Chronopharmacology of antihypertensives

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ABSTRACT

Pharmacological treatments of hypertension are associated with a reduction in cardiovascular risk. The blood pressure of both normotensive and hypertensive patients has a particular pattern associated to the biological clock set according to a circadian rhythm. One of the aims of this study was to test the long acting anti-hypertensive medications, atenolol and perindopril for their chronopharmacological properties in their effect on systolic and diastolic blood pressure levels over a period of 24 hours when administered in the morning or evening. Other aims were to compare blood pressure control in patients on atenolol and perindopril with control and normotensive patients and to obtain hourly systolic and diastolic blood pressure values using the ambulatory blood pressure monitor. An ambulatory blood pressure monitor was applied to the recruited patients for 24 hours and results analysed. Atenolol provides better blood pressure control during the early morning following a morning dose, whilst it results in an elevated blood pressure during the early morning when administered in the evening. Evening administered perindopril did not result in optimum blood pressure control throughout the 24h whilst morning administration resulted in an elevated early morning peak during the critical early morning period.

Keywords: chronopharmacology, hypertension, atenolol, perindopril, ambulatory blood pressure monitoring.

INTRODUCTION

Pharmacological treatments of hypertension are associated with a reduction in cardiovascular risk. Treatment should take into consideration the levels of the patients' risk factors which may include diabetes, cardiovascular or renal damage and target organ damage (Blacher *et al.*, 2009). Within the management of hypertension, aspects of chronobiology are worth considering.

The blood pressure (BP) of both normotensive and hypertensive patients has a particlar pattern associated to the body's biological clock set according to a circadian rhythm. Anwar *et al* in 1998 showed that both the BP and heart rate (HR) of both a normotensive and a hypertensive are higher during the day and lower during the night. Chronobiology as defined by the Dorland's Medical Dictionary (26th edition) is the scientific study of the effect of time on living systems.

CHRONOPHARMACOLOGY OF ATENOLOL VS PERINDOPRIL

Atenolol

Atenolol is a cardioselective, water-soluble βeta-1 selective adrenergic antagonist that lacks membrane-stabilising properties (BNF, 2010). Chronically-administered B-adrenergic antagonists have a greater effect on the heart and vasculature during the day than during the night. However, they appear to be less active at the early morning rise in BP, thus will provide inadequate protection during the most important time of the day (Lemmer, 1996; Morgan *et al.*, 2003).

In 2002, this was confirmed by a study carried out by Curmi. The diastolic BP following an evening dose was found to be significantly lower when compared to the morning dose (Curmi, 2002). This means that an evening dose will result in appropriate decreases in BP during the night, leading to a pronounced lack of BP control during the early morning hours.

Perindopril

Angiotensin-converting enzyme inhibitors (ACEIs) such as perindopril have achieved widespread usage in the treatment of cardiovascular and renal disease. They are adequate in the treatment of hypertension, they decrease mortality in congestive heart failure and left ventricular dysfunction after myocardial infarction, and they delay the progression of diabetic nephropathy (Brown *et al.*, 1998).

In an international study testing the chrono-pharmacological properties of perindopril, 18 male patients were analysed after being administered 4mg perindopril in the morning (0900h) or at night (2100h). Both schedules resulted in a decrease in the early morning peak, more prominent following evening perindopril administration. Perindopril showed an effect greater than 24h after being administered at 0900h, while evening administration only resulted in an effect of 18h following drug administration (Morgan *et al.*, 2007).

AIMS OF STUDY

i. To test the long acting anti-hypertensive medications, atenolol and perindopril for their chronopharmacological properties in their effect on systolic and diastolic BP levels over a period of 24 hours when administered in the morning or evening. Being used on a once daily basis, ability to maintain the 24h BP profile is evaluated.
ii. To compare patients on atenolol and perindopril with control and normotensive patients.
iii. To obtain hourly systolic and diastolic BP values using the ambulatory BP monitor.

METHODOLOGY

Ethics committee approval and patient informed consent were obtained prior to initiating the study.

Setting of Study

Patients in Group 1 were recruited from the Medical Out-Patients (MOP) of Malta's public hospital and from one of the public health centres.

Criteria for inclusion were as follows:

- Primary hypertension
- On once daily atenolol or perindopril to control hypertension
- On no other medication that could influence BP
- Not older than 75 years.

Recruitment of patients

Weekly sessions were attended at the MOP, where a regular consultant physician was always present. Patients attended by appointment.

The investigator discussed with the appropriate patient, drug history regarding hypertension and then provided information on the study. The investigator explained the presence of BP changes during the day. The importance of the right dose to be taken at an appropriate time was also highlighted. Patients were told that since readings were taken regularly throughout the 24-hour period, a more detailed observation of the BP would be attained.

An appointment was fixed for each patient, when the ambulatory BP monitor (ABPM) was applied for twenty-four hours. Upon its removal the following day, the time of drug administration was changed to the evening or vice versa, for the next six days. Exactly a week after the first meeting, a second appointment was fixed where the patient was asked to perform the 24-hour monitoring again. On the following day, data from the two sessions were compared in order to conclude whether there were any differences in BP when the dose was administered in the morning or evening.

The monitor was set to have a systolic BP (SBP) value limit of 140mmHg during the day and of 120mmHg during the night. The diastolic BP (DBP) value limit was set at 90mmHg during the day and 80mmHg during the night.

The hourly readings of SBPs and DBPs were analysed and whenever a distinctively high reading was encountered, the patient was asked what activity he/she was performing. This would determine whether the high reading was a result of exhausting activity.

An explanation of the results was given to participating patients. If readings obtained were above the target for BP, the patient was advised on non-pharmacological measures and referred to the consultant.

The patient was advised on how to change the time of administration of the antihypertensive medication in order to move on to the second reading.

Those patients usually taking their dose in the morning were told to take half the normal dose in the evening of that day, and the other half the next morning. Then, on the evening of the following day, the normal, full dose was to be taken, which was to be carried on for the rest of the evenings until the second appointment was due. This was done to avoid the patient being unprotected for more than twenty-four hours and to allow a more subtle way of changing the time of dosing.

Patients who usually take their medication in the evening were told to take their dose in the evening on that day, and starting as of the following day to take their dose in the morning only.

On the second appointment, the ABPM was fitted again and the recorder was set to take hourly readings for the next twenty-four hours. The patient was asked to return the next day at the same time.

Subjects taking no antihypertensive medications

Withdrawing medication of the recruited patients was not practical due to ethical reasons. Thus, separate hypertensive control subjects (Group 2) were recruited to use their BP values as a baseline. Data from the patient was obtained on his/her consent, and non-pharmacological advice was given. The criteria for inclusion were:

- Primary hypertension
- On no antihypertensive medication
- On no medication which may influence BP.

Normotensive subjects (Group 3) were also examined to obtain the mean variations of BP in Maltese subjects and to show the difference in blood pressure variation as compared to control subjects. The inclusion criteria were:

- Do not suffer from any form of hypertension
- Are on no medication that may affect BP.

Both groups followed the same procedure as Group 1 patients.

RESULTS

Four hundred and ninety-seven patients from Group 1 were screened during weekly sessions at the MOP and the health centre between November 2004 and November 2006.

Reasons that led to patients not completing this study were: unwilling to participate (26%), change of antihypertensive medications (11%), addition of antihypertensive drugs (16%), drop-out after first part (31%), lost data due to a technical error (3%), travel problems (8%) and invalid ABPM readings (5%).

A total of 43 patients successfully completed this study. Twelve were on perindopril (age 55 ± 13.1 years), 9 on atenolol (age 49.9 ± 11.2 years), 18 control patients (age 43.2 ± 13.1 years), and 4 normotensive patients (age 45.6 ± 14.2 years).

Atenolol

Analysis of the 24h Systolic BP (SBP) profile: Morning administration

The SBP during the early morning hours (0600h-1000h) is well controlled and below the target value of 140mmHg. Following atenolol administration at 0800h, a slight decrease in BP is observed, which starts rising again after 0900h. The highest diurnal peak presents at 1500h with BP reading 142.8mmHg, while the lowest peak is seen at 1800h. The most pronounced dip at night is oberved at 0400h, reaching a value of 112mmHg. **Figure 1** compares the 24h SBP profile for patients on atenolol administered in the morning or evening.

Analysis of the 24h SBP profile: Evening administration

A steady morning rise occurs at 0600h, reaching a conspicuous peak at 0900h with a reading of 149.6mmHg. After 0900h, there is a gradual SBP decrease, leading to day-time low value period

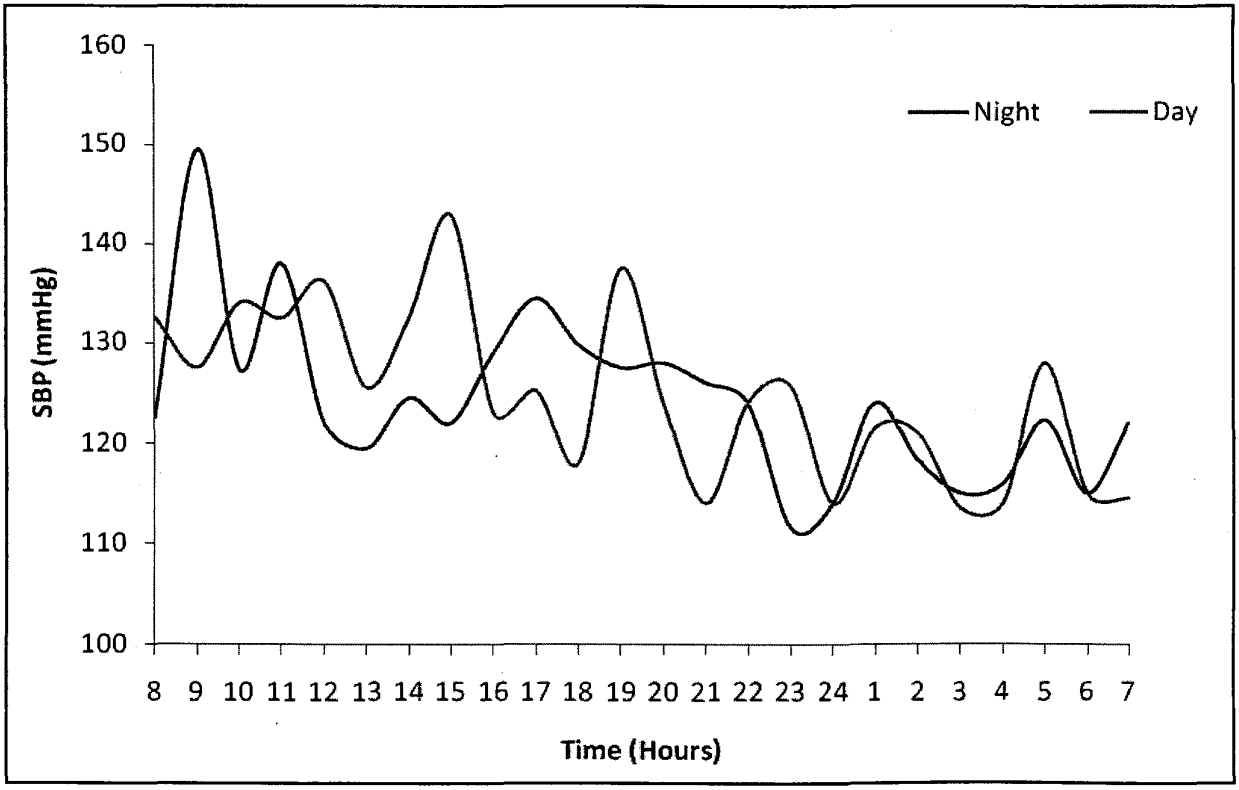

Figure 1. Comparison of the 24h SBP profile for patients on atenolol (n=9) administered in the morning or evening.

between 1200h and 1500h. SBP values are kept below 140.0mmHg throughout day-time and night-time. The night-time nadir is reached at 2300h, after which BP starts increasing again.

Analysis of the 24h SBP profile: Morning vs Evening administration

Better SBP control during the early morning period is present following morning atenolol administration. The majority of peak values during the day-time and night-time period are observed from the morning administration group. Neither morning nor evening drug administration resulted in a prominent nocturnal dip of 10% or more when compared to day-time values (7.8% and 7.2% respectively).

Analysis of the 24h Diastolic BP (DBP) profile: Morning administration

The rise in DBP starts after 0400h, producing a peak at 0500h and decreasing again at 0700h. A steep rise is observed after 0700h, leading to the morning peak at 0900h. DBP values throughout day-time are lower than the morning peak with a gradual BP decrease during 2200h and 0400h.

Analysis of the 24h DBP profile: Evening administration

A steep morning rise which was observed at 0600h results in the highest diurnal peak at 0900h of 97.1mmHg. A sharp decrease in DBP follows till 1100h, after which a more stable pattern is obtained between 1130h and 2100h. A gradual DBP decrease is noted after administration at 2000h, resulting in a night-time nadir at 2400h.

Analysis of the 24h DBP profile: Morning vs Evening administration

The DBP pattern following morning administration showed more changes throughout the day when compared to the evening dosing group. Both resulted in elevated early morning peaks at 0900h, followed by a decline in DBP. Evening drug dosing resulted in lower night-time values until 0200h, after which values becomes similar to the other cohort. Evening administration resulted in a 10% decrease in day-time pressure during the night-time period, resulting in a dipper status unlike morning administration (9.0%).

Perindopril

Analysis of the 24h SBP profile: Morning administration

An immediate sharp rise in SBP is observed at 0500h, reaching a peak of 145.9mmHg at 0800h. A sharp decline is noted following perindopril dosing at 0800h, reaching a value of 126.5mmHg at 1000h. Elevated readings are observed between 1500h and 2000h, with a decrease to night-time pressure starting after 1700h. Nadir was reached at 0300h with a value of 108.1mmHg.

Analysis of the 24h SBP profile: Evening administration

A gradual rise in SBP occured after 0100h. During the early morning readings are kept under 140.0mmHg and no rapid rise is observed. SBP elevation is observed between 1500h and 2000h, with a gradual decrease towards lower night-time values starting at 1800h. Nadir was reached at 0100h.

Analysis of the 24h SBP profile: Morning vs Evening administration

The 0800h peak rise of morning administration was 16.3mmHg more than that following evening dosing. However, this finding was not statistically different ($p=0.3750$; Wilcoxon test). During day-time, SBP following evening administration was generally higher than morning administration. Evening dosing managed to achieve a dipper status (12.6% compared to 8.2% following morning dosing).

Analysis of the 24 DBP profile: Morning administration

A gradual increase in DBP started at 0200h, resulting in an elevated peak at 0800h. DBP values fell following morning administration at 0800h, reaching low values between 1000h and 1100h. DBP elevation is observed between 1500h and 1900h. BP decline in preparation to night-time values started at 1700h, reaching in stable low readings during the night.

Analysis of the 24 DBP profile: Evening administration

The morning peak following evening dosing is observed at 1000h, with a reading of 93.0mmHg. During the early morning (before 1000h), values

below 85.0mmHg are acheived. A general DBP elevation is noted between 1500h and 2100h. The highest diurnal peak is observed at 1800h, followed by a decline that continues after dosing at 2000h. DBP is kept constant throughout night-time, except at 0300h.

Analysis of the 24 DBP profile: Morning vs Evening administration

A BP difference of 14.3mmHg is present between both regimens at 0800h. Both morning and evening perindopril administration led to evident nocturnal dips, reaching DBP decreases of 13.4% and 14.6% respectively.

Comparing Atenolol, Perindopril, Control and Normotensive subjects

Analysis of the 24h SBP profile: Morning administration

A 5% significant difference is present at 0800h when the perindopril and control group are compared to the normotensive group (p=0.0046 and p=0.0080, respectively; Paired t-test). The normotensive group, when compared to the other 3 groups is on the whole markedly lower throughout the day (p=0.300; one-way ANOVA). The paired t-test performed on whole day results in a statistical difference between the control and normotensive group (p=0.0041). **Figure 2** below shows the 24h SBP patterns of morning administered perindopril, control, and normotensive groups.

Atenolol is found to present more BP changes throughout the day than perindopril. Perindopril results in lower SBP control during the early morning period.

The highest peak reached amongst all four groups is that of perindopril at 0800h (152.6mmHg), whilst the lowest dip noted at 0200h resulted from the normotensive group (93.6mmHg). At 1800h, the atenolol group is significantly lower than the control

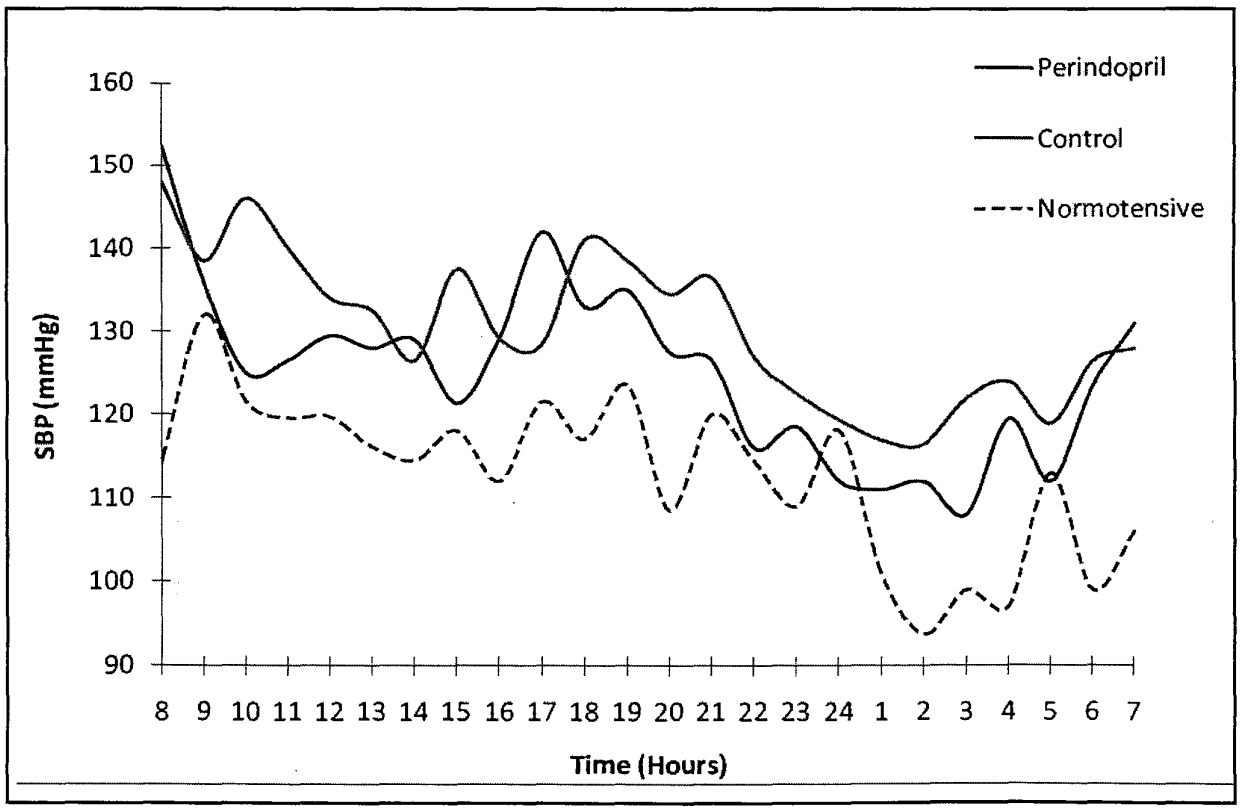

Figure 2. The 24h SBP patterns of morning administered perindopril (n=12), control (n=18) and normotensive (n=5) groups.

group (p=0.0071); Paired t-test). The control group is significantly higher than the normotensive group at 0400h (p=0.0046; Paired t-test) and 0600h (p=0.0094; Paired t-test).

The SBP profile during the day-time period of the normotensive group is similar to the treatment groups, however different from the control group.

Statistical analysis of the four groups for the night-time period does not show any difference between the groups.

Analysis of the 24h SBP profile: Evening administration

The highest peak throughout the day of both the normotensive and atenolol group occured at 0900h having values of 132.0mmHg and 149.6mmHg respectively. One-way ANOVA showed that the overall SBP profile of the normotensive group is generally lower than the other groups and is almost significantly different (p=0.0684).

The lowest night-time nadir is reached by the normotensive group at 0200h, with a value of 93.6mmHg. At 0400h a significant difference is observed between the control and normotensive group (p=0.0047; Paired t-test).

During the day-time period, this effect is reversed since the perindopril group appears to have more frequent higher readings than atenolol when compared to the control group. The elevated perindopril pattern is noted towards the time of dosing.

Perindopril presents with a smoother curve throughout the day when compared to atenolol. Perindopril also presented with better SBP control during the early morning hours, however resulted in an elevated pattern during most of the day-time period till dosing time, when compared to atenolol. Both are similar throughout the day and do not differ.

Analysis of the 24h DBP profile: Morning administration

The lowest DBP value noted during the day-time period in all the four groups was from atenolol at 1300h, with a value of 67.6mmHg. The normotensive group is more similar to the other groups when the DBP mean values are compared. The lowest DBP value during the night is observed at 0400h by the normotensive group (55.0mmHg). The DBP values of all groups decrease during the night with readings ranging from 55.0 – 82.6mmHg.

Analysis of the 24h DBP profile: Evening administration

Both atenolol and the normotensive groups showed an early morning peak at 0900h, which is similarly followed by the control group an hour later. Perindopril, when compared to the control and normotensive groups, results in the best DBP control during the early morning period with a lack of rapid rise in DBP.

At 1800h, a statistically significant difference amongst the four groups is almost detected (p=0.0618; one-way ANOVA), while a statistical difference at the 10% level is detected between the perindopril and atenolol group (p=0.0138; Paired t-test).

Atenolol results in a lower profile during the day-time, especially during the last few hours before drug administration. Atenolol, unlike perindopril, results in a steep morning surge during the early morning period.

CONCLUSION

Atenolol administered in the evening presents a drawback since it results in an elevated BP during the early morning as well as a lack of adequate nocturnal dip in SBP. Atenolol provides better BP control during the early morning following a morning dose.

Evening administered perindopril did not result in optimum BP control throughout the 24h whilst morning administration resulted in an elevated early morning peak during the critical early morning period.

This study shows the value of ambulatory BP monitoring in the management of hypertension. It is of support to physicians and pharmacists during patient monitoring and decision-making processes for pharmacotherapeutic interventions.

Declaration of interest

The authors do not have any interests to declare. Financial support was provided through a University of Malta Research grant.

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