Current and future options for the management of hypertension

In this science article, John Sherwood, Mark Ashton and Hugh Ferriman take a look at current pharmacological treatments for hypertension and examine research and development into new treatments.

Hypertension is a major modifiable risk factor for cardiovascular disease. Prevalence depends on the blood pressure thresholds that are chosen for the diagnosis of hypertension. National Institute for Health and Clinical Excellence guidelines\(^1\) define hypertension as persistently raised blood pressure above 140/90mmHg over three separate clinic visits. Since the risk of cardiovascular events is directly proportional to the level of blood pressure, this is a somewhat arbitrary figure “the lower the better”. However, recently, conventional thinking has always been “the lower the better”. However, recently, there has been some evidence that this is not the case.\(^2\)

**Current treatments**

Traditionally, five main classes of drugs have been used for many years to treat hypertension: thiazide diuretics, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors and alpha-blockers.

In the past few years, there have been few pharmacological innovations in the treatment of hypertension, but the way that the drugs are used together has changed following reports relating to the efficacy of beta-blockers, principally atenolol. It was reported that these drugs were less effective at reducing major cardiovascular events, particularly stroke. There is still debate regarding how appropriate it is that the prescribing of this class of drugs has changed based mainly on the findings of one agent, atenolol. A number of beta-blockers have specific vasodilating properties, for example, carvedilol and nebivolol, and it is argued that these agents may still have a role to play in patients with hypertension.\(^3\)

**The renin-angiotensin system**

The renin-angiotensin system (RAS) is an important mechanism of vasoconstriction and this is the target of a number of drugs used in hypertension. However, in Afro-Caribbean patients, there is a reduced plasma renin activity, so drugs that target this system are less effective. For this reason, beta-blockers, which also affect the RAS, are also less effective for treating hypertension in this group.

Angiotensin II (ang II) raises blood pressure by causing vasoconstriction and releasing aldosterone from the adrenal cortex, which causes sodium and water retention, thus elevating blood pressure. ACE inhibitors prevent ACE converting angiotensin I (ang I) to ang II, thus reducing blood pressure by preventing vasoconstriction and aldosterone release, leading to vasodilation and an inhibition of salt and water retention. They also prevent the destruction of the vasodilator bradykinin by kinase, which is thought to cause the dry cough associated with this class of drugs.

There are 11 ACE inhibitors available in the UK and most are prodrugs, relying on first-pass metabolism in the liver to produce the active metabolite (eg, enalapril is converted to enalaprilat). Ang II receptor blockers (“sartans”) antagonise the effects of ang II at ang II type 1 (AT\(_1\)) receptors, which are found in the heart and blood vessel wall. Unlike ACE inhibitors, they do not affect bradykinin breakdown so do not cause a dry cough.

**Renin inhibitors**

Aliskiren was the first renin inhibitor available in the UK. Renin catalyses the first step of the RAS by breaking down angiotensinogen.\(^4\) This process eventually leads to the production of the potent vasoconstrictor ang II. Since renin catalyses the rate-limiting step in the production of ang II, renin inhibition has long been considered the preferred pharmacological approach to RAS inhibition.

During the past four decades, a number of renin inhibitors were trialled but their large molecular size and lipophilicity resulted in poor intestinal absorption and considerable first-pass hepatic metabolism, which limited oral bioavailability and, therefore, their usefulness in clinical practice.

Aliskiren was developed using molecular modelling based on X-ray crystallographic analysis of renin’s active site rather than on the structure of renin’s substrate, angiotensinogen.\(^4\) Compared with previous renin inhibitors, aliskiren is subject to less intestinal degradation and has a low level of first-pass metabolism, and thus has a much higher bioavailability. It has a long terminal half-life (between 23 to 36 hours) and is, therefore, suitable for once-daily dosing. It is eliminated primarily as unchanged drug in the faeces.

Like any newly launched drug, there is a lack of data on long-term efficacy and safety and it has tended to be reserved for use in patients who have failed to respond...
Exforge HCT and Tribenzor.

US Food and Drug Administration — have recently been granted approval by the different types of antihypertensive medicines apparently waning. Two new and so-called “polypills”, with interest in focused on developing new combination pills, mostly by big Current research and development Combination pills

The use of combinations of drugs is commonplace in the treatment of hypertension and this has important implications for patient compliance and prescribing costs. NICE guidelines suggest combinations of drugs that are thought to complement each other pharmacologically, such as ACE inhibitors and thiazides. Although fixed-dose combination therapies have generally not previously been recommended because of inflexibility of dosing and higher costs compared with the individual generic ingredients, some fixed-dose combination formulations are in use. Exforge, a combination of amlodipine and valsartan, is an example of a recently introduced combination therapy. The combination of a calcium-channel blocker and ang II blocker is claimed to reduce the risk of peripheral oedema caused by the calcium-channel blocker. Current research and development Combination pills

Most of the current activities by big pharmaceutical companies appear to be focused on developing new combination pills, including fixed-dose combination medicines and so-called “polypills”, with interest in developing new classes of antihypertensive medicines apparently waning. Two new combination therapies that combine three different types of antihypertensive medicines have recently been granted approval by the US Food and Drug Administration — Exforge HCT and Tribenzor.

Tribenzor contains olmesartan, amlodipine and hydrochlorothiazide and gained approval with the condition that it cannot be used as an initial treatment. Exforge HCT is an oral medicine that contains amlodipine, valsartan and hydrochlorothiazide, and is available in a range of strengths and has recently been granted a marketing authorisation by the European Medicines Agency. Although the initial suggestion of a polypill containing multiple classes of medicine in a single formulation to reduce multiple cardiovascular risk factors was controversial, the concept now appears to be under serious evaluation. For example, following on from an earlier phase II trial involving “Red heart pill 2b” (contains aspirin, simvastatin, losinopril and hydrochlorothiazide), a phase III trial involving a “Red heart pill, (versions 1 and 2)” is under way and results are expected to be reported in 2013.

LCZ696

One of the few new classes of treatment under investigation is LCZ696, which is under development by Novartis for the treatment of essential hypertension and heart failure. LCZ696, which represents a novel design, combines the active moieties from two different drugs — the ang II antagonist valsartan and the neprilysin inhibitor prodrug AHU377 (neprilysin is an enzyme that cleaves bradykinin, antidiuretic hormone and converts ang I to ang 1–7, which is a competitive inhibitor of ang II). Although LCZ696 is only in phase II trials, it appears to be showing great promise because it produced a greater average reduction in systolic and diastolic blood pressure than valsartan alone.

Vaccine

An interesting and novel approach to the treatment of hypertension that is in the early phase of development is the use of a vaccine. An initial phase II trial of an ang II vaccine (CYT006-Ang-Qb) in a small group of patients with moderate to mild hypertension produced an encouraging result in the group taking the higher dose versus the placebo group, with an average (over 24 hours) reduction in blood pressure of 9mmHg (systolic) and 4mmHg (diastolic). A follow-up study in which the vaccine was administered more frequently than in the first study produced a lower blood pressure reduction (–2.3–0.4mmHg). Further analysis of the biochemical data revealed that the antibody affinities to ang II were significantly lower in the second study group and the amount of ang II sequestered in the blood of vaccinated individuals was one-third lower than in the first study, suggesting that patients whose antibodies had a higher affinity and bound to ang II for longer had a larger reduction in blood pressure. Further studies with CYT006-Ang-Qb are ongoing.

Carotid stimulator therapy

Stimulation of arterial baroreceptors6 located in the carotid sinuses and aortic arch by increased vascular distention causes a decrease in the sympathetic activity to the heart, kidneys and vasculature, heightens parasympathetic tone in the heart, and reduces the release of arginine vasopressin from the posterior pituitary. This results in reductions in heart rate, stroke volume, blood pressure and vascular resistance.

Although the modulation of the baroreflex in controlling hypertension was initially doubted owing to the fact that the baroreflex is reset in response to sustained blood pressure elevation, a lot of work over the past few years has suggested that modulating the baroreflex might provide a means of controlling servo hypertension.

Following the completion of a number of European trials, one such device that is available in Europe is the Rheos Baroreflex Activation Therapy system. The system consists of a device that is implanted into a patient’s body near the collar bone and connected via leads to the carotid sinuses. The frequency of signalling from the device is set externally, allowing modulation of the baroreflex.

Conclusion

During the past two decades, there has been significant progress in the management of hypertension. However, there are a significant number of individuals who have treatment-resistant hypertension and, for these individuals, there is a need for new treatments.

References

3 Pedersen ME, Cockroft JR. What is the role for beta-blockers as initial therapy for uncomplicated hypertension? Current Opinion in Cardiology 2009;24:325–32.