

Modelling analgesia-concentration relationships for morphine to evaluate experimental pain models

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Aims

To develop a population pharmacokinetic-pharmacodynamic (PK-PD) model describing the concentration-effect relationship for morphine on experimental pain caused by skin heat and muscle pressure, and to assess whether these experimental pain models are useful to study the analgesic effects of opioids.

Methods

Thirty-nine healthy volunteers participated in the randomised, double blind, placebo controlled crossover study. After an oral dose of 30 mg morphine hydrochloride or placebo, blood samples were collected and experimental skin heat and muscle pressure was induced repeatedly until 150 min post dose. Nociceptive input was increased until the subjects reported a pain score of 7 corresponding to moderate pain threshold on a 0-10 visual analogue scale, where 5 is the pain detection threshold.

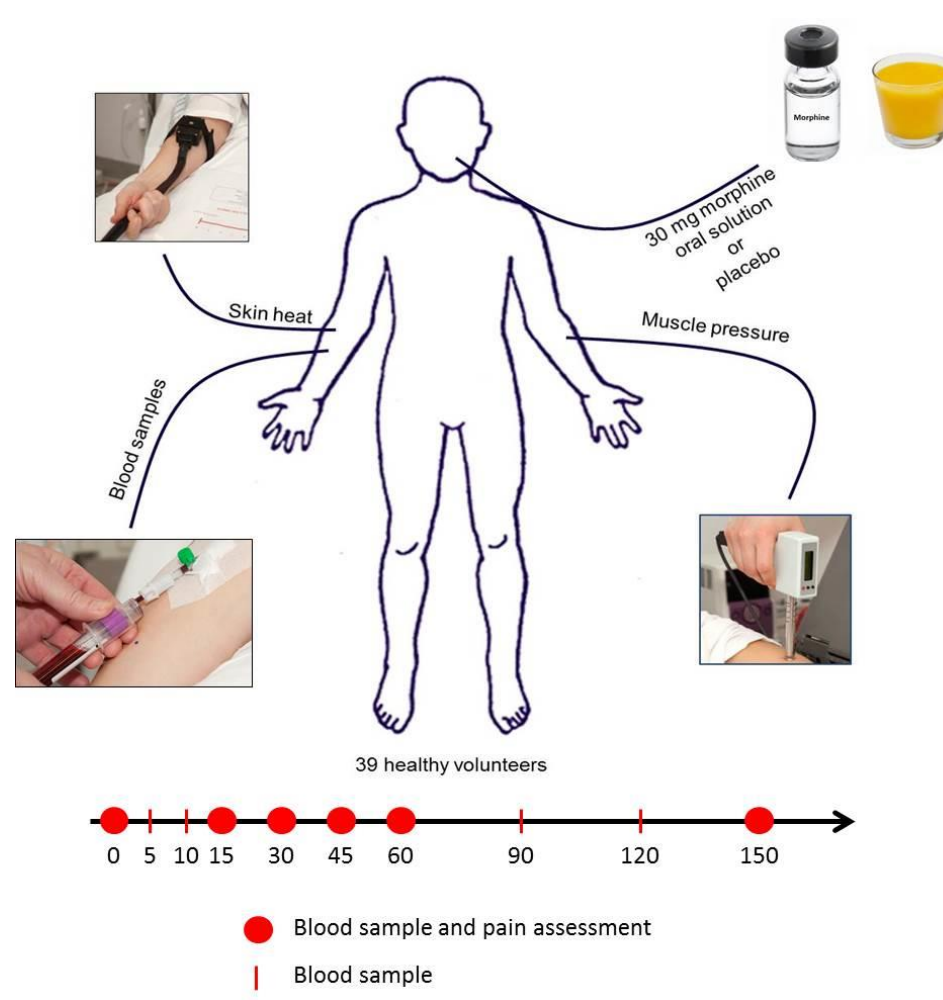


Figure 1. Overview of the study design.

PKPD modelling

A sequential approach was taken to model the data using NONMEM v. 7.2, ICON Plc.

PK modelling

One- and two-compartment models were fitted to morphine, M6G, and M3G plasma concentration-time data, and first order and transit compartment absorption models were tested. The individual parameter estimates were used as input in the subsequent PD modelling.

PD modelling

Placebo response of both pain metrics was fitted to slope 0, linear, and quadratic effect versus time models. Drug effect was fitted to slope 0, linear, and $E_{\max}$ models of effect versus plasma or effect compartment concentration, and was either proportional or additive to placebo response/baseline.

MUSCLE PRESSURE

A	PARAMETER	UNITS	ESTIMATE	%SE
	Θ_1 , baseline	kPa	471	5.6
	Θ_2 , drug slope	% response/(ng/ml)	1.6	37.6
	Θ_4 , k_{e0}	min ⁻¹	0.028	7.9
	ω_1 , BOV baseline	-	0.099	31.4
	ω_2 , BSV baseline	-	0.34	19.0
	ω_3 , BSV drug slope	% response/(ng/ml)	0.30	81.7
	σ , additive error	kPa	71.13	16.5

SKIN HEAT

B	PARAMETER	UNITS	ESTIMATE	%SE
	Θ_1 , baseline	°C	45	0.8
	Θ_2 , drug slope	% response/(ng/ml)	0.0403	44.2
	ω_1 , BOV baseline	°C	0.61	26.4
	ω_2 , BSV baseline	°C	2.33	27.2
	ω_3 , BSV drug slope	% response/(ng/ml)	0.00044	151.8
	σ , additive error	°C	0.81	11.6

Table 1. PD parameters for muscle pressure (A) and skin heat (B). BOV: between-occasion variability. BSV: between-subject variability. SE: standard error.

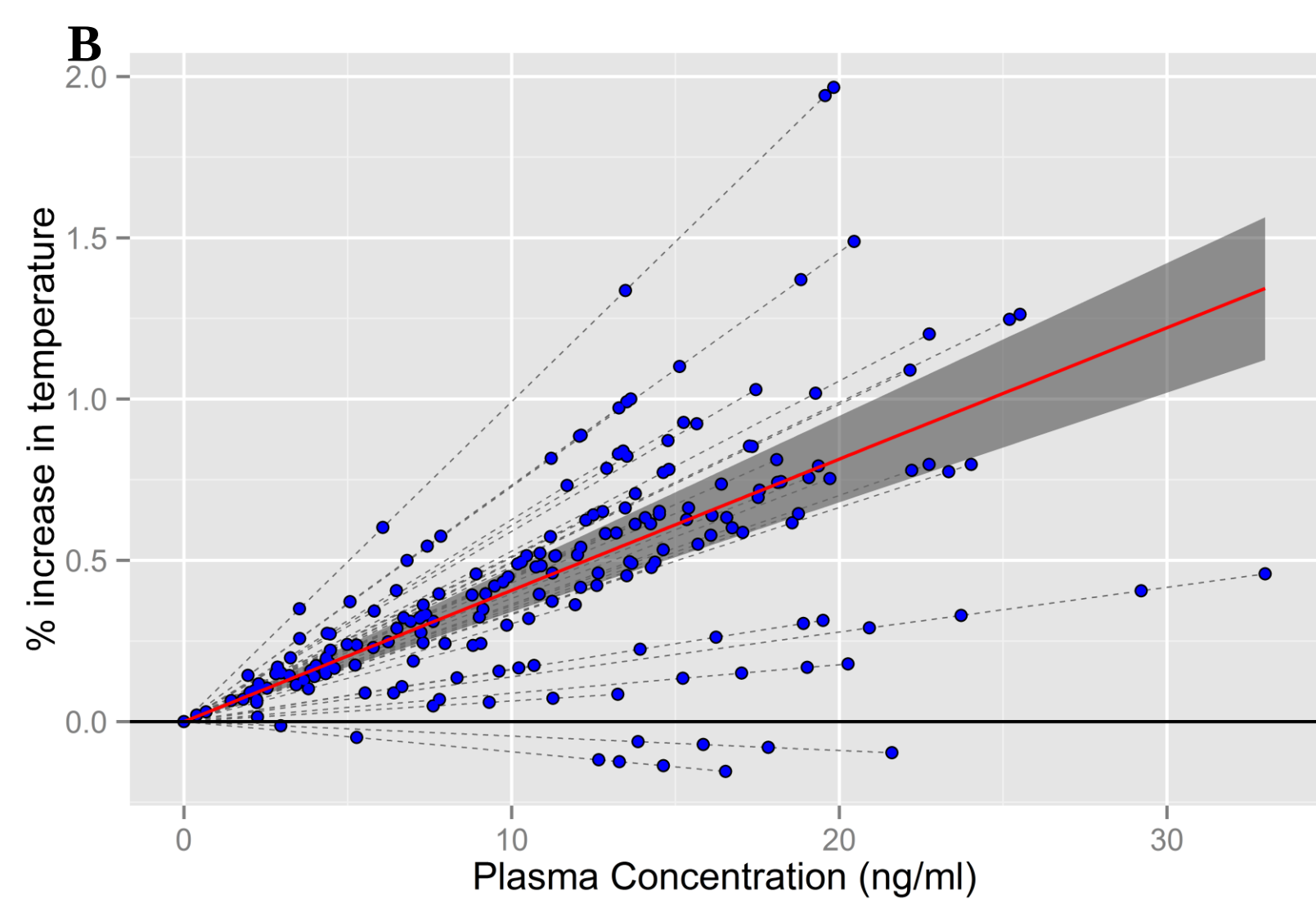
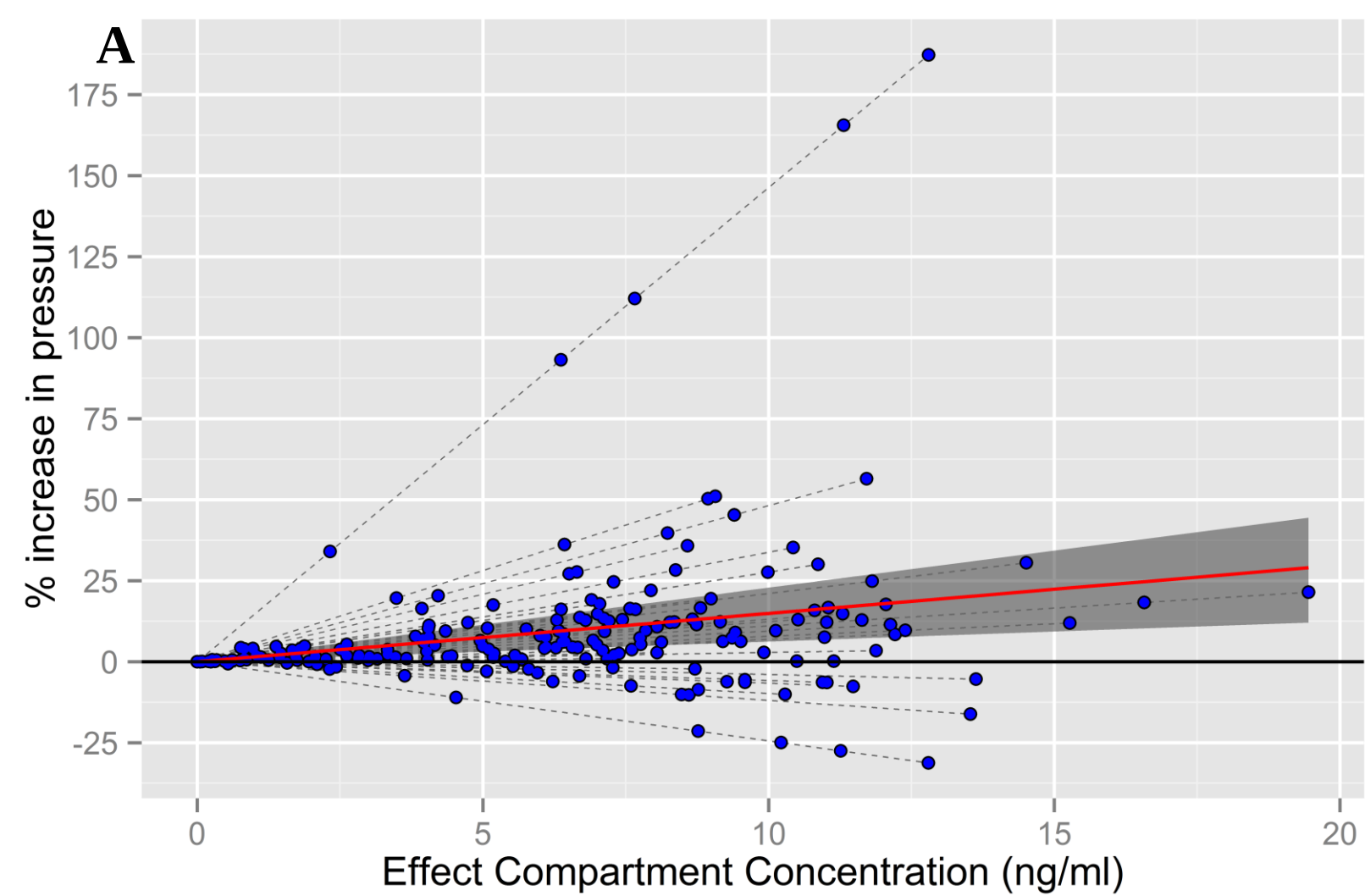


Figure 2. A: Morphine effect (% increase in pressure) vs effect compartment concentration. B: Morphine effect (% increase in temperature) vs plasma concentration. Red line: population drug effect slope. Dashed lines: individual drug effect slopes. Shaded area: 90% confidence interval of population slope.

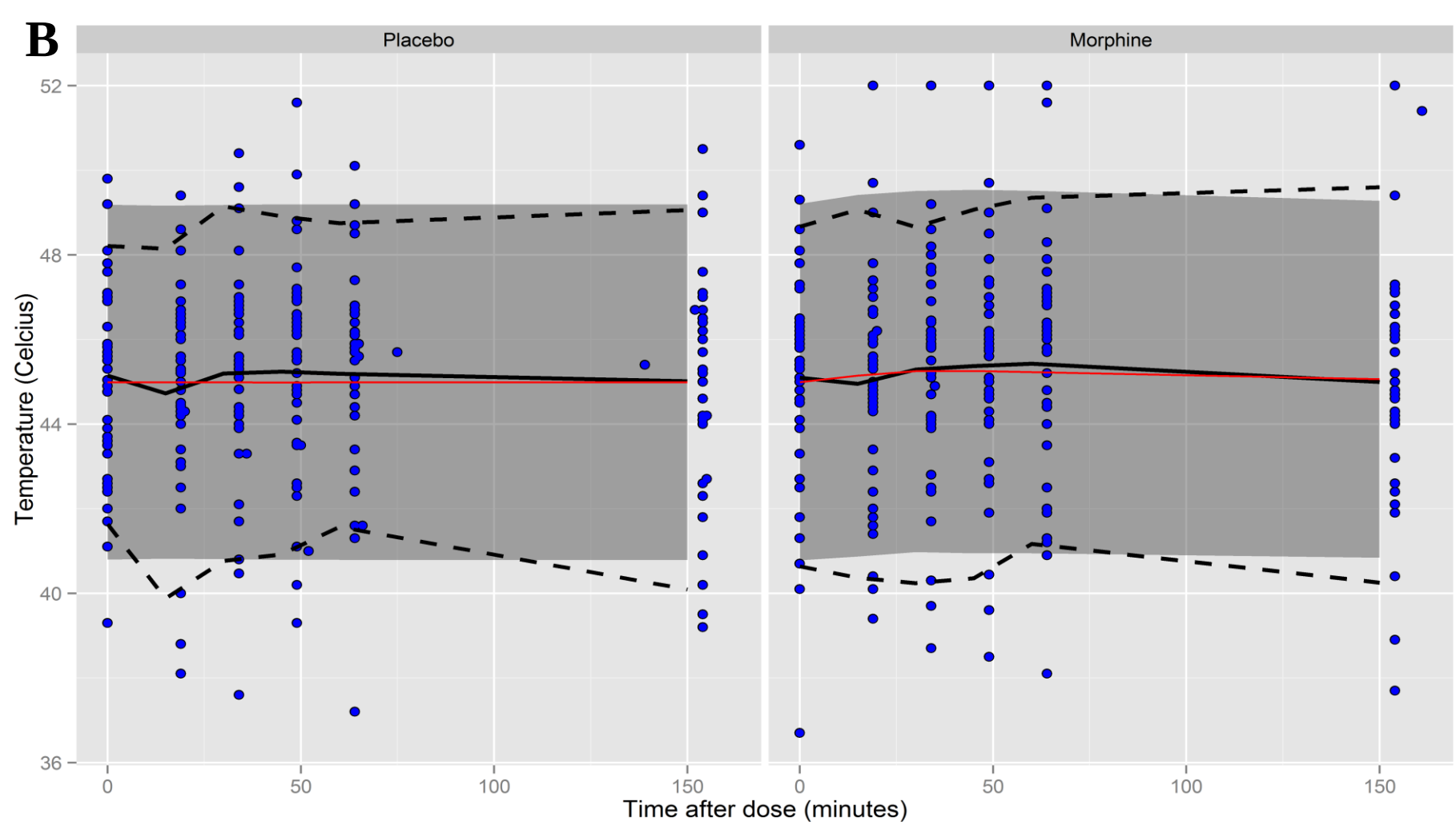
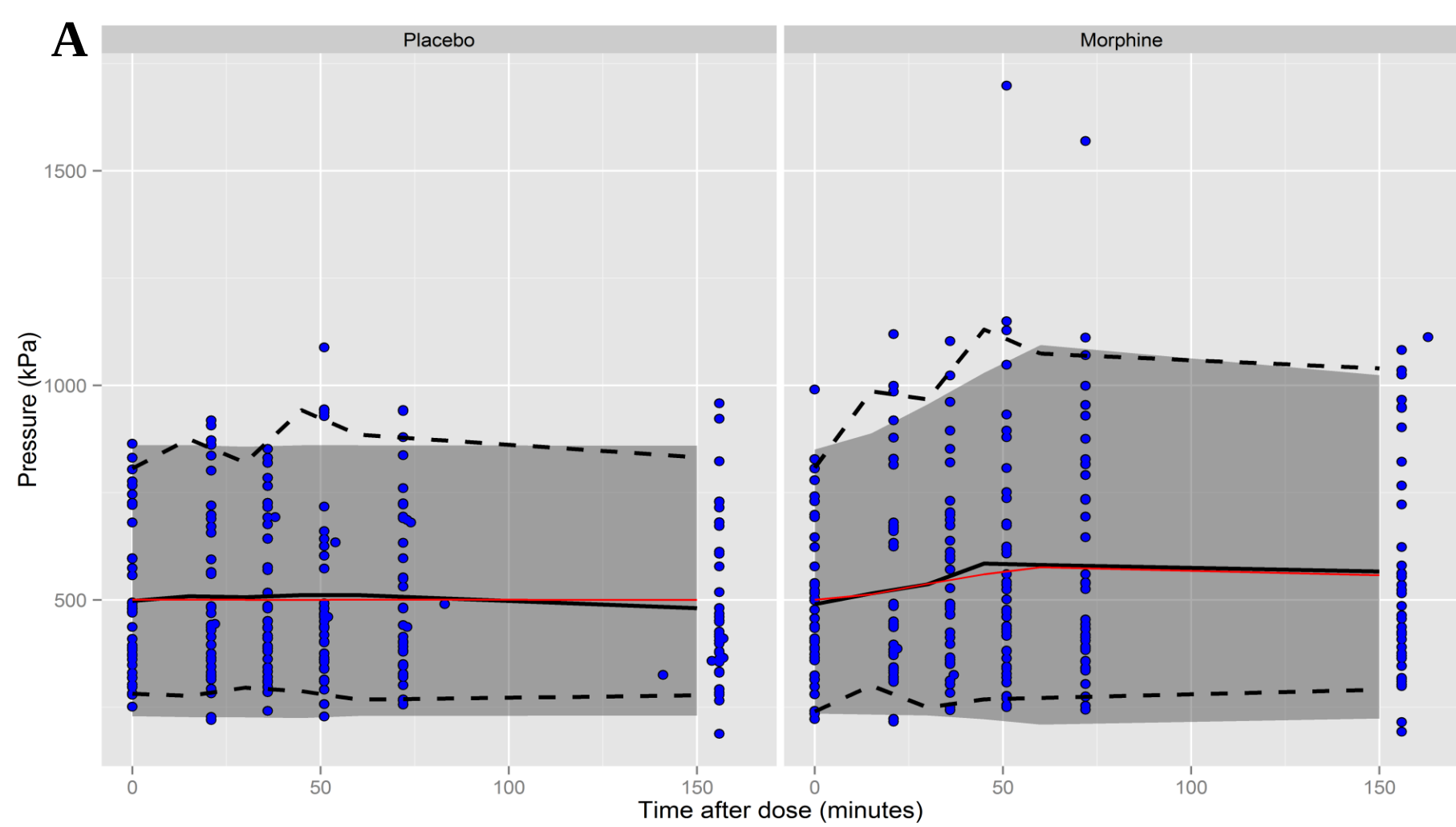


Figure 3. Visual Predictive Check for muscle pressure (A) and skin heat (B) threshold, following oral administration of either 30 mg morphine or placebo. Solid lines: Observed (red) and predicted (black) population mean. Dashed lines: observed 5% and 95% percentiles of the mean. Shaded areas: 90% confidence interval of predicted mean.

$$E = E_{\text{baseline}} \cdot (1 + E_{\text{morphine}}) + \sigma$$

	Muscle pressure	Skin heat
E_{baseline}	$\theta_1 \cdot e^{\eta_1 + \eta_2}$	$\theta_1 + \eta_1 + \eta_2$
E_{morphine}	$(\theta_2 + \eta_3) \cdot k_{e0} \cdot (C_{\text{plasma}} - C_{\text{eff}})$	$(\theta_2 + \eta_3) \cdot C_{\text{plasma}}$
	$\text{VAR}(\eta_i) = \omega_i^2$	

Table 2. PD model (E), baseline models (E_{baseline}) and morphine effect models (E_{morphine}). Θ_1 : baseline. Θ_2 : drug slope. η_1 : between occasion variability on baseline. η_2 : between-subject variability on baseline. η_3 : between-subject variability on drug slope. C_{plasma} : plasma concentration. C_{effect} : effect compartment concentration. K_{e0} : effect compartment equilibrium rate constant.

Results

PK model

- Plasma concentration-time profiles of morphine, M6G, and M3G were best described with a one-compartment distribution.
- Absorption of morphine was best described with a six transit compartment model with a combined additive and proportional residual error model.

PD models

- There was no change in placebo-response with time. However, baseline varied between individuals and occasions and was thus described with between-subject variability (BSV) and between-occasion variability (BOV). For both pain metrics, morphine effect was proportional to baseline and described by a linear model with BSV on drug effect slope and an effect compartment for muscle pressure.
- The models suggest that a morphine concentration increase of 16 ng/ml at steady-state provides a minor increase in skin heat threshold (0.645%) and a substantial increase in muscle pressure threshold (25.6%).

Conclusion

A linear concentration-effect relationship for morphine was identified for both pain metrics. However, the drug effect for skin heat was marginal in relation to clinical relevance, while more than 20% drug response was seen for muscle pressure at clinically relevant plasma concentrations of morphine¹. This could suggest that phasic, deep pain (muscle pressure) is more appropriate for opioid assessment than tonic superficial pain (skin heat).

References

¹ Dahlstrom B, Tamsen A, Paalzow L, Hartvig P. Patient-controlled analgesic therapy, Part IV: pharmacokinetics and analgesic plasma concentrations of morphine. Clin Pharmacokinet 1982 May-Jun;7(3):266-279.