Review Article

Opioid Rotation: The Science and the Limitations of the Equianalgesic Dose Table

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Abstract
Opioid rotation refers to a switch from one opioid to another in an effort to improve the response to analgesic therapy or reduce adverse effects. It is a common method to address the problem of poor opioid responsiveness despite optimal dose titration. Guidelines for opioid rotation are empirical and begin with the selection of a safe and reasonably effective starting dose for the new opioid, followed by dose adjustment to optimize the balance between analgesia and side effects. The selection of a starting dose must be based on an estimate of the relative potency between the existing opioid and the new one. Potency, which is defined as the dose required to produce a given effect, differs widely among opioids, and among individuals under varying conditions. To effectively rotate from one opioid to another, the new opioid must be started at a dose that will cause neither toxicity nor abstinence, and will be sufficiently efficacious in that pain is no worse than before the change. The estimate of relative potency used in calculating this starting dose has been codified on "equianalgesic dose tables," which historically have been based on the best science available and have been used with little modification for more than 40 years. These tables, and the clinical protocols used to apply them to opioid rotation, may need revision, however, as the science underlying relative potency evolves. Review of these issues informs the use of opioid rotation in the clinical setting and defines key areas for future research. J Pain Symptom Manage 2009;38:426–439.

Key Words
Opioid, opioid rotation, relative potency, equianalgesic dose, pain management

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Introduction

Opioid rotation refers to a switch from one opioid to another in an effort to improve therapeutic response or reduce undesirable effects. It is a well-accepted clinical practice and usually is considered as a therapeutic option in the following situations:

- Opioid dose escalation has yielded intolerable and unmanageable side effects, such as somnolence or mental clouding;

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- Severe pain (often with emerging side effects) continues despite repeated dose escalations;
- There may be benefit in a switch to a different route of administration (e.g., transdermal rather than oral), or drug or formulation (e.g., a formulation with once-daily dosing);
- A change in clinical status suggests need for an opioid with different pharmacokinetic properties (e.g., a drug without active metabolites in the setting of progressive renal insufficiency);
- Cost considerations require a change in therapy.

In most situations, opioid rotation is undertaken in the setting of poor opioid responsiveness. The goal is to achieve a better balance between analgesia and side effects, or to allow sufficient dose escalation for satisfactory pain control. The acceptance of this strategy derives from the expectation that a switch to a new drug is likely to yield equivalent or better analgesia and fewer side effects. This expectation has gained support from a small number of observational studies[1–3] and a substantial clinical experience that has accumulated over many decades.

Although the specific mechanisms by which opioid rotation improves the overall response to therapy are not known, the theoretical basis relates broadly to the large individual variation that characterizes the responses to different mu-agonist opioids, and more specifically, to the phenomenon of incomplete cross-tolerance to both analgesic and nonanalgesic opioid effects.[4] Presumably, any change from one opioid to another is likely to yield a different set of effects, sometimes more favorable and sometimes less favorable, and the impact of incomplete cross-tolerance may bias this change toward relative improvement. If cross-tolerance to the analgesic response produced by the first drug is less complete than cross-tolerance to treatment-limiting side effects, the switch will yield a more favorable overall response to therapy. These phenomena of individual variation and cross-tolerance are poorly understood and offer a rich avenue for future research to elucidate the mechanisms underlying the success of opioid rotation.

To implement opioid rotation, a clinician must first calculate an approximate equianalgesic dose between the current opioid and the new opioid. This calculated starting dose must be safe, neither high enough to cause opioid toxicity nor low enough to cause withdrawal, and sufficiently efficacious to produce no worsening of the pain. The dose of the new drug usually must be titrated from this starting dose, hopefully yielding an improved balance between analgesia and side effects.

The calculation of an approximate equianalgesic dose is necessary because the analgesic potency of the various opioid drugs varies greatly. Potency refers to the dose required to produce a given effect. Among the various opioids available for clinical use, potency varies by orders of magnitude (i.e., from micrograms to milligrams). For example, a typical patient with relatively little prior opioid exposure is likely to experience comparable analgesic effects from parenteral administration of a single 100 μg dose of fentanyl (FE) and a single 10 mg dose of morphine. Clearly, there could be no way to switch among drugs safely and effectively unless the relative potencies among them were known.

Relative potency, which may be defined as the ratio of opioid doses necessary to obtain roughly equivalent effects, can be determined through controlled clinical trials that compare different drugs or routes of administration. Relative potency can be calculated for analgesia or any measurable nonanalgesic effect. Relative analgesic potency can be converted into equianalgesic doses by applying the dose ratio to a standard. Historically, 10 mg of parenteral morphine has been considered to be the standard for this determination, and doses equianalgesic to this have been calculated by using the empirically derived relative potency estimates.[5,6]

The first equianalgesic dose table was published more than 40 years ago[5,7] and codified the results of numerous relative potency studies. Although many versions of the table have been published since then, the potency estimates represented by the values in the table have undergone little modification (Table 1).

In addition to their clinical utility in opioid rotation, relative potency estimates are necessary to meaningfully investigate the comparative effects of different opioid drugs. To determine clinical relevance, nonanalgesic effects must be compared at roughly equianalgesic doses. Studies of relative potency, therefore, have been the

Table 1
Values Included in the Original Equianalgesic Dose Table

Drug	Equianalgesic (mg) Doses
Morphine	10 IM/IV/SQ
	60 PO
Hydromorphone	1.5 IM/IV/SQ
	7.5 PO
Oxycodone	20–30 PO
Oxymorphone	1 IM/IV/SQ
	10 PR
	15 PO
Levorphanol	2 IM/IV/SQ
	4 PO
Methadone	10 IM/IV/SQ
	20 PO
Fentanyl	50–100 μg IV/SQ

Some early tables include other drugs, such as codeine and propoxyphene. The original studies were performed with IM dosing and were then extrapolated to IV and subcutaneous dosing. Most tables published subsequently include these values with some modifications: the morphine PO dose often is changed to 20–30 mg, recognizing subsequent work demonstrating that the original, single-dose data did not apply to chronic treatment; recent studies comparing oral doses of oxymorphone and oxycodone have led to modifications in dose-conversion recommendations; and methadone usually is footnoted to highlight that the original ratios do not apply to the clinical setting without large adjustment (see text).
IM = intramuscular; IV = intravenous; PD = by mouth (oral); SQ = subcutaneous; PR = per rectum.

foundation for a better understanding of many issues in opioid clinical pharmacology.

The Methodology of Relative Potency Assays

Although the information collated in the equianalgesic dose table generally is regarded as the best science available, translation of this information to the clinical practice of opioid rotation requires guidelines that are informed by a critical understanding of the nature of the studies from which they were derived. The clinical trial methodology that was developed in the 1950s and 1960s to explore relative analgesic potency represented a landmark in pain research and set a standard for meticulous experimental design and study conduct that remains today.[5,7,8] Nonetheless, like all clinical trials, the specifics must be understood to judge validity, acknowledge limitations, and appropriately apply the data to the clinical setting.

Framework for Controlled Trials of Relative Potency

The original relative potency assays were designed as controlled four-point, single-dose studies. A low dose and a high dose of a study drug were compared with a low dose and high dose of a standard, usually parenteral morphine. Using double-blind technique and random treatment assignment, each patient received one or more of the study doses. Most studies used a partial cross-over design so that each patient received more than one of the study doses, but not all of them. The subjects chosen for these studies either had acute postoperative pain or chronic cancer pain. Postoperative patients were studied on the first day after surgery and typically had minimal opioid exposure. Studies of chronic pain patients typically limited the population to those who had been receiving no more than a relatively low dose of opioid before the study. The intention in developing these entry criteria was to choose a population for study that would be unlikely to have clinically significant tolerance to the analgesic or nonanalgesic effects of the study drugs.

After each dose of the study drugs, analgesia and other effects were evaluated repeatedly for a period of hours, using simple scales. Pain severity and pain relief, for example, were measured on separate 100 mm visual analog scales. The multiple pain measurements were used to calculate metrics that represented the total amount of pain reduction after a dose of study medication. Specifically, total pain reduction was determined as the sum of pain intensity differences (or SPID, which is defined as the sum of the differences between each of the pain severity ratings after the dose and the baseline pain rating before the dose), or the total pain relief (or TOTPAR, which is defined as the sum of the pain relief scores obtained after the dose). The effects produced by the dose of study medication also could be described by other metrics, such as peak effect on pain intensity or duration of effect on pain.

Each dose in the relative potency assay could, therefore, be defined in terms of a summary effect score, such as SPID, or a single meaningful score, such as peak effect. Any one of these outcomes could then be plotted as a simple, two-point dose-response relationship. Because the relationship between plasma drug concentration and the resultant biological effect usually is characterized by a sigmoid curve, which becomes linear when plotted on

a log-linear graph, these dose-response curves for analgesia were plotted with dose on a log scale.[7] The usual approach first calculated a summary measure like the SPID for each dose studied. This SPID score for each of the four doses was then plotted against the log of the doses. The low and the high doses for each drug thereby defined a straight line, and each study usually yielded two such lines, one for the so-called standard—typically morphine—and one for the new study drug (Fig. 1). A relative potency estimate was calculated as the distance between these lines and was expressed as the ratio of doses that would yield comparable analgesic effects.

Indicators of Validity

These relative potency assays included a group of checks, which were reviewed in each study and affirmed the validity of the results.[5,7] First, by incorporating an active control—specifically low and high doses of morphine or another standard—these studies had an "internal measure" of the assay's sensitivity. If the low dose and the high dose of the standard did not separate in terms of the effects produced, the validity of the assay was suspected.[9] Second, the dose-response plots ensured that the two drugs were being compared in a similar effect range. This allows direct measurement, rather than extrapolation, of the ratio of doses yielding roughly comparable effects. Third, the plots could demonstrate whether the dose-response curves calculated from the data were parallel, as they should be if both drugs had similar mechanisms of action- and dose-proportionate effects.

With these checks, and with meticulous conduct of the studies, the relative potency data originally published and adapted for the equianalgesic table are highly credible and give credence to the view that the equianalgesic dose table, as originally developed, represented the best science available. Data reflecting the "best science available" still may be challenged, however, by the impact of specific methodological decisions and the fundamental problem of human variation. Review of the original studies, combined with more recent relative potency data, highlight potential limitations and inform the guidelines that have been developed to safely and effectively apply the equianalgesic table to opioid rotation.

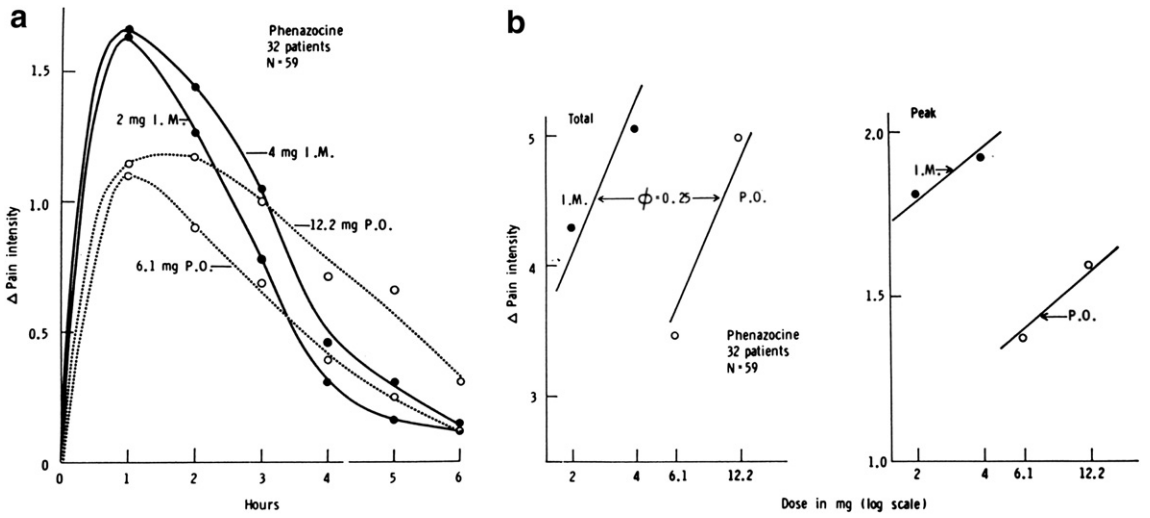

Fig. 1. An example of a four-point relative potency study: a comparison between intramuscular (IM) and oral (PO) phenazocine. a) Pain intensity difference is plotted against time (filled circles: IM preparation and open circles: PO preparation). b) Total (left) or peak (right) changes in pain intensity are plotted against dose. For total scores, PO phenazocine is one-fourth as potent as the IM preparation. For peak scores, no relative potency could be calculated because there was no overlap between the level of response seen with the two routes. Because the time course of response differs between the routes, note that the relative potency calculated for total scores would change according to the length of the study; for example, if only the first three hours were considered, the disparity between IM and PO preparations would have appeared even greater (from Beaver et al., 1966[8]).

Studies of Relative Potency

Although the equianalgesic dose table suggests a simplicity to the pharmacology underlying relative analgesic potency, this is not confirmed by review of the studies that provided the data used to construct it.

Hydromorphone

Standard equianalgesic tables indicate that the equianalgesic dose ratio for total analgesic effect between morphine sulfate (MS) and hydromorphone (HM) is 7:1 for parenteral dosing and somewhere between 4:1 and 8:1 for oral formulations.[6,10,11] Adjusted to a standard of morphine 10 mg parenterally, a typical equianalgesic dose for parenteral HM would be 1.5 mg (roughly the 7:1 ratio noted).

Interpretation of these relative potency ratios has been complicated by more recent data suggesting that these ratios differ depending on the direction of a switch from one drug to another.[12,13] In one retrospective study, for example, the MS:HM ratio for patients who switched from MS to HM was 5.33:1, and the ratio for patients who switched from HM to MS was 3.8:1.[12] These studies indicate that a bidirectional difference in potency between MS and HM may apply to both oral and parenteral dosing, and may be independent of prior opioid exposure. Based on these findings, Bruera et al.[12] recommend a dose ratio of 5:1 for rotation from MS to HM and a dose ratio of 3.7:1 for a switch in the opposite direction. The 5:1 ratio was used safely and effectively in a large survey of patients who were switched from oral morphine to a modified-release, once-daily oral formulation of HM.[14]

Another complexity has been suggested by the finding that the equianalgesic dose ratio of parenteral HM and MS can change over time.[15] In patients undergoing bone marrow transplantation, the potency of HM relative to MS decreased from 7:1 around Day 7 to 3:1 by Day 13 post-transplant. The 7:1 ratio found in standard equianalgesic tables was derived from single-dose studies, which would not reflect time-dependent effects. If the incomplete cross-tolerance that provides a rationale for opioid rotation requires time to develop, this might explain a time-dependent shift in relative potency, and in turn, would suggest that the relative potency estimates that were used to create the conventional equianalgesic dose table usually overestimate the potency of one or more of the drugs involved in the process of opioid rotation.

Oxymorphone

The relative potency between intramuscular MS and intramuscular oxymorphone (OM) has been estimated to be 8.7:1.[16] In the study that determined this ratio,[16] the occurrence of side effects was qualitatively and quantitatively similar for the two drugs at equianalgesic doses. Intramuscular OM has been found to be approximately six times more potent than the oral formulation and 10 times more potent than the rectal formulation.[17] A more recent study observed that the equianalgesic dose ratio between OM extended release and oxycodone (OC) controlled release in patients with cancer pain was OM:OC 1:2.[18] Based on these data, it may be extrapolated that, for clinical purposes, a reasonable oral OM:MS ratio is 1:2–3.

Oxycodone

Early studies estimated the relative potency between parenteral OC and parenteral MS at 0.71:1.[5,19,20] A more recent double-blind, randomized, cross-over study of oral formulations has confirmed this finding.[21] Other studies that have attempted to measure the relative potency between oral OC and oral MS have yielded more variable results, however, presumably because of the large individual variation that characterizes the oral bioavailability of the two drugs. The oral bioavailability of MS ranges from 15% to 64%, and the oral bioavailability of OC is 50% or more.[12,15] This variation alone may result in more than a twofold difference in potency and suggests that oral MS should be considered to be between equipotent and half as potent as oral OC.[12,15,22,23] A study that compared oral modified-release formulations of MS and OC in women undergoing hysterectomy was consistent with this conclusion, finding that the MS:OC ratio was 1.8:1.[24]

Like the relative potency between HM and MS, the ratio between OC and MS may be influenced by the direction of the change. In a controlled trial,[25] patients who received OC first had a potency ratio of MS:OC of 1.5:1, whereas patients who received MS first had

an MS:OC ratio of 1.33:1. This finding suggests that when converting from MS to OC, a 2:1 ratio might be used, but a 1:1 ratio might be more efficient when converting from OC to MS.[26] Although this finding of bidirectionality was not replicated in another study,[21] the ratio of MS:OC was found to range from 1.1:1 to 2.3:1, with a mean of 1.5:1, corroborating findings that OC is more potent than MS.

Methadone

The use of methadone (ME) in opioid rotation has received a great deal of attention in recent years. Initial enthusiasm for a switch to ME based on anecdotal observations suggesting that the potency of this drug is much greater than anticipated has been tempered by recent concerns about serious adverse events related to unanticipated toxicity, inappropriate prescribing, and the newly appreciated potential to prolong the QTc interval (rate corrected electrocardiographic QT interval).[27] Although ME may be very useful in opioid rotation, there is a call for greater caution in the use of this drug, especially by inexperienced clinicians.[28]

In early single-dose relative potency assays, the equianalgesic dose ratio for parenteral MS:ME was 1:1 and the ratio between parenteral ME and oral ME was 1:2.[5,7] More recent studies, however, have confirmed that the potency of ME when patients are switched from another mu agonist is greater than would be anticipated from the early studies.[12,25,29–31] For example, Ripamonti et al.[30,31] reported a dose ratio for oral MS:oral ME of 7.75:1 (range: between 14.1 and 2.5:1). A dose ratio of subcutaneous MS vs. oral ME was reported to range between 5:1 and 7:1.[12,32]

Several studies have found a significant relationship between the relative potency of ME and the dose of the opioid taken at the time that ME is administered.[12,25,30,31] One study noted that the oral MS:ME ratio for patients receiving less than 1165 mg/day was 5.42:1, whereas the ratio for those receiving more than 1165 mg/day was 16.8:1.[12] Another study determined the MS:ME ratios as 3.71:1 if the dose of MS before the switch was 30–90 mg/day, 7.75:1 if the MS dose before the switch was 90–300 mg/day, and 12.25:1 if the prior MS dose was >300 mg/day.[30,31] Another study noted a bidirectional difference in the oral MS:ME ratio, reporting that the ratio was 8.25:1 when switching from ME to MS, and 11.36:1 when switching from MS to ME,[25] whereas the study by Walker et al.[33] reported the mean dose ratio for switching from oral ME to oral MS to be 1:4.7, and intravenous ME to oral MS to be 1:13.5. However, the study did not find a significant relationship between the relative potency of ME and the dose of ME taken by the patient at the time of the switch.

The finding that the potency of ME after a switch from another mu-agonist drug depends on the dose of the prior drug has been explained by the effects of the d-isomer of ME, which comprises 50% of the commercially available racemic mixture. The d-isomer is an antagonist at the N-methyl-D-aspartate receptor, and as such, has the potential to reverse opioid tolerance and to produce nonopioid analgesic effects.[34] Presumably, a relatively high-dose opioid regimen at the time of the switch to ME would be associated with greater tolerance, and initiation of ME therapy would reverse this effect and yield a greater degree of analgesia than a switch to ME from a relatively low-dose regimen.

Together, these more recent studies suggest that the conventional equianalgesic dose ratios derived from a single dose study[5,7] do not apply to opioid rotation using ME without substantial adjustment[12,25,29,30] (see below). This adjustment may take the form of a standardized reduction in the calculated equianalgesic dose in all cases, or a more specific reduction based on the dose of the opioid taken at the time of the switch to ME.

Codeine

The average dose ratio for total analgesic effect between intramuscular and oral codeine has been reported to be 0.6:1;[19] the range in total effect across patients was 0.57:1–0.64:1, and the average ratio for peak effect was 0.49:1.[19] A comparison between parenteral codeine and OC found an equianalgesic dose ratio of 10:1.[20] Codeine is a prodrug of morphine, however, and its relative potency presumably varies with the extent to which it is converted to its active metabolite (see below).

Fentanyl

Transdermal, sublingual, and buccal formulations of FE are now widely used in populations with chronic pain.[35–37] Based on

accumulated evidence from controlled trials, the manufacturer of the transdermal FE citrate delivery system provided a conversion tool that presented dose ratios in broad ranges.[38] For example, the transdermal FE patch delivering 25 μg/hour is suggested to be roughly equianalgesic to oral MS at 60–134 mg/day, whereas transdermal FE at 300 μg/hour was described as equianalgesic to oral MS at a dose between 1035 and 1124 mg.[38] The decision to apply a narrower range at the higher dose of FE was based on very limited data.

In a prospective study of cancer patients receiving modified-release MS who were converted to chronic dosing with transdermal FE, the mean ratio of MS:FE was 70:1.[39] A similar study yielded a ratio of 96.6:1.[40] In a small survey of 11 patients switched from MS or codeine to a subcutaneous FE infusion, the mean relative potency of MS:FE was 68:1, and the range was 15:1–100:1.[41] A study comparing oral MS and subcutaneous FE found the dose ratio to be 84.5:1,[42] and a study comparing subcutaneous MS and subcutaneous FE suggested a ratio of 70:1.[43] These studies demonstrate considerable variability in conversion ratios, both within and across studies, and underscore the need for caution in applying ratios during opioid rotation.[26,44]

Studies of oral transmucosal and buccal FE formulations for breakthrough pain demonstrate no relationship between the dose of the drug and the dose of the baseline regimen.[45] This finding would be unexpected if the potency of the FE were strongly influenced by analgesic tolerance and further reinforces the conclusion that relative potency may be influenced by a variety of factors, such as rapidity of transit across the blood-brain barrier for a highly lipophilic drug, such as FE, or avidity for receptor sites. A study that formally evaluated the relative potency of oral transmucosal FE (OTFC) and intravenous MS in postoperative patients found that the best equianalgesic ratio of intravenous MS:OTFC was 80:1; in this study, 800 μg of the FE produced analgesia roughly comparable to 10 mg MS.[46]

Sufentanil

In patients with chronic pain previously treated with opioids, a controlled trial determined the median potency ratio between an FE infusion and a sufentanil (SF) infusion to be 7.5:1, indicating that SF is approximately 7.5 times more potent than FE.[47] In contrast, a study of two patients with postoperative pain, who were converted from FE to SF, observed that dose ratios of 16:1 and 24:1 were effective.[41] Other investigators[48,49] found the dose ratio between FE and SF to be 10:1. Studies comparing intrathecal FE and SF for labor analgesia identified potency ratios of 4.4:1[50] and 5.9:1.[51]

Buprenorphine

In a randomized, double-blind study that compared epidural buprenorphine (BU) and epidural MS in patients after major abdominal surgery, the MS:BU relative potency ratio was 8:1.[52] A comparison of sublingual BU and intramuscular MS[53] observed an MS:BU equianalgesic dose ratio of 15.5:1, and studies comparing intramuscular BU and intramuscular MS found MS:BU ratios of 33:1 in both.[54,55]

Nalbuphine

In controlled studies, parenteral nalbuphine (NB) was found to be 0.8–0.9 times as potent as parenteral MS,[6] or equipotent to it.[56] A study evaluating intramuscular NB and oral NB found that the equianalgesic ratio was 1:4.[57]

Butorphanol

In patients with postoperative pain, the relative potency of parenteral butorphanol tartrate and pentazocine hydrochloride was 24.3:1.[58] Other studies found this ratio to be 16:1[59] and 20:1.[60]

Tramadol

Comparison of intravenous patient-controlled analgesia with tramadol (T) vs. MS in female patients undergoing reconstructive breast surgery resulted in the potency ratio estimate of 1:11 (MS:T).[61] Given this ratio, it may be surprising that another study, this one in children with postoperative pain, showed that the use of an MS:T equianalgesic dose ratio of 1:10 led to better pain control with the MS.[62] Another study of children with postoperative pain determined an equianalgesic dose ratio for epidural MS:T to be 1:20.[63]

Relative Potency: Interpretation and Limitations

The aforementioned review encompasses both the early relative potency assays and many studies that have appeared in subsequent decades. Although the equianalgesic dose table, which was created using measurements of mean total effect from the original assays, has undergone little modification over the years, the many later trials underscore the elements that were not addressed by the early studies or the equianalgesic dose table derived from them. These studies were not used to describe other estimates, such as peak effect, or to depict the large confidence intervals that surrounded each statistical calculation and objectified the substantial variation around the mean.[7,8,64] They did not assess many of the potential influences on potency that have become relevant with subsequent research, including the direction of the switch from one drug to another, the influence of chronic opioid administration, and the importance of the dose at the time of a change. They could not evaluate formulations and drugs that have come into clinical use since the original equianalgesic table was created, nor did they specifically address responses based on ethnicity, advanced age, concomitant medication use or comorbidities.

Applying Relative Potency Estimates to Opioid Rotation

With the accumulation of relative potency trials, it has become clear that guidelines for opioid rotation based on the use of an equianalgesic dose table cannot ignore the large variability inherent in this pharmacology. It is important to clarify the extent to which the methodology of the trials limits the generalizability of the data they acquire. A critical understanding of the sources of variation, and their impact on the interpretation of the data, may help refine the guidelines for opioid rotation and increase the early effectiveness of a switch from one opioid to another. These sources of variation in relative potency estimates may be divided into those related to the design and conduct of the assays and those related to variation in patient characteristics.

Assay Elements that May Influence the Use of Relative Potency Assays

The specific procedures developed for relative potency assays are intended to control for bias and increase the study's sensitivity to differences between drugs and doses. This positive effect may be balanced, however, by the acquisition of data that lack broad generalizability as a result. Despite the rigor of the relative potency studies, limited generalizability would raise questions about the application of the data to equianalgesic ratios and guidelines for opioid rotation. These questions would necessitate adjustments that acknowledge this uncertainty and increase the safety of the approach. In this regard, the following are important considerations:

- As noted previously, the use of a total effect measurement, such as SPID or TOTPAR, calculated for a defined period after a study dose, means that other parameters, such as time to meaningful pain relief, peak analgesic effect, or duration of effect, are not described. A relative potency estimate, and the equianalgesic dose ratio derived from this estimate, potentially could be calculated for any of these outcomes and could theoretically yield a value with greater clinical relevance. For example, it is possible that an equianalgesic dose linked to peak effect rather than total effect may be most likely to lead to early benefit, particularly if the change from one opioid to another is occurring in the setting of severe pain. The recognition that an equianalgesic dose ratio based on average effect may yield a dose conversion inadequate to address severe pain can be incorporated into a guideline for opioid rotation (see below).
- The use of mean data in developing equianalgesic ratios also may pose problems in the clinical setting. A 10:1 ratio depicted in the table may actually reflect a ratio of 2:1 in some patients and 20:1 in others. Variation may be systematic, such that specific characteristics, like advanced age, are salient influences on potency and may be associated with a relatively higher or lower ratio than codified in the table. Uncertainty about the extent of variation and the potential for systematic influences also must be addressed in a guideline for opioid rotation.
- The four-point, incomplete cross-over method, which increases the sensitivity of the assay by having each patient act as his or her own control, would be difficult

to accomplish and prone to more error if the time courses of effects between the drugs differ greatly, or if the drugs have a long duration of effect after a dose. Although the original relative potency studies tended to avoid these potential problems by studying short half-life drugs, ME was a notable exception and studies of newer, long-acting formulations required other study designs (e.g., Donner et al. and Darwish et al.[39,45]). Guidelines for opioid rotation that apply the traditional equianalgesic dose table to ME or long-acting formulations should acknowledge the uncertainty in this approach and incorporate adjustments for safety.

- Studies of relative potency largely have included populations with little opioid exposure. Given the likelihood that prolonged exposure to an opioid produces changes (including some degree of analgesic tolerance) that will alter the relative potency of the next opioid administered, the dose ratios developed in such populations cannot be directly applied to patients with significantly greater opioid exposure. The recent finding of large potency changes in ME depending on the prior opioid exposure highlight this concern.[12,25,30,31]

Clinical Elements That May Influence the Use of Relative Potency Assays

In addition to these methodological issues, relative potency estimates may be affected by numerous factors that are minimized in the clinical trial setting and similarly affect generalizability of the data. When switching to a new opioid, these potential sources of variation also must be considered.

Major Organ Dysfunction. Physiological disturbances may change the kinetics of a drug or active metabolites, or alter pharmacodynamics. Although these changes may shift relative analgesic potency among opioids in ways that are predictable, studies that would clarify the changes have not been performed.

Renal insufficiency is likely to change the potency of some drugs that depend on renal clearance of the parent compound or active metabolites. Although information about these renal effects on opioid metabolism is incomplete,[65,66] patients with renal insufficiency who undergo opioid rotation generally are given relatively lower starting doses and more cautious dose escalation because of pharmacodynamic changes leading to increased risk of adverse effects, as well as the potential for risk of accumulation of the parent compound or its metabolites.[67–72] The impact of renally cleared metabolites is strongly suspected in the case of drugs with known active metabolites, such as morphine or BU.[68–70,73] A study of BU in the setting of renal impairment, for example, revealed increases of fourfold and 15-fold, respectively, in the plasma concentrations of the metabolites BU-3-glucuronide and nor-BU.[73]

There are even fewer data to clarify the effect of hepatic impairment on opioid potency. A study of butorphanol, an agonist-antagonist opioid, found kinetic changes that would be unlikely to change potency,[74] but a study of morphine noted that the concentration of active metabolites was relatively reduced in cirrhotic patients.[75] The impact of this change on relative potency is unknown. Because severe hepatic disease increases the likelihood of adverse drug effects overall, the usual approach is to exercise caution when rotating opioids in patients with liver disease, notwithstanding the lack of information about specific changes in relative potency.

Patients with adrenal insufficiency and hypothyroidism may show a prolonged and exaggerated response to opioids. Abnormal levels of plasma proteins may change the relationship between protein-bound and protein-free drug, and thereby influence opioid effects.[76] These changes also may influence relative potency estimates when converting from one drug to another, but again, the details are not known.

Demography. Race, age, and gender, each can affect the potency of specific opioids. Although the impact of these characteristics on relative potency estimates between pairs of drugs is not known, data are continuing to emerge and it is possible that future studies will be able to apply this information systematically to guidelines for opioid rotation.

Recent data have underscored the importance of genetically determined racial differences in the response to opioids.[77–83] The best characterized one is the variation in the

activity of the CYP2D6 isoenzyme of the hepatic P450 system, and its encoding gene. CYP2D6 is known to catalyze more than 50 clinically important drugs, including analgesics, antiarrhythmics, antidepressants, antipsychotics, and β-blockers. It is the only one of the drug-metabolizing CYPs that is not inducible, and as a consequence, genetic variation contributes largely to the interindividual variation in the enzyme's metabolic activity.

CYP2D6 is involved in the metabolism of codeine, hydrocodone, OC, T, and a number of other opioids. Codeine is a prodrug and CYP2D6 catalyzes O-demethylation of codeine to morphine, which leads to clinical effect. Different CYP2D6 alleles result in enzyme variants associated with abolished, decreased, normal, or ultrarapid enzyme activity. Clinically, they allow grouping of patients into ultrarapid metabolizers, extensive metabolizers, intermediate metabolizers (IM), and poor metabolizers (PM). PM produce less morphine from codeine and demonstrate relatively poor analgesic response when codeine is administered for pain.[79]

It has been shown that the activity of CYP2D6 is significantly greater in Caucasians than Asian patients. Chinese subjects given codeine have higher mean values of C_{max} and area under the curve, lower plasma clearance, longer plasma half-life, and lower partial clearance by glucuronidation.[83] Similarly, Japanese subjects were found to have a significantly higher frequency of CYP2D6*10 mutation, predicting them to be IM.[80] With these findings, differences between Asians and Caucasians in the relative potency estimates involving codeine are highly likely.

Genetic differences in other metabolic pathways presumably are the cause of variation between Caucasians and Chinese in the pharmacokinetics and pharmacodynamics of morphine.[84] Based on these data, it is likely that Chinese patients will be less efficient metabolizers of morphine, leading to still ill-defined changes in potency. In the absence of a more robust scientific understanding of the impact of race on relative potency estimates, it is prudent to exercise caution when calculating dose conversion from the equianalgesic dose table in patients who are not Caucasian, the population studied in most relative potency assays.

Like racial differences, age also may affect the apparent potency of opioid drugs. Opioid potency may be altered in children aged less than six months[85] and in older patients[86–89] because of pharmacokinetic differences and changes in pharmacodynamic sensitivities compared with older children, and young and middle-aged adults. These shifts tend to increase the potency of these drugs above those that characterize the adult populations included in relative potency assays and would explain, in part, the relatively lower opioid dose requirement for older, compared with younger, cancer patients with chronic pain.[87] Although the different effects of age on relative potencies among various opioids are not known, the concern about excessive toxicity suggests that dose conversion based on the equianalgesic dose table should be undertaken with caution in the very young and in the geriatric age group.

Recent animal and human studies also have indicated sex-related differences in the analgesic effects of opioids.[87,90–93] However, the factors that determine the magnitude and direction of sex differences have not been fully elucidated, and the impact on relative potency remains speculative. In rodents and primates, mu- and kappa-receptor opioid agonists are generally more potent in males than in females, and some drugs can variably function as agonists and antagonists under identical experimental conditions.[93] A study in normal volunteers suggested that morphine may have greater potency but slower speed of onset and offset in women.[91] Overall, the data suggest that there is likely to be an influence of sex on the potency ratios between drugs, but with few exceptions (e.g., switching to or from a kappa agonist), the data are not sufficient to predict the direction or extent of this influence.

These data demonstrate the existence of various factors that may influence opioid potency. Like the methodological strategies that may reduce generalizability, they justify the conclusion that the ratios in the equianalgesic tables are best viewed as broad indicators of relative analgesic potency, and cannot be applied to opioid rotation without adjustment.

Conclusion

The development of clinical trials to evaluate relative potency of opioid analgesics represented a watershed in pain research. Although

the outcome of this work—the equianalgesic dose table—remains a cornerstone of published guidelines for opioid rotation, a review of the science and the clinical practices that have evolved around the use of the table demonstrates substantial limitations. These may be addressed through guidelines that promote safety by introducing routine dose reduction from the calculated equianalgesic dose based on individual patient assessment.[94,95]

Future studies that refine the equianalgesic dose table, and the guidelines for dose conversions, are needed to improve the outcomes associated with the clinical strategy of opioid rotation. Studies would be valuable that assess relative potency estimates in different populations, during treatment with newer formulations, during long-term therapy, and in patients on relatively high doses of opioids. Similarly, the variability in opioid (and metabolite) toxicities among patients requires further investigation to understand both the basis for this variability and means to predict and reduce adverse effects. The potential for bidirectional change in relative potency should be investigated across varied pairs of drugs. The impact of dose range on potency that appears to be particularly important when ME is administered should be studied with other drugs as well. Sources of variation that may systematically alter potency, including pain-related factors, disease-related factors, and demographic factors, remain to be investigated. With existing data, and the results of these future studies, efforts will be needed to adapt the equianalgesic dose table to the continuing accumulation of information about opioid pharmacology.

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