Opioids: Morphine, Hydromorphone, Fentanyl

Intraoperative teaching · CA-1

THE QUESTION

Where the evidence disagrees

This topic was selected because an evidence synthesis beats a textbook on it: the trials disagree, or the guidance has moved recently.

THE EVIDENCE

What each source contributes, and how strong it is

Study design first — a cohort and a randomised trial do not carry the same weight.

Design	Year	Journal	What it found
Other	1983	Clin Pharmacokinet	Fentanyl is 50 to 100 times as potent as morphine
Other	1983	Clin Pharmacokinet	The half-life on the reference card is not the number that predicts when your
Other	2012	Basic Clin Pharmacol Toxicol	These drugs differ at the effect site and not just at the syringe
Other	1986	Br Med J (Clin Res Ed)	Morphine's danger in renal impairment is not morphine but morphine-6-glucuroni
Other	2000	Clin Exp Pharmacol Physiol	Hydromorphone's principal metabolite, hydromorphone-3-glucuronide, carries no
Other	2011	Palliat Med	Equianalgesic tables are estimates rather than conversions

10 resolved citations behind this deck; every point above traces to one of them.

IN PRACTICE

What the cohorts and reviews add

6 findings, each on the slide that follows.

CLIN PHARMACOKINET 1983

Fentanyl is 50 to 100 times as potent as morphine

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CLIN PHARMACOKINET 1983

The half-life on the reference card is not the number that predicts when your

The half-life on the reference card is not the number that predicts when your patient will wake up: reported terminal half-lives for fentanyl range…

BASIC CLIN PHARMACOL TOXICOL 2012

These drugs differ at the effect site and not just at the syringe

These drugs differ at the effect site and not just at the syringe: pharmacokinetic-pharmacodynamic studies give fentanyl and its derivatives a…

BR MED J (CLIN RES ED) 1986

Morphine's danger in renal impairment is not morphine but morphine-6-glucuroni

Morphine's danger in renal impairment is not morphine but morphine-6-glucuronide, an active renally excreted metabolite: three patients with renal…

IN PRACTICE

Fentanyl is 50 to 100 times as potent as morphine

Other · Clin Pharmacokinet

Fentanyl is 50 to 100 times as potent as morphine, and the short duration you see after a single intravenous dose is redistribution-limited rather than clearance-limited, in the same way thiopentone is — which is why repeated or large doses stop being short-acting and can leave a patient with delayed recovery and prolonged respiratory depression.

Mather, Clin Pharmacokinet 1983 · PMID 6226471

IN PRACTICE

The half-life on the reference card is not the number that predicts when your

Other · Clin Pharmacokinet

The half-life on the reference card is not the number that predicts when your patient will wake up: reported terminal half-lives for fentanyl range from about 1.5 to 6 hours in healthy volunteers and up to 15 hours in geriatric patients, and comparing half-lives between opioids is not a rational way to choose one — effect-site concentration and context-sensitive half-time are.

Mather, Clin Pharmacokinet 1983 · PMID 6226471

IN PRACTICE

These drugs differ at the effect site and not just at the syringe

Other · Basic Clin Pharmacol Toxicol

These drugs differ at the effect site and not just at the syringe: pharmacokinetic-pharmacodynamic studies give fentanyl and its derivatives a blood-to-effect-site equilibration half-life of only 0.2 to 9 minutes, while morphine's analgesic time course is observed with a prolonged delay behind its plasma concentration — so a second dose of morphine given because the first one 'is not working yet' is a dose you will meet again later.

Ing Lorenzini et al., Basic Clin Pharmacol Toxicol 2012 · PMID 21995512

IN PRACTICE

Morphine's danger in renal impairment is not morphine but morphine-6-glucuroni

Other · Br Med J (Clin Res Ed)

Morphine's danger in renal impairment is not morphine but morphine-6-glucuronide, an active renally excreted metabolite: three patients with renal failure showed classical signs of morphine intoxication with prolonged respiratory depression while having no measurable morphine in plasma at all, and concentration-effect modelling in volunteers put morphine-6-glucuronide at four to eight times morphine's potency for miosis and for suppression of salivation.

Osborne et al., Br Med J (Clin Res Ed) 1986 · PMID 3087512

IN PRACTICE

Hydromorphone's principal metabolite, hydromorphone-3-glucuronide, carries no

Other · Clin Exp Pharmacol Physiol

Hydromorphone's principal metabolite, hydromorphone-3-glucuronide, carries no analgesic activity and is neuroexcitatory — allodynia, myoclonus and seizures on intracerebroventricular administration — and in anuric haemodialysis patients it accumulated more than twelvefold between treatments while hydromorphone itself barely accumulated at all, though dialysis removed the metabolite effectively.

Smith, Clin Exp Pharmacol Physiol 2000 · PMID 10874511

IN PRACTICE

Equianalgesic tables are estimates rather than conversions

Other · Palliat Med

Equianalgesic tables are estimates rather than conversions: the most consistently supported ratio is about 5 to 1 for oral morphine to oral hydromorphone, no large well-designed randomised trial underpins the tables in common use, and calculating a dose from one of them alone in a patient whose clinical status is changing is an oversimplification of pain management with real potential for harm.

Mercadante et al., Palliat Med 2011 · PMID 21708857

IN THE ROOM

What this changes about the next case

Colour is the strength of the evidence behind each step, not the urgency.

1. **1**
   Fentanyl is 50 to 100 times as potent as morphine, and the short duration you see after a single intravenous dose is redistribution-limited rather than clearance-limited, in the same way thiopentone is — which is why repeated or large doses stop being short-acting and can leave a patient with delayed recovery and prolonged respiratory depression.
2. **2**
   The half-life on the reference card is not the number that predicts when your patient will wake up: reported terminal half-lives for fentanyl range from about 1.5 to 6 hours in healthy volunteers and up to 15 hours in geriatric patients, and comparing half-lives between opioids is not a rational way to choose one — effect-site concentration and context-sensitive half-time are.

3 **3**

These drugs differ at the effect site and not just at the syringe: pharmacokinetic-pharmacodynamic studies give fentanyl and its derivatives a blood-to-effect-site equilibration half-life of only 0.2 to 9 minutes, while morphine's analgesic time course is observed with a prolonged delay behind its plasma concentration — so a second dose of morphine given because the first one 'is not working yet' is a dose you will meet again later.

4 **4**

Morphine's danger in renal impairment is not morphine but morphine-6-glucuronide, an active renally excreted metabolite: three patients with renal failure showed classical signs of morphine intoxication with prolonged respiratory depression while having no measurable morphine in plasma at all, and concentration-effect modelling in volunteers put morphine-6-glucuronide at four to eight times morphine's potency for miosis and for suppression of salivation.

5 **5**

Hydromorphone's principal metabolite, hydromorphone-3-glucuronide, carries no analgesic activity and is neuroexcitatory — allodynia, myoclonus and seizures on intracerebroventricular administration — and in anuric haemodialysis patients it accumulated more than twelvefold between treatments while hydromorphone itself barely accumulated at all, though dialysis removed the metabolite effectively.

KEY TAKEAWAYS

What to carry into the next case

> **Fentanyl is 50 to 100 times as potent as morphine**
> Clin Pharmacokinet 1983

> **The half-life on the reference card is not the number that predicts when your**
> Clin Pharmacokinet 1983

> **These drugs differ at the effect site and not just at the syringe**
> Basic Clin Pharmacol Toxicol 2012

> **Morphine's danger in renal impairment is not morphine but morphine-6-glucuroni**
> Br Med J (Clin Res Ed) 1986

Fentanyl is fast on and, after one dose, fast off because it redistributes rather than because it is cleared; morphine is slow on and, in a kidney that cannot excrete morphine-6-glucuronide, slow off in a way that can stop a patient breathing hours after the dose looked fine.

QUESTIONS I'LL ASK YOU IN THE ROOM

1. You gave fentanyl 45 minutes ago and she is comfortable. Is that dose gone, or is it just somewhere else in her?
2. What does a creatinine of 2.4 change about this choice — and which molecule are you actually worried about?
3. You want to switch her to hydromorphone. What ratio are you using, and where did that number come from?
4. If she becomes obtunded at 3 a.m., which drug did it, and why then rather than now?

ORAL BOARDS STEM

> *A 71-year-old woman with a creatinine of 2.4 mg/dL has just had a hip hemiarthroplasty under general anaesthesia. She is comfortable in recovery on the fentanyl you gave intraoperatively, but she will need something that lasts for the ward. The examiner asks which of morphine, hydromorphone and fentanyl you would choose, how you would convert from what she has already had, and what specifically you are worried about at three o'clock tomorrow morning.*

Fentanyl is fast on and, after one dose, fast off because it redistributes rather than because it is cleared; morphine is slow on and, in a kidney that cannot excrete morphine-6-glucuronide, slow off in a way that can stop a patient breathing hours after the dose looked fine.

SOURCES

[1] Mather, Clin Pharmacokinet 1983 · PMID 6226471
[2] Scholz et al., Clin Pharmacokinet 1996 · PMID 8896944
[3] Ing Lorenzini et al., Basic Clin Pharmacol Toxicol 2012 · PMID 21995512
[4] Osborne et al., Br Med J (Clin Res Ed) 1986 · PMID 3087512
[5] Westerling et al., Ther Drug Monit 1995 · PMID 7624926
[6] Smith, Clin Exp Pharmacol Physiol 2000 · PMID 10874511
[7] Davison et al., J Opioid Manag 2008 · PMID 19192761
[8] Mercadante et al., Palliat Med 2011 · PMID 21708857
[9] Treillet et al., J Pain Res 2018 · PMID 30464578
[10] Patanwala et al., Ann Pharmacother 2007 · PMID 17299011