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Clinical Pharmacokinetics of Nebivolol
A Review

A. Van Peer, E. Snoeck, R. Woestenborghs, V. Van de Velde, G. Mannens, W. Meuldermans and *J. Heykants*
Department of Drug Metabolism and Pharmacokinetics, Janssen Research Foundation, Beerse, Belgium

Summary Nebivolol is the racemic mixture of 2 isomers with 4 asymmetric centres. The *d*-isomer has the SRRR configuration, and the *l*-isomer is RSSS. Animal and human pharmacological experiments demonstrated that the antihypertensive and haemodynamic action of the racemic mixture was superior to that of the isomers alone. Many aspects affect the pharmacokinetics of the parent drug without making a firm impact on the clinical outcome. The absolute oral bioavailability of nebivolol varies from 12 to 96% in subjects characterised as extensive and poor debrisoquine hydroxylators. It is likely that active hydroxymetabolites compensate for the difference in both phenotype subjects. Active drug concentrations reflecting β-blockade by *d*-nebivolol and its hydroxymetabolites can be determined by a radioimmunoassay procedure using enantioselective antibodies. By the use of this method, comparable active drug concentrations were found in extensive and poor metabolisers, which explains why the clinical outcome is the same for both groups.

Nebivolol is a racemic mixture of 2 isomers with 4 asymmetric centres (fig. 1) [Anon 1989]. Animal and human pharmacological experiments (Anon 1989; Van de Water et al. 1988, 1990; Xhonneux et al. 1990a,b) have demonstrated that the racemic mixture of *d*-nebivolol (SRRR) and *l*-nebivolol (RSSS) has antihypertensive action superior to that of the isomers alone.

Isomers in racemates may differ both pharmacodynamically and pharmacokinetically and this may affect the clinical outcome (Lee & Williams 1990). This review summarises the status of the analytical methods used to study the enantioselective pharmacokinetics of nebivolol and looks at the pharmacokinetic findings in humans. Furthermore, current insights into the observed genetic differences as regards nebivolol metabolism and their impact on nebivolol pharmacokinetics are presented.

1. Analytical Methods

Stereoselective assay methodology is an important issue in the understanding of the pharmacokinetics of nebivolol. High performance liquid chromatography (HPLC) with fluorescence detection (Woestenborghs et al. 1988) was used to measure the concentrations of the isomer pair. This method is sensitive to 0.1 μg/L, but is not stereoselective. Chiral chromatography has a detection limit higher than 2 μg/L, and in most patients is not sensitive enough for pharmacokinetic purposes.

Therefore, radioimmunoassay using enantioselective antibodies has been developed (Woesten-

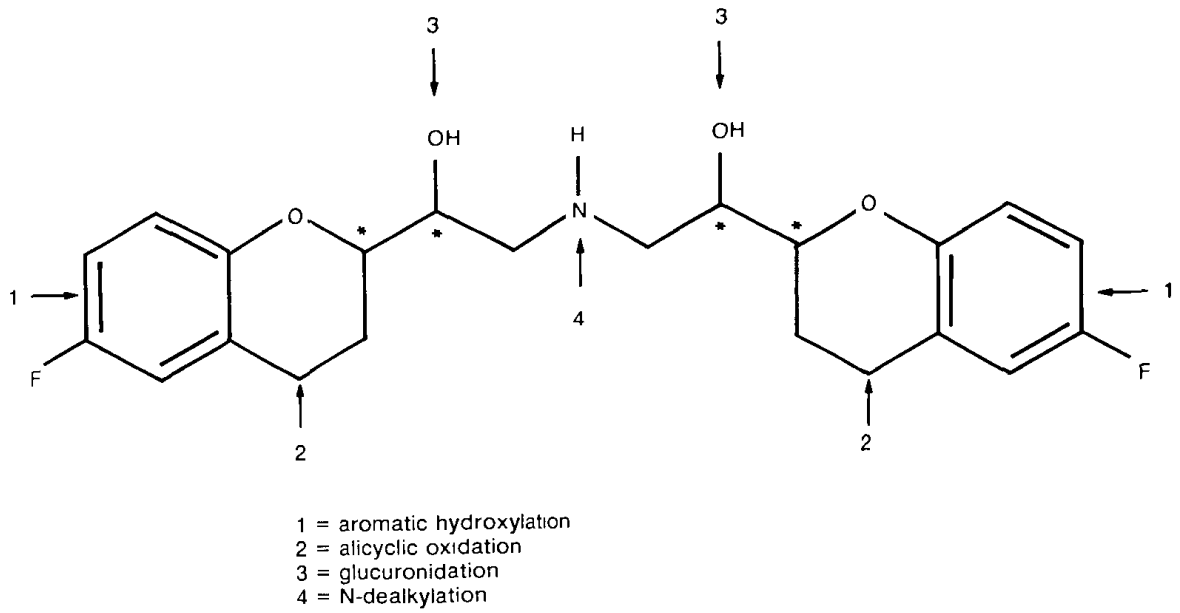

Fig. 1. Nebivolol structure and major metabolic pathways in extensive and poor debrisoquine metabolising subjects. Asterisks denote asymmetric centres. Arrows indicate the major sites of metabolism.

borghs et al. 1990). The enantioselective antibodies were found to crossreact with aromatic and alicyclic hydroxylated metabolites of *d*-nebivolol that have an *in vitro* β_1-adrenergic receptor binding affinity comparable with *d*-nebivolol (data on file, Janssen). Thus, radioimmunoassay is the most feasible method of estimating active drug concentrations in pharmacokinetic studies.

2. Excretion and Metabolism

The metabolic pathways and the excretion of nebivolol have been studied in 6 healthy volunteers receiving a single oral dose of nebivolol 15mg. Two of the subjects were poor hydroxylators of debrisoquine [metabolic ratio (MR) of debrisoquine : 4-hydroxydebrisoquine > 12].

Nebivolol metabolism appeared to be complex, with numerous metabolites formed. Primarily, quantitative differences were found between the metabolic pathways and excretion in the extensive (EMs) and poor (PMs) hydroxylators of debrisoquine (fig. 1). Aromatic hydroxylation was deficient in the PMs, whereas this step was the major pathway in the EMs. Pathways such as alicyclic hydroxylation and glucuronidation of the parent drug and hydroxylated metabolites were important in EMs as well as in PMs. *N*-Dealkylation was less important (table I). Urinary and faecal excretion of the unconjugated parent drug were < 0.5% of the dose in both debrisoquine phenotype subjects.

Table I. Effect of metaboliser phenotype on the metabolism of nebivolol

	Metaboliser phenotype	
	extensive	poor
Aromatic hydroxylation	+++	+
Alicyclic oxidation	++	++
Glucuronidation	+++	+++
N-Dealkylation	+	+

Abbreviations: + = slight; ++ = moderate; +++ = substantial.

3. Absolute Oral Bioavailability

The intravenous pharmacokinetics and absolute oral bioavailability of nebivolol were studied in 10 healthy male volunteers after administration of 0.5mg intravenously and 5mg orally. Two PMs

were included in the study in order to investigate differences in absolute bioavailability.

The elimination rate and absolute oral bioavailability of the parent drug were markedly different in the EMs and PMs (fig. 2). The mean terminal phase half-life of unchanged nebivolol after intravenous administration was 8 hours in the EMs, and 27 hours in the PMs. The difference in half-life was related to the clearance, which was almost 4 times lower in PMs than in EMs (30 L/h *vs* 111 L/h, respectively). First-pass metabolism in EMs reduced the absolute oral bioavailability to 12% whereas, in the PMs, the absolute oral bioavailability averaged 96%, indicating low presystemic elimination.

Formation of hydroxylated metabolites after intravenous nebivolol administration was limited in EMs and PMs. Radioimmunoassay concentrations specifically measuring either *d*- or *l*-nebivolol plus their respective hydroxylated metabolites were half the HPLC concentrations, which reflect the sum of unchanged *d*- and *l*- nebivolol. After oral nebivolol, the radioimmunoassay $AUC_{0\text{-}24h}$ was comparable between EMs and PMs, indicating that substantial first-pass formation of hydroxylated metabolites compensates for the large difference in unchanged drug concentrations between EMs and PMs.

4. Distribution

After an intravenous bolus injection of nebivolol 0.5mg, the plasma concentration-time curve of the parent drug was characterised by a biexponential decay with a similar distribution half-life of 3 minutes in EMs and PMs (fig. 2). The apparent volume of distribution (Vd_{area}) ranged from 695 to 2755L (10.1 to 39.4 L/kg). Because of sensitivity limitations, distribution kinetic parameters could not be calculated for the isomers separately. Plasma protein binding was hardly stereospecific, and concentration independent (98.1 ± 0.2% for *d*-nebivolol and 98.0 ± 0.3% for *l*-nebivolol) [Mannens et al. 1990].

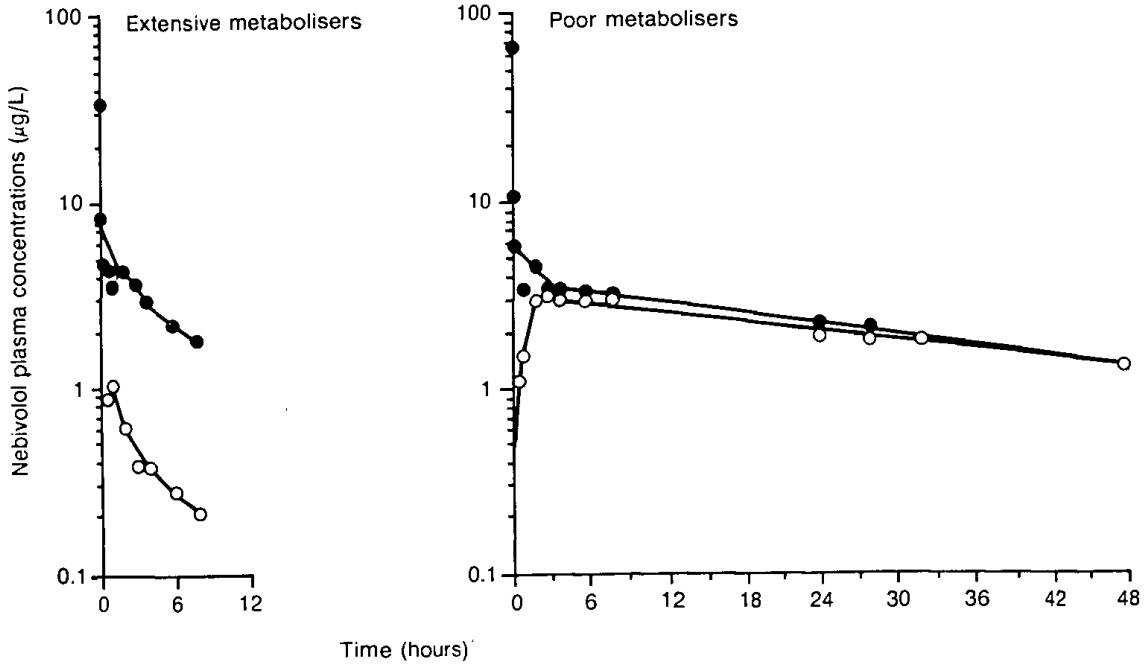

Fig. 2. Mean nebivolol plasma concentrations normalised to a 5mg intravenous (●) and oral (○) dose in 7 extensive debrisoquine metabolising (metabolic ratio < 2) and in 2 poor metabolising (metabolic ratio > 12) volunteers (after Van de Velde 1987).

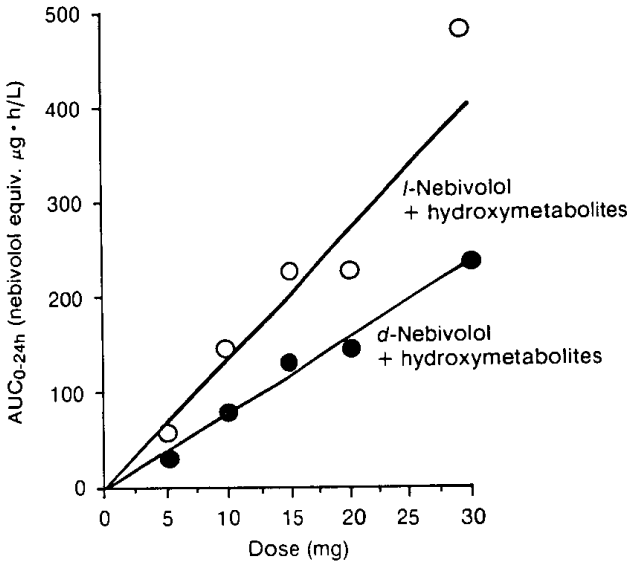

Fig. 3. Dose-linearity after single oral doses of nebivolol to healthy volunteers.

5. *Dose Proportionality*

Nebivolol kinetics after oral dosing were dose-linear in the range 5 to 30mg (fig. 3), but radioimmunoassay-measured AUCs for *l*-nebivolol were almost twice as high as those for *d*-nebivolol. This indicates a lower clearance for the *l*-isomer and also explains the slower decay of the radioimmunoassay plasma concentrations of *l*-nebivolol and its hydroxymetabolites.

6. *Repeated Oral Administration*

After oral administration of nebivolol 10mg on the first day, followed by 5mg once daily (fig. 4) for 7 days to volunteers, plasma concentrations of nebivolol were measured by HPLC and radioimmunoassay. Nebivolol did not accumulate in EMs, as the trough plasma concentrations were generally below the HPLC detection limit of 0.1 µg/L. In the PMs, plasma concentrations were presumably in steady-state. The steady-state $AUC_{0\text{-}24h}$ in PMs was 49 times higher than in the EMs (296 µg • h/L *vs* 6 µg • h/L).

Fewer differences in pharmacokinetics between EMs and PMs were found after radioimmunoassay. After the first 10mg dose, the radioimmunoassay peak plasma concentration of *d*-nebivolol was substantially higher in the EMs than in the PMs, probably due to the important first-pass formation of the hydroxymetabolites. During the following 7 days on 5mg once daily, radioimmunoassay peak plasma concentrations were similar in EMs and PMs. Furthermore, the almost 50-fold difference in steady-state AUC for unchanged drug between EMs and PMs was only 2-fold when the radioimmunoassay AUC was considered (167 µg • h/L in PMs *vs* 73 µg • h/L in EMs for *d*-nebivolol). These findings demonstrate the substantial contribution of the pharmacologically active metabolites of *d*-nebivolol in the blood of EMs and explain the similar cardiac and systemic haemodynamics in EMs and PMs (Van Rooy & De Crée 1990).

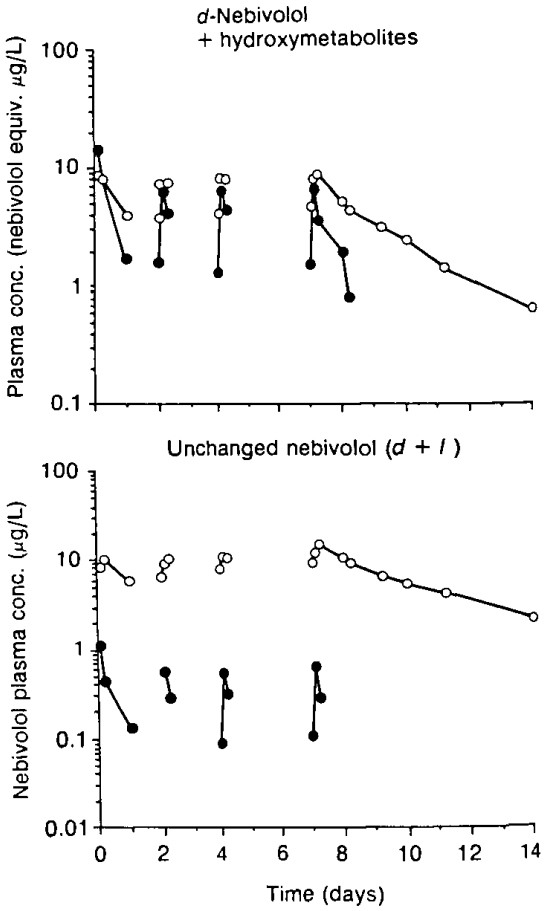

Fig. 4. Mean plasma concentrations of nebivolol in extensive metabolisers (●) [n = 6] and poor metabolisers (○) [n = 6] after oral doses of 10mg on the first day followed by 5mg

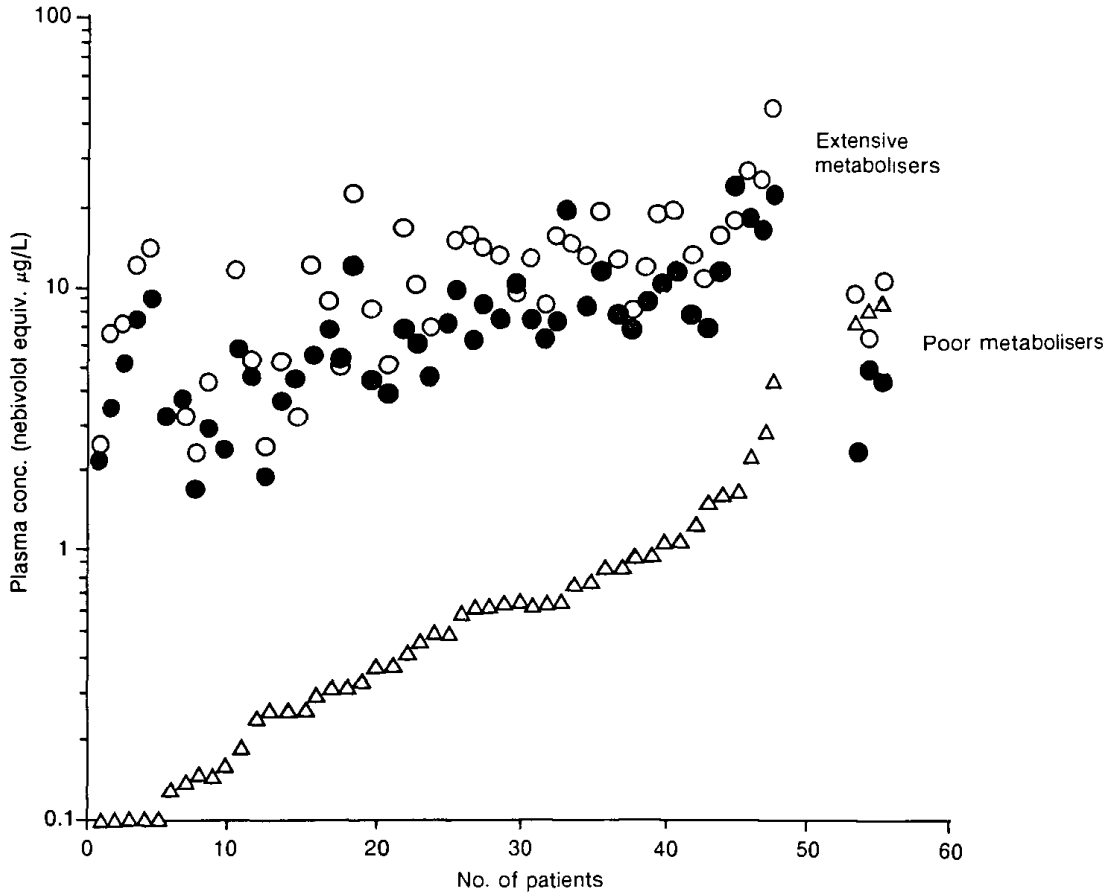

Fig. 5. Plasma concentrations of nebivolol (△), *d*-nebivolol plus hydroxymetabolites (●) and *l*-nebivolol plus hydroxymetabolites (○) in hypertensive patients.

In EMs, the elimination half-life of *d*-nebivolol was difficult to calculate, as the hydroxylated metabolites are rapidly eliminated. In PMs, the AUC and the terminal phase elimination half-life (55 to 100 hours) reflect the kinetics of unchanged nebivolol.

7. *Patients with Hypertension*

The substantial presence of hydroxymetabolites in the plasma of EMs was further demonstrated in samples collected during clinical studies of patients with hypertension. Because the blood samples were taken during the patient's routine clinic visit, plasma concentrations range over various times after drug intake. As a result, HPLC-measured plasma concentrations of nebivolol varied almost 100-fold (fig. 5). The lower concentration range most likely represents predose concentrations, whereas the upper range corresponds to peak concentrations in EMs or concentrations at various times postdose in the 3 PMs. The variation in radioimmunoassay concentrations of *d*- and *l*-nebivolol plus hydroxymetabolites was only 10-fold and ranged between 2 and 20 μg/L. Moreover, there was a considerable overlap in the radioimmunoassay concentrations of each isomer between EMs and PMs, suggesting that active drug concentrations are comparable between both phenotype subjects.

8. *Conclusions*

Nebivolol pharmacokinetics are complex and subject to genetic polymorphism. PMs are unable to adequately hydroxylate nebivolol at the aromatic moiety so that the kinetics in PMs are char-

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