Diamorphine pharmacokinetics and conversion factor estimates for intranasal diamorphine in paediatric breakthrough pain: systematic review

Authors and affiliations

Silke S. Gastine [1], James D Morse [2], Miriam TY Leung [3], Ian CK Wong [3,4,5], Richard F Howard [6], Emily Harrop [7,8], Christina Liossi [6,9], Joseph F Standing [1,6,], Satbir Singh Jassal [10], Richard Hain [11], Simon S Skeen [12], Kate Oulton [13], Siew L Law [4], Wan T Quek [4], Brian J Anderson [14]

1. Infection, Immunity, and Inflammation, Great Ormond Street Institute of Child Health, University College London, London, UK
2. Department of Pharmacology & Clinical Pharmacology, Auckland University, Park Road, Auckland 1023, New Zealand
3. 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
4. Research Department of Practice and Policy, University College London School of Pharmacy, London, UK
5. UCLH-UCL Centre for Medicines Optimisation Research and Education, London, UK
6. Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
7. Helen & Douglas House Hospices, Oxford, UK
8. Oxford University Hospitals NHS Foundation Trust, Oxford, UK
9. School of Psychology, University of Southampton, Southampton, UK
10. Rainbows Hospice for Children and Young Adults, Loughborough Leicestershire, UK
11. All-Wales Managed Clinical Network in Paediatric Palliative Medicine, Cardiff and the Vale University Health Board, Cardiff, UK
12. Surrey Clinical Trials Unit, University of Surrey, UK
13. Centre for Outcomes and Experience Research in Children's Health, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
14. Department of Anaesthesiology, Faculty of Medicine and Health Science, University of Auckland, Park Rd, Auckland 1023, New Zealand

Corresponding author

Prof B.J. Anderson, Department of Anaesthesia, Auckland Children's Hospital, Park Road, Private Bag 92024, Auckland, NZ; Ph +64-9-3074903; Fax +64-9-3078986

Email: briana@adhb.govt.nz

Running head: Intranasal diamorphine

ORCID

James D Morse: https://orcid.org/0000-0001-7500-0062

Christina Liossi https://orcid.org/0000-0003-0627-6377

Emily Harrop: https://orcid.org/0000-0002-2480-2062

Ian Wong: https://orcid.org/0000-0001-8242-0014

Christina Liossi: https://orcid.org/0000-0003-0627-6377

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

Richard Howard: https://orcid.org/0000-0001-9271-0074

Simon S Skene: https://orcid.org/0000-0002-7828-3122

Kate Oulton: https://orcid.org/0000-0002-5778-3849

Brian J Anderson: https://orcid.org/0000-0001-7500-0062

Abstract

Background: Intranasal diamorphine is a potential treatment for breakthrough pain but few paediatric data are available to assist dose estimation.

Aim: To determine an intranasal diamorphine dose in children through an understanding of pharmacokinetics.

Design: A systematic review of the literature was undertaken to seek diamorphine pharmacokinetic parameters in neonates, children and adults. Parenteral and enteral diamorphine bioavailability were reviewed with respect to formation of the major metabolite, morphine. Clinical data quantifying equianalgesic effects of diamorphine and morphine were reviewed.

Review sources: PubMed (1960-2020); EMBASE (1980-2020); IPA (1973-2020) Original human research studies that reported diacetylmorphine and metabolite after any dose or route of administration.

Results: The systematic review identified 19 studies: 16 in adults and 1 in children and 2 neonatal reports. Details of study participants were extracted. Age ranged from premature neonates to 67 years and weight 1.4 – 88 kg. Intranasal diamorphine bioavailability was 50%. The equianalgesic intravenous conversion ratio of morphine:diamorphine was 2:1. There was heterogeneity between pharmacokinetic parameter estimates attributed to routes of administration, lack of size standardisation, methodology and pharmacokinetic analysis. Estimates of the pharmacokinetic parameters clearance and volume of distribution were reduced in neonates. There were insufficient paediatric data to characterise clearance or volume maturation of either diamorphine or its metabolites.

Conclusions: We estimate equianalgesic ratios of intravenous morphine:diamorphine 2:1, intravenous morphine:intranasal diamorphine 1:1 and oral morphine:intranasal diamorphine of 1:3. These ratios are based on adult literature, but are reasonable for deciding on an initial dose of 0.1 $mg.kg^{-1}$ in children 4-13 years.

Key statements

What is already known?

•• Transmucosal diamorphine is an effective, rapid, treatment for pain

•• The conversion ratio between intranasal diamorphine and oral morphine in children is disputed

What are the new findings?

•• Diamorphine has a potency twice that of morphine. The equianalgesic ratio when given intravenously is morphine:diamorphine 2:1

•• Morphine exposure after intranasal diamorphine is half that after intravenous administration and diamorphine intranasal dose should be converted to one third of the oral morphine dose when switching opioids

What are their significance?

A) Clinical: The proposed conversion range (1:3) provides a reasonable starting point for the use of intranasal diamorphine when replacing oral morphine. We suggest an initial dose of intranasal diamorphine 0.1 $mg.kg^{-1}$ in children 4-13 years, prior to a process of titration against the child's changing experience of pain and analgesia

B) Research: Developmental pharmacokinetics and pharmacodynamics of diamorphine and its metabolites are poorly characterised in children. Intranasal absorption parameters require quantification.

Keywords

Diamorphine, Morphine, Intranasal, Transmucosal, Paediatrics, Palliative, Pharmacokinetics, Opioids, Pain, Breakthrough

Introduction

Breakthrough pain in children with life-limiting conditions occurs despite regular background opioid use and is often severe enough to warrant additional opioids.[1] 'Breakthrough' describes pain exacerbation experienced by an individual who is otherwise pain-free, either because the pain source is intermittent or, more often, because the pain is poorly managed using regular 'background' opioids. Although it remains difficult to quantify breakthrough pain [2, 3], management of this pain is possible with analgesia that should be accessible and well tolerated by the individual, rapid in onset and effective. Oral morphine is commonly the first-line management of breakthrough pain [1] but the time until analgesic effect is often more than 30 minutes. Injected (intravenous, subcutaneous and intramuscular) opioids offer more rapid onset, but faced with the possibility of a needle, children and their families often delay asking for pain relief. Palliative care in children demands needle-free, fast acting formulations of analgesia that do not require supervised administration by a practitioner at the bedside (e.g., sanctioning home-based care).

Diamorphine (heroin, diacetylmorphine) is a semi-synthetic diacetylated derivative of morphine. Transmucosal diamorphine may be an alternative to oral morphine because it can be administered by transmucosal (sublingual, intranasal or buccal) routes, where the rich blood supply facilitates rapid systemic absorption of this lipophilic drug with a low molecular weight (369.4 $g.mol^{-1}$). Transmucosal routes provide direct absorption into the systemic circulation, avoiding first pass metabolism. Metabolism of diamorphine to morphine affords analgesia beyond that supplied by the initial metabolite, 6-mono-acetylmorphine, concentrations.[4, 5] The metabolite 6-mono-acetylmorphine is rapidly formed by plasma and erythrocyte esterases [6] resulting in rapid onset of analgesia (maximum effect within 5 minutes). Subsequent metabolism to morphine exerts a maximum analgesic effect within 1 hour.[4, 6-8]

Diamorphine intranasal dosing remains uncertain. The dose of opioid for a child depends on a number of factors that include administration route, body weight, pharmacokinetic changes with age, metabolites, pharmacogenomics, psychosocial issues, receptor type occupancy (e.g., opioid, dopamine, 5-

hydroxytryptamine), pain intensity and tolerance to its effects (adverse and beneficial). The dose needed to treat breakthrough pain also depends on the concurrent dose of background opioid. Current clinical guidelines offer limited dose assistance. The Association of Paediatric Palliative Medicine Master Formulary [9] suggests 10-16% of the total daily opioid, prescribed every 1-4 hours as needed. These recommendations have little basis in evidence because few data are available from clinical studies. Conducting randomized controlled trials in this group of children is challenging.[10, 11] Pharmacokinetic studies, coupled with pharmacodynamics data from observational studies or published literature data, have been used to develop robust models to guide dosing regimens in different patient groups.[12]

This study aimed to review literature concerning diamorphine pharmacokinetics in neonates, children and adults to assess diamorphine practicalities when prescribed by the intranasal route for children with life-limiting conditions. Diamorphine is a prodrug of morphine and the two key pieces of pharmacokinetic knowledge sought were intranasal diamorphine bioavailability and the equianalgesic intravenous conversion ratio of morphine to diamorphine. Quantification of these two indices was based on morphine exposure, a term that relates to the area under the graphical time-morphine concentration curve (AUC). Morphine exposure is a parameter that correlates with analgesic effect, allowing use of clinically determined equianalgesic ratios to assist prediction of conversion factors for morphine to diamorphine.

This current investigation is part of a similar process; the DIamorphine Paediatric Palliative Evaluation of feasibility of Randomised controlled trial (DIPPER) investigations.[10, 11, 13]

Methods

A systematic review of published literature including pharmacokinetic studies of diamorphine and its metabolites administered by parenteral and enteral routes was conducted according to PRISMA guidance.[14] Analgesic equivalence was assessed for diamorphine in relation to morphine.

Conduct of literature review on pharmacokinetics

Pharmacokinetic studies of diamorphine in patients or healthy volunteers were sought. The following electronic databases were included: PubMed (1960-2020), EMBASE (1980-2020), IPA (1973-2020). Databases were searched using the following terms: heroin OR diamorphine OR diacetylmorphine AND (pharmacokinetics OR pharmacokinetic) OR pharmacometric OR pharmacometrics OR PK OR Cmax OR Tmax OR maximum concentration OR serum concentration OR plasma concentration. All searches were conducted up to 23 June 2020.

Eligibility criteria - Inclusion

(1) Original human research studies that reported diacetylmorphine and metabolite pharmacokinetics after administration of diacetylmorphine in any dosage, in single or multiple doses, regardless of route of administration;

(2) Pharmacokinetic data including the maximum concentration of diacetylmorphine in plasma (Cmax) and/or the time to maximum concentration (Tmax), clearance (CL), volume of distribution (V), area under the concentration time curve (AUC), half-life ($t_{1/2}$) or any data that allowed parameter determination;

(3) Studies in children, adolescents and adults without age limits; including patients or healthy volunteers.

Exclusion criteria:

(1) Animal studies;

(2) Review articles;

(3) Abstracts without full text, conference abstracts, unpublished manuscripts, guidelines, manuals and commentaries;

(4) Articles containing pharmacokinetic data not expressed numerically (e.g., graphical displays).

Titles and abstracts of articles were screened by two reviewers (SL and WQ), and full texts of relevant articles were retrieved for further review to identify relevant studies against the inclusion criteria. For quality control purposes extractions were checked by two independent members of the group.

Data extraction

Collected information included routes of administration, number of participants, clinical categories and pharmacokinetic (PK) parameters. Pharmacokinetic parameters were presented in the form: mean, standard deviation (SD); mean, standard error (SE) or range.

The following data were extracted from each paper: authors; published year and country; sample size; age, either individual or population values; weight, either individual or population values; dose or dose range; PK parameters, Area under the concentration time curve (AUC), maximum concentration (Cmax), time to reach maximum concentration (Tmax), clearance (CL), volume of distribution (V), elimination half-life ($t_{1/2}$).

Data analysis

Extracted information concerning pharmacokinetic parameters was analysed using R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). All parameters reported for diamorphine or its metabolites were compared within routes of administration and across the available age and weight range. Analyses were conducted using the extracted parameter mean and standard deviation (SD). Graphical evaluation of mean and standard deviation for all parameters was conducted against the median reported body weight. If no weight was reported in adult studies, a typical weight of 70 kg was assumed.

Opioid conversion

The literature search was extended to include studies which explore equianalgesic doses and bioavailability for oral and intravenous (IV) morphine and transmucosal and IV diamorphine.

Results

There were 4249 publications screened for reporting pharmacokinetic parameters. Full-text articles (n=22) were assessed for eligibility after completion of the PRISMA literature review. Three articles were excluded due to noninformative PK data or data formatting that was unsuitable for extraction, leading to a

total of 19 studies included in the review, of which 16 were in adults, 1 in children and two in neonates. **Figure 1** shows the PRISMA diagram for the performed search. A summary of retrieved parameters is shown in **Supplementary Table S1** (adults) and **Table 1** (children and neonates).

The median (range) age and weight were 32 years (2 days postnatal – 67 years) and 57.7 kg (1.4 – 88.0 kg), respectively. Publications reported one or multiple routes of diamorphine administration. Eleven studies reported parameters for intravenous diamorphine, eight reported on transmucosal, five reported oral formulations, five intramuscular or subcutaneous and two concerned intrathecal administration. Diamorphine concentrations were measured in twelve publications. Morphine was the most studied metabolite (n=17), followed by 6-monoacetylmorphine (6-MAM, n=11), morphine 6-glucuronide (M6G, n=10), and morphine 3-glucuronide (M3G, n=9). Pharmacokinetic parameters reported for the measured diacetylmorphine and metabolites were AUC (n=12), clearance (n=11), Cmax (n=17), half-life (n=15), Tmax (n=16) and volume of distribution (n=10). Parameter estimates across the observed weight range are shown in **Figure 2**.

It was not possible to pool parameter estimates to determine key parameters that might influence bioequivalence ($F_{DIAMORPH}$ or Conversion $_{DIAMORPH\ to\ MORPHINE}$) within this metabolic flow (**Figure 3**). While several individual studies quantified diamorphine and metabolite concentration flow in adults [4, 15], most only quantified morphine exposure using AUC of variable duration and there was only the one study in children and that used a non-compartmental analysis.

There were limited reports of parenteral diamorphine relative bioavailability. The relative bioavailability of inhaled heroin was 53% (95% CI 43.7, 62.3) in opioid-dependent adults.[15] Intranasal diamorphine bioavailability was reported as half that when given by the intramuscular route in adults.[16, 17] The oral bioavailability of diacetylmorphine is dose-dependent and approximately 50% in adults. Opioid naïve users had a bioavailability of only up to 23%.[18] Diacetylmorphine nasal administration in children (aged 4-13 years) achieved an AUC of morphine that was half that in those given intravenous diacetylmorphine.[19]

Figure 2 demonstrates transmucosal administration was associated with a smaller AUC, consistent with lower relative bioavailability (F_{DIAM} <1). Clearance of diacetylmorphine is large, consistent with plasma esterase activity.[20] Both morphine clearance and volume increase with age in childhood and although there are too few data to describe this maturation, this trend is consistent with those reported for morphine in children.[21] Morphine half-life, a parameter confounded by clearance and volume, changed little with age or weight. Morphine metabolite clearance, dictated by renal function, could not be assessed graphically because that covariate was rarely reported.

Table 2 lists literature sources for the conversion between IV and oral morphine. These range between 20 and 50%.[9, 22-25] Equianalgesic doses compare the analgesic effect of an opioid substance, with regards to a comparable analgesia reached by morphine dosing **(Table 3**).[9, 23, 26-29] Analgesia offered by intravenous diamorphine was estimated 200% that of the same dose of intravenous morphine. [23 26, 27, 29]

Information available from the literature review and from equianalgesic equivalence tables was used to create an illustration of metabolic pathways (**Figure 3**). There was insufficient information available in children to estimate values for parameters that could quantify metabolic pathways. **Table 4** illustrates conversion factors for morphine to diamorphine by intravenous and parenteral routes, based on bioavailability and equianalgesia estimates.

Discussion

Intranasal diamorphine is an attractive option for breakthrough pain in children because the drug is rapidly absorbed into the systemic circulation without first pass metabolism. The pharmacokinetics of mucosal diamorphine in children are unknown. Physicians commonly use reported conversion factors to calculate a dose equianalgesic to morphine. Intravenous conversion factors (**Table 3**) allow dose calculation for 'opioid rotation' or 'switch' between different opioids.[30, 31] Equianalgesic dose estimation is difficult when bioavailability of a drug given by a mucosal route is unknown. We describe a relative bioavailability of approximately 50% with a conversion ratio of diamorphine to morphine of 200% consistent with this current literature review and equianalgesic ratios. Based on this information (e.g., intravenous

morphine:intranasal diamorphine 1:1, Table 4), we estimate intranasal diamorphine 0.1 $mg.kg^{-1}$ in a child 4-13 years, prior to a process of titration against the child's changing experience of pain and analgesia. This dose is similar to that used for acute pain in the Emergency Room (0.1 $mg.kg^{-1}$) for bone fracture reduction in children.[7, 8]

Although we predict that diamorphine intranasal bioavailability (F_{DIAZ}) is approximately 50% in children, that estimate is based on children 4-13 years [19] and may change with age because the anatomy of the nose changes with age causing possible consequent absorption characteristic changes. Age is also a covariate for pharmacokinetic parameter estimates; they are immature in neonates.[32] However, opioid clearance maturation is usually complete within the first few years of life [21, 33] and other opioids such as fentanyl have been successfully used intranasally for acute pain in children out of infancy. Concerns that developmental changes related to both central nervous system receptors and opioid passage across the blood-brain-barrier [34] appear confined to infants.[35]

The conversion ratio of 200% for diacetylmorphine to morphine is based on clinical equianalgesia rather than pharmacokinetic examination (e.g., AUC) of this conversion.[36] Use of clinical equianalgesia to define bioavailability is associated with inaccuracy. Morphine, for example has a relative bioavailability in adults of 23.9% after oral solution and 18.7% after a buccal tablet[37]; a relative bioavailability of 30% is reported for elixir in children.[38] Equianalgesia ranges from 1:2.5 to as high as 1:6 in adults.[22-25] This is because empiric studies have shown that a concentration range (10-20 $mcg.L^{-1}$) has analgesic effect [39] and equianalgesia can be achieved over a range of concentrations that are attained by a range of doses. The effectiveness of breakthrough equianalgesic doses can be further complicated by the development of tolerance. [22, 31, 40]

Although PK parameters of diamorphine metabolites, morphine and its glucuronides, have been measured both in children and in single adult studies, those studies involved IV administration of diamorphine in children, while in adults, diamorphine was given orally. Our analysis provides some evidence that extrapolation from adult parameter estimates to children might have some validity. The majority of diamorphine is rapidly converted to 6-mono-acetylmorphine and then more slowly to morphine (**Figure**

3), making it a pro-drug for morphine. The rapid clearance from diacetylmorphine to the active metabolite, 6-mono-acetylmorphine, provides quick onset analgesia that is followed by that provided by morphine.[4, 5] The equilibration half-time ($T_{1/2}keo_{6\text{-}MAM}$) between plasma and effect compartment is unknown but assumed very short duration. Morphine effect is delayed not only by formation clearance from 6-mono-acetylmorphine but also because the equilibration half-time ($T_{1/2}keo_{MORPHINE}$) is a slower 16 min (**Figure 3**).[41, 42] Analgesic effect from morphine 6-glucuronide is further delayed ($T_{1/2}keo_{M6G}$=6-8 h).[43] The high diamorphine clearance is consistent with that described for other drugs cleared by plasma esterases (e.g., remifentanil [20]). Inhaled diamorphine has a relative bioavailability of 52%,[15] similar to that predicted for nasal administration. Morphine clearance in children was similar to the mature value described by others for adults and children.[21, 44, 45] Similarly clearance of metabolites correlated with glomerular filtration rate, a measure of renal function [46] that matures over the first year of life [47].

Most publications (16 of 19) concerned adults and used non-compartment analyses. Only 1 study concerned children.[19] Adult studies could not inform the question of pharmacokinetics in children because diamorphine administration routes differed, pharmacokinetic parameter estimates were incomplete, weight and age standardisation was lacking and the use of non-compartment analyses often ignores parameter variability and the influence of covariates on that variability.[48] Several adult studies did complete compartmental analyses using population pharmacokinetic methodology.[6, 49] where it might have been possible to estimate paediatric parameters from adult using allometric theory and maturation models [50, 51]. Data review (e.g., **Figure 2**) suggested maturation of clearance estimates from neonates [32, 52] to adults, but the lack of paediatric studies made validation difficult.

Pharmacokinetic and pharmacodynamic modelling to explore maturational changes and tolerance could help clarify paediatric pharmacokinetic and concentration-response relationships for diacetylmorphine. This current literature review has shown that a pharmacokinetic model similar to **Figure 3** is possible in adults.[49] While it is currently not possible to populate a paediatric model with parameter estimates, limited paediatric pharmacokinetic studies could be performed to quantify those estimates. A subsequent clinical

validation study could confirm model validity [53], allowing simulation to predict dose determined by administration route, age and weight.[54, 55]

Contributorship Statement

IW is the Chief Investigator of the DIamorphine Paediatric Palliative Evaluation of feasibility of Randomised controlled trial (DIPPER) study and conceived the project and takes overall responsibility for the conduct of this study review. SLL and WTQ screened titles and abstracts of articles and retrieved full texts of relevant articles as shown in Tables S1 and 1. MTYL and JDM created and reviewed PK analysis and graphics. RH, BJA and JDM contributed to the expert consensus and contributed results and wrote the discussion section. SSJ has been involved with ongoing discussions and critically reviewed the manuscript. All other authors (EH, CL, JFS, SSJ, SSS, KO) are involved in DIPPER studies, helped plan this study and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0317-20036). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Declaration of conflicts of interest

IW is the founder of Therakind Ltd which was funded by Wockhardt Pharmaceutical to conduct the clinical studies for Ayendi®. (diamorphine hydrochloride) licensing application. The other authors declare that there is no conflict of interest.

Table Legends

Table 1. Parameter estimates and characteristics of studies from neonates and children

Table 2. Conversion factors reported for oral to intravenous morphine in adults

Table 3. Equianalgesic doses – Conversion of reference is intravenous morphine to intravenous diamorphine in adults

Table 4. Conversion factors for morphine to diamorphine by intravenous and parenteral routes in children. Conversion calculations assumed a diacetylmorphine nasal bioavailability 50%, oral morphine bioavailability 30%, and an equianalgesic conversion factor of 200%

Supplementary Table S1. Parameter estimates and characteristics of studies from adults given diamorphine

Table 1. Parameter estimates and characteristics from studies on neonates and children

Study	PK calculation	Participants (n)	Gestational age (weeks)	Weight (kg)	Route	DAM dose (g/kg)	Chemi-cal	Vd (L/kg)	CL (mL/min/kg)	$t_{1/2}$ (h)	C_{ss} (ng/ml)
Neonates											
Barrett 1991	PCNONLIN	26	30.7 ±3.5	1.56 ±0.61	IV infusion	Loading: 22-50, infusion: 8.8-30/h	MOR	2.7 ±1.0	3.6 ±0.9	8.9 ±3.3	62.5 ±22.8
Barrett 1996	MINIM 2.0.2	19	29.7 ±3.7	1.4 ±0.6	IV infusion	Loading: 50-200, infusion: 15/h	MOR		4.6 ±3.2		86 ±52
							M3G	0.55 ±1.13	2.5 ±1.8	11.1 ±11.3	703 ±400
							M6G	1.03 ±0.88	0.46 ±0.32	18.2 ±13.6	48 ±28
Children											

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	$t_{1/2}$ (min)	C_{max} (ng/ml)	Tmax (min)
Kidd 2009	Excel, linear trapezoid rule	12	8	8.6 (range: 4-13)	30.1 (range: 19-59)	Intranasal	1.8-5.8	MOR	/	/	/	13.8 ±9.8	32.5 ±27.5
				9 (range: 4-12)	33 (range: 16-43)	IV	1.6-4.2	MOR	/	/	/	79.4 ±57.6	3.5 ±1.5

Abbreviations:

AUC: area under the curve, CL: clearance, C_{ss}: steady-state concentration, $t_{1/2}$: half-life, Tmax: time-point Cmax, Vd: distribution volume, IV: intravenous

Table 2. Conversion factors reported for oral to intravenous morphine in adults

Conversion Factor intravenous to oral morphine	Reference
1:2	[9]
1:2 - 1:3	[22]
1:3	[23]
1:3	[24]
1:2 -1:3	[25]

Table 3. Equianalgesic doses – Conversion of reference is intravenous morphine to intravenous diamorphine in adults

IV Morphine	IV diamorphine	Reference
1.5	1	[23]
2	1	[9]
2-4	1	[26]
2	1	[27]
2.5	1	[28]
2	1	[29]

Table 4. Conversion factors for morphine to diamorphine by intravenous and parenteral routes in children. Conversion calculations assumed a diacetylmorphine nasal bioavailability 50%, oral morphine bioavailability 30%, and an equianalgesic conversion factor of 200%

	Conversion	**Factor**
IV Morphine to IV diamorphine	$\frac{IV\ Morphine\ Dose}{2\ Equianalgesic\ Factor}$	1/2
IV Morphine to nasal diamorphine	$\frac{IV\ Morphine\ Dose}{2\ Equianalgesic\ Factor} * \frac{1}{0.5\ Bioavailability\ Diamorphine}$	1
Oral Morphine to nasal diamorphine	$\frac{\frac{Oral\ Morphine\ Dose}{3\ Bioavailability\ Morphine}}{2\ Equianalgeic\ Factor} * \frac{1}{0.5\ Bioavailability\ Diamorphine}$	1/3

REFERENCES

1. Zeppetella G. Evidence-based treatment of cancer-related breakthrough pain with opioids. *J Natl Compr Canc Netw*. 2013; 11 Suppl 1: S37-43.
2. Greenfield K, Holley S, Schoth DE, et al. A protocol for a systematic review and meta-analysis to identify measures of breakthrough pain and evaluate their psychometric properties. *BMJ Open*. 2020; 10: e035541.
3. Liossi C, Greenfield K, Schoth DE, et al. A Systematic Review of Measures of Breakthrough Pain and Their Psychometric Properties. *J Pain Symptom Manage*. 2021.
4. Bourquin D, Lehmann T, Hammig R, Buhrer M and Brenneisen R. High-performance liquid chromatographic monitoring of intravenously administered diacetylmorphine and morphine and their metabolites in human plasma. *J Chromatogr B Biomed Sci Appl*. 1997; 694: 233-8.
5. Gyr E, Brenneisen R, Bourquin D, Lehmann T, Vonlanthen D and Hug I. Pharmacodynamics and pharmacokinetics of intravenously, orally and rectally administered diacetylmorphine in opioid dependents, a two-patient pilot study within a heroin-assisted treatment program. *Int J Clin Pharmacol Ther*. 2000; 38: 486-91.
6. Rook EJ, Huitema AD, van den Brink W, van Ree JM and Beijnen JH. Pharmacokinetics and pharmacokinetic variability of heroin and its metabolites: review of the literature. *Curr Clin Pharmacol*. 2006; 1: 109-18.
7. Kendall JM and Latter VS. Intranasal diamorphine as an alternative to intramuscular morphine: pharmacokinetic and pharmacodynamic aspects. *Clin Pharmacokinet*. 2003; 42: 501-13.
8. Kendall JM, Reeves BC and Latter VS. Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures. *BMJ*. 2001; 322: 261-5.
9. APPM. The Association of Paediatric Palliative Medicine Master Formulary. In: Jassal SS, (ed.). 5th ed.: Association of Paediatric Palliative Medicine, 2020.
10. Jamieson L, Harrop E, Johnson M, et al. Healthcare professionals' views of the use of oral morphine and transmucosal diamorphine in the management of paediatric breakthrough pain and the feasibility of a randomised controlled trial: A focus group study (DIPPER). *Palliat Med*. 2021; 35: 1118-25.
11. Jamieson L, Wong IC, Craig F, et al. Palliative medicines for children - a new frontier in paediatric research. *J Pharm Pharmacol*. 2017; 69: 377-83.
12. Kendall J, Maconochie I, Wong IC, Howard R and study D. A novel multipatient intranasal diamorphine spray for use in acute pain in children: pharmacovigilance data from an observational study. *Emerg Med J*. 2015; 32: 269-73.
13. Harrop E, Liossi C, Jamieson L, et al. Oral morphine versus transmucosal diamorphine for breakthrough pain in children: methods and outcomes: UK (DIPPER study) consensus. *BMJ Support Palliat Care*. 2021.
14. Moher D, Liberati A, Tetzlaff J, Altman DG and Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009; 339: b2535.
15. 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: 86-96.
16. Cone EJ, Holicky BA, Grant TM, Darwin WD and Goldberger BA. Pharmacokinetics and pharmacodynamics of intranasal "snorted" heroin. *J Anal Toxicol*. 1993; 17: 327-37.
17. Skopp G, Ganssmann B, Cone EJ and Aderjan R. Plasma concentrations of heroin and morphine-related metabolites after intranasal and intramuscular administration. *J Anal Toxicol*. 1997; 21: 105-11.
18. Halbsguth U, Rentsch KM, Eich-Hochli D, Diterich I and 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: 781-91.

19. Kidd S, Brennan S, Stephen R, Minns R and Beattie T. Comparison of morphine concentration-time profiles following intravenous and intranasal diamorphine in children. *Archives of disease in childhood*. 2009; 94: 974-8.
20. Eleveld DJ, Proost JH, Vereecke H, et al. An allometric model of remifentanil pharmacokinetics and pharmacodynamics. *Anesthesiology*. 2017; 126: 1005-18.
21. Bouwmeester NJ, Anderson BJ, Tibboel D and Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *Br J Anaesth*. 2004; 92: 208-17.
22. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012; 13: e58-68.
23. Twycross RG. Morphine and diamorphine in the terminally ill patient. *Acta Anaesthesiol Scand Suppl*. 1982; 74: 128-34.
24. Glare PA and Walsh TD. Clinical pharmacokinetics of morphine. *Ther Drug Monit*. 1991; 13: 1-23.
25. Takahashi M, Ohara T, Yamanaka H, Shimada A, Nakaho T and Makoto Y. The oral-to-intravenous equianalgesic ratio of morphine based on plasma concentrations of morphine and metabolites in advanced cancer patients receiving chronic morphine treatment. *Palliat Med*. 2003; 17: 673-8.
26. Reichle CW, Smith GM, Gravenstein JS, Macris SG and Beecher HK. Comparative analgesic potency of heroin and morphine in postoperative patients. *J Pharmacol Exp Ther*. 1962; 136: 43-6.
27. Dundee JW, Loan WB and Clarke RS. Studies of drugs given before anaesthesia. XI. Diamorphine (heroin) and morphine. *Br J Anaesth*. 1966; 38: 610-9.
28. Smith GM and Beecher HK. Subjective effects of heroin and morphine in normal subjects. *J Pharmacol Exp Ther*. 1962; 136: 47-52.
29. Robinson SL, Rowbotham DJ and Smith G. Morphine compared with diamorphine. A comparison of dose requirements and side-effects after hip surgery. *Anaesthesia*. 1991; 46: 538-40.
30. Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev*. 2004: CD004847.
31. Knotkova H, Fine PG and Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table. *J Pain Symptom Manage*. 2009; 38: 426-39.
32. Barrett DA, Barker DP, Rutter N, Pawula M and Shaw PN. Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. *Br J Clin Pharmacol*. 1996; 41: 531-7.
33. Morse JD, Sundermann M, Hannam JA, Kokki H, Kokki M and Anderson BJ. Oxycodone population pharmacokinetics: premature neonates to adults. *Pediatr Anesth*. 2021; 31: xx-xx.
34. Eccleston C, Fisher E, Howard RF, et al. Delivering transformative action in paediatric pain: a Lancet Child & Adolescent Health Commission. *Lancet Child Adolesc Health*. 2021; 5: 47-87.
35. Hain RD, Hardcastle A, Pinkerton CR and Aherne GW. Morphine and morphine-6-glucuronide in the plasma and cerebrospinal fluid of children. *Br J Clin Pharmacol*. 1999; 48: 37-42.
36. Mercadante S and Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. *Palliat Med*. 2011; 25: 504-15.
37. Hoskin PJ, Hanks GW, Aherne GW, Chapman D, Littleton P and Filshie J. The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *Br J Clin Pharmacol*. 1989; 27: 499-505.
38. Dawes JM, Cooke EM, Hannam JA, et al. Oral morphine dosing predictions based on single dose in healthy children undergoing surgery. *Paediatr Anaesth*. 2017; 27: 28-36.
39. Bouwmeester NJ, van den Anker JN, Hop WC, Anand KJ and Tibboel D. Age- and therapy-related effects on morphine requirements and plasma concentrations of morphine and its metabolites in postoperative infants. *Br J Anaesth*. 2003; 90: 642-52.
40. Wiffen PJ and McQuay HJ. Oral morphine for cancer pain. *Cochrane Database Syst Rev*. 2007: CD003868.

41. 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.
42. Murphy MR and Hug CC, Jr. Pharmacokinetics of intravenous morphine in patients anesthetized with enflurane-nitrous oxide. *Anesthesiology*. 1981; 54: 187-92.
43. Hannam JA and Anderson BJ. Contribution of morphine and morphine-6-glucuronide to respiratory depression in a child. *Anaesth Intensive Care*. 2012; 40: 867-70.
44. Knibbe CA, Krekels EH, van den Anker JN, et al. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. *Clin Pharmacokinet*. 2009; 48: 371-85.
45. Holford NH, Ma SC and Anderson BJ. Prediction of morphine dose in humans. *Pediatr Anesth*. 2012; 22: 209-22.
46. Pradhan S, Duffull SB, Walker RJ and Wright DFB. The intact nephron hypothesis as a model for renal drug handling. *Eur J Clin Pharmacol*. 2019; 75: 147-56.
47. 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.
48. Wang Z, Kim S, Quinney SK, Zhou J and Li L. Non-compartment model to compartment model pharmacokinetics transformation meta-analysis--a multivariate nonlinear mixed model. *BMC Syst Biol*. 2010; 4 Suppl 1: S8.
49. 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.
50. Anderson BJ and Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol*. 2008; 48: 303-32.
51. 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.
52. Barrett DA, Elias-Jones AC, Rutter N, Shaw PN and Davis SS. Morphine kinetics after diamorphine infusion in premature neonates. *Br J Clin Pharmacol*. 1991; 32: 31-7.
53. Sheiner LB. Learning versus confirming in clinical drug development. *Clinical Pharmacology & Therapeutics*. 1997; 61: 275-91.
54. Sheiner LB. The intellectual health of clinical drug evaluation. *Clin Pharmacol Ther*. 1991; 50: 4-9.
55. Manolis E, Osman TE, Herold R, et al. Role of modeling and simulation in pediatric investigation plans. *Paediatr Anaesth*. 2011; 21: 214-21.

Figures

Figure 1: Flow diagram of systematic search based on PRISMA guidelines

Figure 2: Distribution of pharmacokinetic parameters extracted in the literature search when standardised to mean total bodyweight. AUC has been corrected to a diamorphine 5 mg dose.

Figure 3: This schematic diagram shows the metabolic flow of diamorphine, 6-mono-acetylmorphine (6-MAM) and morphine. Diamorphine absorption is described in terms of absorption half-times (T_{ABS}) and relative bioavailability ($F_{DIAMORPH}$) by oral or intranasal (IN) routes. Half-times ($T_{1/2}k$) also describe exponential flow between metabolites. The delay between active metabolites (6-MAM, morphine) and the effect compartment is described using equilibration half-times ($T_{1/2}keo$). Morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G) clearance align with renal function. The conversion of diamorphine to morphine (Conversion $_{DIAMORPH\ to\ MORPHINE}$) is assumed 2.