Pharmacological Reports 66 (2014) 448–452

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

Mortality in hypertensive patients with coronary heart disease depends on chronopharmacotherapy and dipping status

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ARTICLE INFO

Article history:
Received 10 August 2013
Received in revised form 30 November 2013
Accepted 16 December 2013
Available online 2 April 2014

Keywords:
Hypertension
Chronopharmacotherapy
Coronary heart disease
Blood pressure profile
Non-dippers

ABSTRACT

Background: The goal of our study was to assess the influence of hypertension chronopharmacotherapy on diurnal blood pressure (BP) profile and mortality.
Methods: Subjects with established coronary heart disease (CHD) (n = 1345, mean age 63.2 ± 9.2 years) were included.
Results: Non-dipping status was related to a lack of nighttime hypertensive drug administration (OR 3.87, 95% CI 3.00–4.98). In a Cox proportional hazards regression model, non-dipping status (HR 1.17, 95% CI 1.02–1.47) and non-nighttime antihypertensive drug administration (HR 1.13, 95% CI 1.01–1.45) were predictors of all-cause mortality.
Conclusions: The non-dipping profile of CHD patients and increased mortality were related to a lack of antihypertensive drug administration at bedtime.

Introduction

The efficacy of hypertension medications is strongly related to their pharmacokinetic and pharmacodynamic properties, and the associated frequency of administration. Ambulatory blood pressure monitoring (ABPM) is especially useful in defining the efficacy of hypertensive medications not only due to the recording of daytime blood pressure (BP) values, but also due to the measurement of nighttime BP values in particular [1–3]. Numerous studies have consistently shown that blunted nighttime BP dipping is related to increased fatal cardiovascular (CV) events [4–6]. Therefore, antihypertensive therapy should focus not only on the normalization of BP values, but also on normalization of BP variability [7]. Previously performed clinical trials have revealed that among subjects taking antihypertensive medications and achieving therapeutic goals, there is group of patients with blunted sleep-time dipping that is related to an high CV risk [8]. This phenomenon might be related to improper time-regimen of antihypertensive drug administration resulting from a disregard for the duration of action of these medications. Moreover, according to previously performed clinical trials, hypertensive subjects with established coronary heart disease (CHD) have a higher probability of blunted sleep-time dipping of BP [6,9]. Therefore, not complying with the principles of hypertension chronopharmacotherapy may be associated with an increased CV risk in already-treated hypertensives, especially those with CHD. Thus, the main purpose of our study was to evaluate the influence of chronopharmacotherapy on diurnal BP control in treated hypertensive patients with CHD. Additionally, we assessed the relationship between diurnal blood pressure profile and total mortality in hypertensives with CHD in over a seven-year observation period.

Materials and methods

Subjects

The observational study recruited 1345 consecutive CHD individuals (between August 2003 and August 2006) with typical angina symptoms and/or signs of myocardial ischemia identified in non-invasive diagnostic procedures (ECG stress test, dobutamine stress echocardiography or myocardial perfusion scyntygraphy stress test) in order to evaluate the indication for invasive treatment (PCI or CABG) in coronary angiography. Subjects with atrial fibrillation or atrial flutter, congestive heart failure of NYHA class III or IV, significant valvular heart disease or valvular heart

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http://dx.doi.org/10.1016/j.pharep.2013.12.009
1734-1140/

disease qualifying the patient for cardiosurgery, renal insufficiency with a creatinine level ≥ 2.0 mg/dL, changes in pharmacotherapy of hypertension within six months before 24-h ambulatory BP monitoring, and other chronic diseases leading to limited life expectancy were excluded.

Blood pressure measurements

To avoid the influence on BP of either hospital conditions or the need for reduced physical activity, in a period of two to four weeks after coronary angiography 24-h ambulatory BP monitoring was obtained (SpaceLabs 90210, SpaceLabs Inc., Redmond, WA, USA) with BP readings set at 20-min intervals (6:00 a.m.–6:00 p.m.) and at 30-min intervals (6:00 p.m.–6:00 a.m.). The non-dominant arm was used for measurement with cuff size adjusted to arm circumference (adult cuff 27–34 cm or large adult cuff 35–44 cm). All BP recordings were obtained on working days, and patients were instructed to maintain their usual activities but to refrain from strenuous exercise and emotional burden. Patients were instructed to hold their arm still by their side during blood pressure measurement and to return to the hospital 24 h later. Participants had no access to their ambulatory BP values. BP measurements recorded between 8:00 and 22:00 were considered as daytime BP values, and BP measurements recorded between 0:00 and 6:00 were considered as nighttime BP values. The percentage decrease in mean systolic BP during the nighttime period was calculated as 100 × [daytime systolic BP mean - − nighttime systolic BP mean]/daytime systolic BP mean. Using this percentage ratio, subjects were classified as dippers or non-dippers (nighttime relative systolic BP decline ≥ or <10%, respectively) [2].

Office BP measurements were performed just before ambulatory BP measurements using a validated oscillometric device (OMRON 705 IT) with the cuff fitted to arm circumference. BP was measured on the non-dominant arm.

Antihypertensive therapy

All subjects were treated with antihypertensive drugs. None of the subjects had had a change in pharmacotherapy in the six-month period before ambulatory blood pressure measurement. Pharmacological therapy had been established by general practitioners or cardiologists who were involved in treatment of hypertension in the subjects' treatment for hypertension. Decisions about the pharmacotherapy of hypertension were made on the basis of clinic BP measurements. All the doctors had European Society of Hypertension guidelines at their disposal. After considering the doses of antihypertensive drugs and their altered effectiveness due to combined therapy, all medications used in the treatment of the included subjects had a trough-to-peak (TTP) ratio (calculated as the ratio between the values of BP at max drop point and just before giving the next dose of antihypertensive drug) in the range of 50–80%.

Laboratory tests

On admission day before a coronary angiography, fasting blood samples were collected in order to measure total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides levels, and serum creatinine level.

Assessment of coronary atherosclerosis

The coronary angiography was performed in the Department of Invasive Cardiology, and angiograms were evaluated independently by two experienced invasive cardiologists. The coronary angiography was used to confirm coronary atherosclerosis.

Follow-up period

Subjects were followed from the date of coronary angiography until December 31, 2011. Follow-up was performed during visits to the clinic, and if patients were unable to attend they were contacted by phone. Data about coronary revascularization (PCI or CABG) was verified by the review of discharge cards and procedure protocols. Stroke diagnosis was performed according to European Stroke Organization guidelines, and acute coronary syndromes (ACS) were diagnosed according to European Society of Cardiology guidelines [10–12]. CV events included acute coronary syndromes (myocardial infarction or unstable angina) and stroke.

Statistical analysis

The overarching goal of the analysis was to create a statistical model to assess the influence of pharmacotherapy on diurnal BP variations. A logistic regression model was used for this purpose. We also performed an analysis of mortality in the follow-up period

Table 1
Basic characteristics the studied groups.

	Total group $n = 1345$	Dippers $n = 600$	Non dippers $n = 745$	p
Male, n	820 (61%)	366 (61%)	454 (61%)	ns
Age, years	63.2 ± 9.2	61.5 ± 9.3	64.0 ± 9.1	<0.01
Diabetes, n	279 (21%)	108 (18%)	171 (23%)	0.04
Smokers, n	208 (15%)	96 (16%)	112 (15%)	ns
Total cholesterol, mg/dL	205.2 ± 52.2	211.7 ± 51.5	202.5 ± 53.2	<0.01
LDL cholesterol mg/DL	120.5 ± 43.0	126.2 ± 44.8	118.3 ± 42.1	<0.01
HDL cholesterol mg/dL	55.3 ± 13.6	55.5 ± 13.3	55.2 ± 13.8	ns
Triglycerides mg/dL	147.6 ± 99.5	153.7 ± 103.5	145.0 ± 98.0	ns
Clinic systolic BP (mmHg)	137.7 ± 20.1	139.1 ± 19.5	137.1 ± 20.3	ns
Clinic diastolic BP (mmHg)	78.3 ± 11.3	80.4 ± 10.4	77.3 ± 11.5	<0.01
Clinic heart rate (bpm)	70.5 ± 12.1	71.2 ± 12.3	70.3 ± 12.0	ns
Daytime systolic BP (mmHg)	127.1 ± 14.0	128.7 ± 13.3	126.4 ± 14.2	<0.01
Daytime diastolic BP (mmHg)	74.3 ± 8.7	76.7 ± 8.1	73.4 ± 8.8	<0.01
Daytime heart rate (bpm)	69.6 ± 10.5	71.4 ± 11.3	68.9 ± 10.1	<0.01
Nighttime systolic BP (mmHg)	119.0 ± 15.4	110.4 ± 11.7	122.7 ± 15.3	<0.01
Nighttime diastolic BP (mmHg)	66.4 ± 8.9	62.8 ± 7.1	67.9 ± 9.1	<0.01
Nighttime heart rate (bpm)	61.9 ± 8.9	62.3 ± 9.6	61.7 ± 8.6	ns
Clinic BP ≥140/90 mmHg, n	496 (37%)	153 (38%)	268 (36%)	ns
Daytime BP ≥135/85 mmHg, n	416 (31%)	222 (37%)	194 (26%)	<0.01
Nighttime BP ≥120/70 mmHg, n	634 (47%)	180 (30%)	454 (61%)	<0.001

LDL – low density lipoprotein, HDL – high density lipoprotein, BP – blood pressure.