

The Bradykinin Challenge Model Translates across Rat, Monkey, and Human

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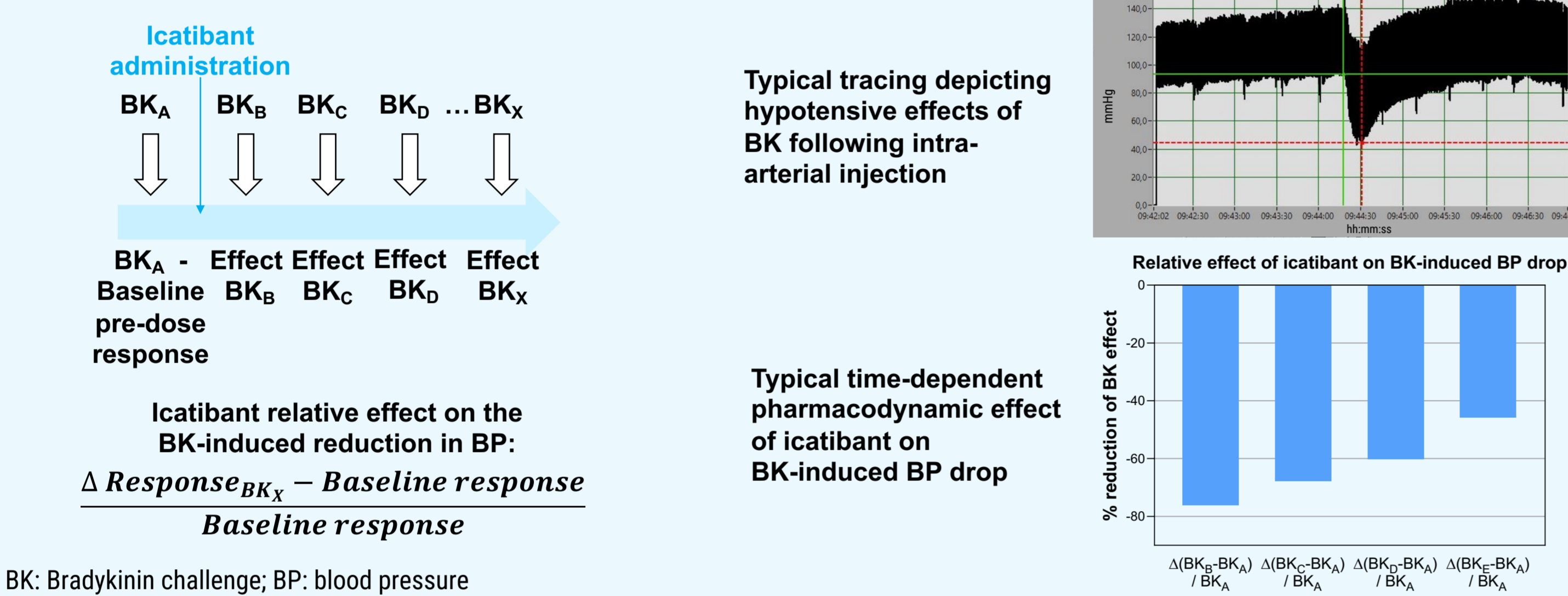
Introduction

- Pharmacokinetic and pharmacodynamic (PK/PD) properties of bradykinin B2 receptor antagonists can be assessed in vivo bradykinin (BK) challenge models.
- In these models, BK is repeatedly administered as a short intravenous (iv) infusion to cause hemodynamic changes such as a reduction in blood pressure (BP). By administering a bradykinin B2 receptor antagonist prior to the BK challenge, the potential of such an agent to prevent the BK-mediated hemodynamic effects can be assessed.
- The BK challenge model has been used in monkeys¹ and in human healthy participants^{2,3}. These models have been used in drug development for prediction of human efficacy but are resource-intensive and require complex set-ups.
- Recently, a BK challenge model in humanized bradykinin B2 receptor transgenic (Tg) rats was developed to provide a new, cost-effective option to evaluate the pharmacological response of bradykinin B2 receptor antagonists⁴.
- It was previously not investigated whether the BK challenge model in Tg rats could serve as a replacement for the monkey BK challenge model for the quantitative nonclinical prediction of the in vivo response of bradykinin B2 receptor antagonists in humans.
- We investigated the translational value of the BK challenge model across Tg rats, cynomolgus monkeys, and humans by comparing the PK/PD relationships of icatibant, a marketed bradykinin B2 receptor antagonist, in all three species.

Materials and Methods - BK Challenge Model

- The effects of icatibant on the repeated BK-induced reduction in BP was determined in BK challenge studies in male Tg Sprague Dawley rats⁴ and male cynomolgus monkeys¹.
- The relative change from the baseline response to BK was calculated to show the antagonistic properties of the test compound (Figure 1).

Figure 1. BK challenge pharmacodynamic endpoint



Pharmacokinetic Data and PK/PD Analysis Methodology

PK/PD data overview

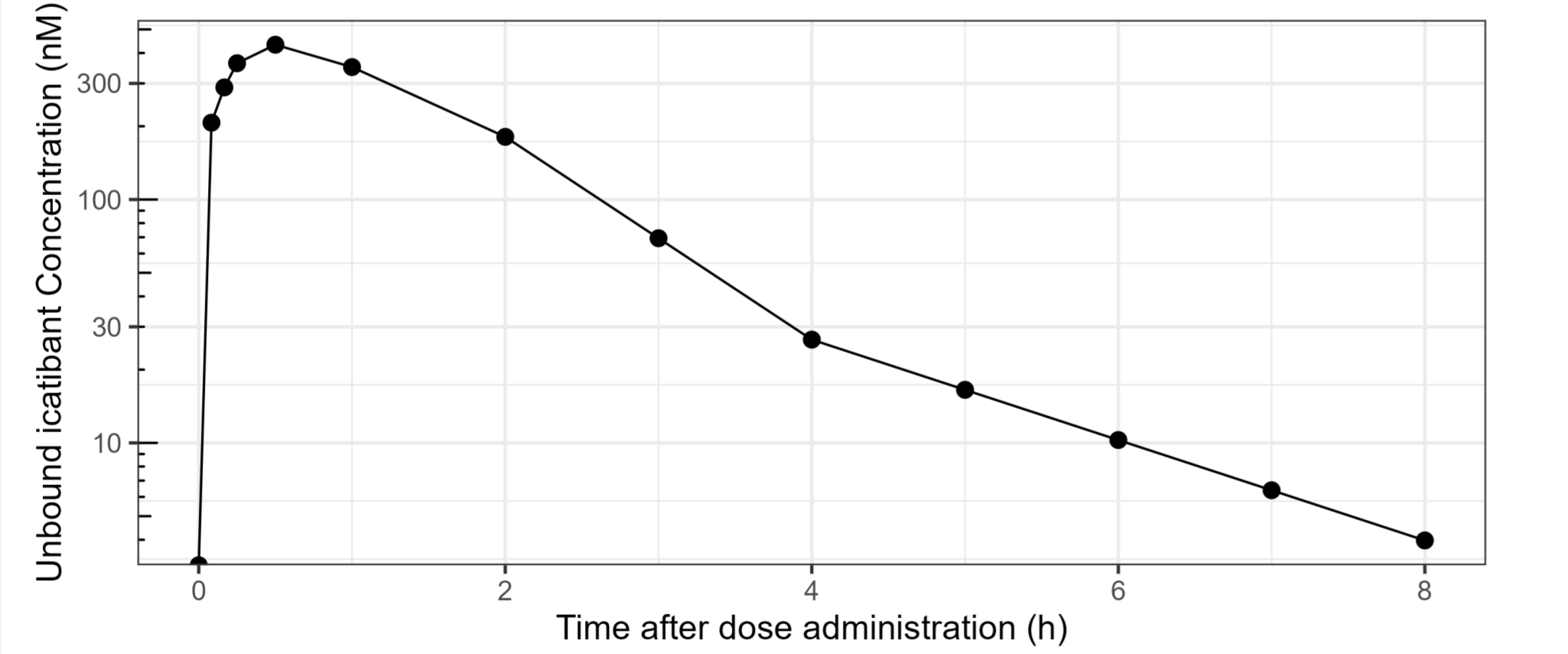
Humanized bradykinin B2 receptor Tg rats

- Icatibant was administered as an iv bolus at 5 dose levels (0.005 – 1 mg/kg) to anesthetized Tg rats.
- The response on the BK-mediated drop in diastolic BP was measured for each BK challenge.
- Plasma exposures to icatibant were determined directly in the study animals closely after each BK challenge.

Cynomolgus monkeys

- Icatibant was administered as a subcutaneous injection at 0.6 mg/kg to freely moving monkeys.
- The response on the BK-induced drop in mean arterial BP was measured by telemetry for each BK challenge.
- The plasma exposure to icatibant after 0.2 mg/kg subcutaneous administration to satellite cynomolgus monkeys was linearly scaled up to the dose used in the monkey BK challenge (0.6 mg/kg).
- Mean plasma concentrations at times corresponding to PD collections were used during PK/PD analysis (Figure 2).

Figure 2. Scaled mean icatibant concentrations in monkeys



Humans - healthy participants

- Population PK/PD analysis parameters for icatibant on a BK challenge study in healthy participants were retrieved from NDA 22-150⁵. While multiple PD endpoints were explored, EC₅₀ and maximal effect (E_{max}) values were similar for diastolic and mean BP PD endpoints. Only the diastolic BP was used for translational comparisons.
- The published human PK/PD parameters were rewritten to a % change from pre-dose to match the PD endpoint used in rats and monkeys.

PK/PD analysis

- The PK/PD relationship on the BP data was quantified in Tg rats and cynomolgus monkeys using a maximal effect model with R software (v4.2.2) and the DoseFinding (v1.0.5) package.
- Unbound plasma concentrations (in nM) versus % change from the pre-dose response was modelled as an E_{max} model to account for the impact of differences in unbound fraction across species.
- The estimated maximal inhibition (E_{max}) and unbound EC₈₅ parameters were then compared across species. The EC₈₅ was selected as a relevant metric to compare icatibant in vivo potency across species because of
 - its relevance to predict efficacy in its primary indication, hereditary angioedema (HAE)⁶.
 - the impact of the Hill coefficient (H) on the ratio between EC₅₀ versus EC₈₅, which limits the cross-species comparison of EC₅₀ estimates.
- EC₈₅ calculations were calculated with Equation 1⁷.

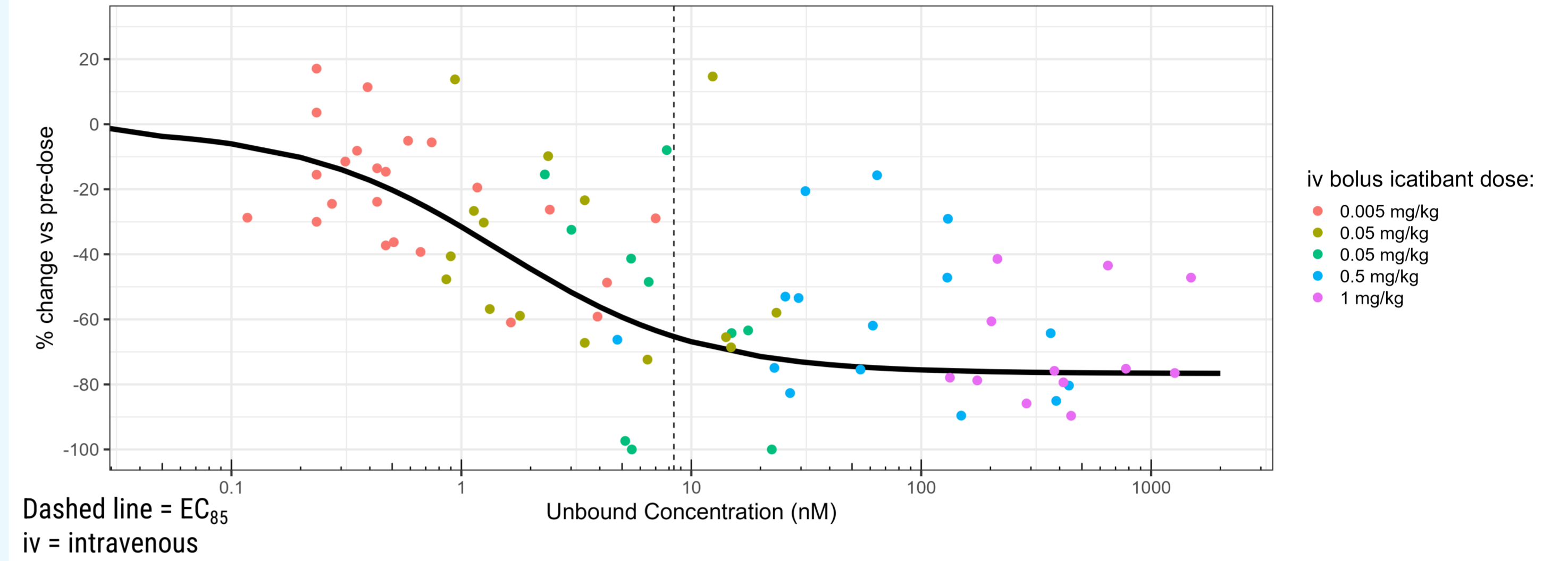
$$\text{Equation 1. } EC_{85} = \left(\frac{85}{100-85} \right)^{1/H} \times EC_{50}$$

Results

Humanized bradykinin B2 receptor transgenic Tg rats

- A robust PK/PD relationship was established for icatibant in Tg rats. The plasma concentrations reflected the full inhibition range of BK-induced changes in diastolic BP (Figure 3).
- The variability in the PD responses across animals is inherent to the complexity of the model readout and the significant inter- and intra-individual changes in response to BK challenges.

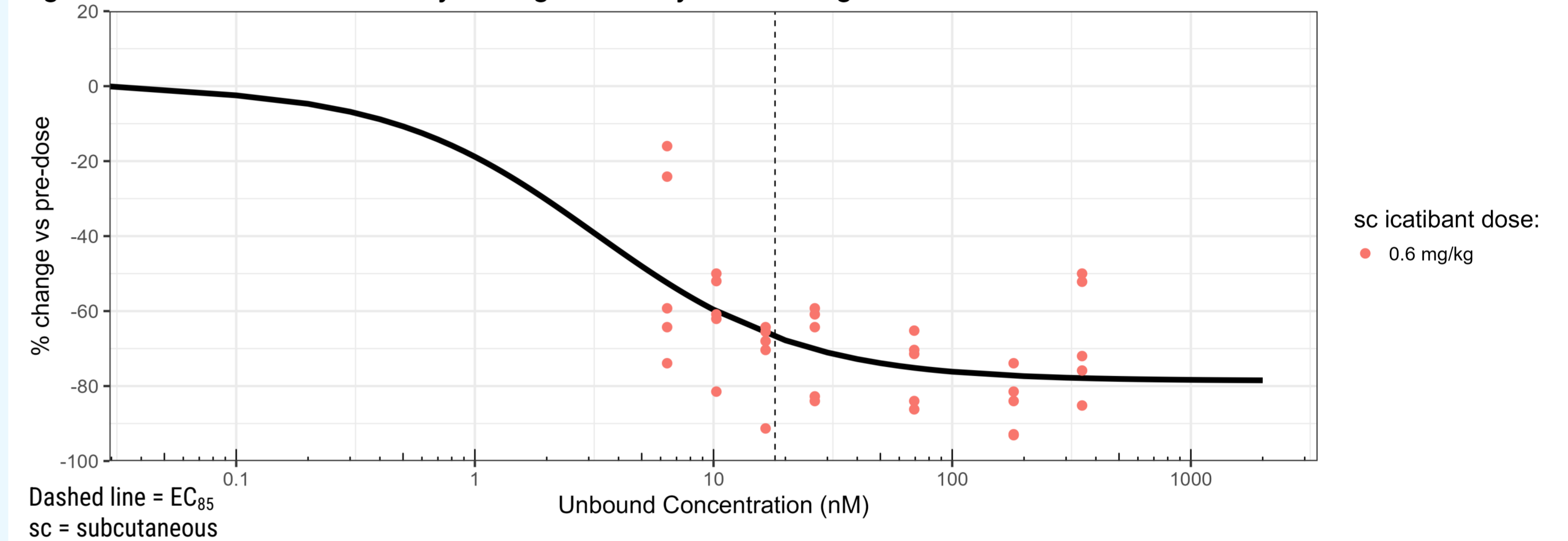
Figure 3. PK/PD of icatibant in Tg rat BK challenge model



Cynomolgus monkeys

- Clear PK/PD response observed for icatibant on the mean arterial BP in monkeys (Figure 4).
- As the BK challenge study in monkeys had not been specifically designed to explore low- or sub-efficacious doses, there are only sparse data below the unbound 5 nM level of icatibant.
- This data gap increases the uncertainty of the exact value of the EC₅₀, but the EC₈₅ approximation is more reliable.

Figure 4. PK/PD of icatibant in cynomolgus monkey BK challenge model



Cross-species comparison

- When comparing the PK/PD of icatibant across species, a very close agreement on E_{max} can be observed, and the EC₈₅ estimates from Tg rat and monkey BK challenge studies are within 2-fold of the human value (Figure 5, Table 1).

Figure 5. Cross-species PK/PD relationship of icatibant on the BK challenge model

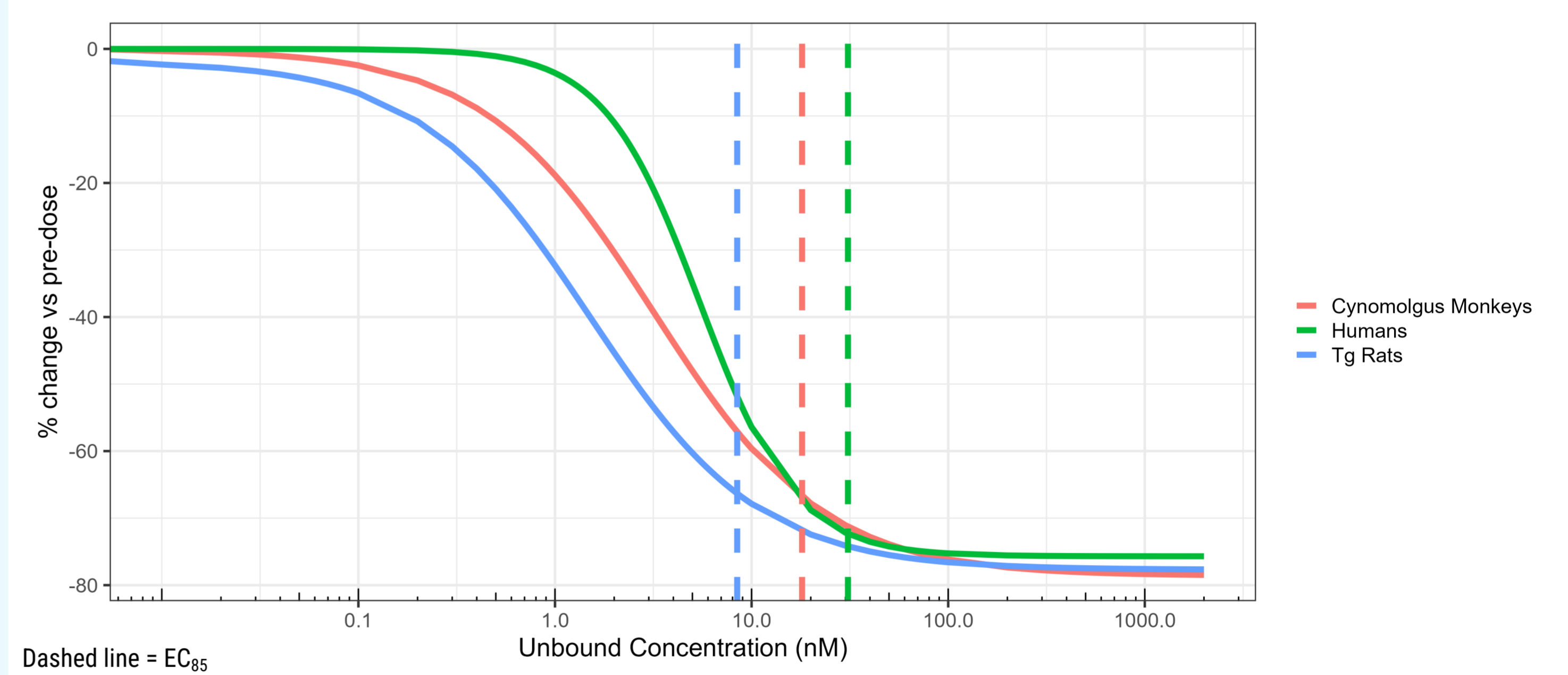


Table 1. Cross-species comparison of PK/PD parameters for icatibant

Species	EC ₅₀ (unbound nM)	EC ₈₅ (unbound nM)	E _{max} (%)	Hill coefficient
Humanized bradykinin B2 receptor Tg rats	1.5	8.4	-75.3	1.00
Cynomolgus monkeys	3.2	18.1	-78.5	1.00
Humans (healthy participants)	5.5	14.5	-75.7	1.77

Conclusions

- Icatibant PK/PD was analysed from BK challenge studies in humanized bradykinin B2 receptor Tg rats, cynomolgus monkeys, and humans and showed a similar PK/PD response in all species.
- The BK challenge model in nonclinical species such as Tg rats and monkeys is predictive of PK/PD outcomes in humans. Differences in experimental setup, potency, and modelling approach between Tg rats and other species might have caused some of the observed differences.
- The Tg rat BK challenge model can serve as a cost-effective replacement for the monkey BK challenge model for the prediction of the in vivo response of bradykinin B2 receptor antagonists in humans.

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