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Pharmacodynamic and -kinetic Behavior of Low-, Intermediate-, and High-Dose Landiolol During Long-Term Infusion in Whites.

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Abstract

Pharmacokinetics, pharmacodynamics, safety, and tolerability of long-term administration of landiolol, a fast-acting cardioselective β-blocker, were investigated for the first time in white subjects in a prospective clinical trial. Blood concentrations of landiolol and its metabolites, heart rate (HR), blood pressure (BP), and electrocardiogram parameters were studied in 12 healthy volunteers receiving continuous infusions of a new 12-mg/mL formulation of landiolol using a dose-escalation regimen (10 µg/kg BW/min for 2 hours, 20 µg/kg BW/min for 2 hours, 40 µg/kg BW/min for 20 hours, 6 hours follow-up). Landiolol blood concentrations were dose proportional. Time until steady state decreased with increasing doses. Pharmacokinetic parameters were t1/2 = 4.5 minutes, VD = 366 mL/kg, and total body clearance = 53 mL·kg·min. Maximal blood concentrations of the inactive main metabolite M1 were 10-fold higher than those of landiolol, with t1/2 = 126 minutes, VD = 811 mL/kg, and total body clearance = 4.5 mL·kg·min. HR reduction from baseline was fast (significant after 16 minutes) and sustained throughout the administration period. Systolic and diastolic BP reductions and electrocardiogram parameter changes were less pronounced and became significant only occasionally. Recovery after discontinuation of infusion was fast with little (HR) or no (BP) rebound. The new formulation showed excellent local and general tolerability.

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