

POPULATION PK-PD MODEL OF SUBCUTANEOUS BUPIVACAINE IN A NOVEL EXTENDED-RELEASE MICROPARTICLE FORMULATION

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Bupivacaine for postoperative pain management

- ◆ Most **local anesthetics** have a duration of efficacy **shorter than 24 hours**¹
- ◆ **Extended-release** formulations have a potential for **improving postoperative outcomes**
- ◆ Epidurally administered **bupivacaine** has previously been shown to have plasma concentration-time profiles with **two peaks**²
- ◆ Here, we studied two formulations of **LIQ865** (hexagonal bupivacaine microparticles produced with PRINT[®]-technology³) for **sub-cutaneous** injection:



- A:** 55% PRINT-bupivacaine + 45% PLGA (n = 16)
- B:** 100% PRINT-bupivacaine (n = 12)

Biphasic absorption modeled as two parallel processes

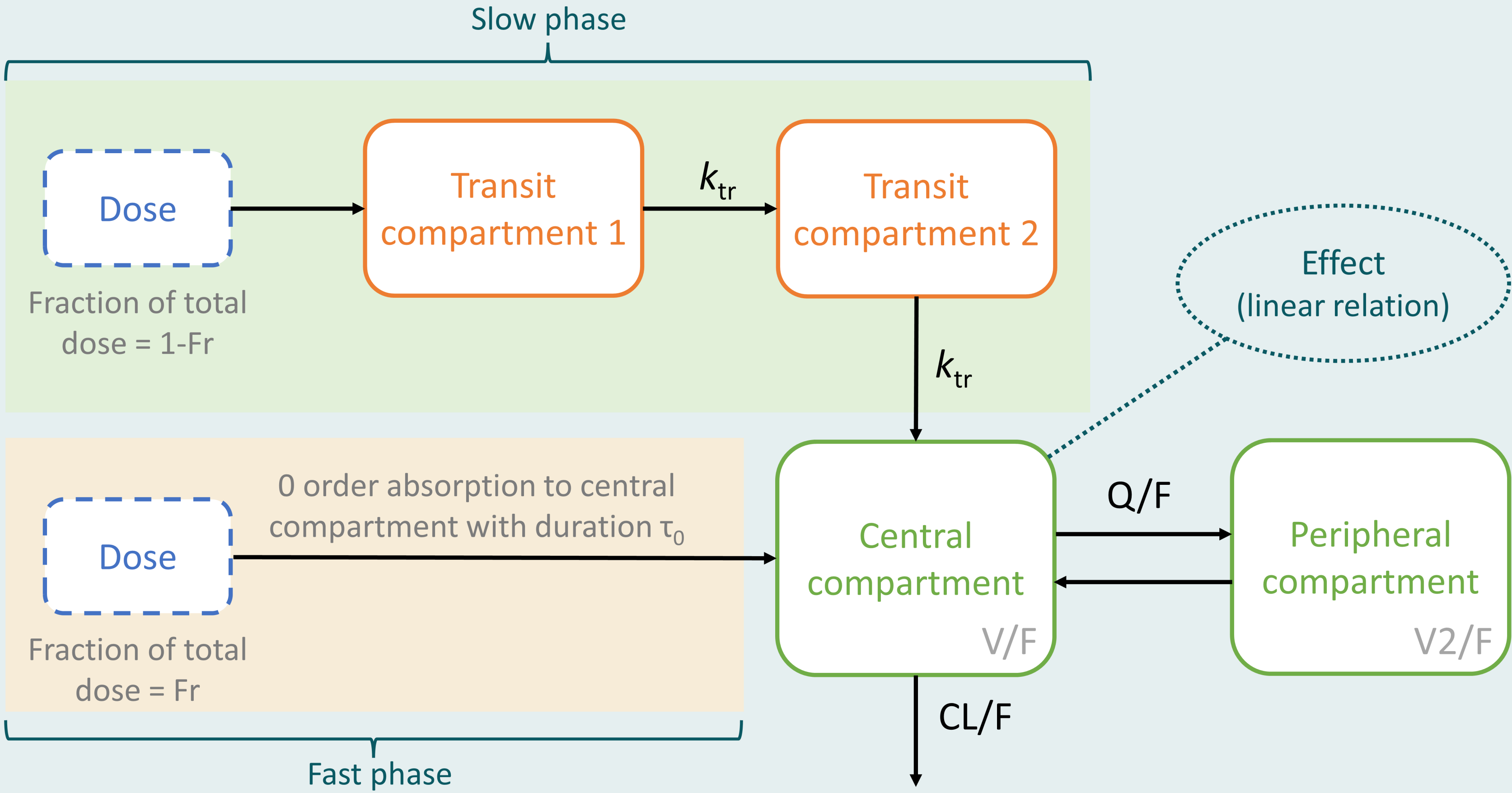


Figure 1. Schematic representation of the structural PK-PD model. k_{tr} = transit rate constant; CL/F = apparent clearance; Q/F = apparent intercompartmental clearance; V/F = apparent volume of the central compartment; $V2/F$ = apparent volume of the peripheral compartment

Population PK-PD model adequately describes biphasic profiles

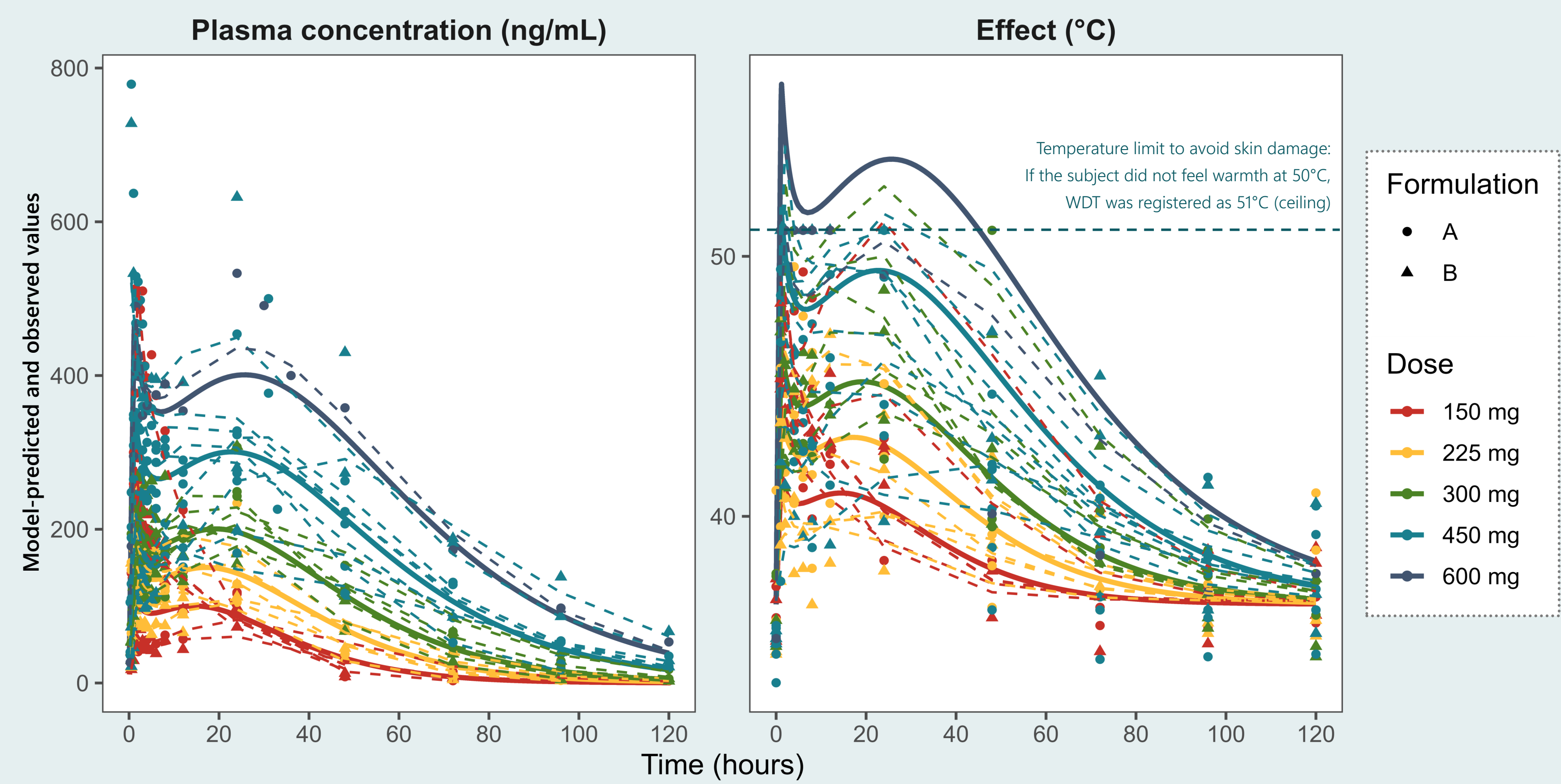


Figure 2. Observed and model-predicted plasma concentration and warmth detection threshold (effect) values for the population (solid lines) and individuals (dashed lines).

Dose-dependent absorption rate appearing to limit clearance

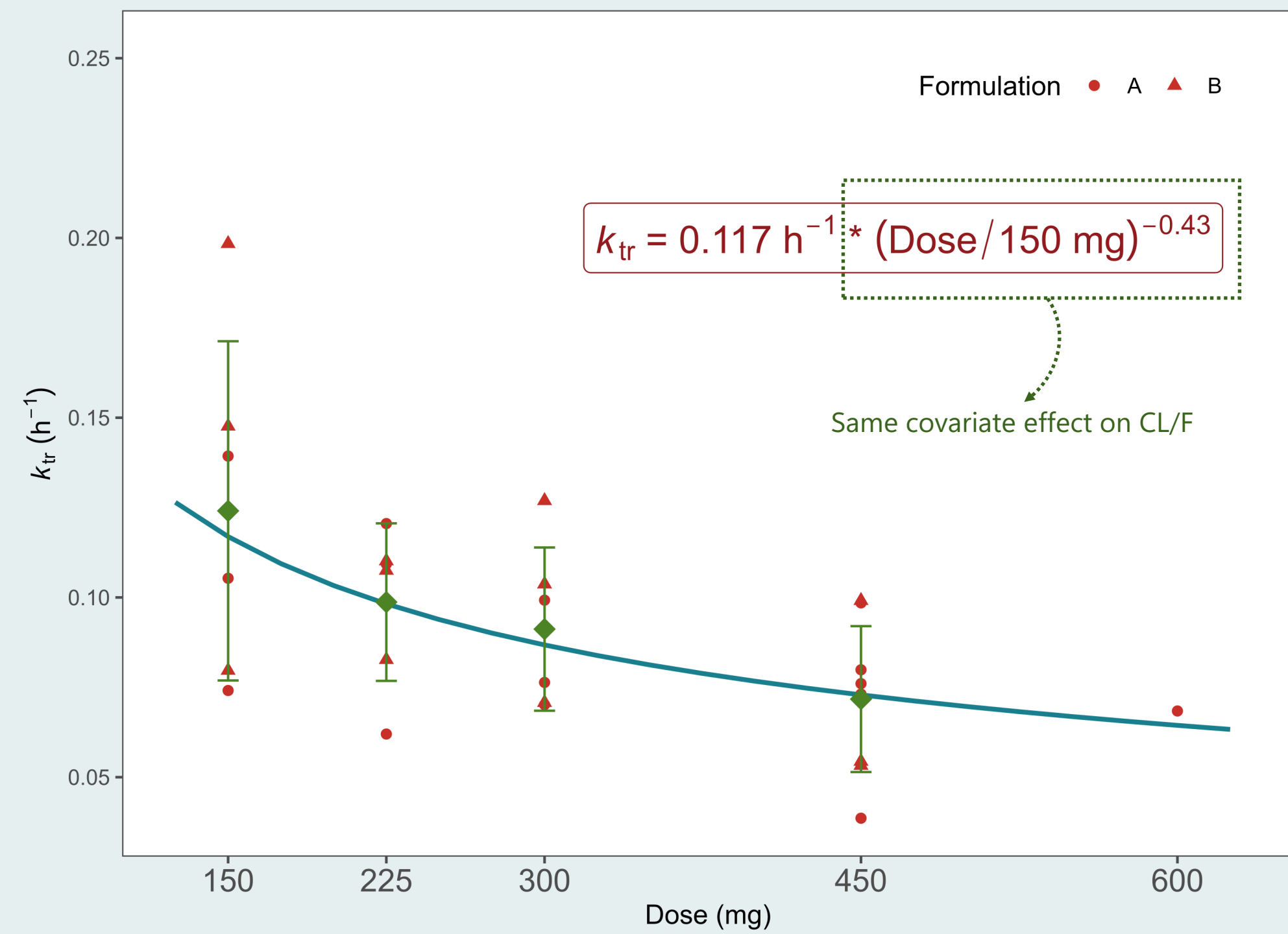
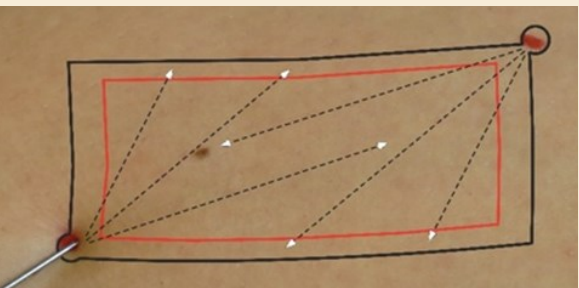


Figure 3. Function of the transit rate constant (k_{tr}) showing its relationship to dose as estimated by the population PK-PD model. The same covariate effect of dose was implemented on apparent clearance (CL/F). Red points are individually estimated parameter values, green points are means, and error bars are standard deviations.

Methods

- ◆ Data from a phase 1 randomized, placebo-controlled, double-blind, dose-ascending study in 28 healthy male volunteers
- ◆ LIQ865 injected in one lower leg, diluent in the other, from two points with fan-like needle trajectories⁴
- ◆ 18 blood samples per subject drawn over 5 days, analyzed for bupivacaine
- ◆ Warmth detection threshold used as surrogate PD endpoint in PK-PD modeling; 12 assessments made per subject over 5 days
- ◆ Bupivacaine plasma concentration-effect-time data fitted to population PK-PD models with non-linear mixed-effects modeling using Phoenix NLME 8.3



References

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3. Xu J, Wong DH, Byrne JD, et al. *Future of the particle replication in nonwetting templates (PRINT) technology*. Angew Chem Int Ed Engl. 2013;52(26):6580-6589.
4. Jensen EK, Borgevig S, Balchen T, et al. *Dose safety and pharmacodynamics of subcutaneous bupivacaine in a novel extended-release microparticle formulation: A phase 1, dose-ascending study in male volunteers*. Basic Clin Pharmacol Toxicol. 2024;134(5):657-675.

Key Points

- ◆ Biphasic absorption of bupivacaine was adequately described as two parallel processes, but with large inter-individual variability on parameters Fr (CV% = 57.4%) and τ_0 (CV% = 51.9%), complicating reliable prediction
- ◆ A linear function best described the relationship between plasma concentrations and warmth detection threshold
- ◆ CL/F and k_{tr} both decreased with increasing doses (with a shared covariate effect of dose on the parameters), possibly due to flip-flop kinetics
- ◆ Formulation (A or B) did not have any significant covariate effect on any parameters

Further reading

Storgaard IK et al. Population pharmacokinetic-pharmacodynamic model of subcutaneous bupivacaine in a novel extended-release microparticle formulation. Basic Clin Pharmacol Toxicol. 2024;134(5):676-685.



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