Original article

Differences in the reduction of blood pressure according to drug administration at activity hours or rest hours

Paola Helena Ponte Márquez a,⁎, Maria José Solé b, Juan Antonio Arroyo c, Laia Matas b, Maria Teresa Benet b, Àlex Roca-Cusachs c

a Servicio de Medicina Interna, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
b Unidad de Hipertensión, Servicio de Medicina Interna, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
c Unidad de Hipertensión, Servicio de Medicina Interna, Hospital de la Santa Creu i Sant Pau, Universidad Autónoma de Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:
Received 18 September 2013
Accepted 12 December 2013
Available online 15 September 2015

Keywords:
Ambulatory blood pressure monitoring
Circadian profile
Treatment efficacy

ABSTRACT

Background and objective: In this study, 123 recordings of blood pressure (BP) obtained by ambulatory BP monitoring were analyzed. These recordings were measured in 2011 in patients from a Spanish tertiary university hospital. All participating patients were treated with 2, 3 or 4 anti-hypertensive drugs. The main aim of this study was to determine differences in BP control, if any, depending on the medication schedule. Thus, BP levels were studied at 3 periods of the day: activity hours, rest hours and 24 h.

Patients and method: We compared subjects taking all anti-hypertensive agents during the day (n = 70, group 1) with those taking at least one at night (n = 53, group 2).

Results: Significant differences were found on diastolic BP, where group 2 patients had lower levels at activity, 24 h periods and sleep-time. Even if it was not statistically significant, lower levels of systolic BP from group 2 were also observed at activity and 24 h periods as well as lower levels of systolic, diastolic and mean BP at rest hours periods. There were also significant group differences in relation to the number of prescribed agents (with the mean being higher for group 2) and the type of agent (beta-blockers and calcium antagonists were more prevalent in group 2). Nevertheless, the multivariate regression analysis done taking into account these variables did not change the observed statistical significance.

Conclusion: The administration of anti-hypertensive drugs at night could be associated with lower BP levels.

© 2013 Elsevier España, S.L.U. All rights reserved.

Diferencias en la reducción de la presión arterial en función de la toma de la medicación en horario diurno o nocturno

RESUMEN

Fundamento y objetivo: Se analizaron 123 registros de presión arterial (PA) efectuados mediante monitorización ambulatoria de PA realizados durante el año 2011 en un hospital universitario español de tercer nivel, con el objetivo de determinar si existían diferencias según la hora de la administración de la medicación en las medias de PA en los 3 períodos (24 h, actividad y descanso) en aquellos pacientes que tomaban 2, 3 o 4 fármacos antihipertensivos.

Pacientes y método: Se compararon aquellos sujetos que tomaban toda la medicación durante el día (grupo 1, n = 70) con aquellos que tomaban al menos uno de los antihipertensivos por la noche (grupo 2, n = 53).

Resultados: Se observaron diferencias significativas, con medias inferiores de PA diastólica en el grupo 2 durante el período de 24 h, actividad y noche; medias inferiores de PA sistólica casual; y medias inferiores de PA media en los 3 períodos, con una tendencia (no significativa) a medias inferiores para PA...
sistolica a favor del grupo 2. En el coiciente de variación noche/día no se alcanzaron diferencias significativas. Sí se encontraron entre ambos grupos en cuanto al número de fármacos utilizado (medias superiores en el grupo 2) y en el tipo de fármaco empleado (betabloqueantes y antagonistas del calcio). Se realizó un análisis multivariante ajustando a estas variables, en el que se mantuvo la significación estadística.

**Conclusión:** La administración de parte de la medicación antihipertensiva por la noche podría contribuir a unas menores cifras de PA, lo que plantea la conveniencia de considerar esta estrategia en pacientes con hipertensión arterial no controlada.

© 2013 Elsevier España, S.L.U. Todos los derechos reservados.

**Introduction**

High blood pressure (HBP) is one of the main risk factors for coronary heart disease, heart failure, cerebrovascular disease, renal failure and atrial fibrillation, and it is in fact considered by the WHO as the cause of death worldwide.1 But what is important is not only a better control of blood pressure (BP) figures, but also correcting altered chronobiological parameters of BP. This is because there are data evidencing that, on the one hand, BP values determined via ambulatory blood pressure monitoring (ABPM) offer a better risk estimation than casual BP measurements2 3 and, on the other hand, because BP control at certain points during a 24 hour period may indicate differences in the clinical benefits to be obtained.4 In this sense, the European Society of Cardiology, together with other scientific societies,5 emphasised in early 2011 the clinical usefulness of measuring BP in hypertensive patients using ABPM. In one of the most recent recommendations of the British National Institute for Health and Clinical Excellence, the issue is taken further and a systemic use of ambulatory monitoring as an essential tool for diagnosis and treatment of HBP is recommended.6 7 The logical reasoning behind these recommendations is that circadian rhythms of the body may affect absorption, distribution, metabolism and elimination of drugs, and, therefore, contribute to the 24 hour BP variations in treated patients.8

Abnormalities in night blood pressure, both absolute and relative (as a non diper circadian pattern) is a frequent finding in hypertensive patients and is related to an increase in subclinical vascular damage and cardiovascular complications,9 associated with a worse prognosis and higher risk both in hypertensive and normotensive patients.9 There are also solid data (Smolensky et al.10) providing a great review of the impact of the change of administration time of 6 different types of antihypertensive drugs over blood pressure control) which document that the administration of at least part of the antihypertensive drugs at night is accompanied by significant differences in the intensity of the reduction of BP, the duration of such effect, the tolerability of drugs and the maintenance of a favourable circadian rate. Therefore, we have proposed to investigate the influence of the different administration times of antihypertensive drugs over the control of BP and the modification of the circadian rhythm.

Another important indicator to consider is pulse pressure (PP) (difference between systolic blood pressure [SBP] and diastolic blood pressure [DBP]), since it represents arterial distensibility. Numerous observational studies, such as Framingham’s, confirmed that PP increases with age, in both men and women. These behavioural changes, based on haemodynamic alterations inherent to ageing, would be the origin of progressive and slow increase of SBP and PP. Different population studies have revealed that a PP over 65 mmHg is associated with a higher cardiovascular morbidity and mortality, and is an independent marker of cardiovascular risk. Despite the works carried out by different authors and the concepts provided by medical literature, current guidelines of European societies of cardiology and hypertension have no recommendations on the administration time of hypotensive medication, and therefore studies that help clarify whether those doubts would benefit a better therapeutic management and an optimal control of patients. The purpose of the study is to determine if, based on the time when the drug is taken, there are differences in the BP medians, both casual and measured through ABPM (in its 3 periods: 24 hour activity and rest), and the circadian rhythm of BP (night/day BP variation quotient).

**Patients and method**

This is a retrospective and observational study. BP measurements were obtained through ABPM in records performed at a third level teaching hospital during 2011 (n = 483). Records from patients receiving 2, 3 or 4 different drugs in 2 or 3 tablets (n = 123) were included, and 2 groups were established: group 1, taking medication during the day (6:00 a.m.–4:00 p.m.) (n = 70); group 2, at least one intake of medication at night (from 7:00 p.m.) (n = 53). Patients treated with more than 4 antihypertensive drugs and/or patients treated with more than 3 intakes, patients with incomplete data and/or with a percentage of readings below 80%; patients with inflammatory bowel disease, rheumatoid arthritis, infection caused by human immunodeficiency virus, pregnant women and those patients under chronic treatment with corticosteroids, biological drugs and antineoplastic drugs.

A diper pattern (considered physiological) occurs when we observe a decrease in night BP of at least 10% in relation to day BP.12 The following variables were compared using the chi-square test: gender, body mass index (BMI, in kg/m²), with 3 categories: normal 18.5–24.9 kg/m²; overweight 25–29.9 kg/m²; obesity >29.9 kg/m², type of antihypertensive drug (diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, alpha blockers and beta blockers, angiotensin II receptor antagonists, renin inhibitors and others such as moxonidine and hydralazine), sleep quality and percentage of dippers (night/day). A Student’s t test was performed to compare independent variables: age, number of drugs and percentage of readings, as well as to compare mean SBP, DBP and mean casual BP (MBP) and in the 3 periods of ABPM readings: period of activity (day), period of rest (night) and 24 hour period, and the PP. A multivariate study was performed to adjust the results to those variables with significant differences among both groups. The SPSS® 20.0 programme was used to perform the statistical analysis.

**Results**

Patients taking the treatment during the day (n = 70) and those receiving at least some antihypertensive drug at night (n = 53) were comparable in the analysed variables: age, gender, BMI, sleep quality during the course of the study and associated cardiovascular factors (Table 1). Among the other variables analysed during the study, there was a higher number of medication intakes in the night group, with a mean of 3.45 tablets, whereas the mean for the day group was 1.93 tablets (p < 0.001).

As regards the category of the drug used as antihypertensive treatment, differences were found among both groups, with significantly higher means in group 2 for beta blockers and calcium
antagonists (Table 1). On casual SBP means, there were no significant differences between both groups, unlike for casual DBP (Table 2).

Significant differences were observed for BP means (SD) obtained during the 24-hour period: DBP 74.46 (9.70) mmHg in the first group compared to 71.08 (7.75) mmHg in the second group ($p = 0.007$); MBB 93.03 (8.41) mmHg (group 1) compared to MBB 90.43 (6.62) mmHg (group 2) ($p = 0.001$). No significant differences were found for SBP.

During the activity period, differences were observed as regards the DBP and MBB in the group taking the medication at night (activity in the first group: DBP 77.43 [10.11] mmHg, MBB 93.03 [8.41] mmHg; activity in the second group: DBP 73.79 [8.36] mmHg, MBB 90.43 [6.62] mmHg). During the period of rest, significant differences were observed on DBP and MBB in group 2 (Table 2). For the first group, DBP was 67.90 (10.57) mmHg, and MBB was 86.71 (10.44) mmHg, while for the second group, DBP was 64.85 (7.76) mmHg, and MBB was 83.64 (7.80) mmHg. When comparing the night/day quotient, no differences were observed in the variation between both groups (dipper/non-dipper pattern (Table 2).

A multivariate analysis was performed to study if the differences obtained in the BP mean depended on the number and family of drugs, and no variation was found on the results. Table 2 contains the $p$ values after making these adjustments.

### Discussion

The BP values obtained through the ABPM offer a more narrow correlation with the risk of cardiovascular events than casual determinations of BP obtained in the consultation; moreover, some of the chronobiological parameters obtained in these records (especially night BP) are more intensively correlated with vascular damage. This is why it is important to take into consideration the changes in BP obtained through ABPM, as well as to consider the values recorded during activity and rest periods. One way of studying this BP is to assess the day/night difference (in other words: the difference between the period of activity and the period of rest), having repeatedly described that patients who do not reduce BP during rest not only have a higher risk of suffering cardiovascular events, but also accumulate a higher organic damage compared to dippers. The non-dipper pattern is highly predominant in high-risk individuals, such as: old age, diabetic, obese, resistant hypertension and established organ damage. Likewise, the probability of having a non-dipper pattern is higher as the number of hypotensive drugs received increases.

The physiological pattern of BP in the 24-hour period (according to measurements via ABPM) evidences that there is a decrease of BP to the lower levels during sleep (night period), and that BP rises abruptly when patients wake up (morning) and reaches its peak and maximum values during first daily activities. The truth is that this finding may be taken as a justification to recommend morning hours to receive the hypotensive therapy. However, taking into consideration that not all commercialised drugs provide the same duration and efficacy homogeneously during the 24-hour period, and that there are (as we have seen before) multiple factors associated with a non-dipper pattern, the fact is that there is a high prevalence of non-controlled hypertension and a high percentage of patients with non-dipper patterns or a bad pressure control during night rest.

There is relatively recent scientific evidence proving that a higher benefit is obtained from administering at least part of the medication at bed time instead of only during the morning, because BP numbers are more intensively reduced and the risk of cardiovascular events is lowered more effectively. This is what we have in fact observed in our study, where even if there were no differences between groups on casual BP after treatment, there were differences in the mean BP with ABPM and a significant difference as regards the DBP and MBB in 2 of the periods analysed (24 h and activity).
The results of the MAPEC study are along the same line. In this study and substudies published in 2010 and 2011, it was suggested to compare the degree of control of BP between 2 groups based on the administration time of the drugs (when waking up or an hour before bed time), and make a prospective assessment of the impact of this different chronotherapy over cardiovascular morbidity and mortality. These authors (mostly in agreement with our results) observed that despite not detecting differences on casual SBP and DBP reached at the end of the follow-up, the proportion of subjects with controlled BP (determined with ABPM) was significantly higher among subjects taking some antihypertensive drug at bed time as compared to those taking all the drugs when waking up (62 against 53%, p < 0.001). Moreover, the night drug group consistently showed a significantly lower incidence of cardiovascular events.

In our results, although it is true that we did not obtain a significantly favourable difference as regards the proportion of dippers when comparing the day drug group with the night administration group, we did prove a better control of DBP and MBP during the 24h, activity and rest periods, with no significant increase of PP (remember that the highest expected benefit in the treatment of HBP is that attributable to the reduction of BP itself). A decrease as that obtained in our study, of almost 10% in night BP, together with a better pressure control during the rest of the day, is a proper clinical control, getting closer to optimal figures to decrease the risk of cardiovascular events.

It should be noted that in this work, unlike the MAPEC study, 2 groups were compared which, although they could be overlapped on their sociodemographic variables, could not be overlapped as regards the consumption of antihypertensive drugs, because the type and number of drugs were significantly different: there was a higher number of tablets administered in the night treatment group, and a higher percentage of use of beta blockers and calcium antagonists in the same group. However, when making a multivariate adjustment, we could dismiss both factors as elements influencing the means obtained. The determinant factor in pressure differences observed consisted of the study group, i.e., the administration time of antihypertensive drugs.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

**References**