Pediatric Anesthesia

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Journal:	*Pediatric Anesthesia*
Manuscript ID	PAN-2021-0452.R2
Wiley - Manuscript type:	Educational Review
Date Submitted by the Author:	19-Jan-2022
Complete List of Authors:	Morse, James; University of Auckland, Anaesthesiology Anderson, Brian; University of Auckland, Dept of Anaesthesiology Gastine, Silk; University College London Institute of Child Health, Department of Pharmaceutics Wong, Ian; University College London Institute of Child Health, Department of Pharmaceutics Standing, Joseph; University College London Institute of Child Health, Department of Pharmaceutics
Key Words:	pharmacokinetics < Drugs, chronic < Pain, opioids < Pain, pharmacodynamics < Drugs

Pharmacokinetic modelling and simulation to understand diamorphine dose-response in neonates, children and adolescents

James D Morse [1], Brian J Anderson [2], Silke Gastine [3], Ian CK Wong [4] AND Joseph F Standing [3]

1. Department of Pharmacology & Clinical Pharmacology, Auckland University, Park Road, Auckland 1023, New Zealand
2. Department of Anaesthesiology, University of Auckland, Park Road, Auckland 1023, New Zealand
3. Infection, Immunity, and Inflammation, Great Ormond Street Institute of Child Health, University College London, London, UK
4. Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Correspondence: Prof B.J. Anderson, Department of Anesthesiology, University of Auckland, Park Road, Auckland 1023, New Zealand; Ph +64-9-3074903; Fax +64-9-3078986; Email: briana@adhb.govt.nz

Key Words: Analgesia, opioids, diacetylmorphine, heroin, children, equianalgesia, pharmacokinetics

Short Title: diamorphine in children

Article category: Pharmacokinetic Review

ORCID

James D Morse; Orcid ID https://**orcid**.org/0000-0001-7500-0062

Brian J Anderson; Orcid ID https://**orcid**.org/0000-0002-2826-3019

Ian Wong; Orcid ID https://**orcid**.org/0000-0001-8242-0014

Joseph Standing; Orcid ID https://**orcid**.org/0000-0002-4561-7173

Abstract

Pharmacokinetic-pharmacodynamic modelling and simulation can facilitate understanding and prediction of exposure-response relationships in children with acute or chronic pain. The pharmacokinetics of diamorphine (diacetylmorphine, heroin), a strong opioid, remain poorly quantified in children and dose is often guided by clinical acumen. This tutorial demonstrates how a model to describe intranasal and intravenous diamorphine pharmacokinetics can be fashioned from a model for diamorphine disposition in adults and a model describing morphine disposition in children. Allometric scaling and maturation models were applied to clearances and volumes to account for differences in size and age between children and adults. The utility of modelling and simulation to gain insight into the analgesic exposure-response relationship is demonstrated.

The model explains reported observations, can be used for interrogation, interpolated to determine equianalgesia and inform future clinical studies. Simulation was used to illustrate how diamorphine is rapidly metabolized to morphine via its active metabolite 6-monoacetylmorphine, which mediates an early dopaminergic response accountable for early euphoria. Morphine formation is then responsible for the slower, prolonged analgesic response. Time-concentration profiles of diamorphine and its metabolites reflected disposition changes with age and were used to describe intravenous and intranasal dosing regimens. These indicated that morphine exposure in children after intranasal diamorphine 0.1 $mg.kg^{-1}$ was similar to that after intranasal diamorphine 5 mg in adults. A target concentration of morphine 30 $\mu g.L^{-1}$ can be achieved by a diamorphine intravenous infusion in neonates 14 $\mu g.kg^{-1}.h^{-1}$, in a 5-year-old child 42 $\mu g.kg^{-1}.h^{-1}$ and in an 15 year-old-adolescent 33 $\mu g.kg^{-1}.h^{-1}$.

Introduction

Diamorphine (diacetylmorphine, heroin) is a strong opioid with rapid onset of effect when given by intravenous, intramuscular and transmucosal routes. It is used for burns and fracture reduction in the acute setting and in palliative care for breakthrough pain in children with life-limiting conditions.[1] Neonatal use is historical and related to management of neonatal abstinence syndrome. Drug use for these indications is limited to the United Kingdom [2], although several European countries continue to use the drug for opioid addiction treatment in adults.[3]

Diamorphine can be considered a prodrug of morphine, with acetylation at two sites of the pharmacophore.[4] It passes through the blood-brain-barrier much faster than morphine [5, 6] due to its higher lipophilicity, with consequent earlier onset analgesia. Metabolism of diamorphine occurs via the active metabolite, 6-mono-acetylmorphine (maximum effect within 5–10 minutes). A more prolonged action is attributable to subsequent metabolism to the major active metabolite, morphine (maximum effect within 1 hour).[7-10]

The lipophilic character of diamorphine also makes it suitable for intranasal administration. Mucosal absorption is rapid with a low first pass metabolism, contributing to the quick onset of analgesia.[5] Despite use in the acute and palliative care settings, the time course of intranasal and intravenous diamorphine concentration profile and sequential effects related to its active metabolites in children are poorly described. Both intranasal and intravenous diamorphine dose are historical, empiric quantities that were guided by clinical acumen and equianalgesic estimates in adults using morphine as the index opioid. Pharmacokinetic-pharmacodynamic modeling and its clinical translation has proven useful for understanding drug disposition and effect in pediatric anesthesia.[11, 12] To demonstrate how modelling and simulation can be leveraged to examine the analgesic's exposure-response relationship, this tutorial demonstrates how a model to describe intranasal diamorphine pharmacokinetics can be fashioned from a model for diamorphine disposition in adults and a model describing morphine disposition in children. This model can be used to inform future clinical studies, interpolated to determine equianalgesia, describe

the time course of diamorphine disposition and consequent effect and inform age-appropriate dosing of intranasal and intravenous diamorphine in children.

What are the parameters in a pharmacokinetic model?

Pharmacokinetic models are mathematical equations that describe the amount of drug in the body over time. A plasma time-drug concentration relationship may be commonly expressed as a one compartment model:

$$Concentration = \frac{Dose \times F}{V} \times e^{time \times {}^{CL}/_{V}}$$

Parameters in this model are clearance (CL), volume of distribution (V) and bioavailability (F). A model such as that for diamorphine will require a number of different clearance parameter estimates such as morphine metabolite formation clearance (e.g., CL to morphine 6-glucuonide, CL2M6G) and elimination clearance of this metabolite (e.g., CLM6G). While volume of distribution (Vd) might be termed for the parent drug in a one compartment model, the diamorphine model requires a volume for the parent drug (V_{DIAM}) and volumes for metabolites; 6-mono-acetylmorphine V_{6MAM}, morphine V_{MOR}, morphine 3-glucuronide V_{M3G}, morphine 6-glucuronide V_{M6G} (**Figure 1**).

In order to account for the delay between concentration and analgesic effect an additional compartment known as the effect compartment is linked to plasma using a rate constant (keo). This rate constant is commonly expressed as a half-life ($T_{1/2}$keo) e.g.,

$$T{}_{1}/_{2}keo_{MORPH} = {}^{Ln(2)}/_{keo_{MORPH}}$$

It is this effect compartment concentration that is linked to pharmacodynamic response (e.g., analgesia)

Compartment models dominate anesthetic pharmacology literature. Drug is administered into and eliminated from a central compartment. This central compartment may be connected to peripheral compartments. A single compartment is often insufficient to characterize the time-concentration profile

and further compartments are required. Drug is administered into a central compartment (V1) and redistributes to peripheral compartments (V2, V3). Drug is eliminated from the central compartment only.

An alternative parameterization for a two-compartment model is to use a central volume and three rate constants (k_{10}, k_{12}, k_{21}) that describe drug distribution between compartments. Another common method is to use parameters such as two volumes (V1, V2) and two clearances (CL, Q). The parameter, Q, is the intercompartment clearance and volume of distribution at steady state (Vss) is the sum of V1 and V2.

Non-compartment analyses have also been used to determine diamorphine pharmacokinetics by interrogating the time-concentration profile. Algebraic equations are used to estimate PK descriptors from the graphical profile such as area under the time-concentration curve (AUC), volume of distribution (V), half-life ($T_{1/2}$), time to maximum effect (T_{MAX}), and concentration at maximum effect (C_{MAX}). The trapezoidal rule, for example, may be used to integrate the area under the concentration time-curve.

The use of population modelling has improved parameter and variability estimation with identification of covariates contributing to variability.[13, 14] A one-compartment model is better served using clearance (CL), volume (V) and absorption parameters (absorption half-time, T_{ABS}, and relative bioavailability, F). rather than confounded parameters (T_{MAX}, C_{MAX}, $T_{1/2}$). Descriptors from non-compartment analyses can be mathematically converted into these one-compartment parameters. Absorption parameters are often dependent on formulation or route of administration and their use prevents the misconception that clearance and volume of a drug change with formulation dose or route.

Bioavailability, exposure and equianalgesia

Aspects of diamorphine pharmacokinetics are often expressed in terms of equianalgesia, exposure and bioavailability. While bioavailability is a parameter, exposure and equianalgesia are descriptive statistics that can be approximated if pharmacokinetic-pharmacodynamic parameters are known.

Bioavailability

Bioavailability refers to the fraction (F) of drug that reaches the systemic circulation and can contribute to effect. Drugs given intravenously commonly have a bioavailability of 100% (F=1). Drugs given by routes other than intravenous generally have lower bioavailability because of processes such as first pass metabolism. Relative bioavailability of enteral drugs is the ratio of the area under the plasma drug concentration curve over a specified time (AUC) and confounded by dose. The ideal specified time is until infinity ($AUC_{0-\infty}$) but time is often truncated to the duration of time used for pharmacokinetic study (e.g., 6 hours, AUC_{0-6}). The relative bioavailability for morphine in adults was estimated to be 23.9% after oral solution and 18.7% after a buccal tablet.[15] Morphine elixir given to children had relative bioavailability of 29%.[10]

The relative bioavailability of intranasal diamorphine is more complex. The drug has two active metabolites, 6-mono-acetylmorphine and that xenobiotic's metabolite, morphine (**Figure 1**).[16] Intranasal diamorphine in children 3-13 years contributed a morphine AUC that was half that given by the intravenous route.[17] However, that relative bioavailability comprises two parts; the relative bioavailability of nasal diamorphine (F_{IN_DIAM}) compared to intravenous administration (F_{IV_DIAM} -= 1) and the conversion of the systemic diamorphine to morphine (Conversion Factor $_{DIAM-MOR}$).

Exposure

The area under the time-concentration curve (AUC) is a measure of exposure. This 'exposure' is dependent on dose and clearance. Clearance changes with age and exposure reflects these age-related changes. Exposure has been used as a measure of effect and for determination of pediatric dose comparative to adult. When used as a measure of effect, 'exposure' may also mean plasma drug concentration. The exposure-effect relationship has also been used to describe concentration-effect relationships such as those described by the Hill equation.[18] This creates confusion when the exposure is used in this context because analgesic drug effect often relates to concentration rather than AUC. Exposure is also a word used to describe previous use of a drug by an individual, particularly when related to opioids.

Equianalgesia

Equianalgesic doses, opioid dose equivalence, analgesic potency tables, opioid conversion guides and opioid dose comparisons guide clinical decision making when switching opioids, with the assurance of similar pain relief.[19] Most guides use morphine as the index opioid against which other opioids are compared. Similar equianalgesic tables also exist for different formulations of morphine. An oral-parenteral (intravenous or intramuscular) potency ratio of 1 to 3 is commonly used, based on first pass metabolism.[20] However, this ratio ranges from 1:2.5 to as high as 1:6, [20-23] and misinterpretation of this ratio variability has resulted in the referenced relative bioavailability of oral morphine formulations to range from 20% to 50%.[20-23]

Most equianalgesic ratios were determined from clinical medicine. It is the dose of a drug that produces the same degree of analgesia as another drug (e.g., morphine, the metabolite of diamorphine). Dose calculations are determined in randomized crossover studies or observational case studies on individuals stabilized with opioids long-term, but can be made with acute dose administrations in patients with little or no previous exposure to the opioids.[24] Equipotency is often used synonymously with equianalgesia. However, potency is defined more as a dose or concentration required to produce a given effect. For example, the concentration at which patients achieve 50% of maximum effect (C_{50}) is used to describe potency among opioids with similar concentration-effect relationships. Potency differs widely among opioids, and among individuals under varying conditions.[25] It is claimed that morphine and diamorphine have similar actions and adverse effects when given orally, although the latter is about 1.5-2 times more potent.[20] Use of potency in this context of dose rather than concentration ignores the relative bioavailability of these two oral formulations, time course of effect, active metabolites (e.g., diamorphine has 6-mono-acetylmorphine, morphine and morphine 6-glucuronide), and pharmacokinetic-pharmacodynamic variability.

Modelling morphine oral bioavailability and its relationship to equianalgesia descriptions

Bioavailability (F) determines dose equivalence, but differs between routes of administration

Bioavailability is usually expressed relative to an intravenous formulation that is assumed to have F=1. The term relative bioavailability is often used to compare an enteral formulation to intravenous. The clinical determination of equianalgesia is difficult because of the nature of pain (e.g., temporal variation and time of assessment, subjective quality) and comparator drugs may be confounded by bioavailability, which is also associated with its own parameter variability.

We use simulation to demonstrate the impact of the relative bioavailability of oral morphine in adults on exposure. Morphine pharmacokinetics are well described in humans [26, 27] and can be used to simulate average concentration (C_{AVG}), concentration in the effect compartment at steady state (Ce_{SS}) and exposure (AUC_{0-24}) when given by both oral (10 mg 4 hourly) and by intravenous (2 mg 2 hourly) routes for 24 hours in a 70 kg individual. The influence of bioavailability (F=0.3 or 0.5) on AUC_{0-24}, C_{AVG} and Ce_{SS} is demonstrated in **Table 1.** These variables change in a dose proportional manner), as expected with linear kinetics.

Empiric studies have taught us that a morphine concentration range (10-20 $\mu g.L^{-1}$) in the opioid naive has effective analgesia [28] without associated adverse effects such as the respiratory depression observed with higher concentrations [29] or postoperative nausea and vomiting reported with higher doses.[30] There is also large between subject variability associated with both pharmacokinetic and pharmacodynamic parameters.[31 32] Consequently analgesic concentrations predicted by the simulation of between 10.1 and 14.1 $\mu g.L^{-1}$ or 14.1 and 17.6 $\mu g.L^{-1}$ will have similar effect (i.e., that associated with effective analgesia, 10-20 $\mu g.L^{-1}$). This observation, determined by simulation (**Table 1**), aligns with clinical equianalgesic estimates that range from 1:2.5 to as high as 1:6 [20-23]. Morphine relative bioavailability is a better pharmacokinetic parameter to use for dose estimation than the clinical measure of equianalgesia dependent on route of administration.

A pharmacokinetic model for intranasal diamorphine

A model to describe diamorphine pharmacokinetics was fashioned using a published model for diamorphine and metabolite (6-MAM, morphine) disposition in adults [9] and a model describing

morphine and its metabolites (M6G, M3G) disposition in children.[26] Additional information was sought from the literature to explain missing parameters. Size was accounted using allometric biological scaling laws.[33]

Parameters for this pharmacokinetic sequential model for diamorphine, 6-mono-acetylmorphine and morphine in adults given diamorphine by both inhalational and intravenous routes [9] were scaled using allometry (size) [34] and maturation models (age),[35] consistent with advice from the European Medicines Agency.[36] (**Supplementary material**: model for intranasal diamorphine in children). The formation clearance of 6-mono-acetylmorphine and of morphine is by plasma and erythrocyte butyryl-cholinesterases and carboxylesterases (hepatic and brain).[8] These are mature at birth and no maturation function was required. Morphine metabolites are cleared by renal function and a model describing the maturation of renal function was used to characterize clearance of the morphine metabolites (M6G, M3G). A scaling factor of 0.74 (F_{VENT}) was used to account for reduced morphine clearance in premature neonates where positive pressure ventilation caused less hepatic blood flow.[37, 38]

Morphine exerts its effects at a site distinct to the plasma. This was described using an additional compartment known as the effect compartment. This plasma-linked effect compartment was added to quantify the delay between morphine concentration in the plasma and that in the effect compartment. An equilibration half-time ($T_{1/2}keo_{MOR}$) for a morphine effect compartment was assumed 16 minutes and scaled using the allometric exponent of ¼ for size.[39, 40] The equilibration half-time for the diamorphine active metabolite, 6-mono-acetylmorphine, ($T_{1/2}keo_{6MAM}$) was unknown but assumed 1 min (**Figure 1**). The relative bioavailability of inhaled diamorphine was estimated to be 53% (95% CI 43.7, 62.3) in adults [10] and the intranasal bioavailability was assumed to be 50% ($F_{DIAM}IN = 0.5$). This estimate was supported by adult data where an Intranasal diamorphine bioavailability was reported half that when given by the intramuscular route in adults.[41, 42]

Usefulness of the Pharmacokinetic Model

Estimation of unknown parameters

A model is not a static entity. New information that is published can be used to improve a model in order to better represent reality. Parameters can be altered so the model better represents observations. "What if" scenarios can be simulated to see what might happen if a parameter is altered by an external factor. Similarly, parameters can be explored to find a model prediction that best fits with results reported by others.

Intranasal diamorphine in children 3-13 years contributed a morphine AUC that was half that given by the intravenous route.[17] However, that relative bioavailability comprises two parts; the relative bioavailability of nasal diamorphine (F_{IN_DIAM}) compared to intravenous ($F_{IV\_DIAM} = 1$) administration and the conversion of the systemic diamorphine to morphine (Conversion Factor $_{DIAM\text{-}MOR}$). The bioavailability of the systemic diamorphine to morphine (Conversion Factor $_{DIAM\text{-}MOR}$) was quantified using modelling to determine comparative morphine AUC when the model for morphine alone was simulated. The bioavailability of the systemic diamorphine to morphine was estimated at 200% (Conversion Factor $_{DIAM\text{-}MOR} = 2$) under the assumption that a dose of both intravenous morphine and intravenous diamorphine generated a similar morphine AUC.

The model was used to estimate equianalgesia for routes of administration, based on relative intranasal bioavailability and the Conversion Factor $_{DIAM\text{-}MOR}$. We estimate equianalgesic ratios of intravenous morphine:diamorphine 2:1, intravenous morphine:intranasal diamorphine 1;1 and oral morphine:intranasal diamorphine of 1:3.

Understanding time-concentration profiles of drug and metabolite

Time concentration profiles for intravenous and intranasal diamorphine and its metabolites were simulated using differential equations in Berkeley Madonna™ modelling and simulation software (Robert Macey and George Oster of the University of California, Berkeley, USA). The concentration of the active metabolite, 6-mono-acetylmorphine, peaks rapidly, followed by a sustained exposure to morphine. The

concentration of morphine at the effect site is protracted compared with that in the plasma. Typical time-concentration profiles for a 2-day term neonate, 5-year-old child and a 15-year-old adolescent given intranasal diacetylmorphine infusion are shown in **Figure 2.** Typical time-concentration profiles for a 2-day term neonate, 5-year-old child and a 15-year-old adolescent given intravenous diacetylmorphine infusion are shown in **Figure 3.**

The model predicted similar diamorphine and metabolite time courses and concentrations to those described in adults.[7] The model also predicted morphine concentrations similar to those observed in 26 premature neonates (26-38 weeks gestation) given diamorphine 50 $\mu g.kg^{-1}$ followed by an intravenous infusion of 15 $\mu g.kg^{-1}.h^{-1}$. The mean observed steady state morphine concentration was 62.5 (SD 22.8) µg/L in that cohort.[43] Simulated drug disposition in a typical child (8 years, 28 kg) given diamorphine 0.1 $mg.kg^{-1}$ by intravenous and intranasal diamorphine was similar to that reported in children 3-13 years observed over 60 min.[17]

Impressions about the nature of diamorphine analgesia

Figures 2 and 3 derived from the model show both parent and metabolite concentration changes that can be related to physiological consequences. Diamorphine is absorbed nasally. The parent drug rapidly crosses the blood-brain-barrier [6] where it is deacetylated by esterases to the active metabolite, 6-mono-acetylmorphine (6-MAM). Observed diamorphine concentrations in plasma are brief and some investigators had difficulty even detecting this parent drug in plasma.[44] The metabolite, 6-MAM mediates an early dopamine response responsible for the initial euphoria. Morphine administration alone creates morphine CSF concentrations similar to those observed shortly after 6-MAM injection, and does not increase CSF dopamine.[16] Morphine is responsible for the slower, prolonged analgesic response.[7] The predicted time-concentration profiles of morphine metabolites, morphine-3-gluronide and morphine-6-glucuronide, is more informative than ratios of these two drugs presented at set time points. Morphine-6-glucuronide concentrations can be correlated with effect relationships to gain a better understanding of

analgesia and respiratory depression.[45] The model provides a mechanistic understanding of the drug effect.

Drug disposition differs in neonates, children and adults. Morphine clearance is immature in neonates, causing higher morphine concentrations and prolonged duration of action (bigger AUC) after doses similar to adults. Metabolism of diamorphine to 6-MAM is not immature; esterase metabolism is mature at birth. Consequently, morphine formation is quicker. The C_{MAX} is not necessarily bigger because that descriptive parameter is determined partially by morphine metabolism and that is slower. Hepatic clearance maturation is usually mature within the first few years of life.[46, 47] Children have bigger clearance estimates than adults (scaled per kilogram). When an adult dose (per kilogram) is administered to a child, then concentrations and morphine AUC are less than observed in adults. These physiological changes for clearance are reflected in the proposed model-based dosing recommendations.

Age-related dosing

The single intranasal dose required to give the same $AUC_{0\text{-}10}$ (70 $\mu g.L^{-1}.h$ that is achieved after 5 mg intranasal diamorphine in a typical adult; 40 years, 70 kg) for these typical individuals is shown in **Table 2**. Simulation was used to estimate intravenous loading and maintenance doses required to achieve a morphine plasma concentration of 30 $\mu g.L^{-1}$ are shown in **Table 2**. This plasma steady-state morphine concentration is that achieved in a typical adult given 30 $\mu g.kg^{-1}.h^{-1}$.

Single dose diamorphine for different ages was calculated using exposure; AUC was similar in all age groups. This methodology is favored by drug regulatory bodies [36] and is commonly used to determine dose in children e.g., brivaracetam [48], diclofenac [49]. Area under the curve (AUC) is directly correlated with the average concentration over the exposure period. Use of another non-compartment descriptive parameter (C_{MAX}) may assist understanding of the shape of the AUC and when concentrations are higher than those associated with some degree of analgesia. Intranasal diamorphine has a lower C_{MAX} and a more flattened morphine AUC compared to that following intravenous administration and we might anticipate longer duration of a lesser degree of analgesia with intranasal administration.

The degree of analgesia, however, often correlates better with concentration than AUC. Concentration in the effect compartment is commonly used to describe analgesic pharmacodynamics. A target concentration strategy [50] that better reflects this concentration-response relationship can be used to determine intravenous infusion or regular intranasal dosing. Consequently intravenous infusion dose was targeted to a morphine steady-state concentration of 30 $\mu g.L^{-1}$. This is a concentration commonly used for acute adult pain but greater than that commonly targeted in children (10-20 $\mu g.L^{-1}$). It should not be used in the opioid naïve.

Application to palliative care

Diamorphine dosing in children is poorly described. While the estimated intranasal single dose in a child (0.098 $mg.kg^{-1}$) was similar to that used for acute pain in the Emergency Room (0.1 $mg.kg^{-1}$) for bone fracture reduction [51, 52], but that dose may not be applicable to children requiring an opioid for palliative care. The use of opioids for chronic pain remains contentious.[53] The dosing recommendations presented in this work serve as an initial guide only. Pain is a complex subjective phenomenon that changes with time. Dose may differ between pain types or in those opioid tolerant therefore titration of dose to clinical effect is important. The intranasal dose predicted in infants and neonates is speculative because nasal anatomy is immature and growing.

The dose needed to treat breakthrough pain or opioid conversion also depends on the concurrent dose of background opioid. Current clinical guidelines offer limited dose assistance. The Association of Paediatric Palliative Medicine Master Formulary [54] suggests 10-16% of the total daily opioid, prescribed every 1-4 hours as needed. These recommendations are based on clinical acumen but have little basis in evidence because few data available from clinical studies. Dose is also compromised by a number of other covariates e.g., opioid tolerance, pain intensity, pharmacogenomic influences and concomitant drug interactions that remain unexplored.[21, 24, 55]

The target concentration in neonates is unknown. Use of diacetylmorphine was commonly for suppression of spontaneous ventilation to reduce difficulties with synchronisation of ventilator-initiated respiration

rather than pain control or neonatal abstinence syndrome. Concentrations were high (60-80 $\mu g.L^{-1}$) [43, 56] and are associated with respiratory depression. Diamorphine has effects in addition to those associated with morphine. Although respiratory depression measured with carbon dioxide response curves or arterial oxygen tension are similar in children from 2 to 570 days of age at the same morphine concentration [29], the additional effects from diamorphine metabolites that are associated with neurotransmitters other than endorphins (e.g., dopamine, 5-hydroxytryptamine) are unexplored in neonates. Dose prediction in neonates, particularly premature neonates, remains speculative. Pharmacodynamic responses are altered in that cohort.[57]

Inform future studies

Pharmacokinetic/pharmacodynamic models can be used to predict outcomes before a child is even enrolled in a study, provided information used to construct the model is accurate.[58] Although this does not obviate the need for clinical study, the focus of the clinical study changes into confirming the model, supporting the model or improving the model by characterizing key elements within the model. This reduces the burden of clinical studies in children effectively by using prior knowledge.[59]

Models are now used extensively to inform future clinical studies. They reduce the burden of studies in children through the use of sparse sampling, extrapolation of adult information to children, and interpolation between pediatric age groups. Optimal design studies which rely on pharmacokinetic models can identify sampling times that allow for the most precise estimates of important pharmacokinetic parameters.[60] Pharmacokinetic-pharmacodynamic models allow critical aspects of drug efficacy to be assessed and provide a design during the development process that can be used for phase 2 studies.

The European Medicines Agency has gained substantial experience in the use of modeling and simulation in pediatric drug development. [61, 62] Such regulators are eager to expand the use of modeling and simulation to elucidate safety issues, to evaluate the effects of disease (e.g., renal or hepatic dysfunction), and to qualify mechanistic models that could help shift the current medicinal development paradigm. [61, 62]

Future studies into diamorphine pharmacokinetics do not need to quantify every metabolite using rich blood sampling techniques in every age group. Instead, sparse sampling can be used in fewer children. Sampling can be designed to confirm or improve aspects of the model; a confirm rather than relearn approach. [59]

Discussion

It is often stated that "all models are wrong, but some are useful". The aphorism recognizes that statistical or scientific models always fall short of the complexities of reality but can still be useful. The tenet is attributed to the statistician George Box (1919-2013) and remains applicable to the field of anesthesia drug modelling.

A pharmacokinetic model for diamorphine and its metabolites was created from a combination of adult and pediatric literature and age and size covariates were added to explain maturation changes.[63] That model was used to demonstrate the time course of diamorphine and its metabolite concentrations, learn about biological principles, estimate relative bioavailability of intranasal diamorphine and predict dosing equivalence using similar exposure at different ages. Simulation using the pharmacokinetic model allowed us to predict intranasal and intravenous doses which achieved the same target concentration in neonates, infants and children.

Diamorphine dosing is empiric for both pain and for use in palliative care; there are few data available in children to guide dose.[17]Analysis of those limited published data used non-compartmental parameters, centered on the morphine metabolite and did not explore age or size covariates.[35, 64] Modelling was used for dose estimation. Validation of the model in children was not possible because there are so few published data in that cohort and prospective clinical evaluation of the model would be required to confirm its validity.[17] However, models can be used for hypothesis testing and can drive decision making during drug development. Modelling and simulation are now integral parts of drug development [61] and

clinical studies can be designed to confirm models rather than undertake further expansive clinical studies.[58]

This tutorial introduces the usefulness of models with diamorphine as an example. This example of a pharmacokinetic model incorporates physiological systems such as renal function and allometry. A model is not a static entity; new information that is published allows pharmacometricians to improve their models in order to better represent reality. The model could be expanded to integrate further available information from experimental data generated for diseases, genetics, drug binding, metabolism, polymorphisms, biological pathways, and inter-relationships between systems. This more advanced modeling is known as quantitative systems pharmacology and is now used at all stages of drug development. Quantitative systems pharmacology focuses on modeling the mechanisms of drug pharmacokinetics (PK), pharmacodynamics (PD), and disease processes using a systems pharmacology point of view.[65]

Reflective Questions

1. Diamorphine is a prodrug of morphine. Why does it have a quicker analgesic onset and a longer duration of action than morphine?
2. Opioids are can be rotated during palliative care in children. How is equianalgesia between opioids assessed?
3. Drug administration route influences the consequent observed time-concentration profile. Is this profile affected by an altered clearance, volume or absorption factors (bioavailability and absorption half time) of the drug?

Disclosures

Conflicts of Interest: James Morse is supported in part by the New Zealand Society of Anaesthetists Ritchie Prize. Brian Anderson serves on the Editorial Board for the journal Pediatric Anesthesia. Ian Wong is the Chief Investigator of the DIamorphine Paediatric Palliative Evaluation of feasibility of Randomized controlled trial (DIPPER) study. Ian Wong is the founder of Therakind Ltd which was funded by Wockhardt Pharmaceutical to conduct the clinical studies for Ayendi®. (diamorphine hydrochloride) licensing application. Joseph Standing and Silke Gastine are co-investigators of the DIPPER study.

Ethics: Human ethics committee approval not required

Funding: This work was funded from institutional resources

Data sharing: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Tables

Table 1. Simulated average concentration (C_{AVG}), concentration in the effect compartment at steady state (Ce_{SS}) and AUC_{0-24} when morphine is given intravenously (2 mg 2 hourly) or orally (10 mg 4 hourly) for 24 hours in an adult 70 kg person. When bioavailability of the oral formulation is simulated using a bioavailability of 30% or 50%, concentrations and AUC_{0-24} change in a dose proportional manner.

Dose	Bioavailability	Total dose 24 h	AUC_{0-24} $\mu g.L^{-1}.h$	C_{AVG} $\mu g.L^{-1}$	Ce_{SS} $\mu g.L^{-1}$
IV morphine 2 mg 2 h	F=1	24 mg	322	13.4	14.1
PO morphine 10 mg 4 h	Foral=0.5	60 mg (=30 mg)	403	16.8	17.6
PO morphine 10 mg 4 h	Foral =0.3	60 mg (=20 mg)	233	9.7	10.1

Table 2. Simulated age-specific dose of diamorphine when given using intravenous or intranasal routes. The intranasal doses target a morphine $AUC_{0\text{-}10}$ of 70 $\mu g.L^{-1}.h$. Intravenous loading and maintenance dose targets a steady-state morphine concentration of 30 $\mu g.L^{-1}$. Intranasal dose in neonates and infants is speculative only; nasal anatomy is immature and the surface area available for absorption not considered. Dose is presented per kilogram for typical weighted individuals of each age.

	Neonate 3.2 kg	Infant 6 month 7.5 kg	Infant 1 years 10 kg	Child 5 years 20 kg	10 years 32 kg	15 years 56 kg	Adult 70 kg
Intranasal							
Dose $\mu g.kg^{-1}$	33	77	98	98	85	75	70
Intravenous							
Loading dose $\mu g.kg^{-1}$	28	29	29	29	29	29	29
Maintenance dose $\mu g.kg.h^{-1}$	14	33	42	42	37	33	31

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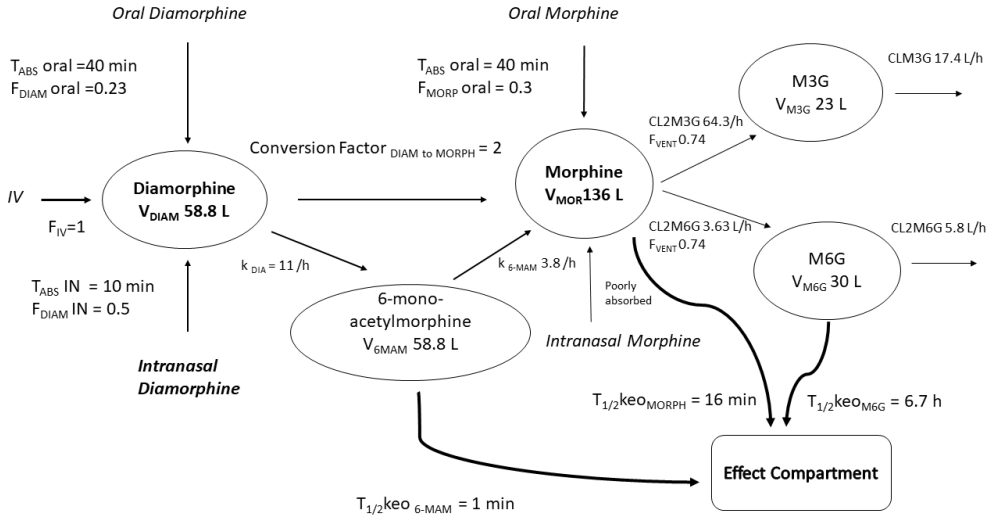
Figure Legends

Figure 1. This schematic diagram shows the metabolic flow of diacetylmorphine, 6-mono-acetylmorphine and morphine using a sequential one-compartment models. Diamorphine absorption is described in terms of absorption half-times (T_{ABS}) and relative bioavailability (F_{DIAM}) by oral or intranasal (IN) routes. Rate constants (k_{DIA}, $k_{6\text{-}MAM}$)) describe flow between metabolites. Morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G) clearance align with renal function. The delay between active metabolites (6-MAM, morphine, M6G) and the effect compartment is described using equilibration half-times ($T_{1/2}$keo). The conversion of diamorphine to morphine (Conversion Factor $_{DIAM\ to\ MORPH}$) is assumed 2. The relative bioavailability of nasal diamorphine (F_{DIAM} IN) compared to intravenous administration was estimated. Clearance (CL) and Volume (V) parameters conform to drug or metabolite they relate to.

Figure 2. Simulated time-concentration profiles for diamorphine and its metabolites are shown for a typical neonate (3.2 kg, PNA 2 days, 40 weeks PMA), child (5 years 20 kg) and adolescent (15 years, 56 kg) given intranasal diamorphine. Simulated concentrations are based on intranasal diamorphine dose shown in Table 2. The target was an $AUC_{0\text{-}10}$ of 70 $\mu g.L^{-1}.h$. Morphine peak concentrations (C_{MAX}) are lower in neonates than in older children, but concentrations are above 10 $\mu g.L^{-1}$ for a longer duration. A 5-year-old child has a bigger C_{MAX} but a shorter duration of exposure.

Figure 3. Simulated time-concentration profiles for diamorphine and its metabolites are shown for a typical neonate (3.2 kg, PNA 2 days, 40 weeks PMA), child (5 years 20 kg) and adolescent (15 years, 56 kg). given diamorphine intravenous infusion for 2 hours. Simulated concentrations are based on intranasal diamorphine dose shown in Table 2. The target steady state morphine concentration was 30 $\mu g.L^{-1}$. Size and immature clearance contribute to rapid achievement of effect compartment concentrations and a

slower reduction of those concentrations in neonates. The active metabolite, morphine-6-glucuronide, is also slowly cleared in neonates.



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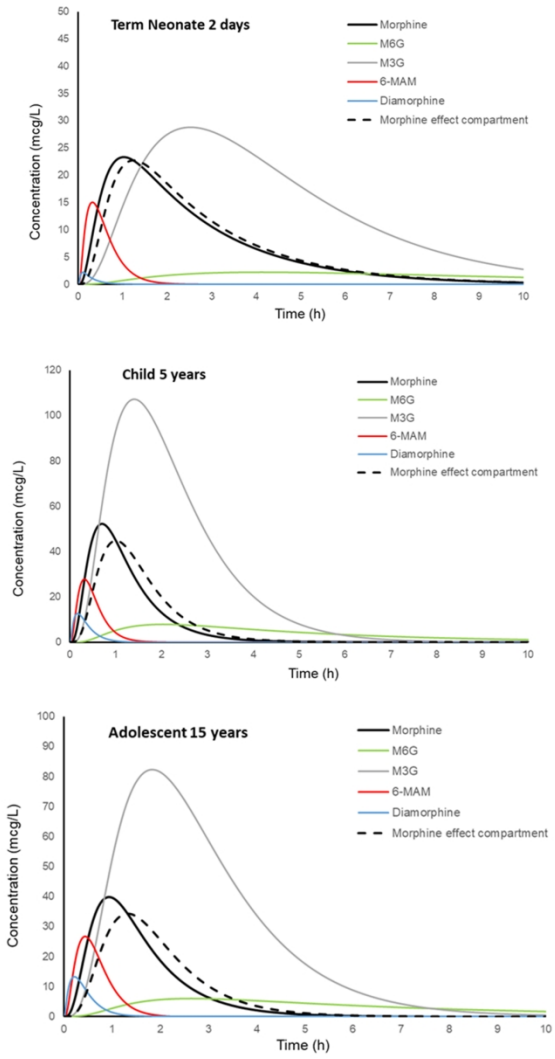
338x190mm (96 x 96 DPI)



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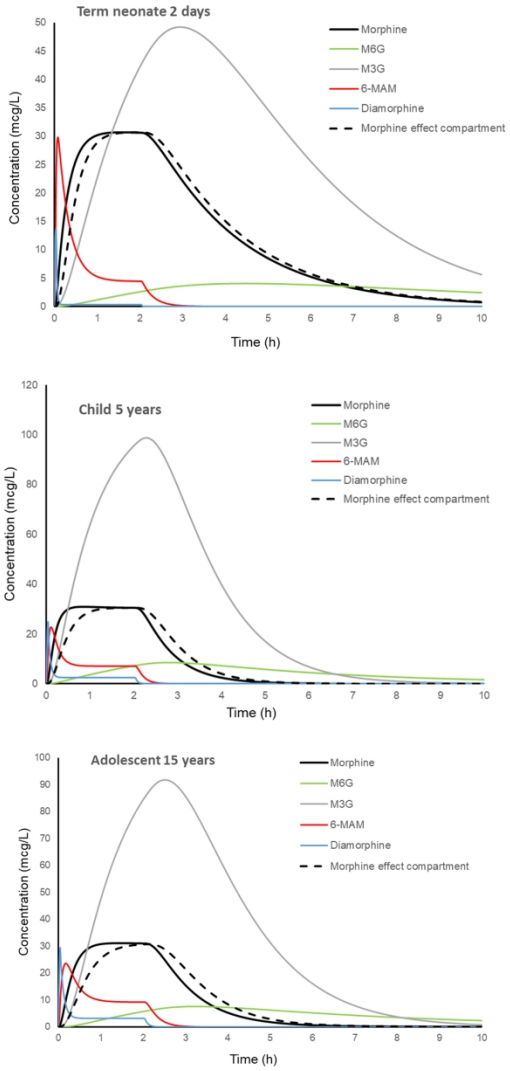
215x279mm (300 x 300 DPI)



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215x279mm (300 x 300 DPI)

Supplementary Material

Model for intranasal diamorphine in children

```
METHOD RK4

STARTTIME = 0
STOPTIME=10
DT = 0.02

DTOUT=0.001 ; output every 0.1 time units
RENAME time=hours ;

WT= 56     ; kg   Teenager 56 kg, 15 years
PMA=40 15*52   ; Postmenstrual age (PMA, weeks)
PNA=15*365     ; Postnatal age (PNA, days)

dose1=75*WT   ;  75 mcg/kg

;; Rook EJ, Huitema AD, van den Brink W, van Ree JM and Beijnen JH. Population pharmacokinetics of
heroin and its major metabolites. Clin Pharmacokinet. 2006; 45: 401-17

VDIAMstd =  2*29.4          ; L  Rook used twin compartments and clearances
V6MAMstd= 2*29.4            ; L
KDIAMstd= 2*5.5             ; /h
K2Mstd=2*1.9                ; /h

TDIAMstd=logn(2)/KDIAMstd
T2Mstd=Logn(2)/K2Mstd  ;  h

TDIAM=TDIAMstd*FSZT
T2M=T2Mstd*FSZT

KDIAM=logn(2)/TDIAM
K2M=logn(2)/T2M

CLDIAMstd=VDIAMstd*KDIAM   ; L/h
CL2Mstd=V6MAMstd*K2M       ; L/h

;; Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine
and its metabolites in neonates, infants and young children. Br J Anaesth. 2004;92(2):208-217
VMstd=136                   ; L
VM3Gstd=23                  ; L
VM6Gstd=30                  ; L

CL2M3Gstd=64.3          ; L/h
CLM3Gstd=17.4           ; L/h
CL2M6Gstd=3.63          ; L/h
CLM6Gstd=5.8            ; L;
```

```
CLEXstd = 3.12          ; L/h  small unaccounted additional clearance


;; size models
;; Anderson BJ and Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008; 48: 303-32.
;; Germovsek E, Barker CI, Sharland M and Standing JF. Scaling clearance in paediatric pharmacokinetics: All models are wrong, which are useful? Br J Clin Pharmacol. 2017; 83: 777-90

FSZT=(WT/70)**0.25
FSZCL=(WT/70)**0.75
FSZV=(WT/70)

;; Clearance of morphine metabolites based on renal function
;; Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009; 24: 67-76.
TMR50=47.6
HILLR=3.4
RF=(PMA**HILLR)/((TMR50**HILLR)+(PMA**HILLR))

;; CL2M maturation based on PMA
;; Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Br J Anaesth. 2004;92(2):208-217
;; Holford NH, Ma SC and Anderson BJ. Prediction of morphine dose in humans. Pediatr Anesth. 2012; 22: 209-22

TMCL50=58.1
HILLCL=3.58
MATCL=(PMA**HILLCL)/((TMCL50**HILLCL)+(PMA**HILLCL))

CLDIAM=CLDIAMstd *FSZCL        ; esterases mature at birth so no maturation
CL2M=CL2Mstd*FSZCL*MATCL    ;

CL2M3G=CL2M3Gstd *FSZCL*MATCL
CLM3G=CLM3Gstd*FSZCL*RF
CL2M6G=CL2M6Gstd*FSZCL*MATCL
CLM6G=CLM6Gstd*FSZCL*RF
CLEX=CLEXstd*FSZCL*RF

:: Morphine effect compartment equilibration
;; 6MAM effect compartment not known but assumed rapid, ignored in this model
;; Inturrisi CE and Colburn WA. Application of pharmacokinetic-pharmacodynamic modeling to analgesia. In: Foley KM and Inturrisi CE, (eds.). Advances in Pain Research and Therapy  Opioid Analgesics in the Management of Clinical Pain. New York: Raven Press, 1986, p. 441-52
;; Murphy MR and Hug CC, Jr. Pharmacokinetics of intravenous morphine in patients anesthetized with enflurane-nitrous oxide. Anesthesiology. 1981; 54: 187-92.

TEOstd=16/60        ; h  16 min
TEO=TEOstd*FSZT
KEO=logn(2)/TEO
```

```
;; nasal diamorphine absorption and conversion to morphine
;; Rook EJ, van Ree JM, van den Brink W, et al. Pharmacokinetics and pharmacodynamics of high doses of pharmaceutically prepared heroin, by intravenous or by inhalation route in opioid-dependent patients. Basic Clin Pharmacol Toxicol. 2006;98(1):86-96.
;; Kidd S, Brennan S, Stephen R, Minns R, Beattie T. Comparison of morphine concentration-time profiles following intravenous and intranasal diamorphine in children. Archives of disease in childhood. 2009;94(12):974-978.
;; Halbsguth U, Rentsch KM, Eich-Hochli D, Diterich I, Fattinger K. Oral diacetylmorphine (heroin) yields greater morphine bioavailability than oral morphine: bioavailability related to dosage and prior opioid exposure. Br J Clin Pharmacol. 2008;66(6):781-791

TABS=10/60    ; unknown but assumed similar to fentanyl
KA=logn(2)/(TABS)  ;
FIN=0.5         ;   estimated for intranasal
F6MAM=2      ; estimated conversion factor diamorphine to morphine

;; morphine volume maturation based on PNA
;; Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Br J Anaesth. 2004;92(2):208-217
BETAV=0.391
TVOL=26.3   ; PNA DAYS
FVOL=1-BETAV*EXP(-PNA*logn(2)/TVOL)

VDIAM=VDIAMstd*FSZV
V6MAM=V6MAMstd*FSZV
VM=VMstd*FSZV*FVOL
VM3G=VM3Gstd*FSZV
VM6G=VM6Gstd*FSZV


dose=PULSE(dose1,0,12)   ; e.g. 12 hourly

;initial amounts in compartments
init(A1)=0   ; depot
init(A2)=0   ; DIAM
init(A3)=0   ; 6MAM
init(A4)=0   ; MOR
init(A5)=0   ; M3G
init(A6)=0   ; M6G
init(A7)=0   ; EFFECT
init(A8)=0   ; AUC

;Concentration in each compartment

CA=A1
CDIAM=FIN*A2/VDIAM
C6MAM=A3/V6MAM
CMOR=F6MAM*A4/VM
CM3G=A5/VM3G
```

```
CM6G=A6/VM6G
CE=A7

; Differential equations for each compartment

  d/dt(A1)= dose -KA*CA
  d/dt(A2)=KA*CA  - CDIAM*CLDIAM
  d/dt(A3)= CDIAM*CLDIAM - C6MAM*CL2M
  d/dt(A4)=C6MAM*CL2M-CMOR*(CL2M3G+CL2M6G+CLEX)
  d/dt(A5)=CMOR*CL2M3G-CM3G*CLM3G
  d/dt(A6)=CMOR*CL2M6G-CM6G*CLM6G
  d/dt(A7)=KEO*(CMOR-CE)          ; morphine effect compartment
  d/dt(A8)=CMOR                   ; AUC, use for exposure
```