

Population pharmacokinetic model for a local sustained-release hydrogel formulation containing bupivacaine for the postoperative pain management after spinal surgery.

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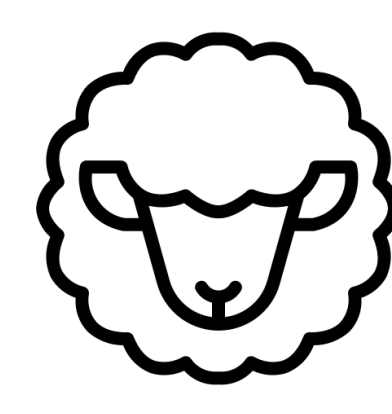
Background

- Spinal surgery often leads to significant postoperative pain.
- Pain is typically managed with opioids**, which have major **drawbacks**:
 - Systemic side effects (e.g., sedation)
 - Impaired rehabilitation^{1,2}.
- Local anesthetics** offer a **non-opioid alternative**
 - But have a short duration of action
- To overcome this, a sustained-release system was developed for bupivacaine:
 - Ring-shaped hydrogel implants
 - Contain crystallized bupivacaine
 - Co-implanted with pedicle screws in a sheep model

Primary objective

To develop a preclinical PK model for the sustained-release formulation of bupivacaine in sheep to predict human exposure.

Methods

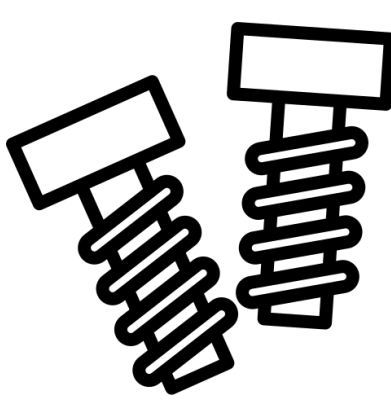


Six preclinical experiments

- 48 sheep
- Six received a s.c. injection
 - to estimate bupivacaine clearance

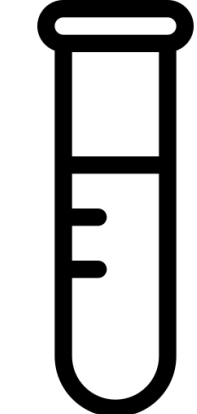
Six ring types, which differed in:

- Dose, buffer, coating, molecular weight of the biopolymer, etc.



Experiments varied in

- Types and combination of rings
- Number of rings/sheep, e.g. 4, 6, 8
- Dose per ring, 5 to 90 mg
- Total amount 100-350 mg per sheep



Sampling regime, ring experiment

- 1 to 16 plasma samples/sheep
- From 0.5 to 360 hours after implant

After 150 mg s.c. injection

- Samples collected at 1, 4, 8, 20, 24, 32, 48, 72 and 96 hours

Results

Different common absorption profiles were tested for model development

- Dual, first- and zero-order, saturable Michaelis-Menten absorption, Weibull function and multiple transit compartment models*

The PK profiles were best described by a **one-compartment model with a first-order absorption process with one transit compartment**

- Evaluation of the PK profiles showed **flip-flop kinetics**, a known phenomenon in modified or extended-release formulations, Figure 1^{3,4}

Parameter estimates are shown in Table 1. Prediction corrected Visual Predictive Check and goodness-of-fit plots, Figure 2&3, showed adequate data description.

Table 1. Pharmacokinetic parameter estimates in sheep scaled to a 70 kg human

Parameter	Estimates	(95% CI - SIR results)
PK parameters		
CL (L/h)	35.2	(28.76 – 42.76)
V _c (L)	435	(345.5 – 569.8)
k _a expt. 1 (h ⁻¹)	0.018	(0.011 – 0.027)
k _a expt. 2 (h ⁻¹)	0.750	(0.428 – 1.413)
k _a expt. 3 (h ⁻¹)	0.797	(0.522 – 1.179)
k _a expt. 5 (h ⁻¹)	0.276	(0.167 – 0.477)
k _a expt. 6 (h ⁻¹)	0.596	(0.393 – 0.915)
k _{tr} (h ⁻¹)	0.818	(0.507 – 1.111)
F s.c.	0.361	(0.229 – 0.534)
IIV		
IIV on CL (CV %)	51.0	(40.32 – 64.72)
IIV on V (CV %)	70.3	(47.42 – 96.42)
IIV on k _a (CV %)	28.2	(16.16 – 44.83)
IIV on k _{tr} (CV %)	101	(63.40 – 148.75)
Correlation ω _{CL} ~ ω _{Vc}	0.55	(0.408 – 0.575)
Correlation ω _{CL} ~ ω _{ka}	0.50	(0.076 – 0.566)
Correlation ω _{ka} ~ ω _V	0.91	(0.604 – 0.747)
Residual unexplained variability		
σ prop. error (CV %)	25.7	(23.37 – 28.48)

CI confidence interval, CL clearance, CV coefficient of variation, F s.c. Bioavailability of the subcutaneous injection, IIV interindividual variability, k_a Absorption constant, Prop. Proportional, V_c volume of distribution central compartment

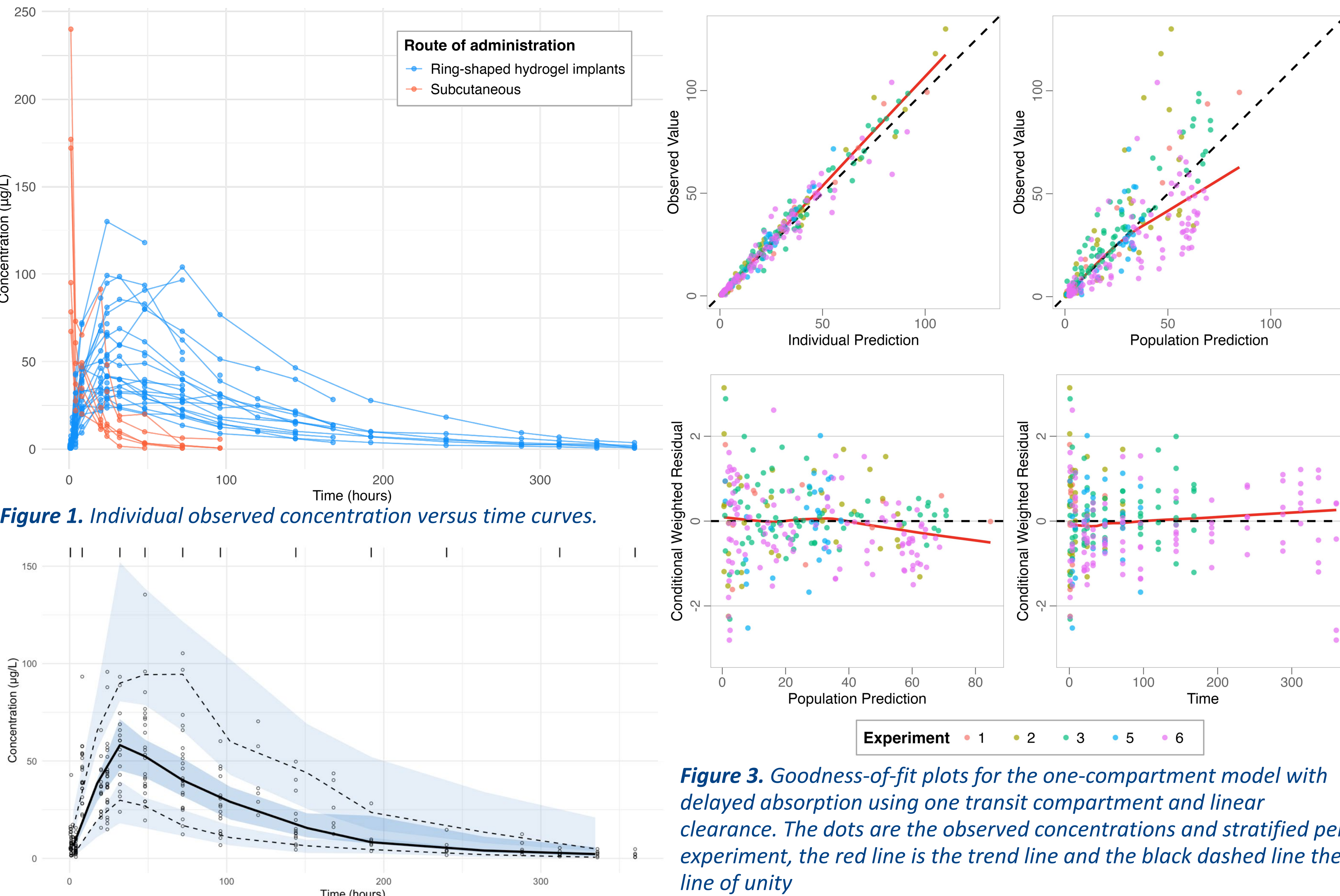


Figure 1. Individual observed concentration versus time curves.

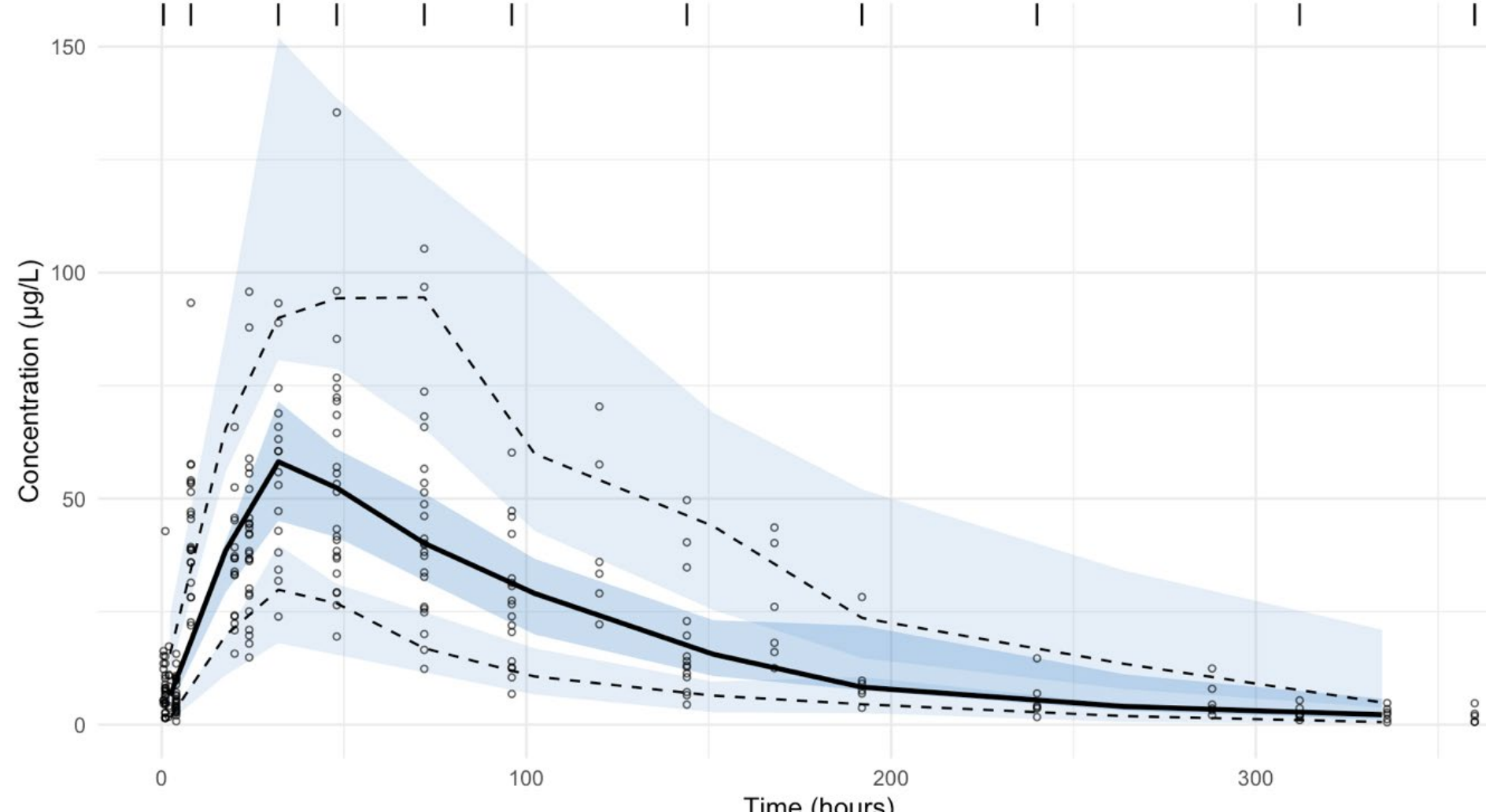


Figure 2. Prediction-corrected Visual Predictive Check (pcVPC) for the final model. Shaded areas are the 95% confidence intervals of the simulated data (n=1000)

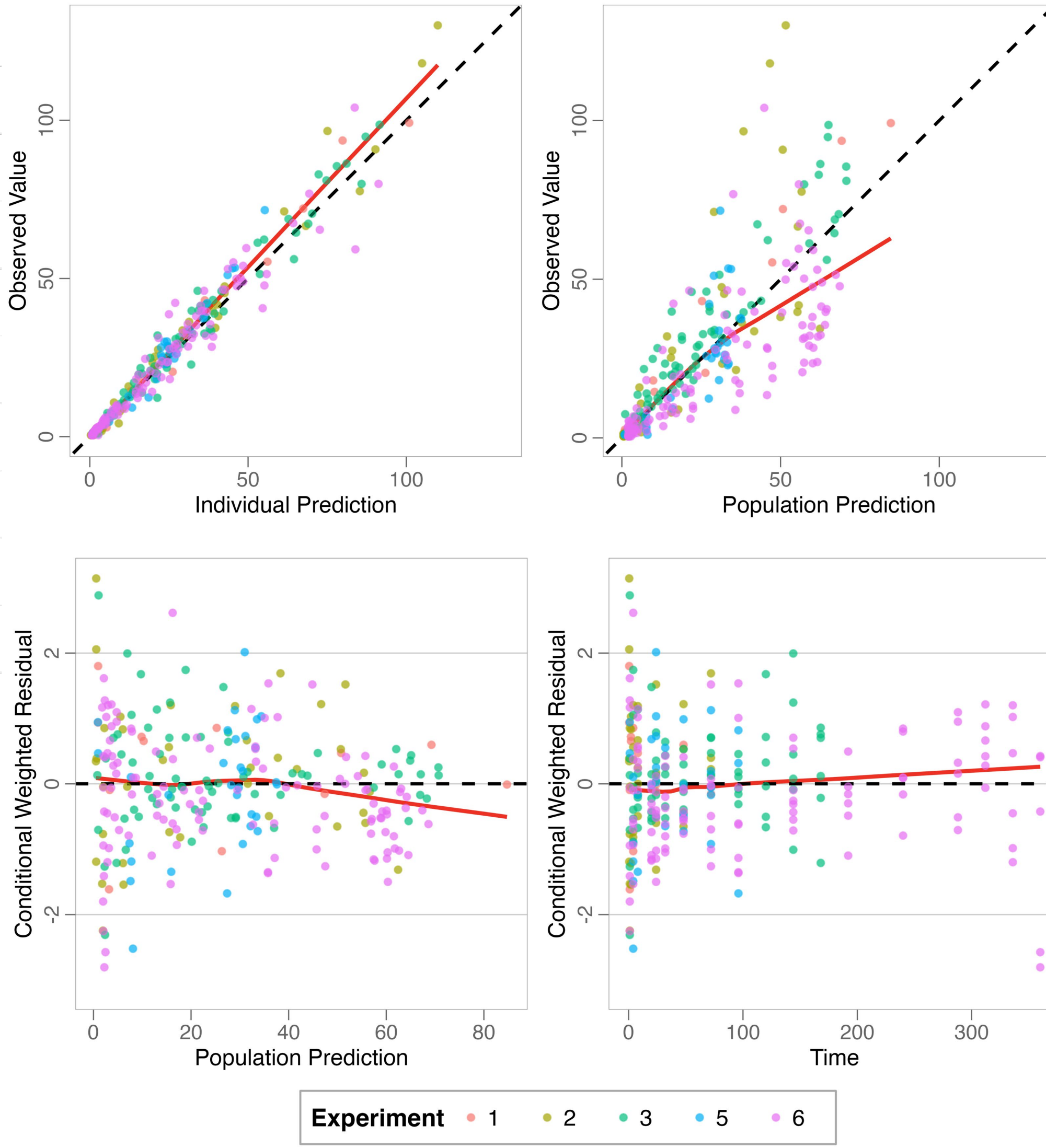


Figure 3. Goodness-of-fit plots for the one-compartment model with delayed absorption using one transit compartment and linear clearance. The dots are the observed concentrations and stratified per experiment, the red line is the trend line and the black dashed line the line of unity

Conclusion

- A novel sustained-release bupivacaine hydrogel was evaluated in sheep.
- The formulation showed a distinct PK profile with flip-flop kinetics.
- These findings offer valuable insights and support further clinical development of hydrogel-based local anesthetic delivery.
 - supporting the potential of this long-acting, localized delivery systems to **enhance postoperative recovery**