

Equianalgesia: Rotating Opioids Makes Me Dizzy

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Disclosure Information

- I have no financial arrangements or affiliations with corporations or organizations having a direct interest in the subject of this presentation or other participants in this continuing medical education activity.

Objectives

- Present the clinical reasons for opioid rotation
- Describe equianalgesia and the development of equianalgesic tables.
- Discuss the pitfalls in relying on equianalgesic tables for opioid rotation
- Offer a rational(?) approach to opioid rotation

In theory, there is no difference between theory and practice.
But in practice, there is.

Jan L. A van de Snepscheut

Introduction

- Pain is present in 50% pts with advanced cancer and >80% of the terminally ill.
- Most feared and distressing symptom of advanced disease
- Opioid analgesics are the mainstay of treatment of moderate to severe pain.
- 85-95% of patients achieve effective pain relief.
 - Majority of pts will require relatively low to moderate doses opioids.
 - Some may require very high doses.

Introduction

- Significant characteristic of opioids is a lack of ceiling associated with their dosing.
- No upper limit to dose that may be required to relieve a patient's pain.
- Clinicians must be prepared to use appropriate doses when required and be skilled in the conversion between opioid analgesics.

Opioid rotation

- The practice of converting a patient from one opioid to another as clinical circumstances warrant with the goal of improving outcomes.
- Calls for the determination of approximate equianalgesic conversions.
- In view of the variability of patient response to individual opioids and conflicting data about equianalgesia, conversion can be problematic especially when involving > 1 opioid analgesic.

Clinical reasons for changing opioids

- Lack of efficacy
 - Worsening of existing pain or underlying disease process
 - Developing of opioid tolerance
 - Inability to tolerate effective dose
 - Dose required to produce analgesia exceeds safe APAP maximum daily dose

Clinical reasons for changing opioids

- Development of intolerable side effects
 - Gastrointestinal - constipation, nausea/vomiting
 - CNS – sedation, somnolence, dysphoria, hallucinations, myoclonus
 - Cardiovascular – hypotension

Clinical reasons for changing opioids

- Change in patient status
 - Inability to swallow
 - Poor peripheral vascular status/poor absorption of transdermal medications
 - Requirement of high dose opioids not practically administered by oral, rectal, or transdermal routes

Clinical reasons for changing opioids

- Practical considerations
 - Availability in local pharmacies
 - Cost/what will insurance pay for
 - Amount of opioid needed
 - Route of administration
 - Problematic drug-drug interactions
 - Opiophobia
 - Fear that one or more opioids may be associated with death or addiction
eg. morphine

Switching from one opioid to another

- Oral to oral
- IV opioid to another IV opioid
- IV opioid to oral opioid
- Oral opioid to IV opioid
- Multiple opioids and routes to one opioid and route

Concepts of potency and equianalgesia

- Potency

- Power of medicinal agent to generate its desired outcome = dose required to produce a given effect.
- More potent agent is beneficial when limiting volume is an issue i.e. subq infusion or where number of units required/dose is excessive and inconvenient.
- Relative analgesic potency – ratio of doses to produce an equivalent degree of analgesia – basis for equianalgesia dose table.

Concepts of potency and equianalgesia

- Equianalgesia
 - Different doses of two opioids (at steady-state) that provide approximately the same pain relief.
 - An equianalgesic dose – a dose that yields roughly equivalent analgesia to the standard set in a given equianalgesic dose table.
 - Miscalculation of equianalgesic doses can lead to over-medication and toxicity or under-medication with unrelieved pain.

Clinical factors that may influence relative potency

- Major organ dysfunction may affect drug kinetics, active metabolites or pharmacodynamics
 - Renal insufficiency
 - Hepatic impairment
 - Adrenal insufficiency and hypothyroidism

Clinical factors that may influence relative potency

- Race

- Best characterized is variation in activity of CYP2D6 isoenzyme of the hepatic P450 system.
- Involved in metabolism of codeine, hydrocodone, oxycodone, tramadol, methadone, and fentanyl
- Activity in Caucasians > Asians

- Age

- Opioid potency may be higher in children <6 months and geriatric patients.
- Pharmacokinetic differences and pharmacodynamic sensitivities
- Lower doses may be required in younger and older patients.

Equianalgesic tables

- The first equianalgesic table was published almost 50 years ago to aid clinicians in converting from one opioid to another.
- Codified results of numerous relative potency studies
 - Much of the information in these tables derived from single dose studies.
 - Subjects either had acute post-op pain (day 1) or chronic cancer pain on relatively low opioid dose before the study.
 - Chosen population for study was unlikely to have clinically significant tolerance to analgesics or non-analgesic effects of study drugs.
 - May have limitations in applicability to repetitive administration

Equianalgesic tables

- Usually standardized to 10mg of parenteral morphine
- Not intended to provide recommended initiation doses for a given opioid or patient
- Simply a tool for determining an estimated equianalgesic dose when switching a patient from one opioid to another

An Equianalgesic Table

<u>PO/PR(mg)</u>	<u>Analgesic</u>	<u>SubQ/IV(mg)</u>
30	Hydrocodone	---
30	Morphine	10
7.5	Hydromorphone	1.5
20	Oxycodone	---
200	Codeine	---

Hydromorphone (HM)

- Standard equianalgesic tables indicate that the equianalgesic dose ratio between MS and HM is 7:1 for parenteral dosing and somewhere between 4:1 and 8:1 for oral dosing.
- Adjusted to a standard of MS 10mg IV, typical equianalgesic dose HM IV would be 1.5mg (~7:1 ratio).
- The disparity between parenteral and oral morphine to hydromorphone equivalents
 - Parenteral equivalents may have been derived from single-dose studies
 - Oral equivalents derived from multiple-dose studies

Hydromorphone (HM)

- More recent data suggest that these ratios differ depending on the direction of switch from one drug to the other
- In one study, MS:HM ratio for pts who switched from MS to HM was 5.33:1, ratio for pts who switched from HM to MS was 3.8:1
- A bidirectional difference in potency between MS and HM may apply to both po and IV dosing and may be independent of prior opioid exposure.
- Suggested a safe dose ratio of 5:1 for rotation from MS to HM and 3.7:1 for switch in opposite direction

Hydromorphone (HM)

- The equianalgesic ratio of IV HM and MS can change over time
 - In study of BMT patients, potency of HM relative to MS decreased from 7:1 on Day 7 to 3:1 by Day 13 post transplant.

Dunbar et al, 1996

Hydromorphone (HM)

- Based on published experiences of hydromorphone to morphine switches
 - The single-dose equianalgesic ratio is 1:7
 - The initial steady-state oral and parenteral equivalence is 1:5
 - Over time with long-term infusions, 1:3

Another Equianalgesic Table

<u>PO/PR(mg)</u>	<u>Analgesic</u>	<u>SubQ/IV(mg)</u>
15	Hydrocodone	---
15	Morphine	5
4	Hydromorphone	1.5
10	Oxycodone	---
100	Codeine	---

Methadone

- Use of methadone in opioid rotation has received a great deal of attention in recent years.
- Potency is much greater than anticipated from early studies.
- A significant relationship between the relative potency of methadone and the dose of the opioid taken at the time that methadone is administered
 - Explained by effects of d-isomer of methadone
 - An antagonist of NMDA receptor → reverse opioid tolerance and produce non-opioid analgesic effects
- Conventional equianalgesic dose ratios from single-dose studies don't apply to opioid rotation using methadone without substantial adjustment.

Conversion ratio of MS po to Methadone po

Daily MS po dose (mg)

Conversion ratio

< 100 mg

3:1

101 - 300 mg

5:1

301 - 600 mg

10:1

601 - 800 mg

12:1

801 - 1000 mg

15:1

> 1000 mg

20:1

Clinical concerns with equianalgesic tables

- Equivalents summed into a single number and placed into use assumes that the population in the study group for which the equivalents were derived and the population for which the equivalents will be applied are similar.
- Equianalgesic tables do not take into account individual differences in opioid metabolism and pharmacogenetics that influence opioid distribution and receptor dynamics.
- Equianalgesic tables assume normal organ function, similar age, and no drug interactions.
- Single numbers without a range for ratios give a false sense of precision.

Clinical concerns with equianalgesic tables

- Bidirectional differences are frequently ignored.
- Conservative ratios for one direction are not conservative when switching in the opposite direction.
- Equianalgesic tables are not meant to provide the initial recommended dose for a given opioid for a given individual
- Equianalgesic tables do provide a guideline for a safe dose in the majority of individuals given the circumstances for which tables were constructed.

Issues to consider before opioid rotation or route conversion

- What are the indications for rotation/conversion?
- Was the opioid given enough time to judge its efficacy before rotation?
- Can the goals of rotation be best achieved by using a different route of administration (conversion) rather than a different opioid?
- Are there any factors that would interfere or change the equianalgesic dose?

Issues to consider before opioid rotation or route conversion

- Can equianalgesia change with dose?
- Is the rotation taking place between opioids with different half-lives?
- Is the equianalgesic dose safe?
- Is the pain syndrome responsive to the new opioid?
- Has the patient been treated with opioids for a short period of time or chronically?

Issues to consider before opioid rotation or route conversion

- Incomplete cross-tolerance
 - The mechanism of action most commonly quoted to explain the perceived benefits of opioid rotation.
 - Analgesic tolerance = reduction in potency after repeated administration = need for higher doses over time to obtain same analgesic effect
 - Tolerance to side effects also seen with time (nausea/somnolence)

Issues to consider before opioid rotation or route conversion

- Incomplete cross-tolerance
 - Postulated as the mechanism whereby a patient remains tolerant to side effects but not analgesic effect of an opioid when rotating from one opioid to another.
 - Underlying mechanism may include preferential binding to different receptor subtypes or different receptor binding properties – difficult to explain at the cellular level.

Issues to consider before opioid rotation or route conversion

- Incomplete cross-tolerance
 - Dose reduction of 25-50% is often suggested after calculating the equianalgesic dose of new opioid based on the equianalgesic table.
 - The calculated equianalgesic dose may understate the actual potency of the new drug due to individual variation
 - How much to adjust based on clinical judgment.

Approach to opioid conversion/rotation

- A thorough assessment will assist clinician in determining severity and type of pain (i.e., worsening of same pain or development of new pain that may not be as responsive to opioid analgesics).
- Evaluation takes into consideration physiologic characteristics as well as impact of pain on patient's quality of life.

PQRSTU of pain assessment

- P Palliating or precipitating factors
- Q Quality of pain
- R Region and/or radiation
- S Severity
- T Temporal nature
- U Impact on “you”

5-step approach to opioid rotation

- Globally assess patient (PQRSTU) to determine if uncontrolled pain is from worsening of existing pain or development of new pain.
- Determine total daily usage of current opioids including all long-acting and breakthrough opioid doses.
- Decide which opioid analgesic will be used as new agent and consult a conversion table to arrive at proper dose of new opioid recognizing limitations of data.

5-step approach to opioid rotation

- Individualize dosage based on assessment information from first step and ensure access to adequate breakthrough medication.
- Patient follow-up and continued reassessment especially in first 7-14 days to fine-tune dosage of long-acting and short-acting opioids.

Clinical guidelines for opioid route conversion and rotation

- Rotation secondary to toxicity requires a dose 30-50% lower than the equivalent dose of the 2nd opioid due to incomplete analgesic cross-tolerance.
- Rotation secondary to uncontrolled pain requires equianalgesic doses.
- 30% of opioids may need an alternative route (nausea/mucositis).
- Before rotation due to toxicity, consider treating side effects, lowering opioid dose (pain controlled), and use of adjuvant analgesics.

Clinical guidelines for opioid route conversion and rotation

- Consider pharmacokinetic change with age, co-morbid conditions, gender, interacting medications, and organ failure in starting or titrating opioids.
- Opioids that are partial agonists have less analgesia per dose increment at higher doses than full agonists or opioids with high intrinsic efficacy (methadone) → equianalgesic ratios will change with dose.
- Rotation between short- and long-acting opioids must be done carefully to avoid withdrawal or overdosing.

Clinical guidelines for opioid route conversion and rotation

- Rotation in the setting of organ dysfunction is potentially disastrous despite recommended doses from equianalgesic tables.
- Opioids may worsen intestinal colic – consider decadron, glycopyrrolate, or octreotide for such pains.
- Opioid-induced toxicity takes time to resolve. Persistent toxicity after rotation may be due to slow clearance of 1st opioid and not the new opioid.
- Rotating to a new opioid before reaching steady-state of the first opioid is pharmacologically meaningless.

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But in practice, there is.

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Questions?

Thank you!

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