different equianalgesic tables, likely result in confusion and inaccurate opioid conversion and rotation. Calculating the median equivalence values based on them may be inaccurate.
3. Computations, rather than data from clinical trials, are sometimes used to estimate or infer the potency ratios between opioids. Such derived ratios are devoid of clinical context and might be grossly inaccurate.
4. Another problem is how to provide calculated equivalents between an opioid and a compounded analgesic that contains an opioid and an adjuvant analgesic (usually a nonsteroidal anti-inflammatory drug). The latter formulations cannot be compared similarly to a single opioid because the adjuvant contributes significantly to pain relief.

Originally, we intended to assess only those tables that used morphine as the reference opioid. This was impossible, as some use other opioids (and varied doses) as the reference opioid. Our survey did not include all published tables, nor was it intended to; however, it documents the wide range of values published in commercially available opioid equianalgesic tables, and illustrates the dangerous inconsistency in recommended doses for both opioid drug rotation and route conversion. Consensus about opioid equianalgesic ratios have been previously published.[18,19] These guidelines did not involve feedback from other specialties (such as primary care physicians) increasingly involved in cancer pain treatment. In a survey among nursing staff, 75% lacked adequate knowledge about equianalgesic

ratios.[20] In another study, 33% of nurses on oncology wards were unable to calculate equianalgesic doses, despite having access to equianalgesic tables.[21] Although nurses are not usually primary prescribers, these findings illustrate problems in using any of the equianalgesic tables and conversion/rotation guidelines. This problem is compounded by the differences we found between tables. For example, a conversion of 20 mg hydromorphone from the parenteral to oral route (as often happens before patients are discharged home) using Table 1 yields 40 mg oral hydromorphone, but using Table 3, results in a 100 mg oral equivalent. This is pharmacologically important and clinically dangerous. It is possible for two physicians working in the same clinical unit to use different tables for conversion or rotation and arrive at markedly different conclusions, and risk serious toxicity. Physicians would likely prefer a single practical table outlining the equivalents of commonly used opioids and singular conversion ratios. This is particularly the case for those who prescribe opioids infrequently or are not pain specialists. The benefits would include convenience, simplicity, and easy access to the desired comparison information. As consensus tables are lacking, those available are useful only as quick references at the time of opioid rotation or conversion.

Most of the tables we reviewed include commonly used opioids. Nevertheless, they must be used cautiously because they do not address critical individual factors. Gender differences and organ dysfunction, bidirectional differences in equivalence with certain opioids, drug interactions, and large inter- and intraindividual differences in pharmacokinetics and pharmacodynamics all may alter equianalgesia. Prescribers must recognize the limitations of existing equianalgesic tables, and proceed with rotation and/or conversion only after a comprehensive assessment that includes patient characteristics and the pain syndrome.

The goal of this study was to report inconsistencies among available equianalgesic tables and other educational materials, not to evaluate them for accuracy or superiority. In our experience, numerous problems and pitfalls in equianalgesic tables exist (Table 5). Variations in equianalgesic dosing will likely persist secondary to the heterogeneous patient

population in which they are prescribed, and a gold standard table applicable in all clinical situations appears unrealistic. Nevertheless, a consistent approach should be achieved by establishing guidelines from expert consensus groups to assist physicians in selecting the most appropriate equivalences, which may then be modified according to the clinical context. Clinical guidelines to approach opioid conversion and rotation based on our experience (and that of others) are outlined in Table 6.[22−31] The current situation is unacceptable, and is a major public health concern.

Conclusions

We have identified wide and clinically important differences in published opioid equianalgesic ratios. The information contained in equianalgesic tables and other educational materials is confusing to physicians and dangerous to patients. Equianalgesic tables should serve to estimate doses that are safe if applied to the general population. This should represent a first step in the clinical decision made on opioid rotation or conversion. Other considerations should include indications for rotation, drug-drug interactions, alternatives to rotation before applying these tables, and host factors that interfere with analgesia. In addition, better presentation of information, separation of ratios for acute and chronic dosing, and mandatory education for those licensed to prescribe opioids and treat cancer pain will help alleviate any confusion. A consensus of multispecialty expert opinion to establish correct and safe equianalgesic dosing for opioid conversion and rotation is recommended. This will maintain quality care without jeopardizing patient safety.

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