Enantioselective pharmacokinetics of nebivolol in patients with chronic kidney disease and in hemodialysis patients

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Introduction: Hypertension treatment with beta adrenoceptor antagonists reduces the rate of decrease of the kidney function and is associated with reduced cardiovascular mortality in chronic kidney disease (CKD) patients undergoing hemodialysis (1). Nebivolol, marketed as a racemic mixture of \textit{d} (SRRR) and \textit{l} (RSSS) enantiomers, is a long-acting and highly selective $\beta_1$ adrenoceptor antagonist ($d$-nebivolol) that also shows nitric oxide-mediated vasodilatory effects ($l$-nebivolol). It is eliminated mainly by metabolism dependent on glucuronidation and hydroxylation mediated by CYP2D6. It is now generally accepted that CKD decreases the nonrenal clearance of drugs, particularly intestinal and hepatic metabolism and transport, due to plasma accumulation of parathyroid hormone, pro-inflammatory cytokines and uremic toxins, which may translate into clinically significant changes in drug response (2-4).

Aim: This study evaluated the influence of CKD and hemodialysis on the pharmacokinetics of nebivolol enantiomers.

Subjects and methods: Forty-three patients, previously phenotyped as extensive metabolizers for CYP2D6 using metoprolol as a probe, were distributed into three groups according to creatinine clearance: $>$ 90 mL/min/1.73 m\textsuperscript{2}, 13 healthy volunteers and 9 hypertensive patients with kidney function within the normal range (control group); $<$ 60 mL/min/1.73 m\textsuperscript{2}, 11 patients with stage 3 and 4 CKD (CKD group); $<$ 15 mL/min/1.73 m\textsuperscript{2}, 10 patients with stage 5 CKD undergoing hemodialysis (hemodialysis group). All participants received a single oral dose of 10 mg racemic nebivolol and serial blood samples were collected up to 48 h after drug administration. Nebivolol enantiomers were analysed in plasma samples using LC/MS-MS. Pharmacokinetic parameters (WinNonlin software) were compared among groups using one-way ANOVA followed by a posteriori Tukey test (p<0.05). The clinical protocol was approved by the local Research Ethics Committees.

Results: The pharmacokinetics of nebivolol is enantioselective with plasma accumulation of the $l$-nebivolol enantiomer in all investigated groups. CKD reduced the oral clearance of $l$-nebivolol (10.24 vs 7.18 L/h/kg) and $d$-nebivolol (16.84 vs 9.77 L/h/kg) and increased AUC of $l$-nebivolol (6.83 vs 9.94 ng.h/mL) and $d$-nebivolol (4.15 vs 7.30 ng.h/mL) when compared with patients with normal renal function. The oral clearance values of 12.45 L/h/kg for $l$-nebivolol and of 15.86 L/h/kg for $d$-nebivolol obtained for the hemodialysis group do not differ from the control group (10.24 and 16.84 L/h/kg, respectively), but are different from those obtained for the CKD group (7.18 and 9.77 L/h/kg, respectively).

Conclusions: The finding of an increase of more than 70% in the exposure of CKD patients to $d$-nebivolol suggests that these patients may be at risk of more prominent bradycardia or arterial hypotension, especially in clinical situations of exacerbated sympathetic activity, such as heart failure, which is frequent in this population. It is therefore prudent that patients with CKD initiate treatment with low doses of nebivolol and that more attention be paid to the monitoring of pharmacodynamic effects. In contrast, hemodialysis, by eliminating uremic toxins, restores the oral clearance values of the nebivolol enantiomers to those observed in the patients normal renal function with suggestion of no dose adjustment.
