2. Zeitz CJ, Campbell DJ, Horowitz JD. Myocardial uptake and biochemical and hemodynamic effects of ACE inhibitors in humans. Hypertension 2003;41:482-7.
3. Campbell DJ, Krum H, Esler MD. Losartan increases bradykinin levels in hypertensive humans. Circulation 2005;111:315-20.
4. Wood JM, Maibaum J, Rahuel J, Grutter MG, Cohen NC, Rasetti V, et al. Structure-based design of aliskiren, a novel orally effective renin inhibitor. Biochem Biophys Res Commun 2003;308:698-705.
5. Campbell DJ. Interpretation of plasma renin concentration in patients receiving aliskiren therapy. Hypertension 2008;51:15-8.
6. Nussberger J, Wuerzner G, Jensen C, Brunner HR. Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (SPP100): comparison with enalapril. Hypertension 2002;39:E1-8.
7. Waldmeier F, Glaenzel U, Wirz B, Oberer L, Schmid D, Seiberling M, et al. Absorption, distribution, metabolism, and elimination of the direct renin inhibitor aliskiren in healthy volunteers. Drug Metab Dispos 2007;35:1418-28.

Dr Campbell holds a Senior Research Fellowship from the National Health and Medical Research Council (NHMRC), and has received research grants from the NHMRC and the National Heart Foundation. He has had research contracts with Solvay and Novartis and has been on an advisory board for Novartis.

Self-test questions

The following statements are either true or false (answers on page 143)

5. Renin inhibitors act at angiotensin II receptors.
6. Renin inhibitors increase the plasma concentration of renin.

Experimental and clinical pharmacology

Clinical implications of renin inhibitors

***Karen Duggan**, Chair, National Blood Pressure and Vascular Disease Advisory Committee, and formerly Director, Hypertension Service, Sydney South West Area Health Service*

Summary

Direct renin inhibition lowers blood pressure by an effective blockade of the renin-angiotensin system. Aliskiren is the first renin inhibitor to be marketed for the treatment of hypertension. At currently available doses it lowers blood pressure to a similar degree as other antihypertensive drugs. Used in combination with thiazides, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists or calcium channel blockers, aliskiren has improved blood pressure control with no appreciable increase in adverse events. Aliskiren has an adverse effect profile comparable to placebo, but its long-term effects are unknown.

Key words: aliskiren, antihypertensives, hypertension.

(Aust Prescr 2009;32:135–8)

Introduction

Hypertension is one of the commonest reasons for general practitioner attendances. Less than 25% of those who are diagnosed attain their recommended blood pressure targets, while some studies place this figure as low as 7%. Although much of this failure to control blood pressure can be attributed to therapeutic inertia, the adverse effects of antihypertensive drugs also contribute. These adverse effects often limit the doses at which antihypertensive drugs can be used. This problem has prompted the ongoing search for more efficacious drugs with fewer adverse effects. One such group of drugs is the direct renin inhibitors which are currently undergoing clinical trials. The first of the drugs to be marketed is aliskiren.

Prorenin and the renin receptor

The discovery of the renin receptor provided a new role for renin, that of a profibrotic agent in its own right. It was subsequently found that the renin receptor also binds

prorenin so it is now termed the (pro)renin receptor. Prorenin is the inactive protein which is converted to renin. Clinically, the incidence of microvascular complications in diabetes is positively associated with prorenin concentrations.

When renin is bound to the (pro)renin receptor, conversion of angiotensinogen to angiotensin I is increased fivefold and there is activation of mitogen stimulated protein kinase which causes fibrosis. As the (pro)renin receptor is present on mesangial cells, renin may be implicated in accelerating glomerular damage and renal failure.

Direct renin inhibitors

Direct renin inhibition has long been a therapeutic aspiration because of the substrate specificity of renin compared with that of angiotensin converting enzyme (ACE). ACE has actions in addition to the formation of angiotensin II.

Early renin inhibitors were peptide analogues of angiotensinogen. They acted by competitively displacing angiotensinogen from the active site of renin. The first synthetic renin inhibitors, enalkiren and remikiren, had low efficacy and very low bioavailability. Further developments have addressed these deficits. Structural modifications have improved bioavailability and efficacy has been improved by making the inhibitory process non-competitive. Non-competitive inhibition means that in addition to stopping the conversion of angiotensinogen to angiotensin I, the stimulation of mitogen activated protein kinase is also prevented.

Aliskiren

While not yet marketed in Australia, aliskiren is available overseas in doses of 75 mg, 150 mg and 300 mg. Doses of 600 mg and 640 mg were also studied but have not been marketed, possibly as a consequence of the plateauing of the dose-response curve above 300 mg. The bioavailability is better than that of remikiren and enalkiren, but remains relatively low. Studies using radiolabelled aliskiren show that only 5% of an oral dose is absorbed. Absorption is rapid with maximal concentrations being reached after 1–3 hours.

In plasma, aliskiren circulates unchanged and is excreted via the biliary route with less than 1% being excreted in the urine. Aliskiren has a long half-life and is therefore suitable for once-daily dosing. The predicted long duration of action has been confirmed in a number of studies using ambulatory blood pressure monitoring.

Efficacy

In patients with hypertension, aliskiren lowered blood pressure more than placebo. The maximum effect was seen after a few weeks of treatment.

Trials of once-daily aliskiren have shown it to be as effective as angiotensin receptor antagonists and ACE inhibitors.

Reductions of the order of 11 mmHg in systolic and 9 mmHg in diastolic blood pressure have been found with aliskiren 150 mg once-daily. The 300 mg dose was associated with decreases of 16 mmHg in systolic and 12 mmHg in diastolic blood pressure. Head-to-head studies over periods ranging from 48 hours to eight weeks have demonstrated equivalent blood pressure reductions for aliskiren 150 mg and irbesartan 150 mg, valsartan 160 mg and enalapril 20 mg. Aliskiren 300 mg is similar to losartan 100 mg.

Many of the trials have focused on changes in the components of the renin-angiotensin system, for example, plasma renin activity is reduced by aliskiren, but increased by losartan. This escape in plasma renin activity and increase in plasma angiotensin II concentrations, which occurs with both angiotensin receptor antagonists and ACE inhibitors, is avoided during treatment with aliskiren. All trials have shown sustained reductions in plasma renin activity and angiotensin II concentrations with aliskiren therapy. It is hoped that this sustained reduction in plasma renin activity may provide better end-organ protection as fibrosis secondary to renin stimulation of mitogen activated protein kinase will be prevented.

Safety and tolerability

In all trials to date, the adverse effect profile of aliskiren in doses up to 300 mg per day has been comparable to that of placebo or of angiotensin receptor antagonists. The most commonly reported adverse effects were fatigue, headache, dizziness and diarrhoea. In contrast, the higher dose of 600 mg per day was associated with an increased incidence of diarrhoea (9.6% vs 1.2% placebo). Unlike the ACE inhibitors, aliskiren does not appear to be associated with cough or angioedema, and in combination with ACE inhibitors aliskiren has been reported to reduce cough.[1]

Although aliskiren is excreted via the biliary route, liver disease did not affect the pharmacokinetics after single dose administration. It has been suggested that dose reductions in patients with concomitant hepatic impairment will not be needed.[2]

As yet no clinical data are available to assess the effects of aliskiren on renal function and plasma potassium concentrations in patients with renal impairment, renal artery stenosis or heart failure. One study in diabetes mellitus found that rates of discontinuation for hyperkalaemia were similar to those of the ACE inhibitor ramipril.

Plasma renin concentrations increase as a consequence of treatment with aliskiren although plasma renin activity and angiotensin II concentrations remain low. Theoretically this could lead to rebound hypertension on sudden withdrawal, but in practice this has not occurred. Blood pressure rises gradually after aliskiren is withdrawn.

Aliskiren is contraindicated in pregnancy. It is unknown if the drug is excreted in breast milk.

Drug interactions

Aliskiren undergoes no significant metabolism, in particular it is not metabolised by cytochrome P450, and it has relatively low plasma protein binding. As a consequence aliskiren could be predicted to cause few adverse drug interactions. The limited number of pharmacokinetic studies have supported this prediction. In healthy volunteers aliskiren was found to have no detectable effect on the pharmacokinetics of warfarin, acenocoumarol, digoxin, lovastatin, atorvastatin, metformin, pioglitazone, fenofibrate, isosorbide-5-mononitrate, celecoxib or cimetidine, but did reduce frusemide concentrations.[3–6]

Patients who have been taking high doses of diuretics may become salt or volume depleted. This may cause symptomatic hypotension when they start taking aliskiren.

Combination therapy

In various studies aliskiren has been used in combination with thiazide diuretics (hydrochlorothiazide), ACE inhibitors (enalapril, ramipril), angiotensin receptor antagonists (irbesartan, losartan, valsartan), beta blockers (atenolol) and dihydropyridine calcium channel blockers (amlodipine). In each study there has been no increase in adverse outcomes compared with monotherapy, and in all instances blood pressure control has been improved. In particular, no significant changes in plasma potassium were seen in combination with ACE inhibitors or angiotensin receptor antagonists, although the patient groups studied and reported on to date have been those with essentially normal renal function. The numbers in these trials have been relatively small and predictions about preferred therapeutic combinations cannot be made.

Prevention of end-organ damage

Aliskiren is highly specific for human renin. This limits the usefulness of animal studies in predicting the protective effect of renin inhibitors on organs such as the heart and kidney. Studies in transgenic hypertensive rats which develop malignant hypertension, heart failure and renal failure show that aliskiren lowers blood pressure to that of non-transgenic rats as well as preventing heart and renal failure.

Small short-term clinical trials have addressed the effects of aliskiren on cardiac hypertrophy, brain natriuretic peptide and diabetic renal disease. ALLAY, which was powered only to show non-inferiority, demonstrated similar effects of aliskiren and losartan on left ventricular mass index at nine months.[7] ALOFT demonstrated a decrease in brain natriuretic peptide when aliskiren was added to therapy with an ACE inhibitor or angiotensin receptor antagonist, but the study was not powered to show a benefit.[8] AVOID showed a decrease in albuminuria when aliskiren was added to losartan compared with placebo.[9] Further insights will have to await completion of large postmarketing clinical trials.

Conclusion

Aliskiren is the first of the renin inhibitors to be approved in Australia. In short-term studies aliskiren has reduced blood pressure to a similar extent as other antihypertensive drugs. It has been well tolerated in these studies, but its long-term safety is unknown. The role of aliskiren in therapy will be unclear until clinical trials report on outcomes such as cardiovascular mortality.

References

1. Uresin Y, Taylor AA, Kilo C, Tschope D, Santonastaso M, Ibram G, et al. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. J Renin Angiotensin Aldosterone Syst 2007;8:190-8.
2. Vaidyanathan S, Warren V, Yeh C, Bizot MN, Dieterich HA, Dole WP. Pharmacokinetics, safety, and tolerability of the oral renin inhibitor aliskiren in patients with hepatic impairment. J Clin Pharmacol 2007;47:192-200.
3. Huang HL, Vaidyanathan S, Yeh CM, Bizot MN, Dieterich HA, Dole WP, et al. Effect of aliskiren, an oral direct renin inhibitor, on the pharmacokinetics and pharmacodynamics of a single dose of acenocoumarol in healthy volunteers. Curr Med Res Opin 2008;24:2449-56. Epub 2008 Jul 24.
4. Vaidyanathan S, Camenisch G, Schuetz H, Reynolds C, Yeh CM, Bizot MN, et al. Pharmacokinetics of the oral direct renin inhibitor aliskiren in combination with digoxin, atorvastatin, and ketoconazole in healthy subjects: the role of P-glycoprotein in the disposition of aliskiren. J Clin Pharmacol 2008;48:1323-38.
5. Vaidyanathan S, Maboudian M, Warren V, Yeh CM, Dieterich HA, Howard D, et al. A study of the pharmacokinetic interactions of the direct renin inhibitor aliskiren with metformin, pioglitazone and fenofibrate in healthy subjects. Curr Med Res Opin 2008;24:2313-26.
6. Vaidyanathan S, Bartlett M, Dieterich HA, Yeh CM, Antunes A, Howard D, et al. Pharmacokinetic interaction of the direct renin inhibitor aliskiren with furosemide and extended-release isosorbide-5-mononitrate in healthy subjects. Cardiovasc Ther 2008;26:238-46.
7. Solomon SD, Appelbaum E, Manning WJ, Verma A, Berglund T, Lukashevich V, et al; Aliskiren in Left Ventricular Hypertrophy (ALLAY) Trial Investigators. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. Circulation 2009;119:530-7.
8. Cleland JG, Abdellah AT, Khaleva O, Coletta AP, Clark AL. Clinical trials update from the European Society of Cardiology Congress 2007: 3CPO, ALOFT, PROSPECT and statins for heart failure. Eur J Heart Fail 2007;9:1070-3.
9. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;358:2433-46.

Conflict of interest: none declared