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Valsartan/Hydrochlorothiazide

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Contents

Abstract

▲ Valsartan/hydrochlorothiazide (HCTZ) combines an angiotensin II AT_1 receptor blocker with a thiazide diuretic to produce additive blood pressure reductions without major effects on heart rate.

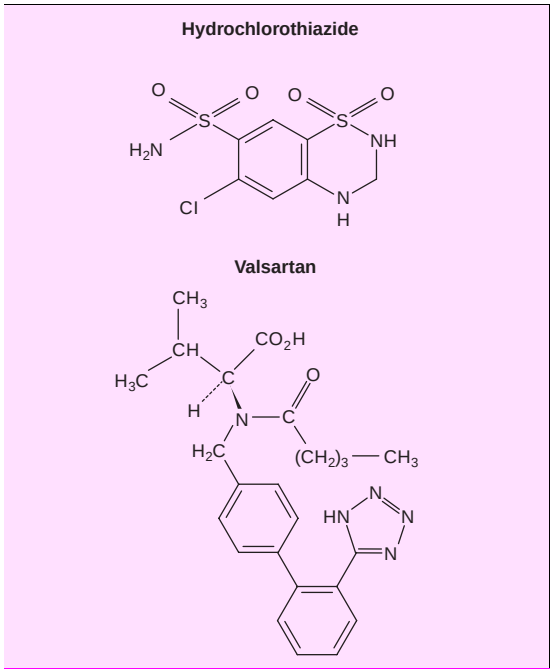
▲ HCTZ did not significantly alter valsartan pharmacokinetics; during combination therapy, HCTZ pharmacokinetics differed from those seen with HCTZ monotherapy.

▲ In clinical trials in patients with essential hypertension, adding HCTZ 12.5 or 25 mg/day to valsartan 80 mg/day resulted in a greater blood pressure reduction than increasing the valsartan dosage from 80 to 160 mg/day.

▲ The valsartan/HCTZ combination was generally more effective than either drug given alone. Efficacy of the combination was maintained during up to 3 years of treatment.

▲ Valsartan/HCTZ was well tolerated in both short and long term trials. The most common adverse events were dizziness, headache and fatigue. The overall incidence of adverse events with the combination was similar to that with placebo. HCTZ-induced hypokalaemia was less common during combination therapy.

Features and properties of valsartan/hydrochlorothiazide	
Indications	
Second-line therapy of essential hypertension in patients whose hypertension is not adequately controlled by valsartan (VAL) monotherapy or hydrochorothiazide (HCTZ) 25mg once daily	
Mechanism of action	
Antihypertensive	Combination of an angiotensin II receptor blocker (VAL) and a thiazide diuretic (HCTZ)
Dosage and administration	
Usual dose in clinical trials	VAL 80 to 160mg plus HCTZ 12.5 to 25mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (*after administration of VAL 160mg plus HCTZ 25mg*)	
Peak plasma concentration	VAL: 2.78 mg/L HCTZ: 0.10 mg/L
Time to peak plasma concentration	VAL: 2.5h HCTZ: 2h
Area under the plasma concentration-time curve	VAL: 21.1 mg/L • h HCTZ: 0.79 mg/L • h
Elimination half-life	VAL: 6.5h HCTZ: 8.1h
Adverse events	
Most frequent	Dizziness, headache, fatigue



Valsartan/hydrochlorothiazide

Valsartan is an angiotensin AT_1 receptor blocker that has been shown to be an effective treatment for mild to moderate essential hypertension.[1]

Early clinical trials in patients with essential hypertension inadequately controlled by valsartan monotherapy (80 mg/day) showed that greater additional reductions in blood pressure ensued when the thiazide diuretic hydrochlorothiazide (HCTZ) 12.5 or 25 mg/day was added to valsartan 80 mg/day than when the valsartan dosage was doubled to 160 mg/day.[2]

Fixed-dose combination therapy for hypertension has been previously noted to provide the potential advantages of convenience for patients, improvements in compliance and overall efficacy, and attenuation of adverse events associated with either component.[3] Therefore, a product combining valsartan 80 or 160mg with HCTZ 12.5mg was developed for use in patients with essential hypertension who need additional blood pressure control beyond that provided by valsartan monotherapy or HCTZ 25mg once daily.

1. Pharmacodynamic Profile

Antihypertensive Effects

- When administered for 2 weeks by continuous subcutaneous infusion from an implanted minipump, additive reductions in mean arterial pressure (MAP) were seen with the combination of valsartan 1 mg/kg/day plus HCTZ 3 or 10 mg/kg/day, whereas synergistic reductions occurred after the combination of valsartan 3 mg/kg/day plus HCTZ 10 mg/kg/day in groups of 4 to 6 spontaneously hypertensive rats (SHR).[4]

- The effects of valsartan 1 mg/kg/day on MAP in SHR were similar to those of benazeprilat 1 mg/kg/day when these drugs were given alone or combined with HCTZ.[4]

Effects on Heart Rate

- In 10 SHR, there was no significant change in heart rate after administration of valsartan 3 mg/kg alone or combined with HCTZ 5 mg/kg daily for 28 days.[5]

- Transient increases in heart rate (of 20 to 30 beats/min from baseline) occurred in SHR receiving valsartan 1 or 3 mg/kg/day plus HCTZ 3 or 10 mg/kg/day, but these were only statistically significant in rats receiving valsartan 3 mg/kg/day plus HCTZ 10 mg/kg/day.[4]

- The lack of significant effects of valsartan 1 mg/kg/day on heart rate in SHR was similar to that of benazeprilat 1 mg/kg/day at the end of 2 weeks' administration with or without HCTZ.[4]

2. Pharmacokinetic Profile

General Pharmacokinetics

- 12 healthy volunteers received single doses of valsartan 160mg, HCTZ 25mg or valsartan 160mg/HCTZ 25mg in a 3-way crossover study of pharmacokinetic interactions.[6] HCTZ had no discernable effect on valsartan pharmacokinetics, but the area under the plasma concentration-time curve (AUC, up to 24 hours after the dose), peak plasma concentration and elimination half-life of HCTZ

were reduced by 22, 26 and 35%, respectively, during combination treatment. As well, 15% less HCTZ was excreted in the urine after the combination than after HCTZ alone (54 *vs* 63% of a dose, p = not significant).

- Valsartan is 95% bound and HCTZ is 40 to 70% bound to serum proteins.[6]

Pharmacokinetics In Special Populations

- When the valsartan/HCTZ combination was administered to elderly (≥65 years) and younger individuals, 'mean exposure' to valsartan was reported to be 53% greater in the elderly and HCTZ clearance was 'lower' (by an unspecified amount) in both healthy and hypertensive elderly study participants than in younger individuals.[2] These changes are said not to warrant reductions in dosages.[5]

- 'Exposure' to HCTZ was reported to be increased in patients with creatinine clearance (CL_{CR}) of <1.8 L/h (<30 ml/min), but valsartan pharmacokinetics were unaffected by renal function after administration of unspecified dosages of the combination of these 2 agents.[2] Caution is recommended in the use of the combination in patients with severe renal impairment.[2]

- Impaired hepatic function did not affect HCTZ pharmacokinetics, and was associated with unspecified increases in the AUC of valsartan, after administration of either drug as monotherapy.[2] It is said that patients already receiving valsartan may therefore be titrated to the fixed combination with HCTZ.[2]

3. Therapeutic Trials

Study in Patients with Essential Hypertension Not Adequately Controlled by Valsartan Monotherapy

- 708 patients with sitting diastolic blood pressure (SDBP) between ≥95 and ≤120mm Hg after 4 weeks' valsartan monotherapy (80 mg/day) were randomised in a double-blind, double-dummy, parallel-group, age-stratified (±65 years), multicentre study.[7] There were 702 patients in the intent-to-treat population, 631 of whom completed a full 8 weeks' treatment with the following daily regimens: valsartan 80mg (n = 179), valsartan 160mg (n = 171); valsartan 80mg plus HCTZ 12.5mg (n = 176); valsartan 80mg plus HCTZ 25mg (n = 176).[7]

- Reductions in SDBP and sitting systolic blood pressure (SSBP) from baseline were statistically significant in all 4 treatment groups ($p < 0.0001$), but reductions were greater in patients receiving either of the valsartan/HCTZ combinations (fig. 1a).

- The percentages of patients responding at the end of 8 weeks' treatment (i.e. SDBP <90mm Hg or a ≥10mm Hg decrease from baseline) were as follows: valsartan 80mg, 36%; valsartan 160mg, 37%; valsartan 80mg/HCTZ 12.5mg, 51% ($p < 0.01$ *vs* valsartan 80mg monotherapy); valsartan 80mg/ HCTZ 25mg, 59% ($p < 0.0001$ *vs* valsartan 80mg monotherapy).

- There were no significant changes in heart rate in any treatment group, and no instances of symptomatic orthostatic hypotension.[7]

Dose-Response Study in Patients with Mild to Moderate Essential Hypertension

- 871 patients with mean baseline SDBP of 95 to 115mm Hg were randomised in a double-blind, parallel-group, multicentre study.[8] There were 865 patients in the intent-to-treat population, 792 of whom completed a full 8 weeks' treatment with the following daily regimens: placebo (n = 94), HCTZ 12.5mg (n = 100), HCTZ 25mg (n = 100), valsartan 80mg (n = 99), valsartan 160mg (n = 99); valsartan 80mg plus HCTZ 12.5mg (n = 96); valsartan 80mg plus HCTZ 25mg (n = 92); valsartan 160mg plus HCTZ 12.5mg (n = 97); valsartan 160mg plus HCTZ 25mg (n = 94).[8]

- Differences in SSBP and SDBP reductions from placebo were statistically significant in all treatment groups ($p < 0.05$), but reductions were greatest in patients receiving valsartan/HCTZ combinations (fig. 1b).[8] There were dose-related increases in efficacy after valsartan or HCTZ monotherapy, but valsartan/HCTZ had a greater effect on blood pressure than an increase in either valsartan or HCTZ monotherapy dosages (fig. 1b).[8] In all

combination therapy groups, differences from relevant monotherapies were statistically significant ($p < 0.05$).[8]

• The percentages of patients responding at the end of 8 weeks' treatment (i.e. SDBP <90mm Hg or a ≥10mm Hg decrease from baseline) were as follows: placebo, 29%; HCTZ 12.5mg, 41%; HCTZ 25mg, 54%; valsartan 80mg, 54%; valsartan 160mg, 59%; valsartan 80mg/HCTZ 12.5mg, 64%; valsartan 80mg/HCTZ 25mg, 81%; valsartan 160mg/HCTZ 12.5mg, 76%; valsartan 160mg/HCTZ 25mg, 81%.[8] Response rates with the 4 combination regimens were significantly greater ($p < 0.05$) than with valsartan monotherapy, and 4 combinations (all but valsartan 80mg/HCTZ 12.5mg) elicited significantly greater response rates than HCTZ monotherapy ($p < 0.05$).[8]

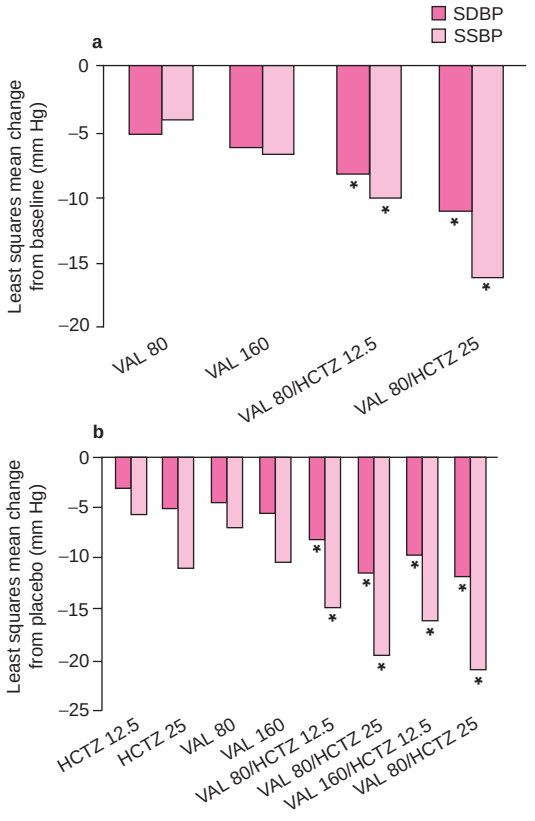


Fig. 1. Antihypertensive dose-response effects of valsartan/hydrochlorothiazide in patients with essential hypertension. Effect of monotherapy or combination therapy with valsartan (VAL) 80 or 160 mg/day and/or hydrochlorothiazide (HCTZ) 12.5 or 25 mg/day on sitting systolic (SSBP) and diastolic blood pressure (SDBP) in two 8-week, randomised, double-blind, parallel group trials: (**a**) least squares mean change from baseline in 708 patients with SDBP of 95 to 120mm Hg after 4 weeks of VAL 80 mg/day monotherapy;[7] (**b**) change in least squares treatment mean from placebo in 865 patients with mean baseline SDBP of 95 to 115mm Hg. * denotes statistically significant difference from tested monotherapy regimens ($p < 0.025$).

• No significant changes in heart rate or bodyweight occurred in this trial.[8]

Long Term Administration

• In an extension of a 6-week double-blind randomised trial, blood pressure reduced further from 6 weeks to 3 years of treatment in 65 patients receiving nonblind combination treatment with valsartan/HCTZ.[9] However, blood pressure reductions observed after 2 years of treatment were stable at the end of 3 years' treatment. All patients received valsartan 80 mg/day. 18 patients required the addition of HCTZ 12.5 mg/day, 52 required the addition of HCTZ 25 mg/day and 3 used HCTZ dosages ranging from 12.5 to 25 mg/day.

• There were no clinically significant differences in antihypertensive effects associated with age or gender, and no discontinuations due to treatment-related adverse events during 3 years' treatment with valsartan/HCTZ.[9]

4. Tolerability

Tolerability in Short Term Trials

• In 2 controlled comparative trials (total n = 1575), the overall incidence of adverse events with valsartan/HCTZ (53.2%) was similar to that observed during monotherapy with valsartan, HCTZ or placebo (50.6, 54.5 and 51.6%, respectively).[2]

• The most common (>2%) treatment-related adverse events with valsartan/HCTZ in the 2 major comparative trials were dizziness (5.9%), headache (4.5%) and fatigue (3.2%).[2]

• A lower incidence of diuretic-induced hypokalaemia occurred in patients receiving the

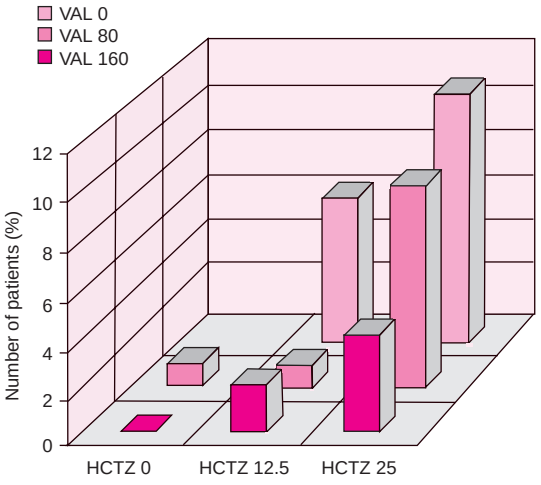


Fig. 2. Effect of valsartan (VAL) on hydrochlorothiazide (HCTZ)-associated hypokalaemia. Number (%) of patients with a >20% reduction in serum potassium levels during an 8-week randomised double-blind placebo-controlled study of monotherapy with VAL 80 or 160 mg/day or HCTZ 12.5 or 25 mg/day or combination therapy with valsartan/HCTZ in dosages of 80mg/12.5mg, 80mg/25mg, 160mg/12.5mg or 160mg/25mg daily in a total of 871 patients with uncomplicated essential hypertension.[6]

combination product than in recipients of HCTZ monotherapy in the placebo-controlled trial (fig. 2).[6]

- Retrospective analysis of 76 patients with mild to moderate renal insufficiency [CL_{CR} 1.8 to 2.1 L/h (30 to 70 ml/min)] who received varying dosages of valsartan/HCTZ for 8 weeks revealed no significant change in renal function after treatment.[2]

Tolerability in Long Term Usage

- Valsartan 80 mg/day plus HCTZ ranging from 12.5 to 25 mg/day was generally well tolerated in 65 patients receiving this combination for up to 3 years.[9] There were no discontinuations due to treatment-related adverse events, no increase in either the type or frequency of adverse events over time and no patients experienced symptomatic orthostatic hypotension during long term use of the combination.[9]

- Retrospective analysis of 60 patients with baseline CL_{CR} of 1.8 to 4.2 L/h (30 to 70 ml/min) who received valsartan/HCTZ revealed no significant change in renal function after up to 3 years' treatment.[2]

5. Valsartan/Hydrochlorothiazide: Current Status

Valsartan/HCTZ combines the antihypertensive efficacy of an angiotensin II AT_1 receptor blocker with that of a thiazide diuretic in a product that has been recently introduced to markets. It has been well tolerated in short and long term use, is more effective in reducing blood pressure than valsartan alone, and appears to be associated with a lower risk of hypokalaemia than HCTZ monotherapy.

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