Canterbury District Health Board
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Clinical Pharmacology Bulletin

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Sacubitril + valsartan for heart failure

Sacubitril + valsartan is now available in New Zealand and fully subsidised under Special Authority criteria. Eligible patients must have NYHA/WHO functional class II, III or IV heart failure; a left ventricular ejection fraction of ≤35%; and be receiving standard heart failure therapy. It can be prescribed by any relevant practitioner and replaces any ACE inhibitor or angiotensin-II receptor blocker (ARB) a patient was previously taking.

What is it?

Sacubitril is a first-in-class neprilysin inhibitor. Neprilysin is an enzyme that degrades peptide hormones including natriuretic peptides such as BNP and ANP. By inhibiting neprilysin, sacubitril increases the concentration of these peptides, which promotes diuresis and vasodilation. However, neprilysin also degrades angiotensin II; hence neprilysin inhibition increases angiotensin II concentrations and reduces sacubitril's therapeutic effect. To solve the problem, neprilysin inhibitors were combined with ACE inhibitors, but this led to high rates of angioedema due to excessive bradykinin concentrations. For these reasons, sacubitril is co-formulated with valsartan, an ARB.

Efficacy

Sacubitril + valsartan (48.6 + 51.4 mg increased to 97.2 + 102.8 mg twice daily) was compared to the ACE inhibitor enalapril (10 mg twice daily) in patients with chronic systolic heart failure. All patients (n=10,513) were taking an ACE inhibitor or ARB prior to enrolment. During a run-in period, they received enalapril for two weeks. If this was tolerated (n=9419), patients were given sacubitril + valsartan for four to six weeks. Only those who could tolerate both medications were then randomly switched to sacubitril + valsartan (n=4187) or enalapril (n=4212) and followed for a median of 27 months. The trial was terminated early due to a 20% reduction in the relative risk of cardiovascular death or heart failure hospitalisation in the sacubitril + valsartan group compared to the enalapril group (21.8% vs. 26.5%). There was also a 16% relative risk reduction for all-cause mortality (17% vs. 19.8%).[1]

Dose

The product is available in three strengths: sacubitril + valsartan 24.3 mg + 25.7 mg, 48.6 mg + 51.4 mg and 97.2 mg + 102.8 mg. If switching from an ACE inhibitor, wait 36 hours after stopping before starting sacubitril + valsartan, to reduce the risk of angioedema. No washout is needed if switching from an ARB. Use an initial dose of 48.6 mg + 51.4 mg twice daily for patients currently stabilised on an ACE inhibitor or ARB. Consider a lower dose (24.3 mg + 25.7 mg twice daily) for patients aged over 75 years; those with an eGFR less than 30 mL/min/1.73m^2 or hepatic impairment (Child-Pugh B or C); and those naive to ACE inhibitors or ARBs. In each case, the dose can be doubled if tolerated after two to four weeks, up to the target dose of 97.2 mg + 102.8 mg twice daily.

Adverse effects

The most common adverse effects in the trial outlined above were hypotension (18%), hyperkalaemia (12%) renal impairment (10%) and cough (9%). Of these, only hypotension occurred more frequently in the sacubitril + valsartan group than in the enalapril group. Blood pressure, renal function and potassium concentrations should be monitored at baseline and periodically during treatment. Angioedema occurred in 0.5% of patients in the sacubitril + valsartan group, compared to 0.2% in the enalapril group. This difference was not statistically significant. Longer term adverse effects are not yet understood; for example, neprilysin metabolises amyloid beta peptides, and increased concentrations of these were found in the cerebrospinal fluid of healthy adults taking sacubitril + valsartan. The clinical relevance of this is unknown.

Drug Interactions (not an exhaustive list)

- ACE inhibitors: contraindicated due to increased risk of angioedema
- Potassium-sparing diuretics and potassium supplements: increased risk of hyperkalaemia
- Non-steroidal anti-inflammatory drugs: increased risk of renal impairment

Pharmacokinetics

Sacubitril is a prodrug, and is rapidly hydrolysed to its active metabolite, sacubitrilat. Fractional oral bioavailability for the combination product is 0.6 for sacubitrilat and 0.4 for valsartan. Elimination is mostly renal for sacubitrilat (60%), and biliary for valsartan (80%). Half-lives in healthy subjects are on average 12 hours for sacubitrilat and 10 hours for valsartan.

Reference

1. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993–1004.