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Eur J Clin Pharmacol. 2017 Apr;73(4):417-428. doi: 10.1007/s00228-016-2176-0. Epub 2017 Jan 13.

Bolus application of landiolol and esmolol: comparison of the pharmacokinetic and pharmacodynamic profiles in a healthy Caucasian group.

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Abstract

PURPOSE:

The aim of this prospective study was to compare in non-Asian subjects the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of two short-acting cardioselective β1-adrenergic antagonists, landiolol and esmolol, after administration of three different bolus dosages.

MATERIALS AND METHODS:

We conducted a single-center, prospective, double-blinded, randomized study in three cross-over periods with 12 healthy subjects (7 women and 5 men, mean age of 24.5 ± 6.9 years) each receiving three doses of landiolol (0.1, 0.2, and 0.3 mg/kg BW) either in a newly developed concentrate i.v. formulation (Rapibloc® 20 mg/2 mL concentrate) or a lyophilized formulation, or three doses of esmolol (0.5, 1, and 1.5 mg/kg BW) in an i.v. formulation (Brevibloc® 100 mg/10 mL). PK and PD parameters, safety, and tolerability were assessed.

FINDINGS:

Results of the two landiolol formulations were reported previously and were similar. For the landiolol concentrate formulation and esmolol, maximum blood concentrations were rapidly reached (mean t max ranged between 1.8 and 3.0 min for landiolol and 1.8 to 2.4 min for esmolol). The parent drugs disappeared very fast from the blood stream, with a t 1/2 of 3.2 ± 1.2 (SD) minutes and 3.7 ± 2.1 (SD) minutes for the low doses of landiolol and esmolol, respectively. Despite comparable injection rates (0.1 or 0.5 mg/kg/15 s for landiolol and esmolol, respectively), the onset of significant heart rate reduction occurred earlier in response to landiolol (1 min) than in response to esmolol (2 min). In addition, significantly lower heart rate values were obtained at every dose level of landiolol, in comparison to esmolol ($p < 0.05$). Both compounds reduced the systolic blood pressure to a comparable degree. Especially at the highest dose, the duration of blood pressure reduction was longer under esmolol compared to landiolol. Seven mild to moderate adverse events occurred after administration of landiolol, and five occurred after administration of esmolol. No serious adverse events were reported in this study.

IMPLICATIONS:

Heart rate reduction induced by a new liquid formulation of landiolol occurred faster, was more pronounced, and lasted longer than the effects of corresponding standard esmolol doses. Both agents reduced systolic blood pressure to a comparable degree, but the blood pressure decrease lasted longer after esmolol infusion. The local tolerance and safety profiles of the two formulations were similar. In summary, compared to esmolol, landiolol shows a more prominent and pronounced bradycardic effect in relation to its blood pressure-lowering effect, an action profile that might be of specific advantage in the perioperative setting.

TRIAL REGISTRATION:

NCT01652898 and 2012-002127-14. https://clinicaltrials.gov/ct2/show/NCT01652898?term=landiolol&rank=7.

KEYWORDS:

Cardioselective β-blocker; Esmolol; Landiolol; Pharmacodynamics; Pharmacokinetics

PMID: 28091703 DOI: 10.1007/s00228-016-2176-0