SUPPLEMENTAL DATA

A pilot study to assess the efficacy of tariquidar to inhibit P-glycoprotein at the human blood-brain barrier with (*R*)–^{11}C-verapamil and PET

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Analysis of scan 1 PET data by PK-PD modeling

To analyze the time course of the effect of tariquidar administration on activity in brain during PET scan 1, an indirect response pharmacokinetic-pharmacodynamic (PK-PD) model was used (Syvänen, 2006). If we assume that the concentration of activity in blood remains constant during the time of the experiment after starting tariquidar infusion, the modulation of P-gp function by tariquidar can be described by the following equations (model 1: tariquidar increases the influx of activity from blood into brain, Eq. (1); model 2: tariquidar decreases the efflux of activity at the BBB, Eq. (2)),

$$\frac{dC(t)}{dt} = E_{\text{kin}} \cdot k_{\text{out}} \cdot C_{\text{ss}} - k_{\text{out}} \cdot C(t) \tag{1}$$

$$\frac{dC(t)}{dt} = k_{\text{out}} \cdot C_{\text{ss}} - E_{\text{kout}} \cdot k_{\text{out}} \cdot C(t) \tag{2}$$

where $C(t)$ is the concentration of activity in brain and C_{ss} is the steady-state concentration of activity in brain. E_{kin} and E_{kout} quantify the effect of tariquidar on the influx rate constant k_{in} and the efflux rate constant k_{out},

$$E_{\text{kin}} = 1 + \frac{E_{\text{max}} \cdot C_{\text{TQD}}^{\gamma}}{\text{EC}_{50}^{\gamma} + C_{\text{TQD}}^{\gamma}} \tag{3}$$

$$E_{\text{kout}} = 1 - \frac{E_{\text{max}} \cdot C_{\text{TQD}}^{\gamma}}{\text{EC}_{50}^{\gamma} + C_{\text{TQD}}^{\gamma}} \tag{4}$$

where we have assumed that tariquidar concentration in blood, C_{TQD}, is representative for its concentration at the BBB. E_{max} describes the maximum change in k_{in} or k_{out}, EC_{50} is the tariquidar concentration for 50% maximum change in k_{in} or k_{out}, and γ is the sigmoidicity factor of the indirect response model.

The function $C_{TQD}(t)$ of the plasma concentration of tariquidar at time t is required in Eqs. (3) and (4) and was obtained by fitting a linear two-compartment pharmacokinetic model for intravenous administration to the measured plasma concentration data of tariquidar,

$$C_{TQD}(t < T) = \frac{A}{\alpha \cdot T} \cdot \left(1 - \exp\left(-\alpha \cdot t\right)\right) + \frac{B}{\beta \cdot T} \cdot \left(1 - \exp\left(-\beta \cdot t\right)\right) \quad (5)$$

$$C_{TQD}(t \geq T) = \frac{A}{\alpha \cdot T} \cdot \left(\exp\left(-\alpha \cdot \left(t - T\right)\right) - \exp\left(-\alpha \cdot t\right)\right) + \frac{B}{\beta \cdot T} \cdot \left(\exp\left(-\beta \cdot \left(t - T\right)\right) - \exp\left(-\beta \cdot t\right)\right) \quad (6)$$

where T is the duration of infusion and A, B, α, β are the corresponding macro constants. The parameters A, B, α, β were estimated by the method of nonlinear least squares as implemented in the *nlin* procedure of the SAS System V9.2 (SAS Institute, Cary, NC, USA). From the estimates of the macro constants A, B, α, β the following parameters of tariquidar plasma pharmacokinetics were calculated (D is the administered dose of tariquidar):

$$V_C = \frac{D}{A + B}$$

$$\mathrm{AUC} = \frac{A}{\alpha} + \frac{B}{\beta}$$

$$\mathrm{AUMC} = \frac{A}{\alpha^2} + \frac{B}{\beta^2}$$

$$\mathrm{MRT} = \frac{\mathrm{AUMC}}{\mathrm{AUC}}$$

$$t_{1/2\beta} = \frac{\ln 2}{\beta}$$

$$\mathrm{CL} = \frac{D}{\mathrm{AUC}}$$

$$V_{ss} = \mathrm{CL} \cdot \mathrm{MRT}$$

Equations (1) and (2) for model 1 and 2 were solved numerically using the *ode15s* solver of MATLAB (Mathworks, Natick, MA, USA). The unknown parameters k_{out}, E_{max}, EC_{50}, and γ were estimated by fitting the respective model to the measured PET data in brain using the method of nonlinear least squares as implemented in the *lsqnonlin* function of the *Optimization Toolbox* of MATLAB. The Akaike Information Criterion (*AIC*) was used to rate the models.

Figure S1 shows tariquidar concentrations measured in venous plasma (open circles) and fits of the linear two-compartment pharmacokinetic model, Eqs. (5) and (6), to the measured data points. Pharmacokinetic parameters as calculated from the estimates of the macro constants A, B, α, β are reported in Table S1. Subsequently, the estimates of A, B, α, β were used for $C_{TQD}(t)$ in the indirect response models, Eqs. (3) and (4).

Figures S2 and S3 show measured activity concentrations in brain after administration of tariquidar (open circles) and predictions of model 1, Eqs. (1) and (3), and of model 2, Eqs. (2) and (4), respectively. Estimates of the parameters k_{out}, E_{max}, EC_{50}, and γ for model 1 and model 2 are summarized in Table S2, together with the corresponding *AIC* values. The *AIC* values for model 2 were smaller than for model 1, indicating better fits of brain activity concentration data by model 2, i.e., efflux (k_{out}) inhibition. On the other hand, activity concentration data in brain are also not inconsistent with model 1, i.e., influx (k_{in}) enhancement at the BBB (*AIC* values for model 1 are not drastically larger than those for model 2, Table S2).

References

Syvänen S, Blomquist G, Sprycha M, Höglund AU, Roman M, Eriksson O, Hammarlund-Udenaes M, Långström B, Bergström M. Duration and degree of cyclosporin induced P-glycoprotein inhibition in the rat blood-brain barrier can be studied with PET. *Neuroimage* 2006;32(3):1134-1141.

TABLE S1

Pharmacokinetic Parameters of Tariquidar

Patient	C_{max} (μg/mL)	*AUC* (μg·h·mL^{-1})	CL (mL·min^{-1})	V_{ss} (L)	$t_{1/2\beta}$ (h)
1	2.692	14.1	198.0	339.1	21.4
2	2.169	14.3	162.7	172.2	12.7
3	2.175	10.9	229.0	264.7	14.3
4	2.427	12.8	189.9	344.9	22.8
5	1.460	13.7	166.8	225.1	16.1

TABLE S2

Parameter Estimates and *AIC* Values for Model 1 and Model 2 (mean±SD)

Model	k_{out} (min^{-1})	E_{max}	EC_{50} (μg/mL)	γ	*AIC*
1	0.053±0.011	1.242±0.356	1.057±0.077	3.908±1.885	-10.729±11.916
2	0.072±0.012	0.820±0.150	1.129±0.092	2.602±0.708	-11.935±8.131

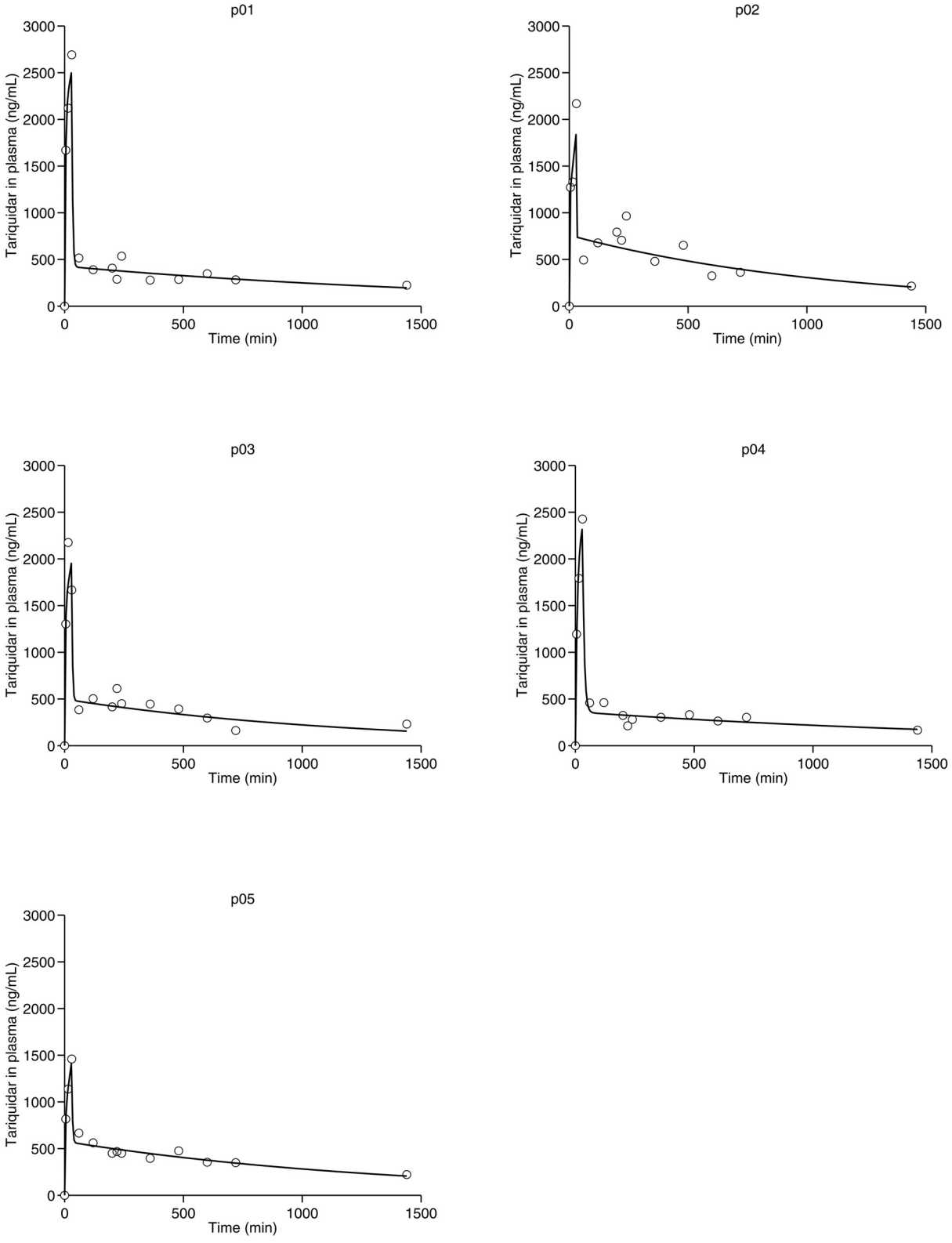

FIGURE S1. Measured tariquidar concentrations in venous plasma (open circles) and fits of the linear two-compartment pharmacokinetic model, Eqs. (5) and (6) (solid lines), for individual study subjects.

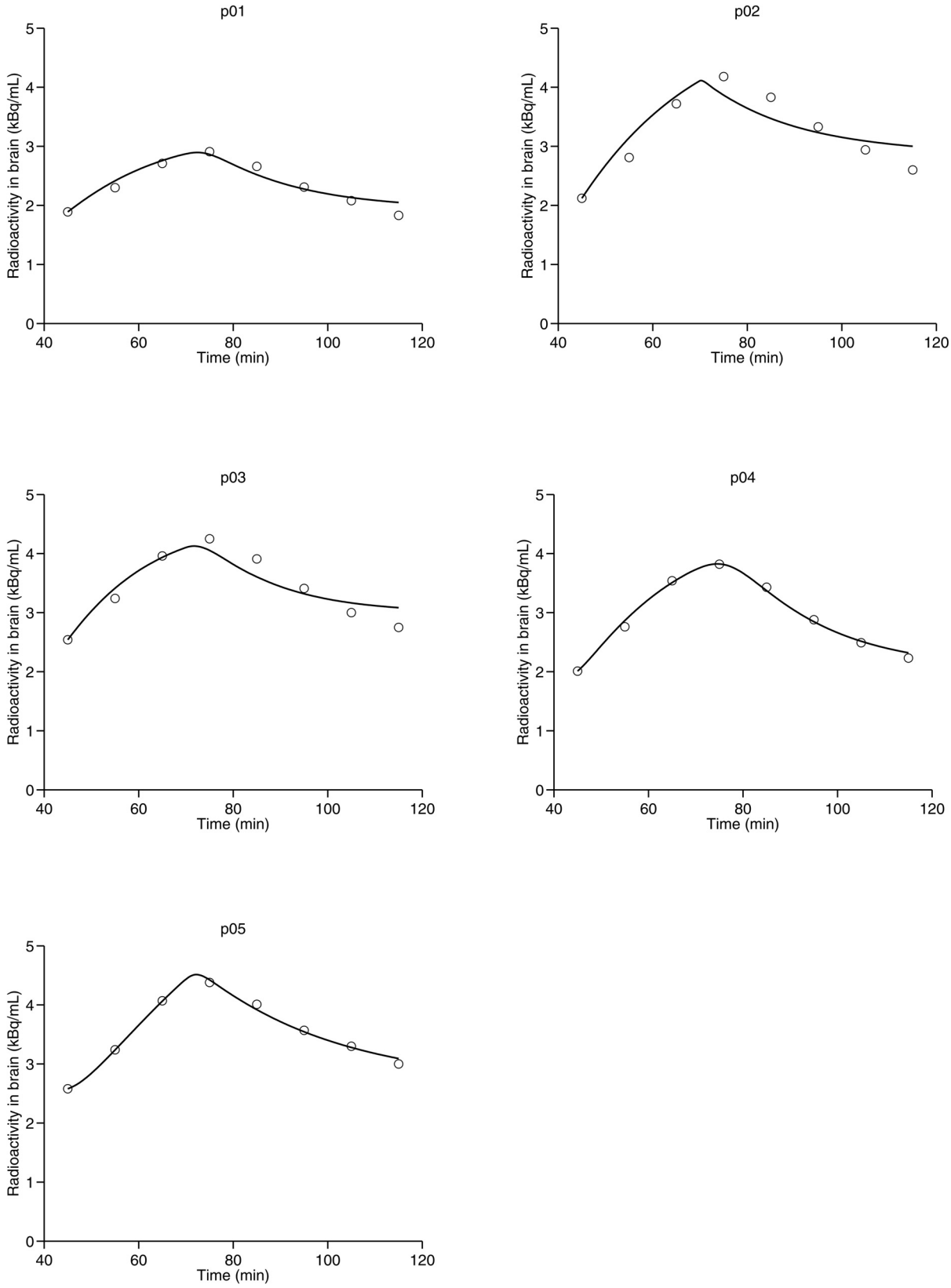

FIGURE S2. Measured activity concentrations in brain after administration of tariquidar (open circles) and predictions of model 1, Eqs. (1) and (3) (solid lines), for individual study subjects.

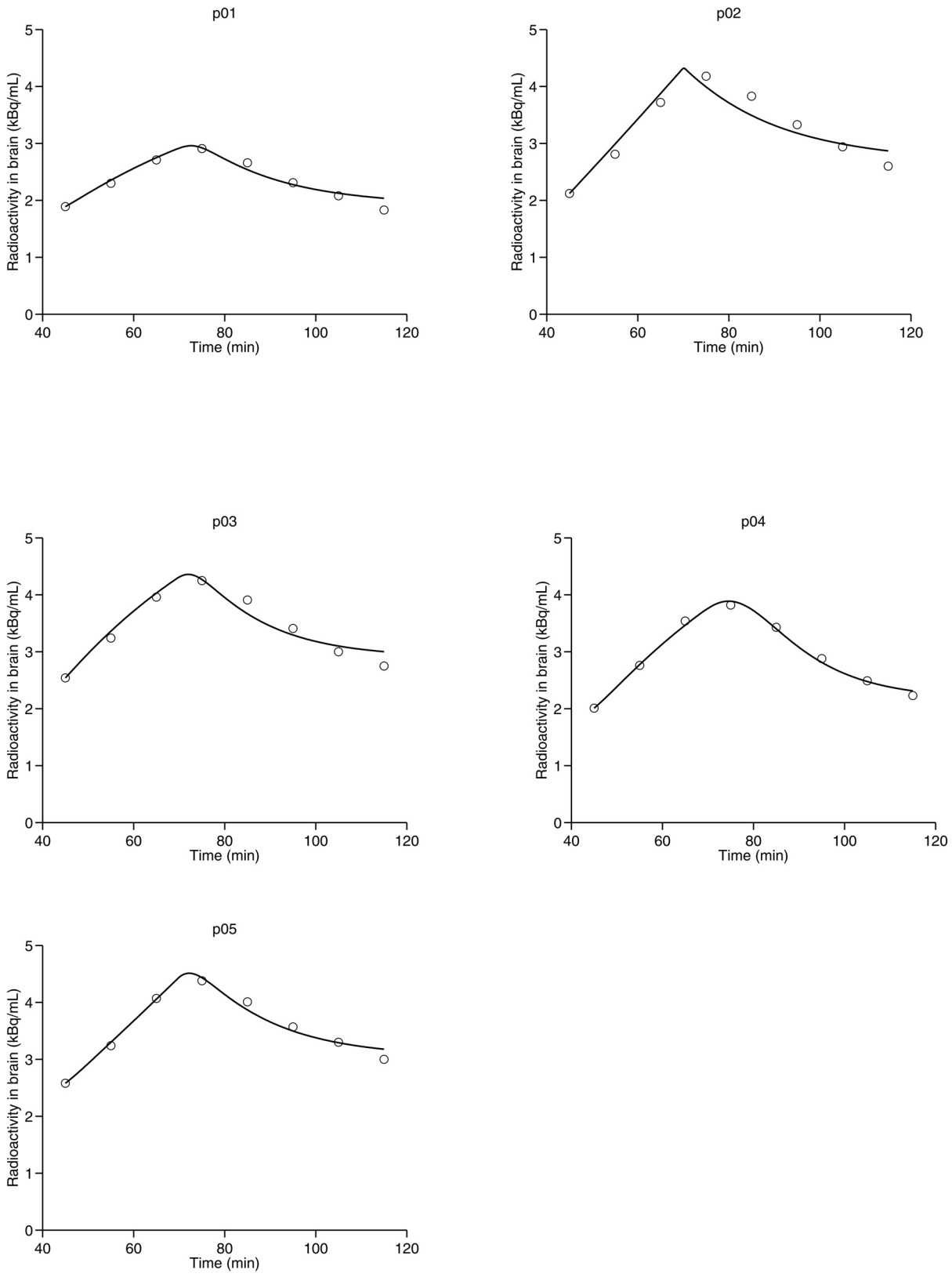

FIGURE S3. Measured activity concentrations in brain after administration of tariquidar (open circles) and predictions of model 2, Eqs. (2) and (4) (solid lines), for individual study subjects.