S1. Mathematical details of model construction

Mathematical basis for relationship between the awakening Cp and maintenance Cp and SE

Based on the sigmoid Emax pharmacodynamic model,

$$SE = SE_{base}\left(\frac{Cp_{50}^{\gamma}}{Cp_{50}^{\gamma} + Cp^{\gamma}}\right)$$

Where,

- Cp is the propofol plasma concentration
- Cp_{50} is the Cp for 50% maximum effect (i.e. when SE = half SE_{max})
- SE is the state entropy (corresponding to Cp)
- SE_{base} is the baseline SE in the absence of any effects from propofol
- γ is the Hill coefficient

Rearranging the above equation and substituting maintenance phase values of SE and Cp, we can calculate Cp_{50}, which can be regarded as a measure of patient sensitivity to propofol.

$$Cp_{50} = \left(\frac{SE_{base}}{SE_{main}} - 1\right)^{-1/\gamma} Cp_{main}$$

Where,

- Cp_{main} is the Cp during the maintenance phase
- SE_{main} is the corresponding maintenance phase state entropy

Inverting the above equation and applying it to the emergence phase, we observe that the awakening Cp (Cp_{wake}) is linearly related to Cp_{50}

$$Cp_{wake} = \left(\frac{SE_{base}}{SE_{wake}} - 1\right)^{1/\gamma} Cp_{50}$$

Using the equation for linear regression and substituting the value of Cp_{50} calculated from the maintenance phase while assuming SE_{wake} is a constant, we obtain an expression for predicting Cp_{wake}

$$Cp_{wake} = a \cdot Cp_{50} + b = a \cdot \left(\frac{SE_{base}}{SE_{main}} - 1\right)^{-1/\gamma} Cp_{main} + b$$

Where,

- *a* and *b* are linear regression coefficients

Finally, by applying least squares fitting to our dataset (Cp_{main}, SE_{main}, Cp_{wake}), we can estimate the values of a, b, γ and SE_{base} that minimises the mean absolute performance error of the above regression equation.

Where,

$$Absolute\ Performance\ Error = \left|\frac{Cp_{observed} - Cp_{predicted}}{Cp_{predicted}}\right|$$

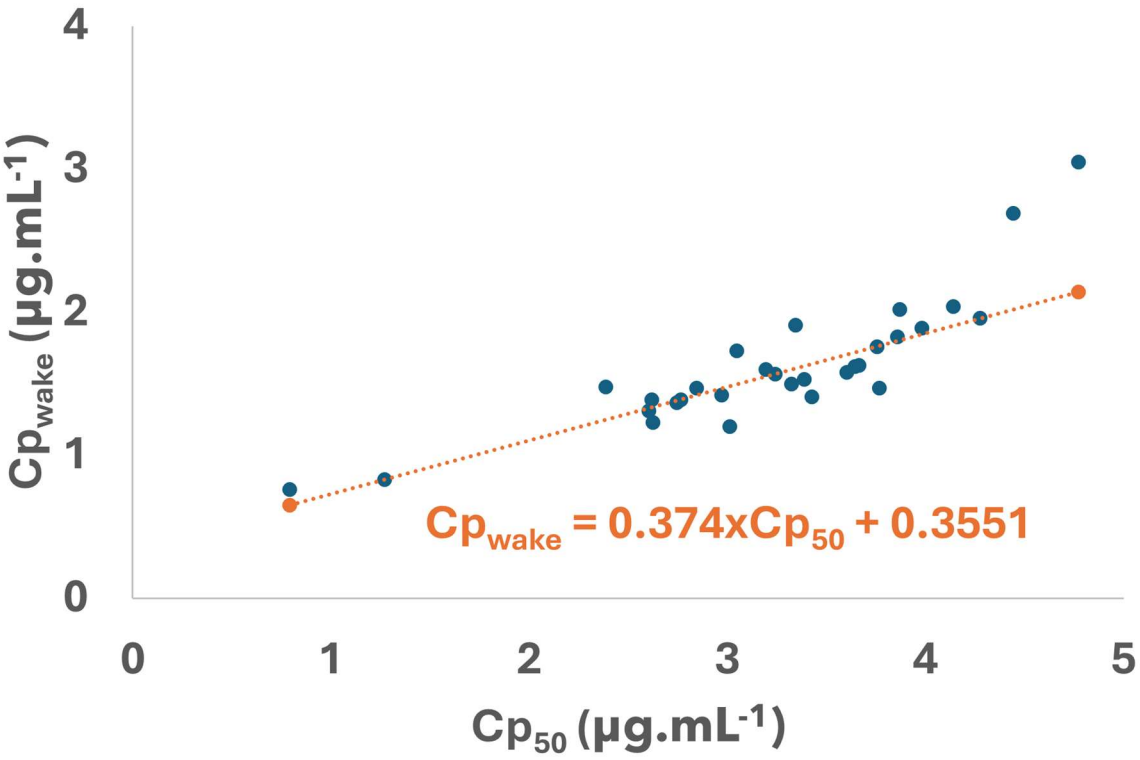
Parameters of the final predictive model

a = 0.3740

b = 0.3551

γ = 5.970

SE_{base} = 99.7



S2. Baseline patient characteristics and anaesthesia details

Table S1 Patient characteristics and model performance across the three study groups. Patients from the Model group was used to construct the predictive model. The validation cohort was categorised into Pain and No Pain groups based on whether additional analgesics were required in the post-anaesthesia care unit. Values are mean (SD), number (proportion), median (IQR [range]) or percentage.

	Model n = 30	No Pain n = 41	Pain n = 59
Age; y	64.4 (11.2)	57.0 (20.2)	48.4 (19.5)
Sex; female	10 (33%)	22 (54%)	38 (64%)
Airway			
Tracheal tube	30 (100%)	17 (41%)	49 (83%)
Supraglottic airway	0 (0%)	24 (59%)	10 (17%)
Surgical time; mins	125 (82.5–160 [60–260])	80 (60–100 [60–270])	90 (60–130 [60–320])
Maintenance Cp; $\mu g.mL^{-1}$	3.4 (3.0–3.9 [1.0–5.0])	3.5 (3.0–4.0 [1.0–5.0])	3.5 (3.2–4.0 [1.5–6.0])
Maintenance SE	42.5 (40–49.5 [20–59])	44 (36–50 [20–61])	42 (37.5–47 [23–65])
Awakening Cp; $\mu g.mL^{-1}$	1.55 (1.40–1.81 [0.76–3.05])	1.66 (1.30–1.85 [0.61–3.05])	1.95 (1.51–2.31 [0.77–3.76])
MDPE	0%	4%	14%
MDAPE	6%	15%	21%

Cp, plasma concentration; SE, state entropy; MDPE, median performance error; MDAPE, median absolute performance error.

Anaesthesia for pulmonary vein isolation

The Model group consisted of 30 patients undergoing pulmonary vein isolation for atrial fibrillation with 15 cases of radiofrequency ablation, 8 cases of cryoablation and 7 cases of pulse field ablation. All procedures were performed under general anaesthesia and managed by the author (GZ) with propofol and remifentanil delivered via target-controlled infusion using the EleMarsh and Minto models, respectively. All patients received rocuronium after induction of general anaesthesia, tracheal tube was inserted and the patient then commenced on positive pressure ventilation. Rocuronium was reversed with sugammadex either prior to cryoablation (to facilitate diaphragm pacing) or immediately following confirmation of successful radiofrequency or pulse field ablation. The intraoperative remifentanil effect site target did not exceed 3 $ng.mL^{-1}$ in our cohort and infusion was ceased following confirmation of successful pulmonary vein isolation. Following ablation catheter removal from the femoral veins, manual pressure used to compress the puncture site, the propofol infusion was ceased and all other stimulation (auditory and tactile) of the patient was minimised until spontaneous eye opening.

S3. Exploratory re-analysis for other TCI models

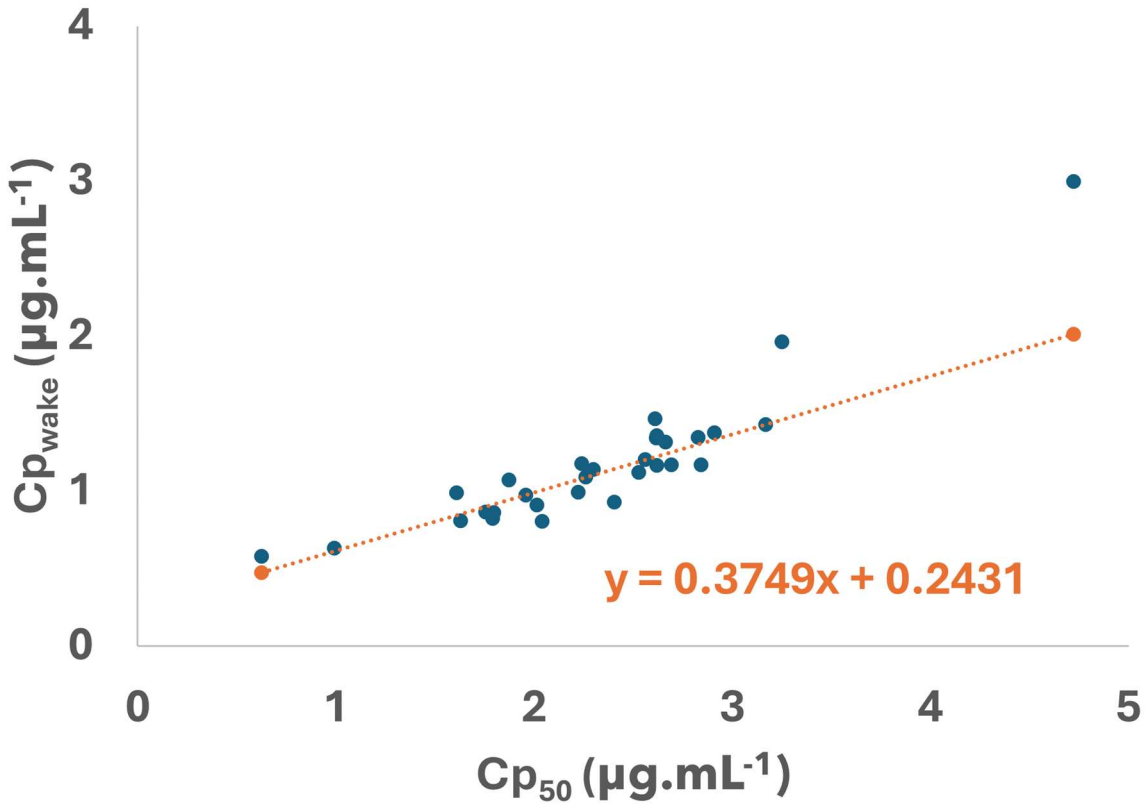
Marsh TCI model using total body weight

As the Marsh TCI model scales linearly with weight, we scaled all maintenance and awakening Cp values of the Model group using the ratio of their total body weight to their EleMarsh adjusted body weight.

The predictive model is constructed in the same manner as above and least squares fitting is used to estimate the best parameters that fit the equation

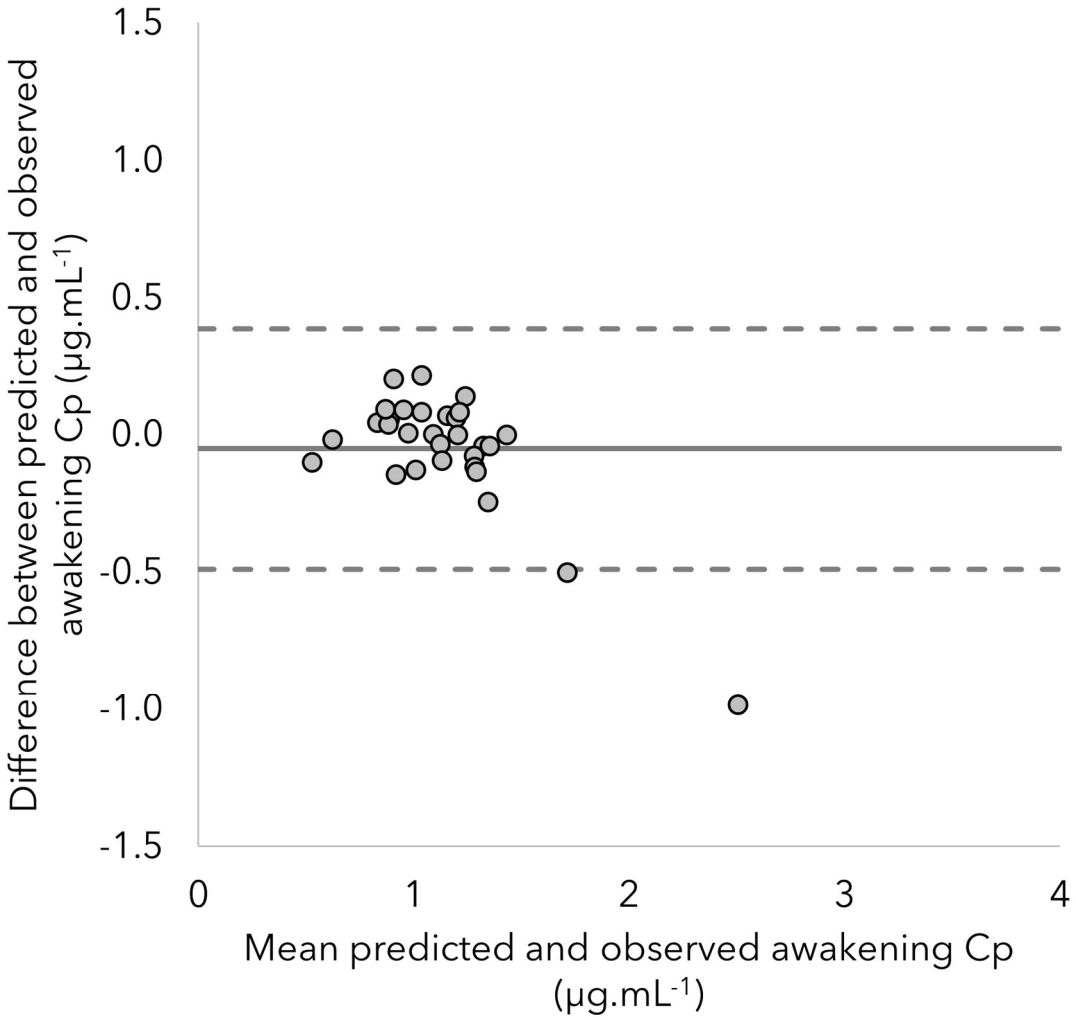
$$Cp_{wake} = a \cdot \left(\frac{SE_{base}}{SE_{main}} - 1\right)^{-1/\gamma} Cp_{main} + b$$

The same linear relationship is again demonstrated between Cp_{50} and Cp_{wake}



The model parameters for the predictive model when total body weight is used with Marsh TCI is given by a = 0.3749, b = 0.2431, γ = 6.929 and SE_{base} = 100.

Bland-Altman analysis revealed good predictive performance within the Model group. MDPE = 0% and MDAPE = 7%. Further studies are required to externally validate these findings.



Eleveld TCI model using effect site concentration values

To explore generalisability of our predictive model construction method to the Eleveld TCI model, we performed the following data transformation:

(1) extracted the TCI time profile for the Model group from the electronic medical records – i.e. the time at which every Cp target changed occurred
(2) use the Cp target changes (Marsh TCI model, EleMarsh ABW) to recreate propofol infusion-time profile in MATLAB (for algorithm source code, see https://github.com/propofoldreams/propofoldreams) – i.e. the instantaneous infusion rate at each time step

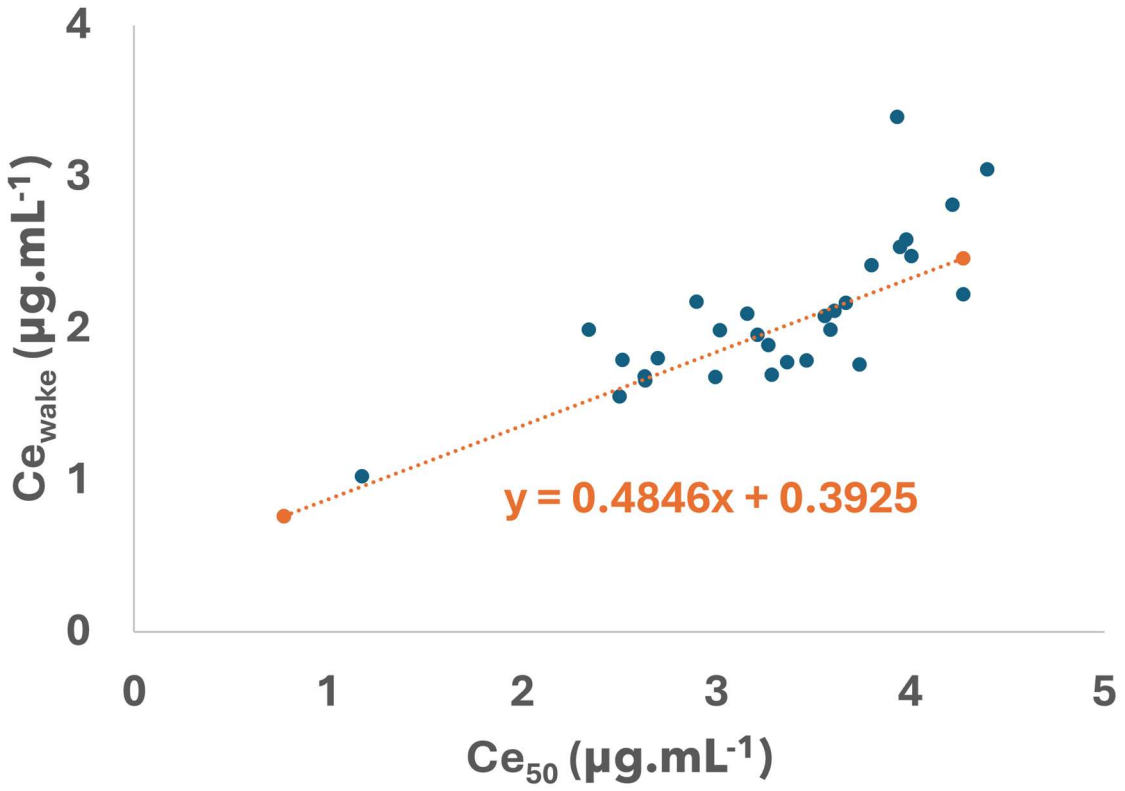
(3) substitute the infusion-time profile into the Eleveld TCI model to recreate the Eleveld effect site concentration (Ce) time profile
(4) use this to calculate the Eleveld maintenance and awakening Ce that would have corresponded to the original Marsh TCI-EleMarsh ABW profile
(5) construct predictive model

The predictive model is again constructed in the same manner as above and least squares fitting is used to estimate the best parameters that fit the equation

$$Ce_{wake} = a \cdot \left(\frac{SE_{base}}{SE_{main}} - 1\right)^{-1/\gamma} Ce_{main} + b$$

Where Ce_{wake} and Ce_{main} are the awakening and maintenance Eleveld effect site concentrations respectively.

The same linear relationship is again demonstrated between Ce_{50} and Ce_{wake}



The model parameters for the predictive model when the Eleveld TCI is used is given by a = 0.4846, b = 0.3925, γ = 4.686 and SE_{base} = 97.8.

Bland-Altman analysis revealed good predictive performance within the Model group. MDPE = 1% and MDAPE = 9%. Further studies are required to externally validate these findings.