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Drug Evaluation

Cardiovascular & Renal

Valsartan: a novel angiotensin Type 1 receptor antagonist

Petra A Thürmann

Philipp Klee-Institute of Clinical Pharmacology, Hospital Wuppertal GmbH, Arrenberger Str. 20, 42117 Wuppertal, Germany

Valsartan is a highly selective, orally available antagonist of the angiotensin Type 1 (AT_1) receptor. It is indicated for treatment of mild to moderate essential hypertension. Experimental studies have confirmed the abolition or attenuation of angiotensin II (AII)-related effects, such as vasoconstriction, cell growth promotion and aldosterone release. In humans, valsartan is rapidly absorbed with maximal plasma concentrations occurring 1 - 2 h after oral administration. The elimination half-life comes to about 7 - 8 h, valsartan is metabolised to a negligible extent and most of the drug is excreted *via* the faeces. There is no dose adjustment required for patients with a creatinine clearance > 10 ml/min. The dose should not exceed 80 mg o.d. in patients with hepatic dysfunction, valsartan is not recommended for patients with severe hepatic dysfunction and/or biliary cirrhosis. At present, no clinically relevant pharmacokinetic drug interactions have been observed. Valsartan produces persistent blood pressure reductions in patients with mild to moderate hypertension, the recommended starting dose is 80 mg o.d. If required, the dose may either be increased to 160 mg o.d. or hydrochlorothiazide may be added. In comparison to other antihypertensive drugs valsartan therapy leads to similar blood pressure reductions, while exhibiting a favourable tolerability profile. Preliminary studies suggest beneficial effects in patients with hypertensive end-organ damage such as renal disease and left ventricular hypertrophy. Furthermore, the drug is evaluated for its efficacy in heart failure and patients post-myocardial infarction.

Keywords: *angiotensin receptor antagonist, heart failure, hypertension, target organ disease*

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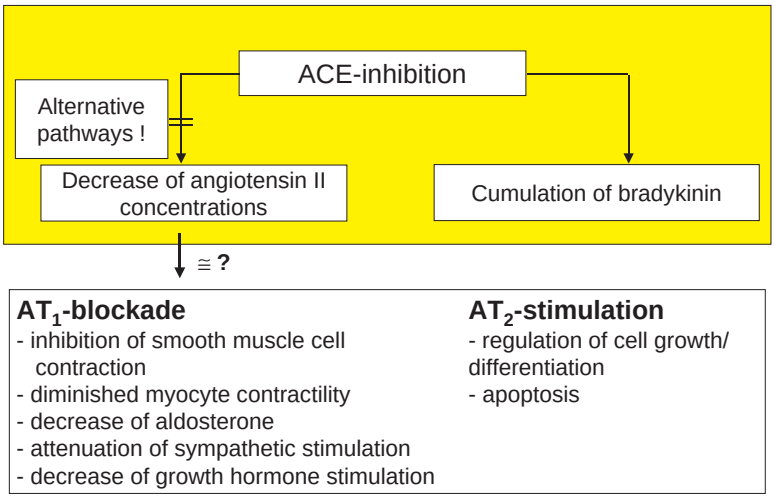
1. Introduction

High blood pressure remains a serious health problem leading to heart disease, stroke, end stage renal failure and retinopathy [1,2]. Heart disease and stroke are the first and third leading causes of death in the USA. Awareness and adequate treatment of hypertension have increased steadily during the last 20 years [3], contributing to a decline in stroke and coronary artery disease mortality. According to the most recent JNC VI guidelines [4] hypertension is defined by a systolic blood pressure above 140 mmHg or a diastolic blood pressure above 90 mmHg. Depending on additional risk factors, e.g., diabetes, dyslipidaemia, smoking, older age and gender, and pre-existing target organ disease (e.g., left ventricular hypertrophy, coronary heart disease, nephropathy, congestive heart failure) drug therapy

Figure 1: Differences and similarities between angiotensin converting enzyme-inhibition and AT_1-receptor antagonist.



- in addition to lifestyle modifications - should be initiated soon after the diagnosis of essential hypertension has been confirmed.

In the absence of relevant co-morbidity initial treatment is generally recommended using diuretics or β-blockers, based on randomised clinical trials showing the benefit of these drugs [5]. In diabetic patients and those with heart failure, angiotensin converting enzyme (ACE)-inhibitors should be considered preferentially, [6-8] whereas patients with isolated systolic hypertension may benefit from long-acting dihydropyrimidine calcium antagonists [9] or diuretics [10]. The goal of antihypertensive therapy is to keep blood pressure below 140/90 mmHg, and if tolerated, even lower [11]. However, diabetic patients should achieve a blood pressure below 130/85 mmHg [12].

Compliance with antihypertensive therapy remains a problem, since most people do not suffer from symptoms of high blood pressure, but rather fear and experience drug-induced side effects as well as an impact of drugs on their quality of life [13]. Optimal treatment and control is therefore maintained only in about one third of hypertensive patients.

Consequently, some of the prerequisites for optimal antihypertensive therapy are [4]:

- sufficient information for the patient about the aims and benefits of therapy
- a simple drug dosing regimen (o.d.)
- low incidence of side effects

2. Rationale for the development of AT_1 receptor antagonists

Experience with ACE inhibitors has shown, that drugs interfering with the renin-angiotensin-system (RAS) are useful for treatment of hypertension [14,15], regression of left ventricular hypertrophy as a major risk factor [16], prevention and treatment of heart failure [6,17,18], treatment of patients with left ventricular dysfunction following myocardial infarction [7,19] and prevention of nephropathy in diabetic patients [8].

As demonstrated below, ACE inhibitors do not only attenuate the unwanted actions of AII, they also increase the levels of bradykinin. The latter substance may be responsible for the ACE inhibitor-related cough, which disturbs about 5% - 10% of treated patients [20]. A more selective approach, namely the direct blockade of the angiotensin receptor, seemed to be a promising way to treat high blood pressure as well as other cardiovascular diseases [21] (**Figure 1**).

ACE inhibitors block the conversion of angiotensin I (AI) to the active AII and thereby attenuate the effects of AII, which are mediated mainly *via* the AT_1-receptor subtype:

- vasoconstriction
- release of aldosterone
- activation of sympathetic nervous system
- stimulation of growth

In addition, the inactivation of the vasodilator bradykinin is prevented. Since alternative pathways exist for the production of AII [22], ACE inhibitors do not completely abolish all the unwanted AII-mediated effects; in contrast, substances, which bind to the AT_1-receptor, are able to prevent these deleterious effects. Following blockade of the AT_1-receptor AII may preferably bind at the AT_2-receptor, moreover, AT_2-receptors may be upregulated in certain disease states. However, the role of the AT_2-receptor subtype is not fully understood. It has been associated with release of NO and subsequent vasodilation, regulation of cell growth as well as apoptosis [21,23].

3. Chemistry of valsartan

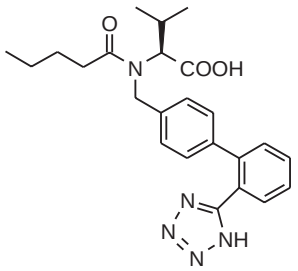
Valsartan (CGP48933) is the *S*-enantiomer of N-valeryl-N-[[2′-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-valine ($C_{24}H_{29}N_5O_3$) and has a molecular weight of 435.5 g [24] (**Figure 2**). The *R*-enantiomer has been reported to have a 170-fold less activity in terms of AT_1-receptor binding. Valsartan is available as a microcrystalline powder with a melting point of 105 - 110°C. It is soluble in water at 25°C and in phosphate buffer at pH 8.0. The hydrophilic character of the compound is indicated by the partition coefficient P with 0.033 (n-octanol/aqueous phosphate buffer pH 7.4) [24] (**Figure 2**).

4. Pharmacology

4.1 *In vitro* experimental studies

AT_1 and AT_2 receptors are expressed by human myometrium membranes as well as vascular smooth muscle cells in rats and are used for binding experiments. Valsartan competes with radiolabelled [^{125}I]-AII at the AT_1-receptor with an inhibitory constant (K_i) of 2.38 ± 0.31 nmol/l and at the AT_2-receptor with a K_i of 57.7 ± 9.4 µmol/l, showing a more than 30-fold higher affinity to the AT_1-receptor than to the AT_2-receptor [25]. Due to differences in AT_1-receptors in different tissues, affinity of valsartan was also shown in human adrenal gland with a K_i of 2.6 ± 0.9 nmol/l, suggesting that the rat tissue experiments are suitable models [26]. Binding of valsartan to the AT_1-receptors achieves steady-state after about 60 min, stability has been proven for 3 h. The dissociation half-life has been calculated to 56 ± 7 min [26]. Affinity and density of AT_1-receptors were unchanged after administration of valsartan to rats and marmosets over 13 weeks, receptor desensitisation following chronic therapy with valsartan seems therefore not to be the case.

Figure 2: Chemical structure of valsartan.



In isolated rabbit aortic rings, serving as a functional assay, valsartan inhibited AII-induced contractions with an IC_{50} of 1.4 nmol/l [26] showing a typical sigmoidal concentration-effect curve.

4.2 *In vivo* studies

Intravenous application of valsartan to renovascular hypertensive rats resulted in a dose-dependent fall in blood pressure. A decrease of 30 mmHg was achieved with a dose of 0.06 mg/kg, higher doses produced persistent blood pressure reduction lasting for 24 h. The effect of 3 mg/kg valsartan was comparable to the effect of 3 mg/kg of the ACE inhibitor enalaprilat [24].

Oral doses of 1 - 30 mg/kg valsartan were given to conscious, freely-moving, sodium-depleted marmosets controlled *via* a telemetric device [24]. The maximum blood pressure lowering response occurred within 1 h after dosing and persisted longer than 24 h after the largest dose. In this model, the hypotensive action of the AT_1-antagonist losartan was markedly shorter. This is due to the fact, that primates are poor metabolisers for the hepatic activating step required for losartan. Neither of the AT_1-antagonists exhibited an influence on heart rate.

Following clipping of the left renal artery hypertensive rats were given 0.3, 3 or 10 mg/kg per day intraperitoneally of the ACE inhibitor benazeprilat or valsartan over 12 weeks [27]. Both drugs produced similar effects on blood pressure as well as on left ventricular volumes, wall stress and ejection fraction. Increase in mRNA for atrial natriuretic factor (ANF) as well as a decrease in the mRNA for the sarcoplasmatic calcium-ATPase are indicators for the development of heart failure. Benazeprilat and valsartan were able to achieve values for these two prognostic markers

Table 1: Pharmacokinetic parameters of valsartan in healthy volunteers (n = 12) after iv. administration of 20 mg and oral application of the 80 mg capsule [34]. Data are given as mean ± SD and median for T_{max}.

	C_{max} (mg/l)	T_{max} (h)	$t_{½el}$ (h)	Ae (% of dose)	f (AUC oral/iv.)
20 mg iv.	4.02 ± 0.43	-	9.45 ± 3.83	28.95 ± 5.82	-
80 mg capsule	1.64 ± 0.63	2	7.05 ± 1.58	7.34 ± 3.02	0.23 ± 0.07

Ae: Urinary recovery; C_{max}: Maximum plasma concentration; f: Oral bioavailability; $t_{½el}$: Terminal elimination half-life; T_{max}: Time of occurrence of C_{max}.

which were comparable to those obtained in healthy control animals.

Furthermore, treatment with valsartan in genetically hypertensive rats induced not only significant regression of left ventricular hypertrophy but also reversal of vascular structural alterations as measured by the media to lumen ratio in resistance arteries [28].

Given to spontaneously hypertensive rats over 48 weeks valsartan significantly reduced urinary protein excretion and prevented development of nephrosclerosis over the dose range from 3, 10 and 30 mg/kg/d p.o. [29]. Furthermore, stroke-related behaviour was observed significantly less under valsartan (*vs.* vehicle control) and survival improved: 14 *vs.* 0 deaths from a total of 30 controls and treated animals, respectively.

The effect of valsartan on haemodynamics after myocardial infarction was compared with that of enalapril in rats following coronary artery ligation [30]. Left ventricular end-diastolic pressures decreased significantly after valsartan, suggesting a beneficial effect on left ventricular dilation following myocardial infarction.

In dogs with moderate heart failure 3 months treatment with valsartan 400 mg b.i.d. ejection fraction was preserved in comparison to control animals receiving no therapy, however, in animals receiving 800 mg b.i.d., ventricular pump function deteriorated [31]. In a pig model of heart failure valsartan treatment prevented the development of pacing-induced left ventricular dysfunction [32], however, significant effects on myocardial collagen content were not observed.

5. Clinical pharmacology

5.1 Pharmacokinetics

The disposition and metabolism of valsartan were studied after oral administration of 80 mg of the [^{14}C]-radiolabelled substance [33]. Maximal concentrations (C_{max}) of valsartan were observed after 1 h and declined with an elimination half-life of about 6 ± 1 h. Only one pharmacologically inactive metabolite (valeryl-4-hydroxy-valsartan) was identified in plasma and represented only 11% of the area under the plasma concentration/time curve (AUC_{0-24h}) of the radioactivity.

At least 51% of the dose was absorbed, 99% of the radioactivity was recovered within 7 days, where the most was excreted in the faeces (86 ± 5%).

Flesch *et al.* [34] investigated the absolute bioavailability of valsartan after administration of a 80 mg single oral dose (capsule and solution) in comparison to 20 mg given intravenously. The pharmacokinetic parameters derived are shown in **Table 1**. The volume of distribution was calculated to be 16.91 ± 6.90 l, the renal clearance came to 0.62 ± 0.12 l/h. The relatively low volume of distribution of the drug may be explained by the protein binding properties of valsartan. About 96 ± 2% of the drug is bound to plasma proteins, preferentially to albumin (92%), only a small percentage is bound to α1-acid glycoprotein (22%), binding to γ globulins is negligible [35].

The area under the plasma concentration *vs.* time-curve increases in a linear and dose-proportional manner in the dose range of 80 - 320 mg [24].

After repeated oral dosing of 200 mg o.d. over 8 days C_{max} increased slightly from 3.46 ± 1.44 mg/l to 3.94 ± 1.38 mg/l and AUC_{0-24h} increased from 21.33 ± 10.22 mg/l.h to 25.75 mg/l.h suggesting only little accumulation with a cumulation factor of 1.21 [36]. The bioavailability of valsartan when given with food is reduced by 46% [24], however, this did not influence the antihypertensive effect in patients.

Mean C_{max} and AUC_{0-24h} increased by 53% and 24%, respectively, in elderly subjects with a mean age of 76 years in comparison to younger volunteers aged 23 years [37]. However, these differences could not be

attributed solely to differences in creatinine clearance (Cl_{CR}), liver function, weight or concomitant medication and appear not to be of any clinical relevance.

The pharmacokinetics of valsartan were studied in 3 patients with mild renal impairment (Cl_{CR}: 78 ± 15 ml/min), 4 patients with moderate dysfunction (Cl_{CR}: 48 ± 8 ml/min), 5 patients with severe renal impairment (Cl_{CR}: 18 ± 7 ml/min) and compared with 7 patients with normal renal function (Cl_{CR}: 126 ± 35 ml/min) [38]. The corresponding $AUC_{0\text{-}48h}$-values came to 10,722 ± 4,862 µg/l.h, 6,123 ± 769 µg/l.h, 14,274 ± 10,880 µg/l.h and 7923 ± 3,703 µg/l.h, respectively. There were no significant correlations between AUC and Cl_{CR} (r = -0.2675) or C_{max} and Cl_{CR} (r = -0.1249). Since renal clearance contributes to < 30% of the total excretion, dose adjustment of valsartan is not necessary in patients with a creatinine clearance above 10 ml/min.

Biliary excretion is the primary elimination route of valsartan, therefore, prolongation of the half-life is expected in patients with hepatic impairment. The pharmacokinetics of valsartan 160 mg orally were studied in 6 patients each with mild to moderate hepatic dysfunction (Child-Pugh grade A and B) and compared with 12 matched healthy volunteers [39]. The AUC was almost twice as high in patients with liver impairment with 46 mg/l.h when compared to healthy controls with 21 mg/l.h. Therefore, the dose of 80 mg should not be exceeded in patients with mild to moderate hepatic dysfunction and valsartan should not be given to patients with severe hepatic failure and biliary cirrhosis.

5.2 Pharmacokinetic-pharmacodynamic investigations in healthy volunteers

After single dose administrations of 40 - 80 mg valsartan, respectively, in 6 healthy volunteers dose-response curves for the inhibition of the AII-induced blood pressure increase were established [40]. 2 h after administration of placebo the dose of AII required to achieve a blood pressure increase of 30 mmHg (D30) came to 5.2 ± 4.0 µg. After valsartan 40 and 80 mg, respectively, the D30 came to 47.4 ± 43.8 µg and 68.2 ± 49.6 µg, respectively. The maximal effect was observed 2 h after dosing of valsartan and lasted up to 24 h. Concentration/effect analysis performed by an E_{max}-model revealed an E_{max} of about 74% inhibition of blood pressure increase and an EC_{50} of 0.37 ± 0.37 µmol/l.

Plasma renin activity (PRA) peaked at 4 and 6 h after application and returned to baseline after 24 h.

Mazzolai *et al.* [40] compared the pressure response to exogenous AII after the recommended starting doses of losartan (50 mg), valsartan (80 mg) and irbesartan (150 mg) in healthy volunteers. At 4 h, losartan attenuated the ANG-induced pressure increase by 43%, valsartan by 51% and irbesartan by 88% ($p < 0.01$ between drugs).

In a repeated dose study with 200 mg valsartan o.d. over 8 days plasma AII levels were measured [36]. The maximum increase in AII concentrations occurred 6 h after dosing, at steady-state, a significant (2- to 3-fold) cumulation of plasma AII concentrations was observed.

The effect of valsartan 80 mg on the pressure response induced by exogenous AII was comparable after single dosing and on the 8th day of once daily dosing with a combined EC_{50} of 85.6 ± 42.3 ng/ml and a corresponding E_{max} of 104% ± 15% [42]. This confirms the experimental findings, that receptor desensitisation does not occur [26].

5.3 Pharmacokinetic interaction studies

The absence of clinically relevant pharmacokinetic interactions with the following drugs has been confirmed: atenolol [43], cimetidine [44], furosemide [45], amlodipine, hydrochlorothiazide (HCTZ), digoxin, warfarin, glibenclamide and indomethacin [Data on file, Novartis, Basle, Switzerland].

6. Clinical trials in patients with essential hypertension

6.1 Clinical trials comparing valsartan and placebo

The safety and efficacy of valsartan in patients with mild to moderate essential hypertension at different dose levels was compared to placebo in several trials (**Table 2**). Pool *et al.* [46] treated 122 patients with placebo, 10, 40, 80 and 160 mg valsartan, respectively, over 4 weeks. Responder rates, as defined by a sitting diastolic blood pressure below 90 mmHg or a decrease in diastolic blood pressure by more than 10 mmHg, came to 16%, 24%, 33%, 46% and 54%, respectively, indicating a clear dose-response relationship (**Figure 3**). The effects observed after the 80 and 160 mg dose were significantly different from placebo for diastolic and systolic blood pressure. The

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