Comparative Pharmacodynamics and Pharmacokinetics of Candesartan and Losartan in Man

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Abstract

The angiotensin II antagonistic effects of candesartan and losartan were compared in-vivo after single and repeated doses. Effects were related to antagonistic activity in plasma.

In this double-blind, crossover study, 12 healthy male volunteers received, in random order, daily oral doses of 8 mg candesartan cilexetil or 50 mg losartan for seven days. On day 1 and day 8, dynamics and kinetics were assessed up to 48 h after dosing. Antagonistic effect was determined from the antagonist-induced rightward shifts of the diastolic blood pressure response curves to exogenously administered angiotensin II measured as the dose ratio (DR). The antagonistic activity in plasma was measured using an ex-vivo/in-vitro radioreceptor assay. Specific high-performance liquid chromatography assays determined plasma concentrations of candesartan, losartan and its active metabolite EXP-3174.

The pharmacokinetic properties of candesartan and losartan were comparable and antagonistic activity in plasma almost identical (ratio candesartan : losartan = 0.97 and 1.2 after single and multiple doses, respectively). However, the antagonistic effects of candesartan and losartan in-vivo were quite different. Twenty-four hours after single dosing with candesartan a clinically relevant rightward shift in the angiotensin II dose−response curve (DR = 3.2) occurred that was more pronounced than that following losartan administration (DR = 2.1, ratio candesartan : losartan = 1.65). Twenty-four hours after multiple doses of candesartan or losartan, the values of the DR were 4.8 and 2.3, respectively (ratio candesartan : losartan = 1.94). The values of DR for candesartan were significantly higher compared with losartan between 6 and 36 h after a single dose and between 3 and 24 h post-dose following multiple dose administration. A counter-clockwise hysteresis was apparent between antagonistic activity in plasma and antagonistic effect.

Despite equivalent angiotensin II antagonistic activity in plasma, the pharmacodynamic effect of candesartan cilexetil was greater than that of losartan. Candesartan appeared to have a slower off-rate from the angiotensin AT1-receptor compared with losartan, nevertheless differences in distributional phenomena or the extent of insurmountable antagonistic activity cannot be ruled out.

Over the last decade, non-peptide angiotensin II antagonists have been developed to inhibit the effects of angiotensin II directly at the receptor site (Brunner et al 1993; Timmermans et al 1993). To date, several angiotensin receptor subtypes have been characterized, of which the AT1 receptor is primarily responsible for the angiotensin II-mediated pathophysiological mechanisms in cardiovascular disease (Dzau et al 1993).

Losartan was the first AT1-receptor antagonist introduced into clinical practice (Brunner et al 1993; Timmermans et al 1993). It is absorbed rapidly and partially transformed to its active metabolite EXP-3174, which is responsible for most of the antagonistic effects. Losartan has been
shown to provide reliable blood pressure reduction at dosages of 50–100 mg, while in the treatment of congestive heart failure, lower dosages seem to be sufficient to reduce systemic vascular resistance and subsequently increase cardiac output (Goldberg et al 1995; Csajka et al 1997). Another AT1-receptor antagonist, candesartan cilexetil, is an inactive prodrug, which is rapidly and completely converted to candesartan, a compound with a long duration of action (Shibouta et al 1993). In healthy volunteers, a long-lasting rightward shift of blood pressure response curves to infusion of angiotensin II have demonstrated a strong antagonistic effect 24 h after single oral doses of candesartan cilexetil at 8 and 16 mg (Malerczyk et al 1998). Initial studies in patients with mild to moderate hypertension confirmed a good antihypertensive efficacy and indicated an excellent tolerability profile (Franke 1997; Heuer et al 1997).

The present study compared the in-vivo antagonistic properties of candesartan and losartan after single and repeated doses: in-vivo in man and on the basis of an ex-vivo/in-vitro plasma radioreceptor assay (preliminary data has been published (Belz et al 1997a)).

The potency of an antagonist can be quantified by measuring its effect on the receptor-mediated responses to different doses of an agonist. After dosing of the antagonist, the agonist dose–response curves are shifted to the right, i.e. higher doses of the agonist are needed to induce an equivalent response. Thus, the rightward shifts of angiotensin II dose–response curves were studied in the presence of candesartan and losartan (the pharmacodynamic effect).

The pharmacokinetics were assessed using high-performance liquid chromatography (HPLC) and a radioreceptor assay, which in contrast to chemical detection assays allows a direct comparison of the activities of various antagonists within the same class. In contrast to HPLC, radioreceptor assay captures only the non-protein bound drug and allows a prediction of receptor-blockade. Due to the lack of specificity of radioreceptor assays, any substance having an appreciable affinity for the receptor displaces the specifically bound radioligand. Correlation of radioreceptor assay and HPLC results clarifies whether active metabolites are present. Therefore, results determined by radioreceptor assay reflect the antagonistic activity present in the biological fluid, no matter which substance is responsible, and in addition takes into account the extent of protein binding. Moreover, results of radioreceptor assay offer a more suitable basis for pharmacokinetic/pharmacodynamic correlations.

Materials and Methods

Materials
All chemicals were supplied by E. Merck (Darmstadt, Germany) unless stated otherwise. [125I][Sar\(^1\) Ile\(^8\)]-Angiotensin II was purchased from ANAWA (Wangen, Switzerland). Candesartan, losartan and EXP-3174 were kindly provided by Takeda (Osaka, Japan). Azosemide was obtained from Sanofi Winthrop GmbH (Munich, Germany) and benoxaprofen from Eli Lilly GmbH (Giessen, Germany).

Subjects
Thirteen healthy male subjects (as assessed from physical examination, electrocardiogram, haematology, clinical chemistry, and urinalysis) were enrolled in the study. All subjects provided informed, written consent. Twelve subjects (mean age 29 years, mean weight 81.3 kg, mean height 1.85 m) completed the study according to the protocol. One subject was withdrawn after his first study day because extrasystoles developed during angiotensin II infusion.

Study design and procedures
The study was performed as a double-blind, randomized, crossover trial which included two study periods of 10 days duration with a wash-out period of at least 13 days between the two treatments. Before enrolment, the subjects underwent screening. This involved clinical examination, electrocardiogram, laboratory analyses and blood pressure measurements at rest and during an isometric stress test. Candesartan cilexetil (8 mg) and losartan (50 mg) were administered as a single oral dose on day 1 of the respective period and pharmacodynamics and pharmacokinetics were measured up to 47 h after dosing. On days 3 to 8 of each period, volunteers received candesartan cilexetil (8 mg) once daily or losartan (50 mg) once daily. During this period, subjects reported to the study centre every morning for supervised drug intake and monitoring of adverse events.

The local ethics committee (Ethikkonimission der Landesa¨rztekarnmer Rheinland-Pfalz) approved the study.
**Pharmacodynamics**

Angiotensin II (5 μg mL⁻¹) was infused in ascending dose steps (0.17–20 μg min⁻¹ flow rate adjusted; duration 3 min each) before and at 3, 6, 9, 12, 24, 36 and 47 h after dosing of the drugs. Dose–blood pressure response curves were fitted individually for each subject, treatment (candesartan cilexetil and losartan), day (single and multiple dose) and time point (0 to 47 h) according to an E_max model (Hill 1910):

\[
E = (E_{max} - E_{min})/(1 + (EC50/x)^a) + E_{min} \quad (1)
\]

where E is the response (y-value, blood pressure), E_max is the asymptotic maximum (arbitrarily set at 500 mmHg), E_min is the asymptotic minimum of response in absence of the agonist (i.e. baseline blood pressure before angiotensin II infusion at the respective time point), EC50 is the concentration of the agonist at which the response is 50% of the maximum, x is the concentration or dose of the agonist, and a is the slope parameter. After administration of the active drugs, rightward shifts of the dose–response curve, quantified as dose ratios (DR), were calculated from the EC50 values after dosing in relation to those before dosing:

\[
DR = EC50 \text{ after dosing} / EC50 \text{ before dosing} \quad (2)
\]

The terminal half-lives of effect were calculated for both treatments (days 1 and 8) using log-linear regression of DR-l data from 6–47 h.

**Radioreceptor assay**

Receptor binding studies at AT_1 receptors were performed using rat lung tissues and [125I](Sar¹ Ile⁸)-angiotensin II as the radioligand as described by Soldner et al (1998). Briefly, membranes (25–50 μg of protein) were incubated at 25°C with 30 μL radioligand (50 pmol L⁻¹), 20 μL unlabelled competitor (0.1 nmol L⁻¹–30 μmol L⁻¹) and 200 μL human plasma for 90 min. For the determination of unknown samples, plasma from the active treatment period was used and the competitor was replaced by 20 μL pure buffer. Free radioligand was separated from bound ligand by rapid filtration through glass fibre filters (GF/C filters, Bibby Dunn Labortechnik GmbH, Asbach, Germany) presoaked with 0.1% aqueous polyethyleneimine solution. The filters were washed with approximately 10 mL ice-cold 0.9% NaCl solution and retained radioactivity was counted for 150 s in a γ-counter (Wallac 1480, Wizard, Turku, Finland).

To avoid inaccuracies due to changes in plasma protein binding, samples were only thawed once for the radioreceptor assay and calibration curves were performed in drug-free plasma of the respective volunteer.

**HPLC determination of candesartan**

After solid-phase extraction from human plasma using CN-N cartridges (Varian Nr. 1210-2007, Varian, Darmstadt, Germany), candesartan was analysed by heart-cut column-switching reversed-phase HPLC with azosemide as the internal standard. Detection was carried out by UV-absorbance at 210 nm yielding a limit of quantification of 3 ng mL⁻¹ as described by Fuchs et al (unpublished data).

**HPLC determination of losartan and EXP-3174**

Losartan and EXP-3174 were extracted from plasma using the same solid-phase extraction method as for candesartan. Analysis was conducted by reversed-phase HPLC (Zorbax CN, 5 μm, 150 × 4.6 mm, Bischoff, Leonberg, Germany and a precolumn 20-mm long filled with the same material) and quantified by measuring the intrinsic fluorescence (λ_exc 280 nm, λ_em 380 nm). Benoxaprofen served as internal standard. For both substances the limit of quantification was 5 ng mL⁻¹.

**Data analysis**

Data were analysed using the non-linear curve-fitting computer program SigmaPlot for Windows, version 2.01. An extended Clark’s equation (Clark 1933) was used to evaluate the concentration–effect relationship according to the law of mass action:

\[
B_{L1} = B_{max} \times L / [K_D (1 + I/K_i) + L] \quad (3)
\]

where B_{L1} is the amount of radioligand bound at concentration L of radioligand and I of antagonist, and B_{max} is the maximal number of binding sites. K_D is the dissociation constant of the radioligand representing the concentration of radioligand at half-maximal receptor occupancy during equilibrium, and K_i is the equilibrium dissociation constant of the antagonist.

Equation 3 was used to calculate the antagonist concentration in positive controls or unknown samples.

If more than one antagonist is present, the equation has to be expanded with an I/K term for each antagonist, e.g. two competitors (I and A):

\[
B_{L1A} = B_{max} \times L / [K_D (1 + I/K_i + A/K_A) + L] \quad (4)
\]

To compare HPLC and radioreceptor assay, a concentration-equivalent (nK_i) was calculated using the following equations:

\[
nK_i (HPLC) = \text{results HPLC} [\text{g L}^{-1}] / \text{MW} / K_i \quad (5)
\]
nKi (radioreceptor assay)

= results radioreceptoe assay [mol L\(^{-1}\)/K\(_i\) (6)

The calculation of the pharmacokinetic parameters of all compounds (maximum plasma concentration (C\(_{\text{max}}\)), time to C\(_{\text{max}}\) (t\(_{\text{max}}\)), plasma half-life (t\(_{1/2}\)) and area under the plasma concentration–time curve (AUC) was carried out using the TOPFIT program, version 2.0 (Heinzel et al 1993). Values are presented as geometric means.

The shifts of the angiotensin II dose–response curves caused by the active treatments relative to those before dosing on day 1 (given as DR-1) were plotted against the radioreceptor assay plasma concentration equivalents (given as n*K\(_i\)) following candesartan cilexetil or losartan for single or multiple dosing (Schild plots).

Statistics

Statistical analyses included descriptive measures and explorative analyses of variance with effects of sequence, subject within sequence, period, treatment, subject*treatment, time and time*treatment at a two-sided \( \alpha \) level of 5% for single and multiple dosing. An “accumulation of concentration” factor was determined for each treatment as the ratio of AUC\(_{nK_i}\) day 8\(0\)–47h/AUC\(_{nK_i}\) day 1\(0\)–47h. Correspondingly, the areas under the effect (DR-1) time profiles were calculated and the “accumulation of effect”-factor was derived as the ratio AUC\(_{DR}\) day 8\(0\)–47h/AUC\(_{DR}\) day 1\(0\)–47h. Statistical significance was accepted when the 95% confidence intervals (CI) of these AUC ratios did not include 1. Comparisons of the plasma antagonistic potency (radioreceptor assay concentration equivalents) of candesartan and losartan were based on the standard bioequivalence approach where bioequivalence was concluded if the values for the 90% CI for AUC\(_nK_i\) were within the [0.80–1.25] interval. The values of the 95% CI were calculated for the overall treatment difference candesartan cilexetil vs losartan and the treatment differences at each time point. Point and interval estimates were determined for the ratio candesartan cilexetil/losartan. Values were deemed to be statistically significant if the corresponding confidence interval did not include 1.

Results

Pharmacodynamics

After the administration of a single oral dose of 8 mg candesartan cilexetil, the maximum in-vivo effect (geometric mean DR = 18.6) was reached 6 h after dosing; after multiple dosing the maximum effect (mean DR = 27.8) was reached at 3 h post-dose (Figure 1). At 24 h post-dose, clinically relevant rightward shifts of the angiotensin II dose–response curves were still present following single (DR = 3.2) as well as multiple dosing (DR = 4.8). Analysis of variance revealed significant treatment effects on day 1 (\( P = 0.008 \)) and day 8 (\( P = 0.003 \)). The pharmacodynamic t\(_{1/2}\) was approximately 6 and 7.5 h following single and multiple dose administration, respectively. The area under the dose ratio–time curve (AUC\(_{DR}\)) following multiple doses of candesartan cilexetil was 33% (95% CI: 0.98,1.81) greater than that following a single dose.

After the administration of 50 mg losartan, the maximum effect was reached 6 h after dosing for the single and multiple dose (DR =10.5 and 13.8, respectively) (Figure 1). At 24 h after single (DR = 2.1) and multiple dose administration

![Figure 1](image-url)
(DR = 2.3), a slight rightward shift of the angiotensin II dose–response curves was still present. Analysis of variance revealed significant treatment effects on day 1 \( (P = 0.008) \) and day 8 \( (P = 0.003) \). The pharmacodynamic \( t_{1/2} \) was 7.2 and 8.9 h after single and multiple dosing, respectively. For losartan, multiple dose administration did not augment the pharmacodynamic effect compared with single dose administration.

Between 3 and 47 h after single dose administration, the DR values for candesartan cilexetil were 1.4–2.0-times larger than for losartan; the difference was statistically significant from 6 to 36 h post-dose. After the administration of the multiple dose the values for DR were 1.5–3.3-times larger for candesartan cilexetil than for losartan; statistical significance was reached from 3 to 24 h post-dose. The \( \text{AUC}_{\text{DR}} \) ratios following single and multiple doses respectively were 1.65–(95% CI: 1.18, 2.30) and 1.94 (95% CI: 1.34, 2.83)-times larger for candesartan cilexetil than for losartan.

**Pharmacokinetics**

**HPLC.** HPLC determination of plasma concentrations of candesartan showed a similar mean \( t_{\text{max}} \) following single and multiple dosing (4.4 and 3.8 h, respectively). The \( t_{1/2} \) increased from approximately 40 h after the single dose to approximately 6.9 h after multiple dose administration. Following a single dose of losartan, \( t_{\text{max}} \) was 1.4 h for losartan and 4.6 h for its active metabolite EXP-3174. Similar values (1.7 and 4.3 h, respectively) were obtained after multiple dose administration. On days 1 and 8, \( t_{1/2} \) values of 3.6 and 2.5 h, respectively, were obtained for losartan and 3.8 h and 4.6 h, respectively, for EXP-3174.

For candesartan, the AUC after multiple dose administration was 39% larger than after a single dose. For losartan and EXP-3174, HPLC data showed no statistically significant difference in AUC between single and multiple doses.

**Radioreceptor assay.** Figure 2 shows the time course of radioligand displacement given as concentration equivalents for candesartan and losartan. For candesartan, \( t_{1/2} \) values were 6.0 and 8.5 h and for losartan the values were 6.9 and 7.0 h following single and multiple doses, respectively. For candesartan and losartan the estimated ratio of \( \text{AUC}_{\text{nK}} \) day 8/day 1 was 1.28 (95% CI 0.81, 2.03) and 1.03 (95% CI 0.88, 1.22), respectively. The ratio candesartan/losartan was 0.97 (90% CI 0.57, 1.65) after a single dose and 1.2 (90% CI 0.76, 1.90) after multiple doses. The large variability in the 90% CI prevented statistical bioequivalence. Nevertheless, the respective point estimates did not differ markedly from 1, indicating that the two compounds induced comparable angiotensin II antagonistic activity in plasma.

The correlations of HPLC data with radioreceptor assay results are depicted in Figure 3. For candesartan the correlation almost corresponds to the line of identity, while for losartan the active metabolite EXP-3174 has to be taken into account in order to yield a line of regression with a slope approximating unity.

**Pharmacodynamic–kinetic relationship**

Individual values of pharmacodynamic effect and plasma concentration determined by radioreceptor assay were linearly related on a double log scale (Figure 4). On day 1, regression lines for candesartan cilexetil were 1.4–2.0-times larger than for losartan; the difference was statistically significant from 6 to 36 h post-dose. After the administration of the multiple dose the values for DR were 1.5–3.3-times larger for candesartan cilexetil than for losartan; statistical significance was reached from 3 to 24 h post-dose. The \( \text{AUC}_{\text{DR}} \) ratios following single and multiple doses respectively were 1.65–(95% CI: 1.18, 2.30) and 1.94 (95% CI: 1.34, 2.83)-times larger for candesartan cilexetil than for losartan.
sartan and losartan showed nearly the same slope. However, despite an equal receptor occupancy candesartan yielded a greater pharmacodynamic effect in-vivo. On day 8 the slope was much steeper for candesartan. Thus, the discrepancy between pharmacodynamic effect and antagonistic activity became even more obvious.

The pharmacodynamic–kinetic relationship yielded a hysteresis curve following candesartan cilexetil different to that following losartan, for which an almost closed loop was apparent (Figure 5).

**Tolerability**

Overall, candesartan cilexetil and losartan were well tolerated. Generally, a reduction in resting blood pressure of 8–12 mmHg was observed. In one volunteer transient orthostatic dysregulation occurred (day 8 of candesartan cilexetil treatment). Occasional headaches and dizziness possibly related to the vasoactive properties of both compounds were reported. No treatment-related clinically relevant changes in electrocardiogram or safety laboratory values were seen.

**Discussion**

In this study, the 24-h DR values, representing the antagonistic activity in-vivo, for candesartan were significantly higher than those for losartan on day 1 and day 8, indicating that candesartan cilexetil exhibited a greater effect. Following a single dose of candesartan cilexetil the extent and time course of the DR values were in good agreement with previous results (Andersson & Neldam 1997; Belz et al 1997b).

The difference in 24-h pharmacodynamic effects between candesartan cilexetil and losartan became more pronounced after multiple doses (AUC$_{DR}$ ratio 1.94 vs 1.65 after single dose). This probably
resulted from a slight accumulation of candesartan after treatment for one week, as indicated by both pharmacokinetic and pharmacodynamic data. Thus, HPLC and radioreceptor assay data showed increased AUC values following multiple doses of candesartan (increased by 39% and 28%, respectively) while the pharmacodynamic data showed that the effect of candesartan was augmented by 33%.

In this study, following losartan administration, pharmacodynamic and pharmacokinetic (radioreceptor assay) t\(_1/2\) values were similar (7-9 h). However, for candesartan, although values were similar after a single dose (approximately 6 h), after multiple dose administration the pharmacokinetic t\(_1/2\) (radioreceptor assay) seemed to be somewhat longer (approximately 8.5 h) than the dynamic one (approximately 7.5 h). In contrast, the pharmacokinetic t\(_1/2\) value for candesartan determined by HPLC was closer to the dynamic value (6.9 vs 7.5 h). The differences between radioreceptor assay and pharmacodynamic t\(_1/2\) values may arise from the high inter- and intra-individual variability.

As expected, HPLC and radioreceptor assay correlated closely suggesting that, apart from candesartan, candesartan cilexetil had no other active metabolites. The inactive metabolite of candesartan, CV-15959 (Shibouta et al 1993), did not contribute to the antagonistic activity in plasma assessed by radioreceptor assay and was therefore not determined by HPLC. In contrast to candesartan, correlation between radioreceptor assay and HPLC data for losartan differed from the line of identity. This was expected, as the active metabolite of losartan, EXP-3174, is responsible for much of its antagonistic activity in vivo. Indeed, addition of HPLC data for EXP-3174 to those for losartan produced a correlation close to 1 (Figure 3).

Antagonistic activity in plasma, as determined by radioreceptor assay, gave similar results for both agents, indicating administration of equipotent dosages. As radioreceptor assay measures antagonistic potency at the receptor site this encompasses any additional active metabolites and therefore reflects bioactivity in plasma. As bioactivity of candesartan and losartan was equivalent, similar pharmacodynamic effects in vivo were expected. However, after multiple dosing, candesartan was significantly more active than losartan (Figure 1).

The time course of the pharmacodynamic-kinetic relationship can be determined from the linear plot. The obtained counter-clockwise hysteresis following candesartan most likely reflects a distributional delay between the concentrations in plasma and the effect site, resulting in a longer in vivo effect than expected from the concentration in plasma. In agreement with our findings, Delacretaz et al (1995) demonstrated a slow onset of the inhibitory effect of the drug on blood pressure while plasma concentration of candesartan was increasing, and a sustained effect when drug concentration was falling, after single as well as after multiple dosing. The link between plasma concentration and observed effect is unknown and therefore resembles a “black box” (Meibohm & Derendorf 1997). One approach to model the relation between kinetics and dynamics is the use of a hypothetical effect compartment, as first introduced by Holford and Sheiner (Sheiner et al 1979). It applies the time course of effect itself to define the rate of drug movement to the effect site. The data
from this study were analysed according to that model and the parameters resulting from single dosing were used to predict the drug concentrations and effects for multiple dosing and checked for consistency with the measured data. The fitted plots resembled the observed data quite well and resulted in good correlation coefficients (0.9994 for candesartan and 0.994 for losartan data). A certain limitation in interpreting the data was the lack of data points for effect in the ascending part of the concentration–time curve. However, it has to be kept in mind that the validity of the relationship has to be established thoroughly, especially in patients, by evaluating data under many different conditions, e.g. different doses and input functions.

There are several possible explanations for the discrepancy between the kinetics and dynamics. Firstly, it may be due to differences in distribution patterns between effect compartment and plasma. Plasma concentrations do not have to resemble the concentrations that are effective at the receptors. Secondly, it may be due to the slow off-rate of candesartan from the receptor, as indicated by in-vitro studies (Inada et al 1997; Ojima et al 1997). Slow dissociation of the antagonist–receptor complex might translate into a longer effect than expected from the respective plasma concentrations. Thirdly, it may be due to a difference in the antagonistic mechanism, as demonstrated in functional studies. Losartan exhibited a classical competitive antagonism whereas candesartan interacted in an insurmountable manner (pD2 9-97). EXP-3174, however, also exerts insurmountable antagonistic activity but in a degree which is 10-times less (pD2 of candesartan 9-97, pD2 of EXP-3174 8-95 (Brunner et al 1993). Receptor mutation studies have demonstrated that competitive and insurmountable antagonists bind to overlapping but distinct regions within the transmembrane segments (Schambye et al 1994). A review of the studies on mutagenesis of angiotensin II type 1 receptor formulated the hypotheses that an antagonist sharing the same dominant binding sites with an agonist reacts competitively, whereas an antagonist which does not share one of the dominant binding sites with the agonist behaves as an insurmountable agonist (Inoue et al 1997). In consequence, a suggestion would be that binding of an insurmountable antagonist impairs, but does not completely prevent binding of an agonist, yet the latter probably does not yield receptor activation. In this case, binding studies and functional investigations would not correlate. Theoretically, insurmountable antagonistic activity can be caused by a slow off-rate from the receptor (pseudo-irreversible antagonism). However, due to different binding sites it is rather unlikely that slow dissociation may be the main reason for the insurmountable pattern of antagonistic activity of candesartan and EXP-3174.

Conclusion
Despite equivalent angiotensin II antagonistic activity in plasma as determined from ex-vivo/in-vitro radioreceptor assay, the pharmacodynamic effect (expressed as rightward shifts in angiotensin II dose–response curves) following candesartan cilexetil administration was greater than that following losartan. Candesartan appears to have a slower off-rate from the AT1-receptor compared with losartan, nevertheless differences in distributional phenomena or extent of insurmountable antagonistic activity cannot be ruled out.

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