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A Comparison of Institutional Opioid Equianalgesia Tools: A National Study

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Abstract

Context: Equianalgesic tools are commonly utilized to guide dose of analgesic therapy, but there is no national consensus on equianalgesic calculations in the United States.
Objectives: To propose a summary of current opioid equianalgesic data that include variations and trends among national institutions.
Methods: Opioid equianalgesic tools were obtained between May and September 2021. For meperidine, tramadol, codeine, hydrocodone, morphine, oxycodone, oxymorphone, hydromorphone, levorphanol, fentanyl, and tapentadol, details of adjustment for incomplete tolerance, opioid equianalgesic ratios, and formulation types were collected and analyzed. Baseline opioid pharmaco kinetic data were obtained through manufacturer labels on FDA databases, including half-life ($T_{1/2}$), volume of distribution (V_d), clearance (Cl), area under the curve (AUC), max concentration (C_{max}), and time to max concentration (T_{max}).
Results: Thirty-two institutions' equianalgesic tools were included with each study opioid appearing on an average of 23 institutions' tools. Few tools contained guidance on levorphanol or tapentadol; or included minimum and maximum recommended doses. All tools included guidance on fentanyl, hydromorphone, oxycodone, morphine, and hydrocodone. A minority of tools included guidance on cross-tolerance considerations ($n = 12$, 37.5%). Oral-tramadol-to-oral-morphine and oral-hydromorphone-to-intravenous (IV)-hydromorphone had the largest variances across equianalgesic tools (6.7 ± 2.8 and 4.06 ± 1.2 mg, respectively).
Conclusion: Opioid equianalgesia tools from across the United States demonstrated significant variation in their inclusion of guidance on adjustment for incomplete cross-tolerance, oral-to-IV, and oral-to-oral opioid equianalgesic ratios, and which opioids and formulations were listed. Tramadol and hydromorphone had the most variation in their equianalgesic guidance among the opioids.

Keywords: equianalgesia; morphine equivalent daily dose; oral morphine equivalent; pain; palliative

Introduction

Moderate to severe pain remains a multifaceted health problem with significant social and economic burdens. Chronic pain is present in >30% of Americans and >40% of elderly patients.[1] The Global Burden of Disease Study 2016 recognized pain and pain-related conditions as one of the leading causes of disability and disease burden globally.[2] The estimated cost of prescribed medications for nonmalignant chronic pain in the United States were $17.8 billion annually from 2000 to 2007, with opioids consisting of 20%, simple analgesics and non-steroidal anti-inflammatory medications consisting of 11%, and adjuvant agents consisting of 69%.[3]

Strategies for pain management are driven depending on the mechanism of pain, the rate of pain chronification, and the

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manifestation of physical and psychological symptoms.[4] Therefore, nonopioid therapies such as tricyclic antidepressants and selective serontonin reuptake inhibitor medications, anticonvulsants, skeletal muscle relaxants, immunologic agents, and steroids comprise the majority of total annual cost of pain medications, as they are used in wide etiologies of pain overall.[5]

Of all analgesics in clinical practice, opioids have been widely considered as the most effective treatment for pain under clinically appropriate guidelines and decisions, and they remain the standard of care for acute and chronic pain associated with advanced illnesses and cancer.[6] Despite this, the selection and dosage of opioids need to be taken into consideration to achieve the balance between adequate pain control and adverse effects. In clinical situations where opioid rotations are necessary, equianalgesic tables have been utilized historically to guide dose of analgesic therapy. 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. The observed reasons for opioid rotations and dose adjustments include inadequate analgesic response, changes in clinical status, feasibility of various formulations, and as a strategy in the management of intolerable side effects.[7]

Equianalgesic dose ratio refers to the dose ratio of two opioids required to produce the same analgesic response. The relative potency between two opioids allows for an estimation of dose for the new opioid while optimizing analgesia and adverse effects.[7] Relative potency can be determined through well-established clinical trials that compare different opioids and routes of administration. Although the specific mechanisms by which opioid rotation improves pain response are not yet elucidated, it is theoretically attributed to variable individual response to different mu-agonists and, therefore, allowing for greater analgesic effects.[8] However, since the first equianalgesic table was published by Houde et al. >50 years ago, the relative potency data between opioids have undergone minimal changes despite numerous publications of modified equianalgesic tables.[9,10]

Although equianalgesic charts imply a simplicity to the pharmacology and the relative opioid analgesic potency, opioid conversions should not be purely a mathematical application but rather a comprehensive patient assessment that takes into consideration relevant patient-specific factors.[11] From their earliest use, equianalgesic tables have been recognized for their limited applications on patients with psychological developments, prior opioid use, sex, and age.[12] Furthermore, most opioid equianalgesic conversion data were solely derived from single-dose studies and pharmacokinetic parameters, which questions the validity of existing recommendations and challenges the generalizability of opioid equianalgesic tables in clinical practice.[6,10,12] Therefore, to effectively provide analgesic therapy, clinicians must clearly understand the weaknesses of opioid conversion tables and appropriately apply the equianalgesic information in various clinical settings.

Although there is considerable research on individual opioids and their pharmacokinetics, there have been fewer studies comparing opioid equianalgesic tables from different institutions using pharmacokinetic profiles of individual opioids. Unlike other areas of medicine where well-defined algorithms dictate clinical practice, there is no widely accepted guideline for opioid equianalgesic conversions. By analyzing opioid equianalgesic tables nationally from different institutions, our primary objective is to propose a summary of current opioid equianalgesic recommendations that include variations and trends among institutions. Our secondary aim is to collect median opioid equianalgesic ranges that may provide clinicians with a more elucidated approach to deal with challenges associated with variable opioid conversions.

Methods

The University of California San Diego (UC San Diego) human research protections program granted institutional review board exemption (Project No. 210339X) contingent on compliance with applicable UC San Diego policies and standards as well as local, state, and federal regulations.

Opioid equianalgesic tables were obtained through social media, organizational LISTSERV, and independent inquiries between May and September 2021. Study data were collected and managed using REDCap™ electronic data capture tools hosted at UC San Diego Health. REDCap (Research Electronic Data Capture)[13,14] is a secure web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Adjustment for incomplete tolerance, opioid equianalgesic ratios, and formulation types were collected from equianalgesic tables for all available opioids and subsequently analyzed using both Excel (Microsoft Corporation, Redmond, WA) and REDCap. Data on which opioids were included on each institution's table were collected for 13 opioids (Fig. 1). Given the complexity of equianalgesic and pharmacokinetic considerations with buprenorphine and methadone, additional equianalgesic data for these opioids were not collected as part of this study.

All baseline opioid pharmacokinetic data were obtained through manufacturer labels on FDA databases. Pharmacokinetic parameters, including half-life ($T_{1/2}$), volume of distribution (V_d), clearance (Cl), area under the curve (AUC), max concentration (C_{max}), and time to max concentration (T_{max}), were collected. Additional data collection included manufacture source and type of opioid formulation. During data gathering, assumptions were established to effectively reflect the data. In instances where ranges were given, mean values were used to give the most accurate estimation of the data.

For example, several equianalgesic tables presented their cross-tolerance dose-reductions estimations in a range format. In instances where equianalgesic ratios varied depending on the dose of an opioid (i.e., fentanyl transdermal), the mean equianalgesic ratio was taken among all doses. The opioids included in this study were meperidine, tramadol, codeine, hydrocodone, morphine, oxycodone, oxymorphone, hydromorphone, levorphanol, fentanyl, and tapentadol.

Results

Thirty-three unique equianalgesia tables were uploaded into the research portal from institutions across the continental United States. One table was eliminated from this analysis due to its complexity. The results presented are for

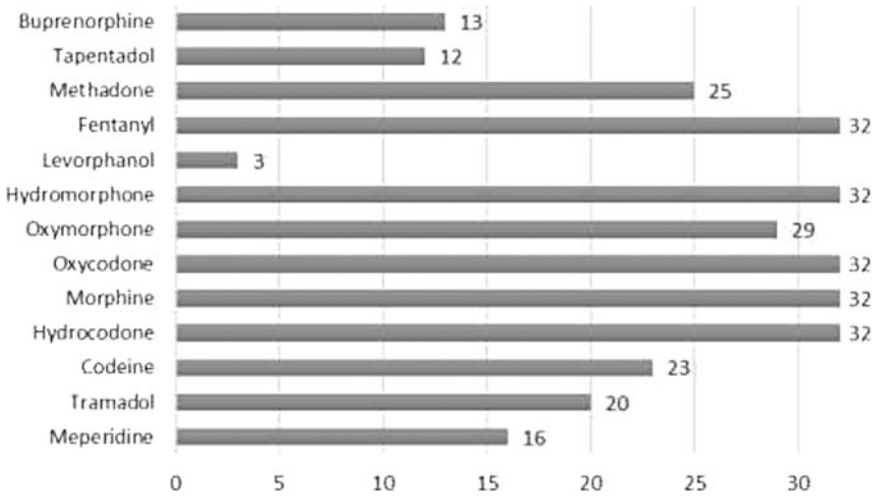

FIG. 1. Number of equianalgesia tables containing each opioid.

the remaining 32-equianalgesic tables. 47.2% (17) of tables were submitted as a result of a call for participation on a LISTSERV, 27.8% (10) due to an institutional contact, and 25% (9) indicated other reason, including social media. The equianalgesia tables had last been reviewed an average of 887 days (median 590 days) before the end of our study period. Package inserts were variable in the level of pharmacokinetic detail listed (Table 1) with $T_{1/2}$, $C_{\max}$, and $T_{\max}$ being most often delineated and AUC most infrequently described.

Of the 11 opioids considered in our study, each opioid appeared on an average of 23 institutional equianalgesia tables (median = 25). Five opioids appeared on every institutional tool (fentanyl, hydromorphone, oxycodone, morphine, and hydrocodone). A minority of tools included guidance on levorphanol or tapentadol. Interestingly, very few institutional tools included information about minimum or maximum recommended doses and only a minority of tools offered guidance related to considerations of opioid cross-tolerance ($n = 12$, 37.5%). The median recommended adjustment for cross-tolerance from 12 institutional equianalgesia tools was 37%.

Oral tramadol had a mean equianalgesic ratio of 6.7 ± 2.8 mg when converting to oral morphine. Oral codeine and hydrocodone had a mean equianalgesic ratio of 7.2 ± 0.9 and 0.99 ± 0.06 mg, respectively, when converting to oral morphine. Oral morphine had a mean equianalgesic ratio of 2.8 ± 0.24 mg when converting to intravenous (IV) route. Oral oxycodone had a mean equianalgesic ratio of 0.72 ± 0.08 mg when converting to oral morphine (Table 2). Oral

Table 1. Opioid Manufacturer Pharmacokinetic Details

Opioid	*Formulation*	*Manufacturer name*	$T_{1/2}$ *(hours)*	*Volume of distribution*	*Clearance (mL/min)*	*AUC*	C_{max}	T_{max} *(hours)*
Buprenorphine	Oral Dissolving	Roxane	33	—	—	10.93	1.25	1.84
Codeine	PO	West-Ward Pharmaceuticals Corp.	3	3	—	—	—	1
Fentanyl	Transdermal	Janssen	17	—	—	—	0.3	27.5
Fentanyl	IV	Akorn	3.6	4	—	—	—	—
Hydrocodone	PO	Allergan	3.8	—	—	—	23.6	1.3
Hydromorphone	IV	Purdue Pharmaceutical	2.3	302.9	117.6	—	—	—
Hydromorphone	PO	Abbott	2.3	4.32	—	23.7	5.5	0.74
Levorphanol	IV	Roxane Laboratories, Inc.	13	11.5	0.94	—	—	—
Meperidine	PO	Validus	8	—	—	—	—	—
Meperidine	IV	Hospira	5	—	—	—	—	—
Methadone	PO	Westward	33	4	63.7	—	675	4
Morphine	PO	Allergan	13	4	1.8	271	15.6	8.6
Morphine	IV	Hospira	1.8	2.8	1.1	—	—	—
Oxycodone	PO	Genus Lifesciences, Inc.	4	2.6	48	—	—	—
Oxymorphone	PO	Endo Pharmaceuticals, Inc.	11.3	—	—	—	0.27	4.54
Tapentadol	PO	Ortho-McNeil-Janssen Pharmaceuticals, Inc.	4	6.8	92	—	—	1.3
Tramadol	PO	Ortho-McNeil	5.6	2.6	0.354	—	308	1.6

AUC, area under the curve; $C_{\max}$, maximum concentration; IV, intravenous; $T_{1/2}$, half-life; $T_{\max}$, time of maximum concentration.

Table 2. Oral Opioid to Oral Morphine Equivalent

Opioid name	n	*Min (mg)*	*Max (mg)*	*Med (mg)*	*Mean (mg)*	*StDev (mg)*
Codeine	23	5.5	10	6.7	7.18	0.92
Hydrocodone	32	0.67	1	1	0.99	0.06
Hydromorphone	32	0.15	0.25	0.25	0.23	0.03
Levorphanol	3	0.07	0.13	0.13	0.11	0.03
Meperidine	16	10	12	10	10.5	0.89
Morphine	32	—	—	—	—	—
Oxycodone	32	0.67	1	0.67	0.72	0.08
Oxymorphone	29	0.33	0.4	0.33	0.35	0.03
Tapentadol	12	2.5	4	3.12	3.12	0.63
Tramadol	20	4	10	4.8	6.73	2.76

max, maximum; med, median; min, minimum; *n*, number of instances; SD, standard deviation.

hydromorphone had a mean equianalgesic ratio of 4.06 ± 1.2 mg when converting to IV formulation, and a mean ratio of 0.24 ± 0.03 mg when converting to oral morphine.

Oral hydromorphone to IV hydromorphone had a significant variation in equianalgesic ratio of 4.23 ± 1.16 mg. Fentanyl transdermal patch had a mean equianalgesic ratio of 0.45 ± 0.08 mg when converting to oral morphine. In addition, IV fentanyl had a mean equianalgesic ratio of 0.04 ± 0.12 mg when converting to oral morphine (Table 3). Oral tramadol had the most variation in recommended conversion factor to oral morphine (standard deviation [SD] = 2.76) and hydromorphone had the most variation in recommended IV:PO conversion (SD = 1.19 mg).

Discussion

This is the first study to evaluate equianalgesic tools from different institutions nationally. Of all the equianalgesic tools captured in our study, there were several opioids where significant variation in equianalgesic ratios were revealed. Notably, there was significant variation in the equianalgesic ratio of oral tramadol to oral morphine as indicated by the SD ranging from 3.9 to 9.5. Although the interindividual variability to pain sensitivity is likely multifactorial, including psychological, social, and environmental factors, one possible explanation for this variation among institutional tools may be due to tramadol's pharmacokinetics profile mediated by pharmacogenetics.

Tramadol produces its analgesic effects through inhibition of monoamine reuptake and the binding of μ-opioid receptors through its active metabolite *O*-desmethyltramadol (M1).[15] Most ultrarapid metabolizers (UM) of CYP2D6 substrates are prone to therapeutic failure during treatment with other concomitant medications metabolized by CYP2D6. However, tramadol, which is a prodrug and demethylated by CYP2D6, may have an exaggerated efficacy and higher incidences of adverse drug reactions due to increased exposure to M1. Therefore, tramadol may require dose reductions in UM and extensive metabolizers (EM) compared with intermediate metabolizers (IM) and poor metabolizers (PM). It is estimated that CYP2D6 UM, EM, IM, and PM compose 3–5%, 70–80%, 10–17%, and 5–10% of White-identified participants, respectively.[16]

Table 3. Oral to Intravenous Equianalgesia Ratios by Medication

Name	n	*Min*	*Max*	*Med*	*Mean*	*StDev*
Meperidine	16	3	4	3	3.24	0.40
Morphine	31	2.5	3	3	2.84	0.24
Hydromorphone	30	2.5	5	5	4.06	1.19
Levorphanol	2	1.5	2	1.75	1.75	0.35

There is a lack of studies in the literature comparing equianalgesic ratios among institutions, including that of oral tramadol to oral morphine. In a study conducted by Stamer et al. analyzing postoperative analgesia using tramadol in 241 EM and 30 PM, it was reported that 47% of PM group were nonresponders compared with 22% in the EM group; and a 1.4-fold higher loading dose was given in the PM group versus the EM group.[17] They suggest tramadol dosing and, therefore, its equianalgesic ratio should be in part driven by genetic polymorphisms of its primary metabolic enzyme. Although Stamer et al. demonstrated the importance of CYP2D6 polymorphisms in the setting of tramadol pharmacokinetics, further studies evaluating the relationship between the dosage of tramadol and drug-metabolizing enzyme activity are warranted to validate findings.

These results also revealed a median equianalgesic ratio of 5 with a significant SD of 1.19 for conversion of IV hydromorphone to oral hydromorphone. Despite its extensive clinical use, there are limited studies regarding the equianalgesic ratio between IV and oral hydromorphone among institutions, which leaves open the potential for inadequate analgesia versus overdose. The ADR profile of hydromorphone is well established, notably due to its analgesically inactive metabolite hydromorphone-3-glucuronide, which is more potent compared with morphine-3-glucuronide in causing neuroexcitation. Clinically, this may present in patients as myoclonus and agitation in a dose- and duration-dependent manner, and is one common reason to perform opioid rotations.[18,19] Houde et al. investigated between parenteral and oral administration of hydromorphone and reported an equianalgesic ratio of 5 with a range of 2.8–14.3, citing extensive first pass elimination and bioavailability ranging from 29% to 95% as reasons for such variability.[9] This suggests the generalizability of current median equianalgesic ratio between IV and oral hydromorphone built upon existing knowledge of wide intersubject variability in pharmacokinetics. Comparatively, Reddy et al. reported a median IV to oral ratio of 2.5 and 2.1 in

147 hospitalized cancer patients receiving <30 mg of IV hydromorphone per day and >30 mg of IV hydromorphone per day, respectively.[20]

The study by Reddy et al. proposed a more conservative equianalgesic ratio, which suggests that patients on higher daily dosages of hydromorphone may require a lower equianalgesic ratio when transitioning to oral regimen of hydromorphone. Although this differs significantly from the median equianalgesic ratio reported in our study, they showed that a ratio of 2.5 from IV to oral hydromorphone can be effective in hospitalized patients with uncontrolled pain in a well-powered sample size. In addition, the ratio by Reddy cannot be generalized to opioid-naive patients in acute pain and this ratio was not studied in the reverse. Given the conflicting data on the appropriate hydromorphone equianalgesic ratio, clinicians should follow their institutional equianalgesic tables when performing IV to oral conversions and applying their clinical judgment to individualize care.

We aimed to reach a consensus on the foundations that opioid rotations should be generalized to a wide population of patients and provide appropriate sufficient flexibility to allow for intersubjective variation seen in various clinical vignettes. The findings indicate while equianalgesic ratios for certain opioids may vary across institutions, there is still a lack of a standardized methodology for applying opioid rotations compared with existing guidelines.[10] For example, clinical influences such as renal and hepatic function have not been emphasized in opioid equianalgesic charts and may provide additional clinical benefit. In addition, common genetic polymorphisms in the population that affect opioid metabolism may contribute to a deeper understanding of the wide interindividual variability in opioid response and, therefore, may offer additional guidance during opioid and dose selection.

Surprisingly, only a minority of tools endorsed a dose reduction when rotating to a new opioid. Given the fluid nature of opioid rotation and the relatively narrow therapeutic window, individualized dose titrations are common and, therefore, initial conservative reductions may have benefit. We suggest a modified table that allows for dose adjustments from preexisting influences that can affect relative potency (see Table 4). In addition, due to the concerns of using current equianalgesic tables without accounting for individual differences, a revised table including ratios driven from clinical judgment and practices may be necessary rather than one utilized from evidence alone.

Table 4. Consensus Opioid Equianalgesia Based on the Median Conversion Factors from 32 Institutions' Equianalgesia Tables

	PO (mg)	*IV (mg)*
Codeine	200[a]	—
Fentanyl	—	0.135 (135 mcg)
Hydrocodone	30	—
Hydromorphone	8[b]	2
Levorphanol	4	2
Meperidine	300	100
Morphine	30	10
Oxycodone	20	—
Oxymorphone	10	—
Tapentadol	90[a]	—
Tramadol	140[a]	—

[a]Rounded to the nearest tenth.
[b]Consider more conservative conversion for those on >30 mg IV hydromorphone.[20]
PO, oral.

Limitations

These data are limited by the various presentation of equianalgesic ratios among institutions. In efforts to standardize the way the data are presented, our analysis of equianalgesic ratios may have led to skewed interpretations. Many of the studies did not disclose the data from which their equianalgesic ratios derived. As such, equivalency data may not fully apply to specific situations such as in the setting of chronic pain. In addition, we have not considered opioid rotations that may have continued after hospital discharge, the ratios of which were not captured in our data. Therefore, we may have missed descriptive data such as ambulatory opioid rotation habits, outpatient equianalgesic patterns, and opioid conversions in the setting of opioid use disorders.

Conclusion

Opioid equianalgesia tools from across the United States demonstrated significant variation in their inclusion of guidance on adjustment for incomplete cross-tolerance, oral-to-IV and oral-to-oral opioid equianalgesic ratios, and which opioids and formulations were listed. Tramadol and hydromorphone had the most variation in their equianalgesic guidance among the opioids. Future research should focus on cross-institutional equianalgesic elements of buprenorphine and methadone, user factors in relationship to equianalgesia tool design that would encourage the safest and effective practice, and the role of equianalgesic factors in opioid prescribing guidelines. The authors are happy to share our research database with others interested in studying or collaborating on the important question of equianalgesia in clinical practice.

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Author Disclosure Statement

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