Association for Paediatric Palliative Medicine

6th APPM Formulary 2024: New Opioid Ratios

The 6th APPM formulary includes new recommended dosing regimens for opioid naïve babies and children as well as new recommended opioid potency ratios for converting between routes and between morphine and diamorphine.

This briefing paper outlines the rational for the new recommendations and the supporting evidence base.

What are the "drugs used differently" in paediatric palliative care?

Some drugs are used differently in paediatric palliative care for a variety of reasons. Drugs are more frequently administer drugs by alternative routes including subcutaneous infusions, buccal, intranasal or sublingual routes. Drugs are often converted to different routes during a course of treatment. Drugs are used for different indications compared with other areas of medicine including using opioids for palliation of dyspnoea and antipsychotics for their anti-emetic properties. The paediatric palliative care patient population is also different. Our patients are often sicker and with multiple co-morbities. Our patients are frequently atypical in terms of body weight and/or composition for age. Polypharmacy is common. Our patients are more frequently being treated in non-hospital settings.

Why are APPM 2024 recommended doses for morphine and diamorphine different to the British National Formulary for Children?

Important new evidence has been published since the monographs for morphine and diamorphine in the British National Formulary for Children (BNFc) (1) were last updated. It is possible that when these monographs are updated the BNFc -recommended potency ratios will also change. However, as the new evidence is of greatest relevance to paediatric palliative care, it is possible that the editors of the BNFc, which relates primarily to general paediatrics, may not consider the evidence of sufficient relevance for their target population.

The BNFc 2023-24 dose recommendations for morphine and diamorphine include a number of important inconsistencies when viewed from the perspective of how these drugs are used in paediatric palliative care. These include subcutaneous morphine bolus doses up to twice the oral dose in the 6 – 11 month age range, and different dosing frequencies for oral versus intravenous/subcutaneous bolus morphine in the 3 – 5 month age range. An editorial decision was therefore taken to not to adopt the BNFc dose recommendations for the 6th APPM formulary reverting instead to a "back to basics" approach.

Why are the APPM 2024 recommendations for morphine and diamorphine different to the Adult Palliative Care Formulary?

Important new evidence has been published since the monographs for morphine and diamorphine in the Adult Palliative Care Formulary (2) were last updated. It is possible that when these monographs are updated, the adult PCF recommended potency ratios will also change. As the new evidence is of greatest relevance to paediatric palliative care, it is possible that the editors of the adult PCF may not consider the evidence of sufficient relevance for their target population.

What do we already know about morphine pharmacokinetics in children?

Morphine and diamorphine are important drugs that are frequently used differently in paediatric palliative care. However, the primary research evidence to support dosing recommendations is sparse. The greatest experience and evidence in babies is with intravenous morphine in the post-operative and intensive care settings. There is relatively more published evidence for oral morphine in palliative care in older children and adults.

Established evidence suggests that oral absorption of morphine is more variable, and may be higher in neonates. Volume of distribution is also higher in preterm babies and neonates, particularly during days 2 – 5 of life. Morphine is converted to active metabolites in the liver, and then excreted by the kidneys. Maturation to adult pharmacokinetics occurs by approximately 6 months of age. Clearance of morphine may be higher in some younger children. Diamorphine is a pro-drug which is converted to morphine by serum esterases (3).

What new evidence is available?

The new edition of the APPM formulary also takes into account important new evidence derived from two independent systematic reviews and a pharmacodynamic modelling study (3–5). This evidence is outlined in the new approximate equianalgesic ratios for morphine and diamorphine in the table.

From	To	Ratio
Oral morphine (3–5)	IV/SC morphine	3:1
IV/SC morphine (4,5)	IV/SC diamorphine	2:1
IV/SC morphine (4,5)	Intranasal diamorphine	1:1

APPM dosing recommendations for morphine and diamorphine are informed by the established and new evidence. Dose recommendations for oral and bolus dosing in younger children have been extrapolated from infusion doses because these recommendations have remained relatively static and can be traced back to primary research, providing the strongest evidence base. We recognise that equianalgesic data is derived largely from single doses, and is therefore likely to underestimate

potency relative to infusions. For older children, greater emphasis has been placed on oral dosing evidence as the research base is stronger.

How has the APPM decided on the recommended starting doses for morphine and diamorphine in the new formulary?

The recommended starting doses for morphine and diamorphine in the new formulary are derived as far as possible from primary evidence. In babies and younger children, the strongest evidence base is from neonatal and paediatric intensive care and surgery. In older children there is also some primary evidence for enteral dosing. Whilst these recommendations are mainly for acute rather than chronic pain, they are a safe and sensible starting point. Dose recommendations for these routes and indications have not significantly changed over time further suggesting that they are appropriate.

The APPM recommendations for other routes ensure a consistent dosing ratio between oral and intravenous or subcutaneous routes and between intermittent bolus doses and infusions, recognising the way morphine and diamorphine are used differently in paediatric palliative care.

Why are the potency ratios used to derive the new starting doses different to the potency ratio for converting different routes?

The available evidence means that slightly different equianalgesic ratios for oral: intravenous/subcutaneous morphine have been used to derive dose recommendations for opioid naïve patients. However, once patients are established on morphine, an oral: intravenous subcutaneous ratio of 3:1 should be used for in all patients.

Potency ratios used to derive starting doses take account of known differences in pharmacokinetics and pharmacodynamics of morphine and diamorphine in babies and younger children. These differences are less likely to be relevant once a baby or child has been commenced on regular morphine or diamorphine. Therefore, for safety and simplicity the APPM recommends using the same potency ratios for babies and children of all ages when converting between routes or drugs in patients already established on regular morphine or diamorphine.

Why did APPM update both diamorphine and morphine when the newest publications relate to diamorphine?

Diamorphine is a pro-drug which is converted to morphine by serum esterases (3–5). The newest publications include important information regarding both morphine and diamorphine.

We have always used a potency ratio of 2:1 when converting oral to IV/SC morphine and not had any problems, why should we change?

The APPM can only make recommendations based on the available evidence and peer reviewed nationally and internationally by appropriate subject matter experts. It is up to individual practitioners to decide whether to follow these recommendations. Using the previously established potency ratio of oral morphine: iv morphine 2:1, may result in over-dosing when converting from enteral to intravenous or subcutaneous routes, and under-dosing when converting from intravenous or subcutaneous to enteral routes.

What are other paediatric teams and services doing nationally and internationally?

A potency ratio of 3:1 for oral: intravenous or subcutaneous morphine has been well established internationally for several years. Some units in the UK were also using this ratio before the publication of the APPM 2024 formulary.

Should we also be using different potency ratios for intravenous versus subcutaneous morphine and diamorphine?

There is some unpublished evidence, primarily drug company data on file, that bioavailability in adults may be slightly lower for subcutaneous versus intravenous administration of morphine. However, at present the APPM Formulary team is of the opinion that there is as yet, insufficient evidence to make a recommendation for a different potency ratio for subcutaneous versus intravenous morphine in our population. The APPM formulary currently assumes 100% bioavailability for both intravenous and subcutaneous routes, recognising that this is likely to be safer, and that subsequent doses can be titrated according to response.

References

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3. Thigpen JC, Odle BL, Harirforoosh S. Opioids: A Review of Pharmacokinetics and Pharmacodynamics in Neonates, Infants, and Children. Eur J Drug Metab Pharmacokinet. 2019 Oct;44(5):591–609.

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