Oral morphine dosing predictions based on a single dose in healthy children undergoing surgery

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Introduction

- **Oral morphine** has been proposed as an effective and safe alternative to codeine for after-discharge pain in children following surgery, but there are few data guiding an optimum safe oral dose.
- **Current recommended doses** of oral morphine (1) are extrapolated from small paediatric studies of the pharmacokinetics (PK) of IV, IM or SR morphine. Such inferences may be inaccurate as they ignore the extensive biotransformation of oral morphine before it reaches the central circulation and effect sites, and slower enteral absorption.
- **Serum morphine concentrations** after an oral dose for acute pain in healthy children are not well investigated. Clinical experience suggests a target of 10-20 mcg.l^{-1} (2) and concentrations > 20 mcg.l^{-1} are associated with increased respiratory depression (3).
- **Study Aim:** To characterise the absorption PK of enteral morphine in order to simulate time-concentration profiles in children given common oral morphine dose regimens.

Method

- Randomised observational PK study.
- REB approval and written informed parental consent.
- ASA I-II subjects, aged 2-6 years undergoing elective surgery with a minimum hospital stay of 4 hours and requiring opioid analgesia.
- 34 children randomised to receive one of three doses of morphine PO pre-operatively.

Group 1	Group 2	Group 3
100 mcg.kg^{-1}	200 mcg.kg^{-1}	300 mcg.kg^{-1}

- Blood sampling at 30, 60, 90, 120, 180 and 240 minutes.
- Serum morphine concentrations determined by liquid chromatography-mass spectroscopy.
- PK parameters calculated using nonlinear mixed effects models.
- Current data pooled with published time-concentration profiles from children (n=1059, age 23 weeks postmenstrual age – 3 years) administered IV morphine (4,5).
- Used to determine oral bioavailability (F), absorption lag time (T_{LAG}) and absorption half-time (T_{ABS}).
- Parameter estimates used to predict concentrations in children given oral morphine (100, 200, 300, 400, 500 mcg.kg^{-1}) at different dosing intervals (3, 4, 5, 6, 8, 12 hours).

Results

- **Demographics:** Mean (SD) age 4.1 (1.2) yr, weight 17.0 (3.2) kg, BMI 16.1 (1) kg.m^{-2}.
- **Adverse Drug Effects:** None during 4 hour study period.
- **PK analysis:**

Parameter	Description	Estimate	PPV	95% CI
T_{ABS} (h)	Absorption half-time	0.71	0.550	0.557, 1.04
T_{LAG} (h)	Absorption Lag-time	0.145	0.636	0.106, 0.152
F	Oral bioavailability	0.298	0.365	0.276, 0.380

Table 1. Absorption parameter estimates. PPV (population parameter variability) is the apparent co-efficient of variation of between subject variability; CI is the confidence interval for the population parameter estimate.

- PC-VPC plot (Figure 1) confirms the adequacy of model predictions, showing no apparent deviations between model and data.

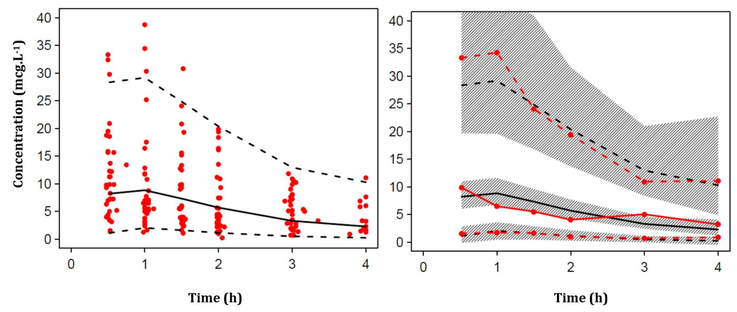

Figure 1. Population prediction corrected visual predictive checks (PC-VPC). Dashed black lines = 5th and 95th percentiles, solid black line = model predicted median. Shaded grey area = range between 5th and 95th percentiles of simulated medians, reflecting uncertainty range in the median of the observations. 90% prediction interval and median for observed data shown as lines with closed circles.

Age (yr)	Dose (mg)	C_{MAX}	$C_{MAX\ ss}$	C_{SS}	$C_{MAX\ ss}$	C_{SS}	$C_{MAX\ ss}$	C_{SS}
100 mcg.kg^{-1}		**Loading**	**3 hourly**		**4 hourly**		**6 hourly**	
1	1	9.6	20.1	17.7	16.2	13.1	12.6	8.9
3	1.5	10	22	19.5	17.6	14.5	13.6	9.8
5	2	10.2	23.5	20.8	18.7	15.5	14.3	10.5
10	3	10.5	25.6	22.8	20.3	17	15.4	11.5
15	5.5	11.1	29.1	26.1	23.1	19.6	17.3	13.2
Age (yr)	**Dose (mg)**	C_{MAX}	$C_{MAX\ ss}$	C_{SS}	$C_{MAX\ ss}$	C_{SS}	$C_{MAX\ ss}$	C_{SS}
150 mcg.kg^{-1}		**Loading**	**3 hourly**		**4 hourly**		**6 hourly**	
1	1.5	14.4	30.2	26.5	24.2	19.9	18.9	13.3
3	2.25	14.9	33.1	29.3	26.4	21.9	20.3	14.7
5	3	15.3	35.2	31.3	28.1	23.5	21.5	15.7
10	4.5	15.8	38.3	34.2	30.5	25.7	23.1	17.3
15	8.25	16.6	43.7	39.2	34.6	29.6	25.7	19.8
Age (yr)	**Dose (mg)**	C_{MAX}	$C_{MAX\ ss}$	C_{SS}	$C_{MAX\ ss}$	C_{SS}	$C_{MAX\ ss}$	C_{SS}
200 mcg.kg^{-1}		**Loading**	**3 hourly**		**4 hourly**		**6 hourly**	
1	2	19.2	40.2	35.4	32.3	26.5	25.2	17.8
3	3	19.9	44.1	39	35.2	29.2	27	19.6
5	4	20.4	47	41.7	37.4	31.3	28.4	21
10	6	21.1	51.2	45.6	40.7	34.3	25.2	19.1
15	11	22.2	57.4	52.2	46.2	39.4	15.5	12

Table 2. Concentrations achieved from simulations after a loading dose and at steady-state (SS) for 100 mcg.kg^{-1}, 150 mcg.kg^{-1} and 200 mcg.kg^{-1} oral morphine dosing. All concentrations measured in mcg.L^{-1}

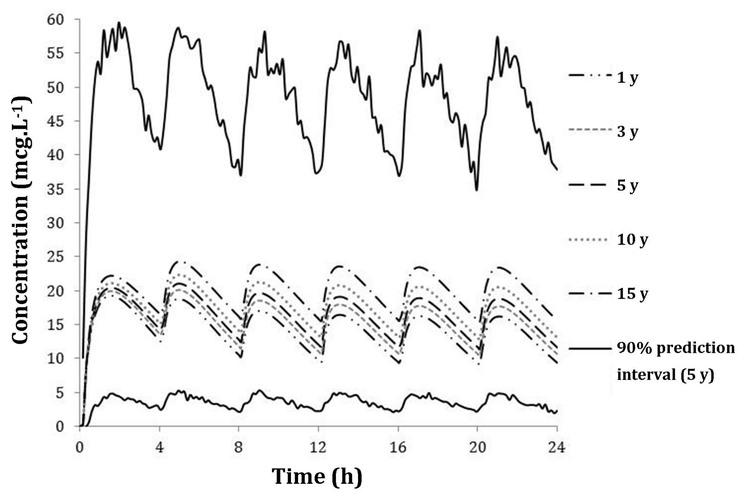

Figure 3 Time concentration profile for a loading dose 200 mcg.kg^{-1} followed by a maintenance dose of 100 mcg.kg^{-1} 4 hourly given to children 1 year, 3 years, 5 years, 10 years and 15 years. The 90% prediction interval for the 5 year old child, derived from 1000 simulations, is also shown (black solid lines).

Discussion

- Oral morphine **200 mcg.kg^{-1} then 100 mcg.kg^{-1} 4 h** or **150 mcg.kg^{-1} 6 h** achieves mean concentrations associated with analgesia.
- The morphine dose prescribed will depend on the **indication** for use and 100 mcg.kg^{-1} 6 h may be satisfactory for mild to moderate pain.
- **Clearance decreases with age** in children and this is reflected in higher observed concentrations in older children (Table 2). This is why the upper dose is limited to 5 mg by some authorities.
- There was **high serum concentration variability** suggesting that respiration may be compromised in some children given these doses.
- Pharmacodynamic variability may lower (or increase) the minimum effective concentration and/or therapeutic index. This highlights the problem of a "One-Dose-Fits-All" approach.
- Pain scores are not described due to the wide range of surgery performed and anaesthetic regimens used.

References

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