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Research Article

Pharmacokinetic-Pharmacodynamic Analyses of the Antidiabetic Drug, Nateglinide, in Goto-Kakizaki Rats Based on Pharmacological Mechanism

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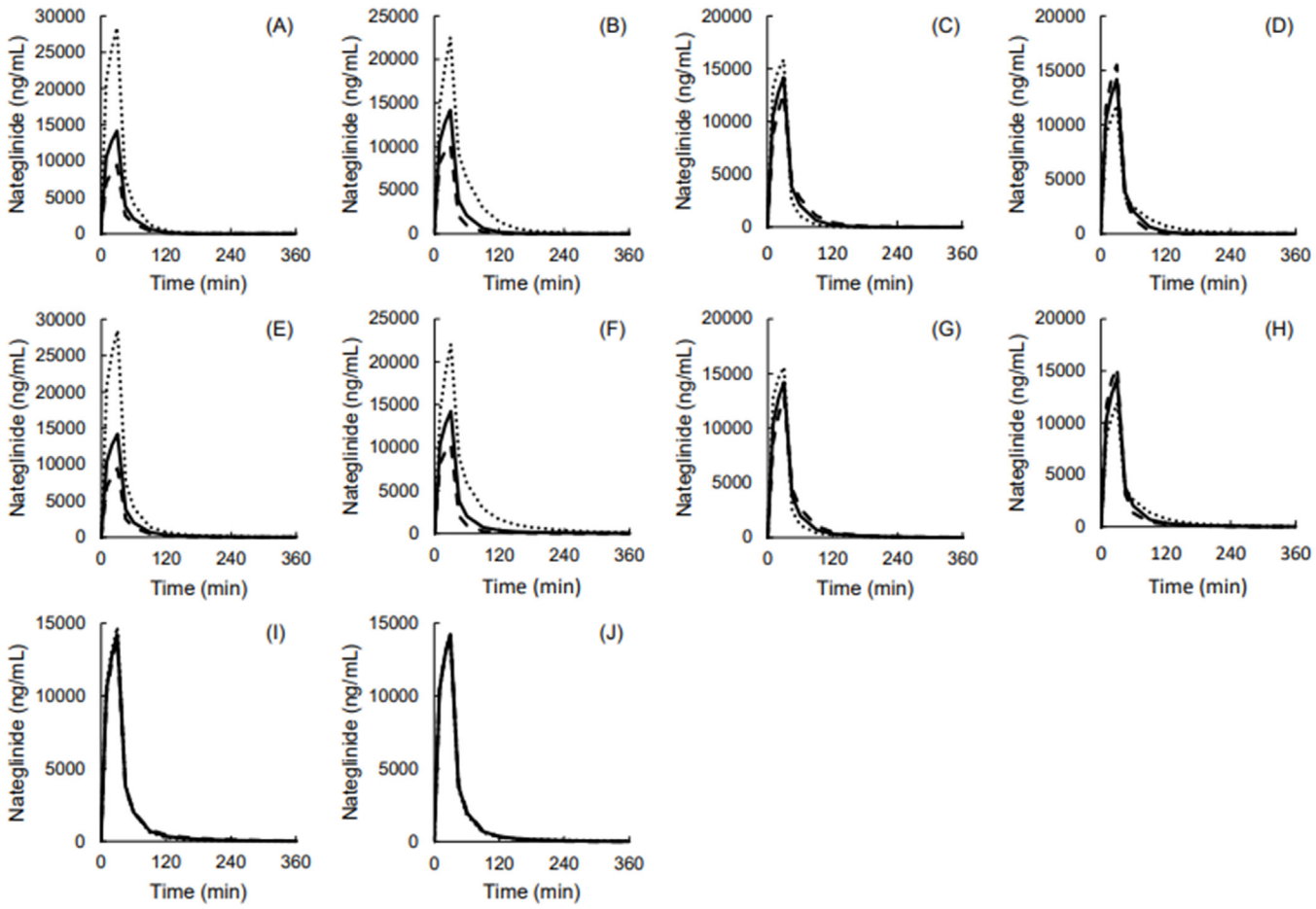

Figure S1: Sensitivity of pharmacokinetic parameters calculated by two -(A-D) and three-compartment (E-J) pharmacokinetic models of nateglinide. The pharmacokinetic model is illustrated in Figure 1. **Note:** A and E: V_1 (distribution volume of the central compartment); B and F: k_{10} (first-order elimination rate constant); C and G: k_{12} (first-order rate constants from central compartment to peripheral compartment); D and H: k_{21} (first-order rate constants from peripheral compartment to central compartment); and I and J: k_{13} and k_{31} (first-order rate constants between secondary peripheral (third) and central compartments) Symbols: solid line, simulated profile using calculated parameters; dotted line, parameter reduced to 50% of its original value; and dashed line, parameter increased to 150% of its original value.

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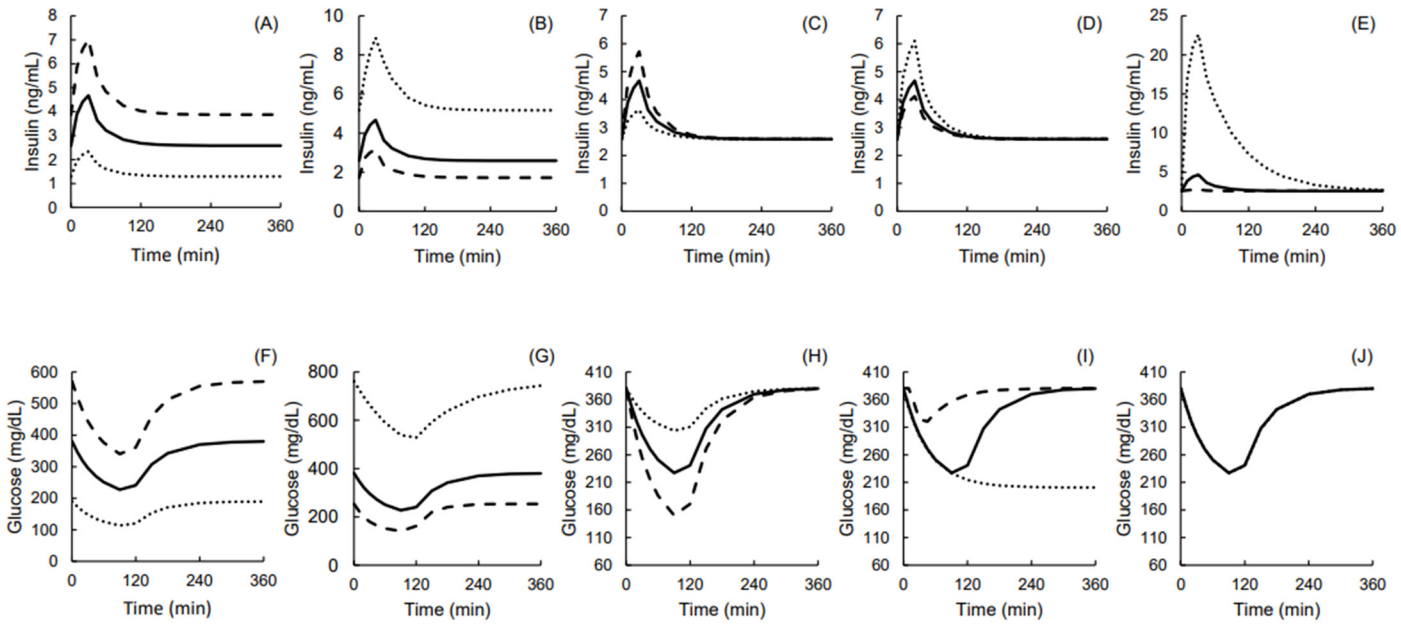

Figure S2: Sensitivity of pharmacodynamic parameters of nateglinide following intravenous infusion to rats. The PK-PD model is illustrated in Figure 1.
Note: A-E: effect of nateglinide on insulin profile; and F-J: effect of insulin on glucose profile.

A and F: K_{inI} and K_{inG} (zero-order rate constants of the formation of insulin and glucose, respectively); B and G: k_{outI} and k_{outG} (first-order rate constants of the degradation of insulin and glucose, respectively); C and H: E_{maxI} and I_{maxG} (the maximum drug and insulin effects on insulin and glucose levels, respectively); D and I: EC_{50I} and IC_{50G} (drug and insulin concentrations at the half-maximum effect, respectively); E and J: γ_I and γ_G (Hill constants for ordinary sigmoid E_{max} models); Symbols: Solid line, simulated profile using calculated parameters; dotted line, parameter reduced to 50% of its original value; and dashed line, parameter
increased to 150% of its original value.