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Clinical pharmacokinetics of angiotensin II (AT_1) receptor blockers in hypertension

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Angiotensin II receptor blockers (ARBs) represent a new class of effective and well tolerated orally active antihypertensive agents. Recent clinical trials have shown the added benefits of ARBs in hypertensive patients (reduction in left ventricular hypertrophy, improvement in diastolic function, decrease in ventricular arrhythmias, reduction in microalbuminuria, and improvement in renal function), and cardioprotective effect in patients with heart failure. Several large long-term studies are in progress to assess the beneficial effects of ARBs on cardiac hypertrophy, renal function, and cardiovascular and cerebrovascular morbidity and mortality in hypertensive patients with or without diabetes mellitus, and the value of these drugs in patients with heart disease and diabetic nephropathy.

The ARBs specifically block the interaction of angiotensin II at the AT_1 receptor, thereby relaxing smooth muscle, increasing salt and water excretion, reducing plasma volume, and decreasing cellular hypertrophy. These agents exert their blood pressure-lowering effect mainly by reducing peripheral vascular resistance usually without a rise in heart rate. Most of the commercially available ARBs control blood pressure for 24 h after once daily dosing. Sustained efficacy of blood pressure control, without any evidence of tachyphylaxis, has been demonstrated after long-term administration (3 years) of some of the ARBs. The efficacy of ARBs is similar to that of thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors or calcium channel blockers in patients with similar degree of hypertension. Higher daily doses, dietary salt restriction, and concomitant diuretic or ACE inhibitor administration amplify the antihypertensive effect of ARBs. The ARBs have a low incidence of adverse effects (headache, upper respiratory infection, back pain, muscle cramps, fatigue and dizziness), even in the elderly patients. After the approval of losartan, five other ARBs (candesartan cilexetil, eprosartan, irbesartan, telmisartan, and valsartan) and three combinations with hydrochlorothiazide (irbesartan, losartan and valsartan) have been approved as antihypertensive agents, and some 28 compounds are in various stages of development.

The ARBs are non-peptide compounds with varied structures; some (candesartan, losartan, irbesartan, and valsartan) have a common tetrazolo-biphenyl structure. Except for irbesartan, all active ARBs have a carboxylic acid group. Candesartan cilexetil is a prodrug, while losartan has a metabolite (EXP3174) which is more active than the parent drug. No other metabolites of ARBs contribute significantly to the antihypertensive effect.

The variation in the molecular structure of the ARBs results in differences in the binding affinity to the receptor and pharmacokinetic profiles. The differences observed in lipid solubility, absorption/distribution, plasma protein binding, bioavailability, biotransformation, plasma half-life, and systemic elimination influence the time of onset, duration of action, and efficacy of the ARBs. On the basis of the daily mg dose, the antihypertensive potency of the ARBs follows the sequence: candesartan cilexetil $>$ telmisartan $\simeq$ losartan $>$ irbesartan $\simeq$ valsartan $>$ eprosartan.

After oral administration, the ARBs are rapidly absorbed (time for peak plasma levels = 0.5–4 h) but they have a wide range of bioavailability (from a low of 13% for eprosartan to a high of 60–80% for irbesartan); food does not influence the bioavailability, except for valsartan (a reduction of 40–50%) and eprosartan (increase). A limited dose-peak plasma levels/areas under the plasma level-time curve proportionality is observed for some of the ARBs. Most of these drugs have high plasma protein binding (95–100%); irbesartan has the lowest binding among the group (90%). The steady-state volumes of distribution vary from a low of 9 L (candesartan) to a high of 500 L (telmisartan). Plasma elimination half-life is short for candesartan cilexetil and losartan (1–4 h), intermediate for eprosartan and valsartan (5–10 h), and longer for candesartan, irbesartan and telmisartan (11–38 h); the active metabolite of losartan has a longer half-life than for the parent drug. The drugs and their active metabolites do not accumulate to a significant extent after repeated dosing, except for telmisartan (100%). Most of the orally administered dose of ARBs is excreted via bile into the faeces; from 2% (telmisartan) to 33% (candesartan) of the oral dose is excreted in the urine. In most cases, changes in pharmacokinetic parameters due to aging, mild to moderate renal disease and heart failure do not require dosage modification; dosage has to be individualised for eprosartan, losartan, telmisartan and valsartan in patients with hepatic disease. In general, pharmacokinetic drug–drug interactions are rare, with the exception of combination of digoxin and telmisartan.

The ARBs are an important treatment option for hypertension, being relatively safe and efficacious. The beneficial effects of the ARB therapy go beyond blood pressure control. They may prove to have beneficial haemodynamic and neurohormonal effects in heart failure and provide renoprotection in diabetic nephropathy.
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Keywords: angiotensin receptor blockers; candesartan; eprosartan; irbesartan; losartan; telmisartan; valsartan; pharmacokinetics

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Introduction

Angiotensin II receptor blockers (ARBs) represent a new class of effective and well tolerated orally

active antihypertensive drugs[1–15] that inhibit the renin-angiotensin system by selectively blocking the AT_1 subtype of angiotensin II receptor.[1,16,17] A number of studies have demonstrated the efficacy of ARBs (used as monotherapeutic agents or in combination with other antihypertensive drugs) in the treatment of hypertension.[1–15,18–63] Initial studies indicate that ARBs, either alone or in combination with angiotensin-converting enzyme (ACE) inhibitors, are also useful in the management of heart failure.[64–75] Several large, long-term studies are in progress (Table 1) to assess the beneficial effects of ARBs on cardiac hypertrophy, renal function, and cardiovascular and cerebrovascular morbidity and mortality in hypertensive patients with or without diabetes mellitus, and the value of these drugs in patients with heart failure, acute myocardial infarction, and diabetic nephropathy.

Angiotensin receptor blockers as antihypertensive drugs

As antihypertensive agents, the ARBs are as effective as ACE inhibitors, thiazide diuretics, beta-blockers or calcium channel blockers, often with a better tolerability profile.[2–15,21,25,29,35,43,60] The ARBs are effective and relatively safe in the elderly hypertensives,[2–15,42,52,63] and in patients with isolated systolic hypertension.[76] The antihypertensive efficacy of ARBs is enhanced when combined with diuretics, ACE inhibitors, calcium channel blockers, beta-blockers, or alpha-blockers.[2–15,37,52,54,55,57] In combination with other classes of antihypertensive drugs, the ARBs are also efficacious in the treatment of JNC-VI Stage III (severe) hypertension.[77–80] In general, the blood pressure lowering efficacy of ARB monotherapy is lower in black than in white hypertensives.[14,15] However, addition of a diuretic to the therapeutic regimen abolishes the ethnic difference in blood pressure control.[14,15,79]

Advantages of angiotensin receptor blocker therapy in hypertension

Most of the ARBs control blood pressure for 24 h after once daily dosing.[2–15,19,21,24,25,31–33,36–40,42,44,47,50,54,56,58–60,62] Sustained efficacy has been shown with long-term therapy with ARBs, with no tachyphylaxis.[36–38,42,47,48,50] Age or gender have no effect on blood pressure response to ARBs.[2–15,42,52,63] The ARBs do not alter the circadian rhythm of blood pressure.[24,31,34,40,53,62] Therapy with the ARBs does not cause first dose (excessive) hypotension or significant orthostatic hypotension.[2–15,27,49,50,59,60] Cessation of treatment with ARBs causes no rebound hypertension.[2–15,59]

ARB therapy does not have any effect on heart rate and cardiac output or electrocardiographic data.[2–15,19,24,34,38,39,49,50,52,58,59] The ARBs do not impair cerebrovascular regulation, and may even improve cognitive function. Treatment with the ARBs does not result in clinically significant alterations in laboratory measurements of serum chemistry, haematology and urinalysis.[2–15,19,23,39,44,50,59,62,81] The ARBs do not impair glucose or lipid metabolism.[2–15,19,81–83] These drugs have no adverse effect on renal function.[2–15,36,39,45,84–89] As a result of favourable safety profile, discontinuation rate with ARBs is low. In a study, it was shown that ARBs had the highest 1-year compliance rate among five major classes of antihypertensive drugs.[90]

The benefits of ARB therapy of hypertension go beyond the reduction in blood pressure. The additional advantages of ARB therapy include: (1) reduction in left ventricular hypertrophy;[5,22,48,91–95] (2) improvement in diastolic function;[96] (3) decrease in ventricular arrhythmias;[97] (4) reduction in the abnormal QT dispersion;[98] (5) improvement in endothelial dysfunction;[99] (6) improvement in large artery compliance;[95] (7) reduction in microalbuminuria;[29,35,45,89,100,101] (8) preservation of or improvement in renal function;[36,39,45,84–89] except in patients with severe congestive heart failure or renal artery stenosis; (9) increase in insulin sensitivity;[102,103] and (10) decrease in serum uric acid levels (by only losartan);[104–106] hyperuricaemia is associated with increased risk for stroke and heart attack in hypertensive patients.[107]

Commercially available angiotensin receptor blockers

After the introduction of the prototype drug, losartan, six more ARBs were approved for treatment of hypertension (Table 2); of these, tasosartan (*Verdia*) was withdrawn by the pharmaceutical company due to liver enzyme elevation. The available ARBs and their combinations (with hydrochlorothiazide) are

Table 1 Large scale ongoing clinical trials of angiotensin receptor blockers (ARBs)

Trial	*ARB*	*CV Disease*[a]	*Trial*	*ARB*	*CV Disease*[a]
ABCD-2V	Valsartan	HTN/DN	CHARM	Candesartan[c]	HF
ELITE[b]	Losartan	HF	ELITE II	Losartan	HF
IDNT	Irbesartan	DN	IRMC	Irbesartan	
LIFE	Losartan	HTN/LVH	OPTIMAL	Losartan	AMI, HF/LVD
RAAS	Losartan	HF/LVD	RENAAL	Losartan	DN
RESOLVD[b]	Candesartan[c]	HF/LVD	SCOPE	Candesartan[c]	HTN
SILVER	Irbesartan	HTN/LVH	SPICE	Candesartan[c]	HTN
STRETCH	Candesartan[c]	HF	TEES	Telmisartan	HTN
ValHeFT	Valsartan	HF	VALIANT	Valsartan	AMI
VALUE	Valsartan	HTN	VLIG[b]	Valsartan	HTN

[a]Cardiovascular (CV) diseases in patients: hypertension (HTN), heart failure (HF), left ventricular hypertrophy (LVH), left ventricular dysfunction (LVD), acute myocardial infarction (AMI), diabetic nephropathy, (DN); [b]partial results have been published; [c]cilexetil.

Table 2 Angiotensin receptor blockers approved for the treatment of hypertension

Candesartan cilexetil (*Atacand, Kenzen*, TCV-116); candesartan, CV-11974)
Eprosartan (*Teveten*, SK&F 108566); eprosartan mesylate (SK&F 108566J)
Irbesartan (*Avapro, Aprovel*, SR 47436, BMS-186295); [*Avalide*]
Losartan potassium (*Cozaar, Tenserpil, Cormac*, DuP 753, MK-954, L-694, 491); [*Hyzaar, New Hyzaar*]
Telmisartan (*Micardis*, BIBR 277 SE, BIBRO277 SE)
Valsartan (*Diovan, Nisis, Tareg*, CGP 48933); [*Diovan HCT*]

Tasosartan (*Verdia*, ANA-756; WAY-ANA-756) was approved, but has been withdrawn due to adverse effects.

Table 3 Angiotensin receptors blockers available for the treatment of hypertension

Atacand, Astra AB (**candesartan cilexetil**) *Kenzen*
Avapro, Sanofi/Bristol-Myers Squibb (**irbesartan**) *Aprovel*
Cozaar, DuPont-Merck (**losartan** potassium salt) *Tenserpil, Cormac*
Diovan, Novartis/Ciba-Geigy (**valsartan**) *Nisis*, *Tareg*
Micardis, Boehringer Ingelheim Pharmaceuticals, Inc. (**telmisartan**)
Teveten, Smith Kline Beecham (**eprosartan**)

*Combinations with **hydrochlorothiazide***

Avalide, Sanofi/Bristol-Myers Squibb (**irbesartan**)
Diovan HCT, Novartis/Ciba-Geigy (**valsartan**)
Hyzaar, New Hyzaar DuPont-Merck (**losartan**)

listed in Table 3. At least 28 compounds are currently under investigation as potential ARBs (Table 4).

The structures of angiotensin receptor blockers

The ARBs are non-peptide compounds with varied structures (Figure 1). There are some structural similarities among the ARBs: (a) candesartan, irbesartan, losartan, and valsartan have a common tetrazolobiphenyl structure; (b) candesartan and telmisartan have a common benzimidazole group; (c) with the exception of irbesartan, all active ARBs have a free carboxylic acid group. The structure of eprosartan is distinct from other ARBs.

The variation in the molecular structure of the ARBs results in differences in lipid solubility, binding affinity to AT_1 receptor (giving rise to differences in potency), and pharmacokinetic profile (rate and extent of absorption, distribution, oral bioavailability, effect of food on absorption, protein binding, plasma half-life ($t_{\frac{1}{2}}$), biotransformation and systemic elimination) of the ARBs. These differences result in variations in the time of onset, duration of action, and efficacy of the individual ARBs.

Mechanism of blood pressure lowering action of angiotensin receptor blockers

The ARBs interfere with the renin-angiotensin-aldosterone system by selectively blocking the binding of angiotensin II to its receptor subtype 1 (AT_1),[1,16,17] causing an insurmountable inhibition, thereby inhibiting the main physiological effects of angiotensin II. The blockade of angiotensin receptor AT_1 results in relaxation of smooth muscles, increase in salt and water excretion, reduction in plasma volume, and decrease in cellular hypertrophy. The antihypertensive effect of ARBs is mainly due to the reduction in peripheral vascular resistance.

Doses and potencies of angiotensin receptor blockers used in the treatment of hypertension

The ARBs vary in potency and duration of action. The recommended starting and maintenance dosages of these drugs for the treatment of high blood pressure are given in Table 5. Lower initial doses are recommended in volume- and/or salt-depleted patients, and in patients with severe renal or hepatic disease for some ARBs.

The antihypertensive potency of the ARBs, based upon the starting dose in milligrams follows the sequence:

candesartan cilexetil > telmisartan ≃ losartan > irbesartan ≃ valsartan > eprosartan.

If the dose is expressed in millimoles, the potency order follows the sequence:

candesartan cilexetil > telmisartan > losartan > valsartan > irbesartan > eprosartan.

Although, most of the ARBs control blood pressure for 24 h after single daily doses, some patients may require twice daily dosing. Often, a diuretic may be added for increased efficacy; combination with drugs from other classes of antihypertensive agents also increase the efficacy of ARBs in controlling blood pressure (see above).

Pharmacodynamic characteristics of angiotensin receptor blockers

Candesartan cilexetil is a prodrug which is bioactivated in the body to candesartan.[14,15] A dose-depen-

Table 4 Compounds under investigation as potential angiotensin receptor blockers

1. **Abitasartan** (Tisartan)
2. **Elisartan**
3. **Fonsartan** (HR 720)
4. **Forasartan** (SC-52458)
5. **Milfasartan**
6. **Saprisartan** (GR 138950C)
7. **BAY 10–6734**
8. **BIBS 39**
9. **BIBS 222**
10. **BMS-183920**
11. **CGP 48369**
12. **CS-866**
13. **DuP 532** (L-694,492)
14. **E4177**
15. **GR117289 C**
16. **KR31080**
17. **KRH-594**
18. **L-158,809**
19. **L-163,017**
20. **LRB081**
21. **MK-966**
22. **SB 203220**
23. **TA606**
24. **TAK-536**
25. **TH-142177**
26. **UP269-6**
27. **XR510**
28. **YM358**

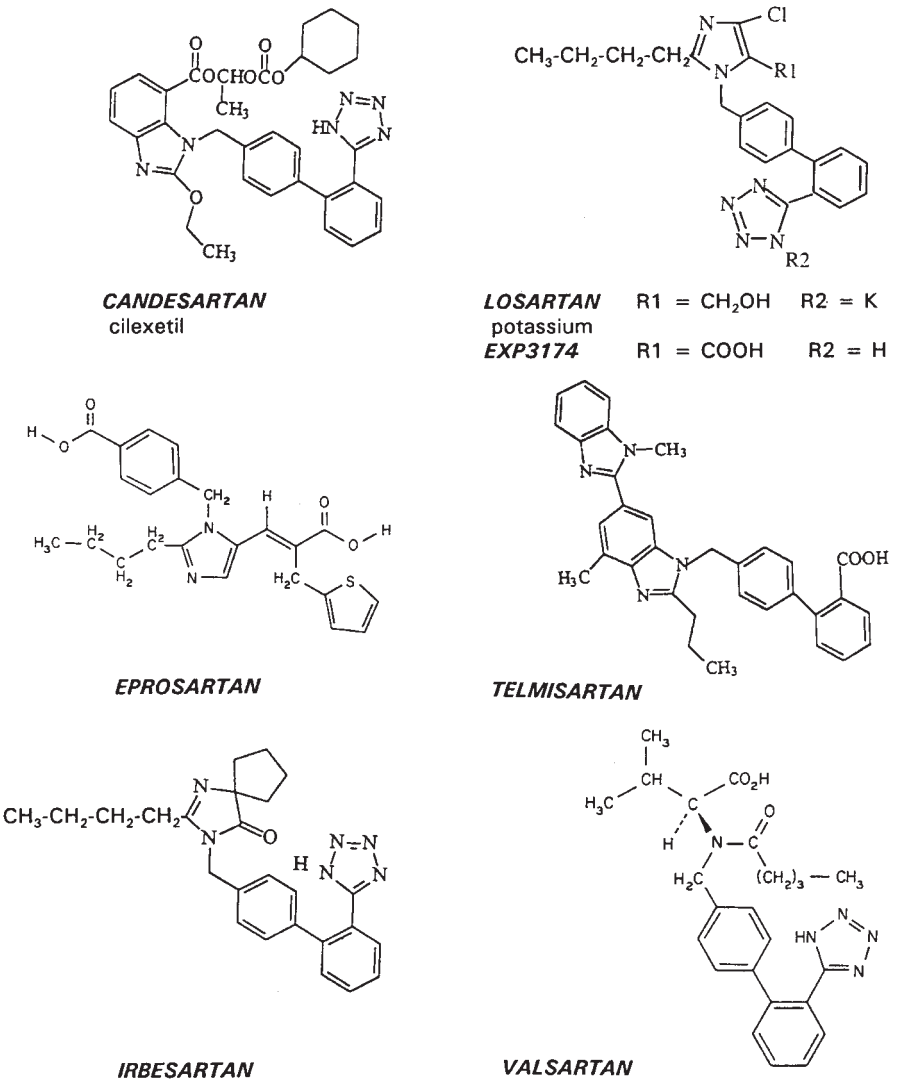

Figure 1 Structures of angiotensin receptor blockers.

Table 5 Recommended doses of angiotensin receptor blockers in hypertensive patients[a]

Angiotensin receptor blocker	*Total daily dose*			*Dosage adjustment*
	Initial[b]		*Maintenance*[c]	
	mg	*mMol*	*(mg)*	
Candesartan[d]	16	0.026	8–32	No[1,2,3]
Eprosartan	400	0.707	400–1200	No[1,2] Yes[3]
Irbesartan	150	0.350	75–300	No[1,2,2s,3]
Losartan	50	0.108	25–100	No[1,2] Yes[3]
Telmisartan	40	0.078	40–80	No[1,2] Yes[3]
Valsartan	80	0.176	80–320	No[1,2,3] Yes[2s,3s]

[a]Patients: 1 = elderly; 2 = with mild to moderate renal impairment; 3 = with mild to moderate liver disease; s = with severe disease.
[b]Lower initial doses in volume- and/or salt depleted patients.
[c]Twice-a-day doses may be needed in some patients.
[d]cilexetil.

dent (blood pressure lowering) response has been observed for 4–32 mg dose.[5,12,14,15,30,49] Maximum antihypertensive effect occurs at 4–6 h after an oral dose.[14,53] A trough plasma level-response relationship is found after repeated dosing, irrespective of age, weight, or gender of the patient.[12,14] The trough/peak ratios of blood pressure are in the range of 0.7–1.0.[12,30,49,62] The antihypertensive effect is well maintained for 24 h after 8–16 mg daily dose of candesartan cilexetil;[12,14,15,20,31,53,62] peak efficacy of antihypertensive effect is reached in 4–6 weeks of daily dosing.[12,14,15]

The basic structure of eprosartan is different from other ARBs (Figure 1). The drug does not require metabolic activation.[11,56] Maximum blood pressure lowering effect occurs in 4–6 h after the oral dose;[11] blood pressure may not be controlled for the full 24 h with once daily dosing. Eprosartan has no dose-response relationship in the therapeutic dose range.[11] Peak efficacy of blood pressure lowering effect is reached in 4–6 weeks.

Irbesartan does not require metabolic activation.[6,10,14,15,27] The drug exhibits nearly linear dose-response (blood pressure lowering) relationship for 50–300 mg dose.[6,10,23,27,32,46] After oral dosing, maximum blood pressure lowering effect occurs at 3–6 h.[6,14,15] Peak efficacy of blood pressure lowering effect is reached in 4–8 weeks.[6,10,14,15] Irbesartan is effective in hypertensive patients, irrespective of

age or gender.[14,15] Long-term blood pressure control can be achieved (in many patients) with monotherapy, since trough/peak ratio of blood pressure is in the range of 0.7–1.0.[6,14,15,27,32] There is no difference in the efficacy of irbesartan between the morning dose and the evening dose.

Most of the antihypertensive action and the long duration of action of losartan is due to its active metabolite EXP3174, which is 10–40 times more potent than losartan.[2,3,9,14,15] The time for maximum effect (4–6 h) coincides with the time for peak plasma level (T_{max}) of the metabolite.[2] Although, dose-response relationship is observed for the 40–120 mg dose of losartan or plasma level-response relationship for the metabolite in blocking the pressor effect of exogenous angiotensin II in normotensive subjects,[108] no such relationship exists for the blood pressure lowering effect in hypertensive patients.[14,15] The minimum dose of losartan to produce significant day-long blood pressure control in hypertensive patients is 50 mg; larger doses are no more efficacious.[3,26] A daily dose of 100 mg of losartan may have a slightly higher response rate or longer duration of action.[59] Peak efficacy of blood pressure lowering effect is reached in 3–6 weeks.[4,14,15] The antihypertensive response to losartan is independent of age or gender.[14,15] In some patients once daily dosing may not be sufficient to control blood pressure, although, the reported trough/peak ratio of blood pressure is in the range of 0.5–0.9.

Telmisartan is inherently active.[13,15] The blood pressure lowering effect of the drug is related to the dose (20–80 mg).[15,58] However, doubling of dose (from 40 mg to 80 mg) does not result in additional blood pressure reduction.[60] Telmisartan has a rapid onset of action (0.5–1.0 h),[13,15] and maximum blood pressure effect occurs at 4–6 h after the oral dose.[13,15] Once daily doses of 40–80 mg provide 24-h blood pressure control.[13,15,40,52,60] The trough/peak ratio of blood pressure is in the range of 0.7–1.0,[15] although, plasma trough/peak level ratio is 0.1–0.25. Peak efficacy of blood pressure lowering effect is reached in 1–4 weeks.[15] The antihypertensive effect of telmisartan is unaffected by the age or gender of the patient.[15]

Valsartan does not require metabolic activation.[8,14,15] The trough/peak ratio of blood pressure is in the range of 0.6–0.7.[15] Once daily dosing of valsartan is usually sufficient to control blood pressure for 24 h.[14,15,25] The peak efficacy of blood pressure lowering effect is reached in 4–6 weeks.[14,15] Maximum efficacy of valsartan is achieved at 80 mg dose, although, 160 mg dose may have a higher overall response rate.[59]

Adverse effects of angiotensin receptor blockers

The ARBs have a low incidence of adverse effects,[2–15,21–40,42,44,46–59,62,63,76–81,88,109,110] even in the elderly.[29,42,52,63] The adverse effect profile is often similar to that of placebo. Some of the adverse effects include, headache, dizziness, non-specific pain, upper respiratory tract infection, viral infection, asthenia/fatigue, sinusitis, and diarrhoea.[2–15] The side effects are not dose related.[2–15] First dose hypotension is uncommon (except in salt- and/or volume-depleted patients). Cough, the main adverse effect of ACE inhibitors,[111] occurs much less frequently with ARB therapy, and angioneurotic oedema is relatively rare.[112–116]

Pharmacokinetics and metabolism of angiotensin receptor blockers

Candesartan cilexetil: Candesartan cilexetil, an inactive racemic prodrug, is rapidly and completely metabolised (by ester hydrolysis) in the gastrointestinal tract to the active achiral candesartan.[12,14,15] The absolute bioavailability of candesartan (Table 6a) is about 15%.[14,15,109] Food with high fat content does not have any effect on its absorption or bioavailability.[14,15] Plasma levels of candesartan are proportional to the dose and peak at 2–5 h after the dose of candesartan cilexetil.[12,14,109] Candesartan is highly bound to plasma proteins (>99%).[14,15] The apparent volume of distribution (Vd) of candesartan is quite small (9 L).[14,15] Total plasma clearance (Cl_T) of candesartan is 26 mL/min, and its plasma elimination $t_{\frac{1}{2}}$ is approximately 9 h (range = 6–13 h).[12,14,15,109,117] The dose-pharmacokinetic relationship is linear for candesartan cilexetil for doses of 8–32 mg.[12,14,15] A nonsignificant accumulation (up to 20%) is observed (Table 6b) after repeated dosing.[14,15,109] The drug does not distribute into red blood cells to an appreciable extent.[14,15]

Candesartan is not metabolised by the cytochrome P450 system, but is de-ethylated and glucuronidated to a small extent.[14,15,117] After an oral dose, candesartan is excreted (Table 7) mainly unchanged in faeces (via bile) and in urine (26–33%);[14,15,20] a minor inactive metabolite formed by de-ethylation is also excreted.[14,15]

Eprosartan: After oral administration, eprosartan is fairly rapidly absorbed (T_{max} = 1–3 h), but its bioavailability (Table 6a) is low (about 13%) due to incomplete absorption.[11,118,119] High fat food increases bioavailability [increase in peak plasma levels (C_{max}) by 80% and in the area under the plasma level-time curve (AUC) by 55%], but slows its absorption, possibly by prolonging residence time in the gastrointestinal tract;[11,118,120,121] these changes do not require dosage adjustment in the fasting state.[11] The dose-C_{max} and dose-AUC relationships for single doses in the range of 100–800 mg of eprosartan, are less than proportional due to saturation of absorption.[122] Eprosartan is highly bound to plasma proteins (98%),[11,120,123] and has a small steady-state Vd (13 L).[11,118] It has a low systemic Cl_T (Table 6b; 130 mL/min).[89] The terminal $t_{\frac{1}{2}}$ of orally administered eprosartan is 5–9 h (about 2 h after intravenous administration).[11,118–120] The drug does not accumulate after repeated dosing.[124] Eprosartan is metabolised to a small extent, by enzymes other than cytochrome P450.[125] Most of the oral dose is excreted unchanged in the faeces (Table 7).[11,118,120,125]

Irbesartan: After an oral dose, irbesartan is rapidly and completely absorbed.[6,14,15,32,41,126] The absolute

Table 6 Pharmacokinetic parameters of angiotensin receptor blockers

(a)	T_{max} (h)	*Bioav. (%)*	*Effect of food*	*Protein binding*[a]	*Vd (L)*	$T_{½}$ *(h)*
Candesartan cilexetil		15	No	99.5		3–4
Candesartan[M]	2–5			99.5	9	6–13
Eprosartan	1–3	13	↑ $C_{max/AUC}$	98.0	13	5–9
Irbesrartan	1.3–3	60–80	No	90.0	53–93	11–18
Losartan	1–1.5	29–43	↓ C_{max}	98.7	28–47	1–3
EXP3174[M]	3–6			99.8	10–12	5–10
Telmisartan	0.5–1	30–60	Min	99.5	500	21–38
Valsartan	2–4	10–35	↓ C_{max}/AUC	95.0	17	6–10

(b)	*Dose (mg)*	C_{max} *(ng/mL)*	$AUC_{0-\infty}$ *(ng.hr/mL)*	*Clearance (mL/min)*	*Accum*[b] *(%)*
Candesartan[M]	12[P]	100	1000	26	20
Eprosartan	350	1250	5050	130	no
Irbesartan	150	3300	16600	167	15
Losartan	50	250	420	600	no
EXP3174[M]	50[P]	220	1330	50	no
Telmisartan	80	280	1970	>800	100
Valsartan	80	2000	6480	37	20

M = active metabolite; Min = minimum; [a]protein binding (%) mainly to albumin; [b]after repeated dosing; P = parent drug.

Table 7 Elimination of angiotensin receptor blockers (as % of oral dose)

Angiotensin receptor blockers	*Faecal*	*Renal*	*Metabolism*
Candesartan	67	33	Min
Eprosartan	90	10	Min
Irbesartan	80	20	9
Losartan	65	35	14[a]
Telmisartan	98	2	15
Valsartan	80	20	20

[a]Metabolised to the active compound EXP3174.
Min = minimum.

bioavailability is in the range of 60–80% (Table 6a).[14,15,32,126,127] Food does not influence neither the absorption nor bioavailability of the drug.[6,14,15,32,126,127] Peak plasma levels of irbesartan are achieved at 1.3–3 h after oral dosing.[6,32,41,61,110,126–129] Irbesartan displays linear dose-related pharmacokinetics over the dose range of 50–600 mg.[6,14,15,110] The drug is 90% bound, mainly to albumin (binding to alpha 1-acid glycoprotein = 22%).[6,14,15] Steady-state plasma levels are reached in 3 days after daily dosing, and no clinically important accumulation (<20%) occurs (Table 6b).[6,14,15,110,129] The Vd of irbesartan is between 53 L and 93 L, and it has a Cl_T of 157–177 mL/min (Table 6b).[14,15,126] Irbesartan has a long plasma elimination $t_{½}$ (11–18 h).[6,14,15,32,41,61,110,126–128]

The hepatic extraction ratio of irbesartan is low (0.2),[126] and the drug is partially metabolised (6% of the dose) by oxidation (by cytochrome CYP2C9) and glucuronidation to form eight inactive metabolites.[14,15,130] The metabolites account for only 9% of the circulating drug, 5–10% in urine and 6% in faeces.[14,15,131] Most of the administered dose (80%) is excreted in faeces via bile (Table 7), and the remainder in urine.[6,14,15,126]

Losartan: Losartan is pharmacologically active, but its major metabolite EXP3174 (10–40 times more potent than losartan) is responsible for most of its pharmacological activity (see above),[2,3,14,15,133] and long duration of action.[2,3,133] After oral administration, losartan is rapidly absorbed, and undergoes substantial first-pass metabolism by cytochrome P450 enzymes.[14,15,135] The T_{max} (Table 6a) of losartan and EXP3174 are 1–1.3 h and 3–6 h, respectively.[14,15,132–134] Systemic bioavailability of losartan is 33% (range = 29–43%).[132–134] About 14% of an oral or intravenous dose of losartan is converted to EXP3174.[14,15,133,134] The C_{max} and AUC of losartan and EXP3174 are linearly related to the dose of losartan (25–200 mg).[18] The C_{max} AUC of EXP3174 is two to four times higher than for losartan.[18,132–134] Food delays the absorption of losartan and lowers its C_{max}, but the AUC of losartan or EXP3174 are not significantly altered.[14,15,132] Losartan and EXP3174 are highly bound (Table 6a) to plasma proteins (98.7% and 99.8%, respectively), primarily to albumin.[14,15,135] The apparent Vd of losartan and EXP3174 is in the range of 28–47 L and 10–12 L, respectively.[14,15,133,134] The Cl_T of losartan and EXP3174 is about 600 mL/min and 50 mL/min, respectively (Table 6b).[14,15,133,134] Plasma elimination $t_{½}$ of losartan and EXP3174 ranges from 1–3 h and 5–10 h, respectively.[14,15,133,134,136–138] No significant accumulation of losartan or EXP3174 occurs after repeated dosing.[133]

Losartan is oxidized by cytochromes CYP2C9 and CYP3A4 to the active carboxylic acid metabolite EXP3174.[14,15,136,138,139] In addition, hydroxylation and glucuronidation result in several metabolites which are much less active than losartan.[14,15,139] Faecal excretion accounts for about 65% of the oral dose (Table 7) and 50% of the intravenous dose of losartan; the remainder is excreted in urine.[14,15] Biliary route contributes significantly to the total elimination of losartan and EXP3174. In the urine, 4–5% of the dose is present as losartan and 6–8% as EXP3174.[14,15,133–134]

Telmisartan: The drug is rapidly absorbed (T_{max} = 0.5–1 h)[13,15,58,140] following oral administration.

Telmisartan has an absolute bioavailability of 43% (range 30–60%; Table 6a).[13,15,140] Food has minimal effect on the bioavailability of telmisartan.[13,15] It is highly bound (>99%) to plasma proteins.[13,15,141] Telmisartan has a very high Vd (approximately 500 L).[15] Plasma elimination $t_{\frac{1}{2}}$ of telmisartan is about 24 h (range 21–38 h), and Cl_T is >800 mL/min (Table 6b).[13,15,58,142] The pharmacokinetics of telmisartan are nonlinear over the dose range of 20–160 mg, with greater than proportional increases in plasma levels with increasing doses.[15] Upon repeated dosing, telmisartan accumulates in plasma (150–200%).[15] The drug is not metabolised by cytochrome P450 system,[13,15,143] and almost all of the oral dose is excreted unchanged in faeces (Table 7), mainly by the biliary route.[13,15,143] A small amount of a glucuronide (11%) of telmisartan is found in the circulation.[15]

Valsartan: When given as a capsule, 19–23% of the dose of valsartan is absorbed.[8,14,15,144,145] Oral bioavailability (Table 6a) is about 19% (range 10–35%) if given as a capsule, but 39–51% if given as a solution.[8,14,15,145,146] The T_{max} of valsartan is 2–4 h after the administration of a capsule;[8,14,15] the absorption is more rapid if the drug is given as a solution (T_{max} = 1 h).[145] Food decreases C_{max} by 50% and AUC by 40%.[14,15] The C_{max} and AUC increase linearly with increasing dose (range 80–320 mg).[8] Protein binding of valsartan is high (94–97%, mainly to albumin),[14,15,147] and its Vd is 17 L.[14,15,145] The Cl_T of valsartan is 37 mL/min (Table 6b), and plasma elimination $t_{\frac{1}{2}}$ is in the range of 6–10 h.[14,15,144–146,148] The drug does not accumulate significantly (<20%) after repeated dosing.[8,14,15]

Valsartan is eliminated mainly by biliary excretion as unchanged drug in faeces (Table 7; 80–85%).[8,14,15,148] Urinary excretion (mainly unchanged drug) accounts for 7%, 13% and 29% of the dose given as a capsule, as a solution or intravenously, respectively.[145,148] Valsartan is not metabolised by the cytochrome P450 enzymes,[14,15] but is converted to inactive compounds (15–20% of the dose),[14,15,145] with only 9% in the circulation.[146,148]

Pharmacokinetics of angiotensin receptor blockers in special populations (Table 8)

No gender differences are observed in the pharmacokinetic parameters of candesartan,[12,14,15] eprosartan,[11,149] EXP3174,[14,15] irbesartan,[6,14,15,32,41,150] and valsartan.[14,15] But, female subjects were found to have twice as high C_{max} for losartan[14,15] and telmisartan[15] as in males; the AUC of telmisartan is also higher (250%) in females than in males.[15] However, these differences do not require adjustment of doses in female patients.[15]

Elderly patients have higher AUC and C_{max} of candesartan (by 50% and 80%, respectively), compared to young subjects, however, no initial dosage adjustment has been recommended based on age.[12,14,15] In mild to moderate renal insufficiency, higher serum levels of the drug are observed, and in severe disease, C_{max} and AUC are increased two-fold.[14,15] The drug is not removed by haemodialysis.[14,15] In mild to moderate hepatic disease, the changes in the pharmacokinetics are minor.[14,15,109,117] No dosage adjustment is needed in mild to moderate renal or hepatic disease.[14,15,117]

The elderly have about two-fold higher C_{max} and AUC (for both total and unbound eprosartan in plasma) compared to young (most likely due to increased bioavailability of the drug in the elderly);[149] the T_{max} is also higher (by 2.5 h) in the elderly.[119,149] However, no initial dosage adjustment is necessary in the elderly.[119,149] Hypertension has no effect on the pharmacokinetics of eprosartan.[119] In subjects with severe renal impairment, higher C_{max} (by 35%) and AUC (by 55%) are found, and a decrease in Cl_T by 95%,[119,120] however, dosage adjustment is not necessary in patients with renal impairment.[119,120] Hepatic disease causes an increase in AUC (40%),[123] and it is recommended to individualise the dose of eprosartan, based on tolerability and response, in patients with liver disease.[123]

Ethnic differences have been noted in the pharmacokinetic parameters of irbesartan: compared to Whites, Blacks have a higher AUC (25%; NS, P = 0.11), C_{max}, and plasma trough levels, and $t_{\frac{1}{2}}$ (20%) of irbesartan.[14,15,151] The elderly patients have higher AUC (20–43%) and C_{max} (50%) of the drug than young patients, but the $t_{\frac{1}{2}}$ is not changed.[14,15,150] The renal clearance of irbesartan is decreased in elderly females.[150] However, these changes are not clinically significant and no dosage adjustment is recommended based on ethnicity, gender or age.[6,14,15,27,32,150] Mild-to-moderate renal insufficiency does not influence the pharmacokinetics of irbesartan,[14,15,27,152,153] and significant drug accumulation does not occur.[153] Irbesartan is not cleared by haemodialysis.[14,15,153] Based on pharmacokinetic data, the starting dose need not be adjusted in subjects with mild-to-severe renal impairment or in patients undergoing haemodialysis.[14,15,152,153] However, dose adjustment may be necessary in volume- or salt-depleted patients.[153] No significant differences were found in the pharmacokinetic parameters of irbesartan in patients with hepatic insufficiency and healthy subjects,[61,152] hence, no dosage adjustment is necessary in these patients.[14,15,61,152]

Aging does not influence the pharmacokinetics of losartan.[14,15] Rare cases of poor metabolisers of losartan (who convert only 1% of the dose of losartan to EXP3174) have been have been reported.[14,15,154] In these individuals, plasma EXP3174 levels are very low and the $t_{\frac{1}{2}}$ is long.[155] The pharmacokinetics of losartan or its active metabolite EXP3174 in patients with heart failure are similar to those in healthy subjects, and hence no dosage adjustment is needed in these patients.[133] In patients with severe renal disease, the AUC and $t_{\frac{1}{2}}$ of losartan increase by 50%; but these parameters are not affected for EXP3174.[14,15] Renal excretion of both losartan and EXP3174 decrease significantly.[137] Neither losartan nor EXP3174 are removed by haemodialysis.[14,15] No dosage adjustment is needed in patients with renal impairment, unless they are also volume-depleted.[9,14,15] The pharmacokinetics of losartan are altered in hepatic disease. In patients with mild to

Table 8 Pharmacokinetics of angiotensin receptor blockers in special populations

Angiotensin receptor blockers	T_{max}	C_{max}	*AUC*	*Clearance*	*Accum*[a]
Candesartan cilexetil		↑ 50%[1]	↑ 80%[1]		No[1]
		↑	↑	↓[2s]	
	nc[3]	100%[2s]	100%[2s]	nc[3] ↓[3s]	20%[3]
		nc[3]	nc[3]		
Eprosartan	↑[1]	↑ 100%[1]	↑ 100%[1]		
	nc[2s]	↑[2s]	↑ 55%[2s]	↓ 95%[2s]	No[2s]
		↑[3]	↑ 40%[3]		Yes[3]
Irbesartan	↓[1]	↑ 50%[1]	↑ 40%[1]	↓[1]	No[1]
	nc[2,2s,3]	nc[2,2s,3]	nc[2,2s,3]	nc[2,2s,3]	No[2,2s,3]
Losartan	nc[1,2,4]	nc[1,2,4]	nc[1,2,4]		nc[1,2,4]
		↑[2s]	↑[2s]	↓[2s]	
		↑ 500%[3]		↓ 50%[3]	
Telmisartan		nc[1,2]	nc[1,2]	nc[1,2]	No[1,2]
		↑ 100%[3]	↑ 100%[3]	↓[3]	
Valsartan			↑ 70%[3]	↓[1]	
		nc[2]	nc[2]	nc[2]	No[2]
	↑[3]	↑[3]	↑ 100%[3]	↓[3]	

[a]After repeated dosing; nc = no change.
Patients: 1 = elderly; 2 = with mild to moderate renal impairment; 3 = with mild to moderate liver disease; 4 = with heart failure; s = with severe disease.

moderate liver cirrhosis, plasma levels of losartan and EXP3174 are five- and 1.7-fold higher, respectively, than in normal controls.[14,15] Compared to normal subjects, patients with liver disease have a two-fold higher oral bioavailability and 50% lower Cl_T of losartan.[14,15] Based upon pharmacokinetic data, a lower starting dose of losartan is recommended in patients with hepatic impairment.[14,15]

The pharmacokinetic parameters of telmisartan do not change with age, hence, adjustment of doses of telmisartan are not needed in the elderly patients.[13,15] Mild to moderate renal insufficiency does not influence pharmacokinetics of telmisartan.[13,15] The drug is not removed by haemodialysis.[15] In patients with hepatic disease, plasma concentrations increase as a result of increased bioavailability.[15] Telmisartan should be avoided or used with caution in patients with severe renal impairment, renal artery stenosis, impaired hepatic function, severe congestive heart failure, and in volume- and/or salt-depleted patients, since doses lower than 40 mg are not available.[13,15]

Valsartan pharmacokinetics is altered in the elderly patients; the AUC increases by 70% and $t_{½}$ is prolonged by 35%,[8,14,15] however, no dosage adjustment is necessary.[8,14,15] The pharmacokinetics of valsartan is not related to the degree of renal impairment, hence no dosage adjustment is recommended for mild to moderate renal insufficiency.[8,14,15] However, pharmacokinetic data are not available to make recommendations in patients with severe renal impairment. The drug is not removed by haemodialysis.[14,15] In patients with mild to moderate hepatic disease, a two-fold increase in AUC is observed and the $t_{½}$ is prolonged,[14,15,156] but, no dosage adjustment is needed in such patients.[14,15] No pharmacokinetic data are available in patients with severe hepatic diseases.

Interactions of angiotensin receptor blockers with other drugs (Table 9)

No significant drug interactions occur when candesartan cilexetil is co-administered with glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, oral contraceptives.[14,15] Since candesartan is not metabolised by the cytochrome P450 system and it has no effect on these enzymes, inhibitors and inducers of the P450 enzymes are not expected to interact with candesartan.[14,15]

Eprosartan has no clinically significant effect on the pharmacokinetics of digoxin[157] or the coagulation parameters of warfarin.[158] Similarly, eprosartan has no effect on glucose profile in non-insulin-dependent diabetic patients stabilized on glyburide.[159] Hence, no dosage adjustment of warfarin, digoxin or glyburide is necessary if co-administered with eprosartan.

Since eprosartan is not metabolised by cytochrome P450 system, it has a low potential for interaction with drugs which inhibit or are substrates for this enzyme system.[11] For example, fluconazole[124] or ranitidine[160] do not have a significant effect on the pharmacokinetics of eprosartan.

Administration of hydrochlorothiazide to hypertensive patients[14,15,128] or nifedipine to normal volunteers[14,15,161] has no effect on the pharmacokinetics of irbesartan. Irbesartan does not alter the pharmacodynamics or pharmacokinetics of warfarin,[14,15,162] or digoxin.[14,15,27] hence no dosage adjustment of warfarin or digoxin is necessary.[27] Fluconazole, at a dose of 200 mg/day, significantly increases the AUC (63%) and C_{max} (19%) of irbesartan without affecting the T_{max};[129] dosage adjustment may be needed if the two drugs are co-prescribed.

Losartan does not alter the pharmacokinetics of digoxin[163] or pharmacokinetics and pharmacodyn-

Table 9 Drug interactions with angiotensin receptor blockers

Other DRUG:→ *Angiotensin receptor blocker↓*	*Warfarin*[a]		*Digoxin*[a]		*Glyburide*[a]		*HCTZ*[b]		*Phenobarbital*[b]		*Cimetidine*[b]		*Ketoconazole*[b]	
	Pk	*Act*	*PK*	*Act*	*PK*	*Act*	*PK*	*Act*	*PK*	*Act*	*PK*	*Act*	*PK*	*Act*
Candesartan	no	no		no		no	no	↑						
Eprosartan	no		no	no	no	no	no	↑						
Irbesartan	no	no	no	no				↑				no		no
Losartan	no	no	no	no			no	↑	min	no	min	no	no	no
Telmisartan	min	no	yes	↑			no	↑						
Valsartan		no	no	no	no	no	no	↑	yes	no	yes	no		

[a]Effect of ARB on the drug; [b]effect of the drug on ARB; min, minimum; PK: pharmacokinetic interaction; Act, effect on activity; HCTZ, hydrochlorothiazide.

amics of warfarin,[164] hence, no dosage adjustment of digoxin or warfarin are needed. There is no clinically significant pharmacokinetic interaction between losartan and hydrochlorothiazide in hypertensive patients.[165]

Inhibitors of drugs metabolised by the cytochrome P450 system have variable effects on the pharmacokinetics of losartan. For example, erythromycin,[136] ketoconazole,[166] or fluvastatin[167] do not have any significant effect on the steady-state pharmacokinetics of losartan and EXP3174. Cimetidine does not cause a significant change in the pharmacokinetics (18% increase in AUC) or pharmacodynamics of losartan.[168] On the other hand, grapefruit juice (an inhibitor of dug metabolism) increases the AUC of losartan (by 14%), and decreases the AUC of EXP3174 (by 19%),[169] while fluconazole, decrease the conversion of losartan to EXP-3174.[124,170]

Among the inducers of drug metabolism, phenobarbital[171] has minimal effect on the pharmacokinetics (20% increase in the AUC) of losartan or EXP3174. However, both rifampin and phenytoin alter the pharmacokinetics of losartan. Rifampin increases the clearance of both losartan and EXP3174 (decrease in AUC and $t_{\frac{1}{2}}$, and increase in oral Cl_T).[136] Phenytoin increases the AUC of losartan by 66% and decreases the Cl_T by 32% (due to competitive inhibition of metabolism of losartan to EXP3174); it also decreases the AUC of the metabolite by 64% (by simultaneous induction of the metabolism of EXP3174);[172] the $t_{\frac{1}{2}}$ of losartan is not altered.

Thus, pharmacokinetic interactions of losartan with certain inducers and inhibitors of cytochrome P450 enzymes may be clinically significant.

There are no clinically significant drug interactions of telmisartan with warfarin, acetaminophen, amlodipine, glibenclamide, ibuprofen and hydrochlorothiazide.[13,15] Warfarin has no effect on the pharmacokinetic parameters of telmisartan.[13,15,173] Telmisartan reduces the trough plasma levels of warfarin, but without affecting coagulation parameters.[13,15,173] Since telmisartan causes variable increases in serum digoxin levels, digoxin levels should be monitored in patients taking this drug combination.[15] As telmisartan is not metabolised by cytochrome P450 enzymes and it has no effect on the activities of cytochrome P450 enzymes, it is not expected to interact with drugs metabolised by these enzymes.[15]

There are no pharmacokinetic interactions of valsartan with amlodipine, atenolol, digoxin, furosemide, glyburide, hydrochlorothiazide, indomethacin and warfarin.[14,15,174] Cimetidine increases the C_{max} of valsartan (due to enhanced absorption) by 51%, but the increase has no clinical significance; valsartan has no effect on the pharmacokinetics of cimetidine.[14,15,144]

Pharmacokinetic differences among the angiotensin receptor blockers

(1) Most of the antihypertensive activity of candesartan cilexetil and losartan is due to the metabolites, while eprosartan, irbesartan, telmisartan and valsartan are inherently active. (2) The systemic bioavailability varies widely among the ARBs, from a low of 10% for valsartan to as high as 80% for irbesartan. (3) Food alters the bioavailability of only eprosartan and valsartan, and not that of other ARBs. (4) Despite high plasma protein binding of ARBs, their Vd vary widely, from 9 L (candesartan) to 500 L (telmisartan). (5) There is a large variation in plasma elimination $t_{\frac{1}{2}}$ of ARBs: shortest for candesartan cilexetil and losartan (1–4 h) and longest for telmisartan (21–38 h). (5) Only candesartan and eprosartan are not metabolised to a significant extent. (6) Only eprosartan and telmisartan do not display dose related pharmacokinetics. (7) Gender differences exist in the pharmacokinetics of only irbesartan, losartan and telmisartan. (8) The pharmacokinetics of only irbesartan, losartan and telmisartan are not altered in renal disease. (9) The pharmacokinetics of only candesartan and irbesartan are not altered in hepatic disease. (10) The only clinically important pharmacokinetic drug–drug interaction requiring dosage adjustments is for the telmisartan-digoxin combination.

Conclusions

The angiotensin II receptor blockers (ARBs) represent a relatively new class of effective and well tolerated, orally active antihypertensive agents. The beneficial effects of therapy with the ARBs go beyond blood pressure control. Although, the ARBs share the same mechanism of action, their pharmacodynamic and pharmacokinetic profiles vary from compound to compound. The ARBs may prove to have beneficial haemodynamic and neurohormonal

effects in heart failure and provide renoprotection in lgA and diabetic nephropathy.

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