Bedtime dosing of amlodipine and a diuretic improves blood pressure control

Patients with high blood pressure need time to accept the diagnosis and the need for treatment

Lowering blood pressure has benefits in patients without high blood pressure who have cardiovascular disease

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Administration of a fixed-dose combination of amlodipine and hydrochlorothiazide at bedtime resulted in lower 24-hour mean blood pressure than administration in the morning (Zeng J, Jia M, Ran H, *et al*. *Hypertens Res* 2011; 34: 767-772). Eighty patients in China with essential hypertension were randomised to receive a single pill containing amlodipine 5mg and hydrochlorothiazide 25 mg at 8am in the morning or 10pm at night for 12 weeks. Blood pressure was measured by ambulatory monitoring (ABPM) every 20 minutes during the day and every 30 minutes at night for 24 consecutive hours before and after the 12 weeks of treatment. At the end of the treatment period, patients receiving bedtime dosing had lower 24-hour mean blood pressure (P<0.05), lower night-time mean blood pressure (P<0.01), and greater minimisation of the morning blood pressure surge (P<0.01) than patients receiving morning dosing. The percentage of patients with controlled blood pressure according to ABPM criteria was 80% in the bedtime group and 75% in the morning group after 12 weeks of treatment. A fixed-dose combination of amlodipine and hydrochlorothiazide has different blood pressure lowering efficacy dependent on treatment time, and suggests that administration at bedtime could optimise the blood pressure lowering effects of this combination.

*Expert Comment*
In the present article, Zeng *et al*., showed that the fixed-dose combination amlodipine 5mg plus hydrochlorothiazide 25mg administered at night reduces the morning surge and increase the number of patients with good nocturnal dip. Furthermore, 24h BP reduction was also significantly greater among patients randomized to receive the fixed-dose combination at bedtime than in those who had the same combination in the morning. This concept is especially important in patients with resistant hypertension who have uncontrolled BP despite of 3 or more antihypertensive medications and usually take all drugs in the morning. Small clinical randomized studies have shown greater BP reduction when one medication is taken at night. This strategy can also reduce drug interactions, e.g. episodes of hypotension. It is known that morning surge and nocturnal BP are related with cardiovascular (CV) morbidity and mortality. However, it is unknown if decreasing morning surge or inducing nocturnal dip with antihypertensive medications translate into better outcomes independently of overall BP reduction. Furthermore, it is unclear if exaggerated nocturnal dip (“overdipping”) is related to increased CV risk. It would also be interest to know about side effects and quality of life in the study performed by Zeng *et al*. Hydrochlorothiazide is a thiazide diuretic and nocturia may be present when this medication is taken at bedtime. Changes in the time of administration of antihypertensive agents can effectively improve BP control and reduce medication interactions, particularly in patients on multiple medications. However, these modifications need to be focused on overall BP reduction which is known to reduce CV events.

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Patient adherence to blood pressure lowering medication is influenced by the experience of living with high blood pressure and the ability to accept the diagnosis and its treatment (Marx G, Witte N, Himmel W, et al. *Patient Educ Couns* 2011; May 18). Group discussions were held with 43 patients with high blood pressure from 19 general practices in Germany who were receiving antihypertensive medication. The study identified four basic phenomena associated with patients living with high blood pressure: fear of the diagnosis, ignorance about the illness, the impact of illness experiences, and a reluctance to discuss the illness with the doctor. The four phenomena were found to be interwoven and to result in patients acting in one of three ways: to seek information about high blood pressure or medication (the assertive actor), to not seek information about high blood pressure and simply accept the prescribed medication (the unconscious avoider) or to not accept high blood pressure as a lifelong condition and only accept medication as an interim solution (the inconsistent actor). However, these three action patterns did not have implications for medication adherence. Patients newly diagnosed with high blood pressure need time to accept the diagnosis and the need for treatment prior to initiation of medication, and an ongoing dialogue with the doctor is needed to support medication adherence.

**Expert Comment**
This qualitative study sought to identify patient beliefs and attitudes to the diagnosis and treatment of hypertension and the implications of these for adherence to medication. Eight focus group discussions involving four to six hypertensive patients (total sample size = 43) from 23 general practice surgeries in Germany were recorded and subjectively interpreted by the researchers. All patients had been prescribed antihypertensives but only 18 were classified as adherent. Other relevant participant factors such as education level, duration of treatment, comorbidities etc. were not provided.

The results identified patient perspectives about living with hypertension, including fear of risks related to disease, ignorance, reluctance to ask the doctor for information, and impact of the illness experiences. The authors used these phenomena to develop categories of patient "action patterns" suggesting that there are six types of patient, depending on how they act and react in managing their diagnosis. However, these patterns had no demonstrated implications for medication adherence and exactly how they were developed was not clearly presented. There was no evidence to support the claim that the phenomena have “different impact on patients’ acceptance of having hypertension”.

While the study provides a useful first step in identifying issues of concern to hypertensive patients, the results should be interpreted cautiously due to the subjective nature of the analysis and the limited sample size. Further research is needed to empirically test the validity of these action patterns and to ascertain whether or not they have relevance for adherence.

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Patients without high blood pressure but with a history of cardiovascular disease that were
treated with antihypertensive medication had a decreased risk of stroke, heart failure and death (Thompson AM, Hu T, Eshelbrenner CL, et al. JAMA 2011; 305(9):913-922). A meta-analysis of 25 clinical trials has found that antihypertensive treatment reduced the risk of stroke by 23%, myocardial infarction by 20%, heart failure by 29%, cardiovascular events by 15%, cardiovascular death by 17% and death by all causes by 13% in patients with a history of cardiovascular disease with normal or pre-hypertensive blood pressure levels, compared with controls. The 25 studies included in the meta-analysis incorporated data from 64,162 patients without high blood pressure, 76% of whom were men and with a mean age of 55-68 years. It was noted that a clinical history of myocardial infarction, heart failure, diabetes, stroke and coronary artery disease at baseline varied between studies. The meta-analysis included trials with a range of antihypertensive agents including diuretics, ACE inhibitors, beta-blockers, calcium channel blockers and angiotensin II receptor blockers. The use of antihypertensive medication in patients with a history of cardiovascular disease can provide significant benefits in terms of secondary prevention of cardiovascular events even in the absence of high blood pressure.

Expert Commentary
In aiming for 130/80 mmHg for patients with diabetes, renal disease or pre-existing cardiovascular disease, doctors are following the practice recommended by the National Heart Foundation of Australia. The sense of this recommendation is supported by the meta-analysis by Thomson et al of trials treating such patients with entry blood pressures of less than 140/90 mmHg, i.e. without hypertension. It was good news all round with benefits for stroke, myocardial infarction and all-cause mortality. One would imagine that those currently drafting BP guidelines, such as the Europeans (ESH/ESC) and the Americans (JNC8), would also welcome this analysis. Indeed, the Europeans have been expressing doubts recently (Mancia et al J Hypertens. 2009;27:2121-58) about their own existing recommendations for treatment to 130/80 mmHg in high risk patients. With the reassurance from the Thomson meta-analysis, only evidence of distinct harm should cause any reversal of current targets – and there is no hint of this emerging. Guidelines also need to speak to the “targetless” approach to blood pressure reduction. In appropriate circumstances (high cardiovascular risk with known atherosclerosis or diabetes in the HOPE Study, cerebrovascular disease in the PROGRESS Study and diabetes in the ADVANCE Study) treatment with blood pressure lowering drugs irrespective of blood pressure have been of benefit. For blood pressure, this approach is analogous to cardioprotection using aspirin irrespective of bleeding times. Although these studies were also included in the Thomson meta-analysis, to date, guidelines don’t provide doctors with recommendations for this mode of treatment. Hopefully this will be rectified soon.

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