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Chronotherapy of hypertension: Time really is of the essence in treating high blood pressure

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ABSTRACT

Essential hypertension is a common condition, affecting approximately one in four adults, and a major risk factor for stroke and coronary heart disease. The evidence that vigorous treatment of hypertension prevents cardiovascular complications is incontrovertible, however in approximately one in three hypertensive patients blood pressure remains suboptimally controlled despite treatment, and cardiovascular morbidity and mortality in such patients remains high. Recent evidence suggests that the time at which antihypertensive medications are taken can have an important effect not only on degree of blood pressure control but also on outcome: both are improved dramatically if the medications are taken at bedtime rather than on first waking. The reasons for this remain unclear, since most modern antihypertensive drugs have long duration of action with high trough / peak ratio, but contributors could include better medication adherence as well as restoration and / or enhancement of nocturnal dipping of blood pressure. In this article, we will review the evidence that timing of blood pressure medication taking has an important influence on both hypertension control and cardiovascular outcomes, and the clinical implications of implementing chronotherapy in the treatment of hypertension.

Hypertension management: What are the barriers to optimal treatment?

Hypertension is an important preventable risk factor for cardiovascular disease. Stroke and ischaemic heart disease are increased by 10% and 7% respectively with each 2 mmHg increase in systolic blood pressure, and hypertension is the leading cause of premature death and disability after smoking[1]. In the United Kingdom, 25% of adults are diagnosed with hypertension, as defined by the National Institute for Health and Care Excellence (NICE) criteria[2], and this figure rises to 50% in the over 65 age group[3]. Indeed, due to the ageing population, the prevalence of hypertension is on the rise[3].

Hypertension treatment targets vary between different guidelines across the world, but whatever the target the principal goal of hypertension treatment is to reduce blood pressure with the goal of preventing cardiovascular morbidity and mortality. A relatively small reduction in pressure is needed to give rise to reduced cardiovascular disease risk: It is estimated that a 5 mmHg systolic blood pressure reduction can lead to 7% decrease in all-cause mortality, with a 14% and 9% decrease in mortality from stroke and coronary heart disease respectively[4]. Therefore, any intervention that can augment the efficacy of antihypertensive treatment, however small, can have a profound effect on cardiovascular complications and patient outcome, with resultant benefits not only in mortality and quality of life, but also in financial savings for the health economy and for society more generally.

The normal blood pressure response is to decrease, or 'dip', during the hours of sleep. In many hypertensives, dipping is decreased or lost, and in some cases blood pressure can actually increase

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during sleep (so-called reverse dipping). Long-term observational studies have shown that non-dippers have worse cardiovascular outcomes than dippers, and even where dipping is present there is an inverse relationship between incidence of cardiovascular complications and degree of dipping[5-8]. This suggests that, in order to optimise cardiovascular outcomes, not only is the degree of blood pressure lowering important but so is its 24 hour pattern. Hence for a number of years there has been considerable interest in whether timing of antihypertensive medication is an important facet of treatment.

Another barrier to optimal treatment is the frequent occurrence of medication non-adherence. Although precise figures vary between different studies, it is widely recognised that poor adherence to antihypertensive medication is common, and especially so in those with apparently resistant hypertension where figures of 25-50% have been reported (reviewed recently by Poulter et al.[9]). The reasons for poor / non-adherence are multiple and complex, but one factor is complexity of treatment regime – not only related to number of tablets but also to patients being instructed to take them at various different times of the day. For example, diuretics are generally advised to be taken in the morning, to mitigate the possibility of potentially troubling nocturia, whilst alpha blockers are usually advocated to be taken last thing at night, to avoid the possibility of falls due to their potential to cause orthostatic hypotension. Simplifying medication regime by standardising when all tablets should be taken is likely to improve adherence, and hence blood pressure control and hypertensive complications.

Such considerations as the above have sparked interest in chronotherapy, that is to say the role of timing of therapy, in the management of hypertension.

Chronotherapy in hypertension: is it important?

Over the years, a number of trials have suggested that night-time administration of antihypertensive drugs may improve overall 24 hour blood pressure profile and also may reduce cardiovascular events, although results have been inconsistent and most such studies have been small and have involved patients with varying co-morbidities (reviewed recently by Bowles et al.[10] and Hermida et al.[11]). Very recently, however, a new large multicentre, controlled, prospective endpoint trial in 19,084 ambulatory blood pressure-proven hypertensive patients, The Hygia Chronotherapy Trial, was conducted over 6.3 years median follow up in primary care in Spain[12]. This trial was specifically aimed to compare the effectiveness of administering all antihypertensive drugs upon waking or at bedtime, both in terms of blood pressure reduction and prevention of cardiovascular endpoints. Randomised patients, widely ranging in age, co-morbidities and other demographic characteristics, received all antihypertensive treatments either at bedtime (n = 9.552) or upon waking (n = 9.532). There were 1.732 primary cardiovascular outcomes in the study (cardiovascular death, myocardial infarction, coronary revascularization, heart failure, or stroke). After adjustment for age, sex, type 2 diabetes, chronic kidney disease, smoking, high-density lipoprotein cholesterol, asleep systolic blood pressure mean, sleep-time relative systolic blood pressure decline, and previous cardiovascular events, there was a 45% reduction in the primary composite endpoint when medications were all taken at bedtime compared to upon waking [hazard ratio 0.55 (95% CI 0.50-0.61), $P < 0.001$]. Large reductions were also seen in cardiovascular death [HR 0.44 (0.34-0.56)], myocardial infarction [0.66 (0.52-0.84)], coronary revascularization [0.60 (0.47-0.75)], heart failure [0.58 (0.49-0.70)], and stroke [0.51 (0.41-0.63)].

The upshot of this study is that, for a wide range of patients with hypertension, and unless there is a specific reason to the contrary, all antihypertensive medications are best given at bedtime: this gives rise to better overall blood pressure control (in terms of enhanced decrease in asleep blood pressure and increased blood pressure dipping during the hours of sleep), substantially reduces events, is safe and has no additional adverse effects. One interesting and potentially important piece of information from the trial is that, although there were no significant differences in baseline characteristics, patients taking medications on waking ended up having more treatments (mean number of medications 1.80 versus 1.71, $p < 0.001$), but despite this ended the study with higher blood pressures and worse renal function and were more likely to be non-dippers. All of these data suggest that night-time treatment is more protective in the longer term.

Although by far the largest trial of timing of blood pressure-lowering treatments, the Hygia trial is in line with other studies and hypotheses. The HOPE study suggested that night-time ramipril was safe and effective, but this was against placebo[13]. In Syst-Eur, nitrendipine and enalapril were given at

night, and hydrochlorothiazide in the morning[14], but no analysis comparing outcomes has yet been published. No other large trials have been published comparing identical initial treatment strategies with only the timing of the medication being variable. Notably, the UK-based Treatment in the Morning versus Evening (TIME) study has randomised > 10.000 hypertensive people to morning or evening dosing. The trial began in 2014 with a planned 4 year follow up and is fully recruited. Results are expected in the next 1-2 years.

Conclusions

It has been well established that the incidence of acute coronary syndrome, stroke and sudden cardiac death all peak in the morning hours soon after waking; and a meta-analysis by Cohen et al. showed that approximately 1 of every 11 acute myocardial infarctions and 1 or every 15 sudden cardiac deaths are attributable to the excess morning incidence[15]. These early hours after waking coincide with the period during the day when blood pressure surges most markedly[16,17]. Giving antihypertensive drugs at night rather than during the early part of the day is likely to dampen this surge, and this may have contributed to the decrease in cardiovascular complications seen in Hygia. Although this is speculation, this chimes with other literature suggesting that control of morning hypertension is clinically feasible and should be an important therapeutic target[18].

Regardless of the mechanism of benefit, it seems clear that there is much to be gained by giving all blood pressure-lowering drugs at night, with very little if anything to be lost, unless there are clinical reasons for giving antihypertensive drugs in a different way (such as troublesome nocturia in elderly patients treated with diuretics). The time surely has now come for physicians to take time into account in treating their hypertensive patients.

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