Drug therapies in older adults (part 2)

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ABSTRACT

In this, the second of two articles, we continue our evaluation of drug therapies in older adults. Having previously described the pharmacokinetic and pharmacodynamic consequences of physiological ageing, along with the challenge of appropriate prescribing, we proposed four key questions which should be considered when prescribing for this cohort of the population. Does this agent reflect the priorities of the patient? Are there alternatives – with greater efficacy, effectiveness or tolerability – that might be considered? Are the dose, frequency and formulation appropriate? How does this prescription relate to concurrent medication? We also highlighted the reliance on subgroup analysis to demonstrate the efficacy of drug therapies for older adults in osteoporosis and the underutilisation of appropriate treatments for patients with Alzheimer's disease as a result of flawed guidelines. Here we describe current drug therapies in systolic heart failure, noting the limited inclusion of older adults in key trials, while also reviewing the pharmacological treatment of orthostatic hypotension. In doing so, we advocate the intermittent use of midodrine as a first-line treatment for orthostasis in older adults, counter to the generic guidelines produced by various learned societies, but in keeping with the scant trial data available.

KEYWORDS: Pharmacology, elderly, orthostatic hypotension, postural hypotension, systolic heart failure, left ventricular dysfunction

Introduction

Diseases of the heart and circulatory system are the commonest cause of morbidity and mortality in the UK.[1] While ischaemic heart disease (IHD) continues to represent the single largest disease entity within this, cardiac failure, particularly left ventricular systolic dysfunction, is often a consequence in the long term.[1] Over two decades, antagonists of the renin–angiotensin–aldosterone system, along with those targeting β–adrenoceptors, have revolutionised outcomes for such patients. However, despite the incidence and prevalence data, landmark trials in this field have disproportionately overlooked the cohort most frequently affected – older adults. This is equally true of the newer agents, ivabradine and LCZ696.

The treatment of orthostatic hypotension (OH) among older adults is equally problematic. Notwithstanding issues relating to the challenge of consistent diagnosis and the prognostic significance of the disease, treatment options are poorly evidenced, particularly for adults aged over 65 years. Here we discuss drug therapies in both disease states, with a particular focus on older adults.

Orthostatic hypotension

OH is currently defined as 'a sustained reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table'.[2] It is common among older adults with a prevalence of 6–30% in those aged 65 years and over.[3,4] This variability highlights a significant issue which must be considered prior to treatment: the challenge of diagnosis. When completing four distinct assessments for OH in new nursing home residents, 50% of subjects had no readings suggestive of OH, 20% had one reading consistent with the diagnosis, 20% had two or three 'positive' readings and only 10% had four readings consistent with OH.[5] A second issue is the variability of symptoms experienced; in 205 patients with a systolic BP drop of at least 60 mmHg, 43% had typical symptoms, 24% had atypical symptoms (eg backache or headache) and 33% were asymptomatic.[6] Third, is the issue of prognostic importance. In 1998, the Honolulu Heart Program reported that OH was a significant independent predictor of 4-year all-cause mortality in elderly ambulatory men – a paper cited over 300 times.[7] Two years later, many of the same authors reported that there was no significant correlation with morbidity or subsequent mortality, again as part of the Honolulu Heart Program – this paper has been cited twice.[8]

A number of age-related physiological changes increase the likelihood of OH, especially in the presence of related pathology.[9–11] The compliance of the arterial tree diminishes with age, diastolic filling may be impaired and the tortuosity of the venous system increases.[9,10] The renal conservation of sodium declines, as do renin, angiotensin and aldosterone levels.[9,10] Similarly, the circulating concentration of arginine vasopressin falls, while cerebral blood flow is reduced.[9,10] Although these changes may account for some of the increased burden of OH among older adults, it is also associated with a multitude of causes, which can be broadly categorised into

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primary autonomic failure (eg pure autonomic failure), secondary autonomic failure (eg diabetes mellitus), drug-related disease (eg antihypertensive use), volume depletion (eg haemorrhage) and idiopathic OH.[9–11]

Asymptomatic OH does not require treatment and only rarely is a treatable cause identified eg vitamin B12 deficiency.[12] In other instances a number of non-pharmacological methods have been employed, including dietary changes, abdominal compression, lower limb bandaging and drinking increased volumes of water.[9] Most of the pharmacological agents which have been trialled in this setting, including dihydroergotamine, midodrine, fludrocortisone, octreotide, yohimbine, domperidone and Korodin, have been limited in their application by studies which are methodologically flawed.[11–13] Only two are currently recommended in the 2009 European Society of Cardiology (ESC) guidelines: fludrocortisone and midodrine.[14] The 2006 guidelines produced by the European Federation of Neurological Societies (EFNS) make similar recommendations, while also recommending dihydroxyphenylserine and octreotide for the treatment of dopamine β-hydroxylase deficiency and post-prandial OH, respectively.[15]

Fludrocortisone

Fludrocortisone is a synthetic (0.1–0.3 mg, once daily) mineralocorticoid, devoid of almost all glucocorticoid activity. It is thought to raise blood pressure by promoting the renal retention of sodium and increasing plasma volume.[16] However, persistent exposure may lead to the normalisation of both the plasma volume and the degree of sodium retention; despite this, a sustained increase in blood pressure is observed.[17] This suggests that fludrocortisone may sensitise the α-adrenergic receptors of blood vessels, leading to an indiscriminate increase in peripheral vascular resistance and a risk of supine hypertension,[17] in addition to the more frequent adverse effects of dependent oedema, hypokalemia, headaches and congestive heart failure (HF).[12,18]

Although guidelines from the ESC and EFNS suggest that fludrocortisone be considered first-line therapy for OH, the trial data supporting these recommendations are weak.[14,15] The first double-blind crossover study of fludrocortisone and placebo was reported in six patients with diabetes (mean age: 52 years; range: 33–64 years); symptomatic improvement was observed in four subjects.[19] Subsequent studies, published in the English language, adopted an observational approach, whereby fludrocortisone was utilised in combination with head-up sleeping. In the first instance, six patients were studied (mean age: 52 years; range: 23–65 years), in the second, eight (mean age: 50 years; range: 23–65 years).[20,21] While both studies suggest that fludrocortisone may help some younger patients with OH, the absence of older adults is notable.[20,21] Whether such a bias exists in the double-blind trial published in German is unclear (n=60); the study also reported haemodynamic benefits and improved symptom control among those receiving fludrocortisone.[22]

Midodrine

Midodrine (5–20 mg, three times daily) is currently the only drug approved for the treatment of OH in both the US and Europe, although not in the UK.[11] A prodrug, it is converted by enzymatic cleavage to its active metabolite, deglymidodrine; a selective α1-adrenoceptor agonist that does not cross the blood–brain barrier.[23] It is thought to increase peripheral vascular resistance and venous return by promoting the vasoconstriction of arterioles and venous capacitance vessels.[23] Intermittent use is likely to be more effective than regular use as this avoids tachyphylaxis;[10] the drug is variably contraindicated if patients have significant IHD, acute kidney injury, an underlying phaeochromocytoma, thyrotoxicosis or problems with urinary retention (a particular issue for older males).[9]

Although four double-blind, placebo-controlled trials and a number of smaller studies have demonstrated the apparent effectiveness of midodrine in OH, a number of systematic reviews have highlighted key issues with the evidence.[12] Criticisms include a failure to conclusively demonstrate symptomatic improvement and an exaggeration of supine blood pressure.[12,13] In keeping with studies of fludrocortisone, the trials are also notable for the mean age of participants (60–65 years), although the range extends from 22 to 86 years.

In light of the evidence, it is difficult to concur with the guidelines generated by the ESC and EFNS, particularly when treating older adults experiencing OH.[14,15] The intermittent use of midodrine, as a first-line treatment, as opposed to fludrocortisone, would follow the limited evidence more closely in this cohort.

Heart failure

HF is largely a disease of older adults, characterised by objective evidence of cardiac dysfunction and a triad of symptoms: dyspnoea, fatigue and fluid retention.[24] The median age at diagnosis is 76 years;[25] the British Heart Foundation recently estimated the prevalence to be approximately 3% among adults between the ages of 25 and 74 years and 12.5% in those aged over 75 years.[26] Incidence data follows a similar pattern; in the UK, the annual incidence of HF is 102.5 cases per 100,000 person years among those aged between 55 and 64 years and 327.3 cases per 100,000 person years in those aged over 85 years.[26] With an ageing population, improved survival from associated cardiovascular diseases, eg IHD, and advances in the treatment of HF itself, both the prevalence and incidence of chronic HF are set to increase.[24]

However, prior to treatment, the underlying cause must be established, as the condition may be reversible, may provide some indication of prognosis and may have consequences for family members.[24] While there are significant variations in the causes of HF between the industrialised and non-industrialised worlds, IHD with associated left ventricular systolic impairment remains the primary cause of HF worldwide, particularly among older adults,[27] despite the recent interest in diastolic dysfunction, which frequently co-exists with systolic dysfunction.[24]

The key aims of therapy for systolic HF secondary to underlying IHD are to relieve symptoms and prolong survival. Integral to this approach are a series of lifestyle measures, which include a graded exercise programme, salt and alcohol restriction, along with weight loss in overweight patients. However, it is antagonists of the renin–angiotensin–aldosterone system and β-adrenoreceptors that have revolutionised outcomes for this cohort of patients – a product of large, randomised controlled trials. More recently, ivabradine, an inhibitor of electrical pacemaker activity in the sinoatrial node,

has proved promising, as has LCZ696: a neprilysin inhibitor coupled with valsartan.

ACE inhibitors and angiotensin II receptor antagonists

A number of landmark trials have demonstrated the efficacy of angiotensin-converting-enzyme inhibitors (ACEi) in both symptomatic and asymptomatic HF.[28–30] However, these trials primarily recruited younger adults; the mean age of trial subjects in the SOLVD study was 60 years, while the mean age of participants in the 'Heart Outcomes Prevention Evaluation' (HOPE) trial was 66 years.[28,30] Nonetheless, subgroup analysis of HOPE demonstrated a greater risk reduction among older adults (>65 years old) as compared with the wider trial population;[30] results from subgroup analyses of the SOLVD studies were broadly comparable.[28]

Angiotensin II receptor antagonists (ARBs) are considered an effective alternative for those who are intolerant of ACEi, although the mortality benefit may not be as large as that observed with ACEi.[31,32] While the CHARM-Alternative trial, confirms the mortality and morbidity benefits of candesartan in patients with a left ventricular ejection fraction (LVEF) of 40% or less, only 23.3% of the trial population were aged ≥75 years, leaving the authors reliant upon subgroup analyses to demonstrate that the benefits among older adults were broadly akin to those reported for ACEi.[33,34] When combined with ACEi and β-adrenoreceptor antagonists, the ARBs, valsartan and candesartan have demonstrated additional mortality and morbidity benefits in patients with HF.[32,35] However, caution must be exercised when considering application of this trial data in older adults, as the physiological decline in renal and musculoskeletal function may increase the likelihood of adverse effects, particularly as the target doses for most ACEi and ARBs are independent of age.[36] Despite this, sub-maximal dosing is likely to be beneficial in patients with severe left ventricular systolic dysfunction, albeit not as effective as maximal doses.[37]

β-adrenoreceptors antagonists (β-blockers)

There is now unequivocal evidence that bisoprolol, carvedilol, nebivolol and sustained-release metoprolol, also provide mortality and morbidity benefits for patients with HF, regardless of its severity.[38–41] Many consider these results to have been fully validated among older adults, where a meta-analysis of 12,719 patients found no difference in benefit between those defined as 'elderly' in the constituent trials and their younger counterparts.[42] However, the oldest patient in the individual trials analysed was 71 years old.

While β-blocker therapy should only be initiated when patients are euvolaemic, practical concerns relating to those agents with a known vasodilatory effect (eg carvedilol and nebivolol) may be overstated.[43] Data from the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, suggests that carvedilol is extremely well tolerated, even among patients with a baseline systolic blood pressure of 85 mmHg.[44] Similarly, β-blockers are not contraindicated among those with chronic obstructive pulmonary disease; the association with broncho-constriction is only observed with reversible airways disease, which may be excluded by performing spirometry pre- and post-bronchodilator therapy.[43]

Aldosterone antagonists

The aldosterone antagonists, spironolactone and eplerenone, reduce mortality and morbidity in patients with moderate to severe HF (New York Heart Association classes III and IV).[45,46] However, the landmark trials in this field again failed to target the population most frequently affected by HF: the median age of patients in the Randomized Aldactone Evaluation Study (RALES) trial was 67 years, while the mean age at enrolment was 64 years among those recruited to the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.[45,46]

However, when used in older adults, renal chemistry should be monitored closely, as there is a tendency for aldosterone antagonists to cause renal impairment, thereby exaggerating age-associated changes. Concurrent use of these agents with high-dose ACEi or ARBs also increases the risk of hyperkalemia in patients with a creatinine clearance of <50 ml/min.[47] Similarly, the age-associated decline in serum testosterone levels predisposes older men to an increased risk of spironolactone-related gynaecomastia.[48]

Ivabradine

Ivabradine is a selective inhibitor of the hyperpolarisation-activated, cyclic-nucleotide-gated, funny current I(f) expressed at the sinus node. It does not affect atrioventricular or intraventricular conduction times, myocardial contractility or ventricular repolarization.[49] Current guidance from the National Institute for Health and Care Excellence (NICE), recommends that ivabradine be used in the treatment of adults with 'stable' HF, who are in sinus rhythm, have a heart rate of ≥75 beats per minute and a LVEF <35%.[50] The landmark study demonstrating the efficacy of ivabradine, received the acronym SHIFT – systolic HF treatment with the I(f) inhibitor ivabradine trial.[51] This demonstrated an 18% reduction in the primary endpoint of cardiovascular death or hospital admission with progressive HF among those treated with ivabradine, when compared with patients receiving placebo.[51] Significant improvements were observed throughout all pre-specified subgroups, including patients below and above 65 years of age. However, the average age of patients recruited to the trial was 60.4 years (standard deviation 11.4) and only 722 (11%) patients were aged ≥75 years.[51] Again it was a post hoc, subgroup analysis that led the authors to conclude that the safety and efficacy of ivabradine was comparable across all age groups.[52]

Neprilysin inhibitors

Neprilysin is a neutral endopeptidase which degrades a variety of vasoactive peptides, including natriuretic peptides, bradykinin and adrenomedullin.[53–55] Inhibition of neprilysin increases the circulating concentration of such peptides, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention and maladaptive attempts at physiological remodeling.[56,57] Neutral endopeptidase inhibition was evaluated as a possible antihypertensive mechanism, but proved ineffective; trials were never conducted on its efficacy in cardiac failure.[58] In preclinical studies, the combined inhibition of neprilysin and the renin–angiotensin system had effects that were superior to

either approach in isolation;[59,60] however, in clinical trials, such agents were associated with serious angioedema.[61,62]

LCZ696, which consists of the neprilysin inhibitor, sacubitril (AHU377), and the ARB, valsartan, produced morbidity and mortality benefits superior to those observed with enalapril, in patients with chronic HF and a reduced ejection fraction.[63] However, in keeping with many of the previous landmark trials, older adults were underrepresented in the study. Of the 8,399 patients randomised to either treatment arm, only 1,563 were aged 75 years and above (18.7%).[62] Among this cohort neither the primary outcome (a composite of death from cardiovascular causes or hospitalisation for HF) nor death from cardiovascular causes alone, achieved statistical significance. By contrast, in those under 75 years old, statistical significance was noted.[62] Whether this is a function of the trial design or LCZ696 has yet to be determined.

Concluding thoughts

The utilisation of drug therapies is increasingly evidence based; however, this process is at its most tenuous at the extremes of age. As with osteoporosis, there is often a reliance on subgroup analysis to demonstrate the efficacy of pharmacological treatments for older adults experiencing systolic HF, despite incidence and prevalence data demonstrating the propensity of these disease states for this growing cohort of the population. While Alzheimer's disease highlights the issue of underutilisation of appropriate treatments, for this oft-neglected group, the current guidelines for the management of OH highlight a failure on the part of researchers and clinicians to undertake meaningful trials of treatment for diseases which predominantly afflict older adults. ■

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