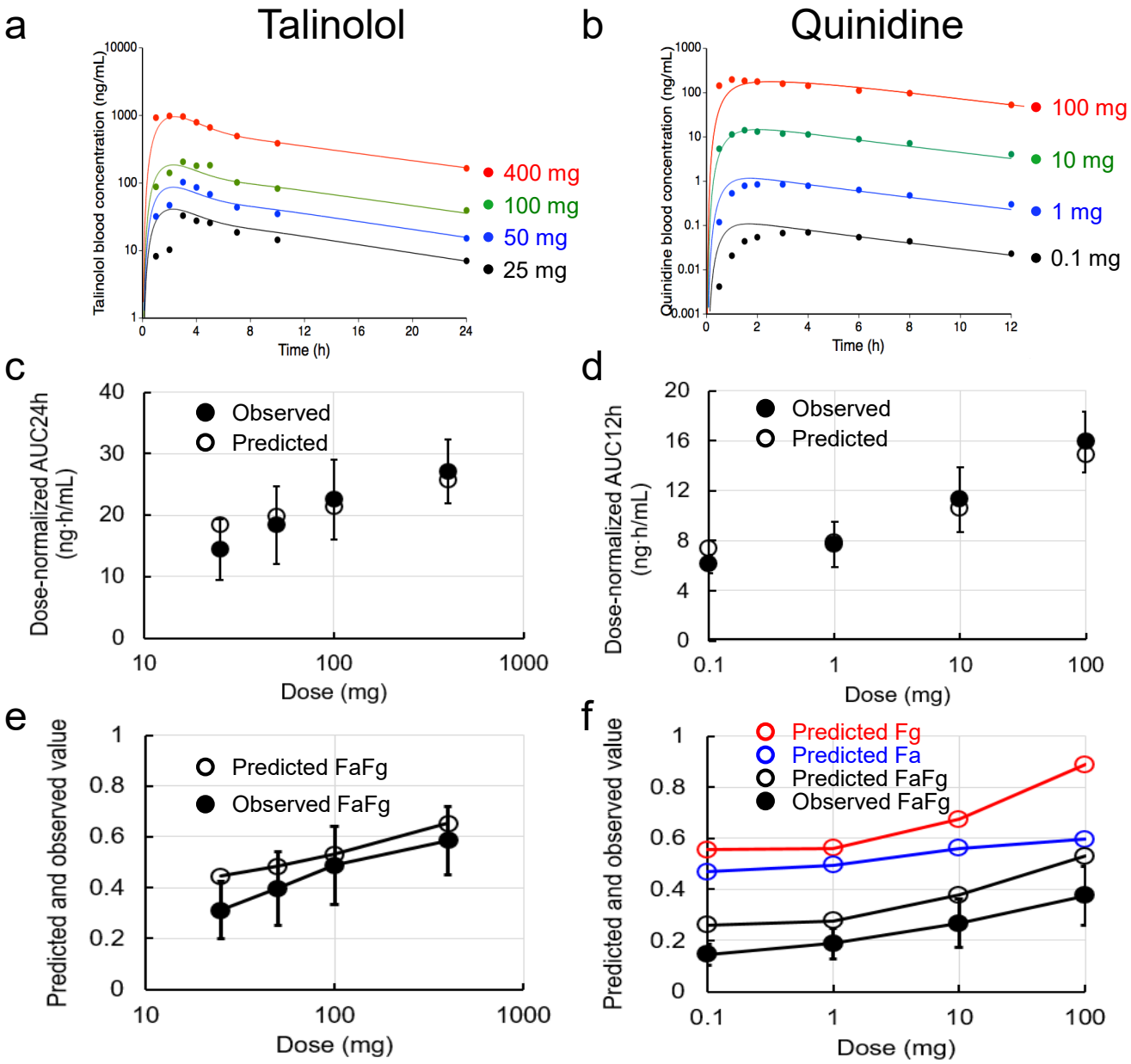

Figure S1 Predicted and observed non-linear pharmacokinetics of talinolol and quinidine.
(a) Closed circles and solid lines represent observed and predicted non-linear blood profiles of talinolol after single oral doses of 25 mg (black), 50 mg (blue), 100 mg (green), and 400 mg (red) talinolol. To describe the non-linearity, saturable P-gp efflux in the intestine, liver, and kidney was incorporated. The predicted talinolol profiles were shown with the hepatic β value of 0.5 because no major differences was observed with three β values of 0.2, 0.5, and 0.8. (b) Closed circles and solid lines represent observed and predicted non-linear blood profiles of quinidine after single oral doses of 0.1 mg (black), 1 mg (blue), 10 mg (green), and 100 mg (red) quinidine. To describe the non-linearity, saturable P-gp efflux in the intestine and kidney and saturable CYP3A metabolism in the intestine and liver were incorporated. (c-f) Closed and open circles represent observed and predicted dose-normalized AUC (c-d) and F_aF_g (e-f) of talinolol (c and e) and quinidine (d and f). The observed values are shown as mean ± SD. The predicted values of talinolol and quinidine were calculated from Figures S1a and S1b, respectively. (e) Since the intestinal metabolism of talinolol is negligible (Fg = 1),[6] only FaFg (= Fa) is shown. AUC, area under the plasma/blood concentration-time curve; CYP, cytochrome P450; F_a, fraction of dose absorbed from gut lumen; F_aF_g, intestinal availability; F_g, fraction available after intestinal metabolism.