Editorial article

Chronotherapy with anti-hypertensive drugs to improve blood pressure control and reduce the vascular risk

Cronoterapia con antihipertensivos para mejorar el control de la presión arterial y reducir el riesgo vascular

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Blood pressure (BP) has a daily variation, mostly predictable, resulting from the interrelation of several physiological, neuroendocrine and environmental factors: (i) changes in behaviour associated with the activity–rest pattern; (ii) difference in relation to the light–dark cycle at room temperature, humidity and noise, and (iii) endogenous circadian rhythms (≈24 h) in neuroendocrine, endothelial, vasoactive and haemodynamic parameters, for instance, plasma noradrenaline and adrenaline (autonomous nervous system), atrial natriuretic peptide and calcitonine, renin, angiotensin and aldosterone (renin–angiotensin–aldosterone system [RAAS]). Different circadian rhythms in functions and physiological and biochemical processes also significantly affect the pharmacokinetics and pharmacodynamics of antihypertensive drugs, as it has been widely described.3–5

The diagnosis of hypertension and the clinical decisions regarding its treatment are usually based on a limited number of BP values obtained at the clinic, occasionally supplemented with domiciliary self-measurement always during the activity cycle.6 However, the correlation between the BP level and the risk of damage to solid organs and cardiovascular events (CV) is much higher for ambulatory BP monitoring (ABPM).7,8 One of the additional advantages of ABPM is that it allows description and quantification of the circadian BP variation profile.

During the last decades, the value of different parameters calculated from ABPM as biomarkers or mediators of damage to solid organs and risk of CV events has been explored. Specifically, many independent prospective studies have demonstrated that the BP mean at rest (sleep period) is a better marker for CV risk than the conventional clinical BP and the activity or 24 h means derived from ABPM.8–12 In general, these studies prove that when the activity and rest means adjusted with variables of significant influence (including gender, age, diabetes, chronic renal disease [CRD], smoking, prior CV event, etc.) are analysed together, only the rest mean, but not the activity mean, is a significant and independent marker of CV morbidity and mortality.

However, most ABPM studies carried out up to date have many limitations, including: (i) the use of arbitrary clock time slots to define day/night, hence, the calculated values do not represent the actual rest and activity BP means of each individual, and (ii) most of the published results derive from studies based on one ABPM record of each patient at the moment of inclusion, under the apparent and erroneous assumption that ambulatory BP profile remains unchanged during the follow-up years, despite the effect of antihypertensive treatment, ageing and the development of target organ damages or concomitant diseases.8,12 Thus, the potential change of CV risk associated with the normalisation of the circadian BP profile with the antihypertensive treatment, i.e., the specific reduction of the mean BP at rest or the increase in depth (percentage of BP drop during sleep period in relation to the BP mean during the activity period) towards a more dipper profile is still open for debate.

In this sense, the Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, MAPEC) study was designed to prospectively investigate: (i) the comparative diagnosis value of several parameters derived from ABPM, and (ii) if the intake of the complete dose of at least one antihypertensive drug at bed time provides a better control of BP and reduction of CV risk than the conventional treatment based on administering all medications during the morning.11,13–16 There were 3344 subjects participating in this prospective study. 2610 of which were hypertensive patients according to ABPM criteria.8,17 At the moment of inclusion, and then annually (or more frequently, depending on whether it was necessary to adjust the antihypertensive treatment based on ABPM results) during a median of 5.6 years of follow-up, the BP and physical activity (wrist actigraphy) were monitored simultaneously for 48 h in order to determine in a precise and individualised way the activity and rest BP means. The results of the MAPEC study, the first and only study published so far with participants periodically assessed via ABPM, indicate that the mean at rest, but not the activity mean, of systolic BP (SBP) is the most significant predictor of CV events in a survival model adjusted by

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the significant variables of gender, age, diabetes, anaemia and CRD (for each 1 - DT of elevation, hazard ratio 1.63 [95% CI 1.44 – 1.85], p < 0.001 for the rest mean; 0.94 [0.81 – 1.08], p = 0.348 for the activity mean). More importantly, the analysis of changes in ambulatory BP during the follow-up years revealed a 17% decrease in CV risk for each 5 mmHg of reduction in the rest mean of SBP, regardless of the changes in the clinical BP or the activity mean calculated based on the ABPM.8,11,12 These results, altogether, indicate that the mean BP during rest could be a new treatment objective to reduce CV risk, which obviously requires a precise assessment of patients using ABPM.17

The evident question based on these results is whether the mean BP during rest can be reduced as a specific treatment objective with the antihypertensive drugs available. Many randomised clinical trials with 6 different classes of antihypertensive drugs (angiotensin-converting enzyme inhibitors [ACE inhibitors], angiotensin II receptor antagonists [ARA-II], calcium antagonists, alpha blockers, beta blockers and diuretics) have documented relevant differences in their efficacy to lower BP, duration of the action, security profile and effects over the circadian BP pattern which depends on the administration time (chronotherapy).3–5 For instance, the intake in monotherapy of ACE inhibitors or ARA-II at bed time, instead of during the morning, reduces the BP during sleep to a greater extent without losing efficacy during activity hours, which is accompanied by a significant increase of depth towards a more dipper profile. These results are also independent from the terminal half-life of the drug (generally calculated only on the basis of the studies in which patients were treated in the morning) and seem to be more related to the activation of RAAS during the second half of the sleep period.2 Recently, a higher reduction of the BP during sleep with bed time intake has also been documented more consistently, as compared to morning intake, of several fixed combinations, including captopril-hydrochlorothiazide (HCTZ), valsartan-amlopidine, fosinopril-amlopidine, olmesartan-amlopidine, amlodipine-HCTZ and valsartan-HCTZ.4

In this issue of Medicina Clinica, Ponte-Márquez et al.18 conclude, based on a cross-sectional study with 123 hypertensive patients, that the administration of part of antihypertensive drugs at night contributes, to a certain extent, to a better control of ambulatory BP. Despite the fact that the lack of randomisation leads to differences in several variables, especially the mean number of drugs taken by the patients of each group, the authors came to the same conclusion after repeating the analysis of their data with a multivariate adjustment ruling out the potential influence of this and other variables. The size of the study does not allow discriminating the effects of the different antihypertensive families taken at night, or if the results would apply to different subgroups of interest based on high CV risk, including elderly patients and patients diagnosed with diabetes, CRD or resistant hypertension, among other conditions associated with a high prevalence of night hypertension.19

The results of the work of Ponte-Márquez et al.18 are consistent with those reported by Crespo et al.,19 among many other studies, starting with a cohort of 2659 hypertensive patients with CRD assessed using 48 h ABPM and participants in Hygia Project,19–22 a multicentre, prospective and controlled study, where currently 290 researchers participate through a network of 42 health centres in Galicia. Hygia Project was designed to assess the prognostic value of ABPM and the influence of the treatment time in CV risk.22 Among the patients with CRD studied, 1446 took all the medication on awakening, 359 took it all at bedtime, and 854 took the complete dose of some drugs at bed time and the rest on awakening. The mean BP at rest was significantly higher, the depth was lower and, therefore, the prevalence of the non dipper profile was higher with all the medication on awakening (68.3%) than with one or more drugs at bed time (54.2%; p < 0.001), and still lower in patients taking all the medication at bed time (47.9%; p < 0.001). The prevalence of the riser pattern (mean at rest higher than mean at activity), associated with the higher CV risk among other potential circadian BP profiles, was much higher (21.5%) in patients taking all the medication on awakening than in those taking some (17.8%) or all the drugs at bed time (10.6%; p < 0.001).19

Moyà et al.21 investigated, in turn, the effects of antihypertensive treatment time over ABPM in 2429 hypertensive patients with type 2 diabetes participating in Hygia Project. Out of those patients, 1176 took all their medication on awakening, 336 took all the medication at bed time, and 917 took the complete dose of some drugs at bed time and the rest on awakening. The intake of medication at bed time reduced the mean BP during rest to a greater extent. Thus, the prevalence of the non dipper profile was significantly higher for those taking all the medication on awakening (58.6%) than for those taking at least one drug (55.8%) or all of them (49.7%; p < 0.001) at bed time. This last group also presented the highest prevalence of controlled ambulatory BP, reached with a significantly lower number of drugs.4

On the other hand, the results of a reduced number of prospective clinical trials allow for the assessment of the impact of the antihypertensive treatment time over the CV risk. Thus, in the studies Syst-Eur,23–25 Syst-China,24 Heart Outcomes Prevention Evaluation26 and Controlled Onset Verapamil Investigation of Cardiovascular Outcomes (CONVINCE),26 the drug under investigation (nitrindipine, ramipril, verapamil-COER) was administered at night. The purpose in CONVINCE was to reduce BP in the first hours of the morning and not the rest mean; in fact, the delayed release formulation of verapamil administered at bed time reduces the activity BP by a much greater extent than rest BP,27 and therefore its most convenient administration time could be other than bed time. Despite all of the above, the comparison of the results of these studies of night intake of medication with those of the 170 clinical trials in which the investigation drug was administered in the morning28 indicates a 46% reduction (p = 0.008) in the relative risk of a CV event when the medication is taken at bed time instead of on awakening. Unfortunately, the medication investigated in those 4 trials with night treatment was not randomised in order to assess the effects of the same medication taken in the morning. The MAPEC study is therefore the first prospective study of the impact of antihypertensive chronotherapy over CV risk; patients randomised to take the medication at bed time were characterised for having in their last assessment using ABPM, after 5.6 years of follow-up, lower rest BP mean, higher depth, lower prevalence of the non dipper pattern and higher prevalence of controlled ambulatory BP than patients taking all the medication on awakening.14 Patients treated at bed time had a hazard ratio of total CV events significantly lower than those treated on awakening (0.39; 95% CI [0.29 - 0.51]; p < 0.001). The difference between groups was also significant for the total of major events, i.e., CV death, myocardial infarction and stroke (0.33; 95% CI [0.19 - 0.55]; p < 0.001). These results were validated in subgroups of elevated CV risk, including patients with diabetes, resistant hypertension13 and CRD.16

The purpose of the antihypertensive treatment is to reduce the BP to prevent damage to target organs and decrease the risk of CV events. Current treatment strategies, almost exclusively focused on reducing the clinical BP,6,10 do not allow eliminating the risks associated with high BP; on the contrary, they allow reducing CV risk by approximately 33%, a clearly suboptimal result.29 These therapeutic strategies still fail to take into consideration that: (i) the correlation between the BP level and the CV risk is much higher for ABPM than for clinical BP measurements7,8; (ii) the mean BP at rest is a better marker of CV risk than the activity or 24h means6–12; and (iii) the efficacy to reduce the level and improve the circadian BP profile of a good number of medications and their
combinations depends greatly on its administration time in relation to the patient’s activity and rest cycle.\(^1\)\(^2\) as proved by the study carried out by Ponte-Márquez et al.\(^3\) The results of the MAPEC study, pending potential confirmation by other prospective studies such as the ongoing Hygia Project, indicate, further, that the intake of the complete dose of one or more antihypertensive drugs at bed time significantly reduces the risk of CV events. In this sense, it is worth noting that the American Diabetes Association has acknowledged the clinical relevance of antihypertensive chronotherapy by recommending that diabetic hypertensive patients should be treated with one or more drugs at bed time.\(^4\) This same recommendation was recently extended to other groups, including elderly patients, patients with CRD and resistant or secondary hypertension.\(^5\)

**Conflict of interest**

The author declares that there are no conflicts of interest. The author is the only person responsible for the contents of this publication.

**References**