HYPERTENSION

Taking diltiazem ER in the evening reduces morning blood pressure and heart rate more than ramipril

Background

Several attributes of the cardiovascular system, including blood pressure and heart rate, undergo predictable changes during a 24 hour period, usually in line with cycles of rest and activity. People whose blood pressure does not reduce by 10% to 20% at night are at increased risk of cardiovascular events. There is growing interest in how to tailor the treatment of hypertension according to circadian blood pressure patterns. Long-acting (LA) diltiazem is an agent designed to parallel the circadian rhythm of blood pressure and heart rate.

Objective

White and colleagues compared the effect of graded-release delivery of long-acting diltiazem versus ramipril at bedtime on blood pressure and heart rate during the first four hours after waking and over a 24 hour period.

Method

Forty-one centres in the United States and Canada took part in this double-blind, titration-to-effect randomised trial between July 2002 and June 2003.

Participants

Participants were 261 adults with untreated sitting diastolic blood pressure of 90 to 109 mmHg and ambulatory daytime diastolic blood pressure of 85 to 109 mmHg. Mean age 54 years; 38% were women. Exclusion criteria were recent coronary disease or stroke; congestive heart failure; secondary hypertension; cardiac conduction problems; uncontrolled diabetes; malabsorption syndromes; and chronic renal failure.

Intervention

Each evening for ten weeks participants received either diltiazem LA graded release tablets (240 mg titrated to 360 mg and to 540 mg) or ramipril (5 mg titrated to 10 mg and to 20 mg). Titration was based on blood pressure goals of less than 140/90 mmHg. 76% of participants in each group were titrated to the highest possible dose.

Main results

After 10 weeks, diltiazem LA was associated with greater reductions in early morning blood pressure and heart rate compared to ramipril. Diltiazem LA was also associated with reductions in mean 24 hour diastolic blood pressure and heart rate. Reductions in 24 hour systolic blood pressure were similar in both groups. Adverse effects were minor, and were similar between groups.

Authors’ conclusions

Taking diltiazem LA at bedtime is more effective than ramipril for improving blood pressure and heart rate control in the morning.

Commentary

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Nocturnal hypertension, characterised by the loss or even reversal of the expected 10% to 20% blood pressure decline during sleep, increases the risk of cardiovascular and cerebrovascular events, nephrosclerosis, and progression to end-stage kidney failure in renal patients. These blood pressure patterns are more frequent in hypertension that is secondary to specific medical conditions, such as chronic renal failure, diabetes, and autonomic nervous system dysfunction. However, more than 35% of people with uncomplicated essential hypertension may have these ‘non-dipper’ patterns. Normalising the circadian blood pressure rhythm is an important clinical goal of pharmacotherapy because it may slow the advance of renal injury and avert end-stage renal failure. It is therefore important to know about the effects of antihypertensive medications on the circadian blood pressure pattern.

Caveats

This study assumes that cardiovascular events are more frequent in the first hours after awakening, and that this increase in events is somehow related to the morning rise of blood pressure. However, an increase in morning stroke onset could be due to people awakening with neurological deficits as a result of a stroke that occurred during the night.

Unfortunately, most authors have reported their results in terms of clock hour, and not in circadian time based on the rest-activity cycle. Lower blood pressure and heart rate during the night may contribute to stroke onset during sleeping hours, particularly in thrombotic stroke. Recent studies suggest that thrombotic and lacunar strokes have a higher onset during sleeping hours.

With regard to circadian variation of blood pressure, blood pressure increases in the morning are an independent risk factor of stroke in older people with hypertension. The highest rate of both fatal and non-fatal strokes occurs in people with mean nocturnal blood pressure above the diurnal mean (so-called reverse-dippers or risers). Interestingly, reverse-dippers are characterised by a morning decrease, not surge, in blood pressure. Although appealing, there is little prospective evidence that slowing morning blood pressure peaks decreases cardiovascular risk.

Many prospective studies have suggested that the extent of nocturnal blood pressure decline influences cardiovascular injury and risk. The potential reduction in cardiovascular risk associated with normalising the circadian variability of blood pressure (converting a non-dipper to dipper) remains uncertain. A HOPE substudy suggested that the benefits of administering ramipril at bedtime on cardiovascular morbidity and mortality may be related to the 8% increase in the diurnal/nocturnal ratio of blood pressure.

White’s study suggests that the effect of diltiazem LA and ramipril on nocturnal blood pressure is similar. Diltiazem LA is more effective than ramipril for reducing mean diurnal blood pressure, thus resulting in a more ‘non-dipper profile’ after treatment. Evaluating the effects of both antihypertensive drugs on nocturnal blood pressure and on the diurnal/nocturnal ratio could have added valuable information.
Prospective studies are needed to assess whether normalising circadian blood pressure patterns reduces cardiovascular risk beyond the reduction in the blood pressure itself.

Overall quality

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References


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Results abstracted by Debbie Singh.