# Diuretic drugs benefit patients with hypertension more with night-time dosing

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***Abstract:***

**Objectives:** Night-time chronotherapy in antihypertensive drugs has been shown to produce better blood pressure control and protect from cardiovascular morbidity and mortality. To date, this has been proven for several drug classes excluding thiazides diuretics. Given the peculiar response of blood pressure to thiazides in black people we sought to determine whether night-time chronotherapy with thiazides produces better control as already shown with other drug classes.

**Methods:** A subanalysis of a larger chronotherapy study with antihypertensive drugs in Nigerian Africans was done. The subpopulation of those whose disease was controlled after 12 weeks of diuretic monotherapy was analysed. Those who received drugs in the morning and at night were compared along control lines and some cardiac indices.

**Results:** Both groups were similar on all scores at baseline. After 12 weeks of monotherapy patients who received drugs at night had significantly lower systolic and diastolic blood pressure though control was achieved with both morning and night-time dosing. Also the left ventricular posterior and septal walls regressed better as well as left ventricular mass in the night-time group.

**Conclusion:** Though equally effective in reducing blood pressure and cardiac indices related to hypertension, patients taking their drugs at night recorded better values. This makes diuretics equally amenable to night-time chronotherapy as other drug classes. This effect should be explored to reduce the morbidity and mortality consequences of hypertension.

***Keywords:*** Africans, benefit, night-time therapy, thiazide diuretics

## Introduction

Hypertension is a major cardiovascular disease (CVD) risk factor [Svetkey *et al.* 2009] and the leading cause of global mortality in most World Health Organization (WHO) regions [WHO, 2002], including Africa. Africans in sub-Saharan Africa and in the Americas bear a greater brunt of hypertension. They are reported to have higher blood pressure (BP) levels [Gombet *et al.* 2007], present earlier [Ferdinand, 2008] and have more target organ effects [Salako *et al.* 2007].Pharmacological and nonpharmacological treatments of hypertension are central to curbing the adverse health statistics related to hypertension [Psaty *et al.* 1997]. This is irrespective of drug types used [Turnbull *et al.* 2003]. Recently emerging chronotherapeutic studies have demonstrated better BP control and a significant reduction in cardiovascular events with night-time dosing [Hermida and Smolensky, 2004]. This timing is known to attenuate morning pressure surge and returns day and night-time BPs to a normal circadian pattern resulting in better night-time cover when most cardiovascular and brain events occur [Elliot, 1998]. In a recent study we showed that native Africans also benefit from chronotherapeutic manipulations of antihypertensive drugs [Okeahialam *et al.* 2011]. Patients with hypertension of African descent are known to benefit more from thiazide diuretics unless contraindicated by comorbidities [Ferdinand and Ferdinand, 2008], and thiazide use as first-line drug in hypertension is recommended [Wright and Musiu, 2009]. Only one

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study with a diuretic has tried chronotherapeutic manipulations and confirmed better control with bedtime ingestion [Hermida *et al.* 2008]. Another study, combining hydrochlorothiazide with valsartan after valsartan monotherapy, proved unsuccessful and also confirmed better control with night-time dosing [Hermida *et al.* 2011]. The paucity of chronotherapeutic studies using diuretics was not surprising given that most of the studies have been done in the West where diuretics are considered only as add-on therapy or when certain complications develop. Given the unusual need and use of diuretics in the treatment of patients with hypertension of African descent, we decided to study chronotherapy with diuretics in this native African population. We documented any benefit which would go a long way in improving the devastating morbidity indices in this population in which hypertension starts earlier, runs a more aggressive course and damages target organs. This could then be extended to Africans in diaspora and contribute to improvement in control rates globally.

## Patients and methods

Between the last quarter of 2007 and the first quarter of 2008, we performed an interventional randomized controlled clinical trial involving 181 patients with grade 1 or 2 hypertension consecutively recruited from the Cardiology Unit medical outpatients' clinic of Jos University Teaching Hospital, Jos, Nigeria. Details of the enrolment and randomization into morning and night-time ingestion groups were published previously [Okeahialam *et al.* 2011]. Briefly, the following exclusion criteria were applied to consecutive patients with hypertension presenting over the study period: current smoking, chronic alcohol abuse, grade 3 hypertension, clinical or laboratory evidence of secondary hypertension, serum creatinine in excess of 200 μmol per liter, pregnancy and lactation. The resulting 181 patients who had grade 1 or 2 hypertension were divided into two groups by means of a table of random numbers (A, ingestion time 10.00 am; and B, ingestion time 10.00 pm) and received once-daily antihypertensive medication. As this was an African cohort, all patients started on diuretics (either amiloride 5 mg/hydrochlorothiazide combination or only hydrochlorothiazide 50 mg) unless contraindicated by an associated clinical condition when another single drug was given (calcium channel blocker, β adrenergic blocker or blocker of the renin–angiotensin system). Patients underwent a full physical examination on enrolment as well as electro- and echocardiography. The first and second postenrolment visits (at 2 and 6 weeks respectively) were devoted to a drug review if control had not been achieved, ensuring compliance and ascertaining if any complications had developed. On the third and last visit 12 weeks after initiation of treatment, all investigations performed at enrolment were repeated.

A secondary analysis was performed of data for patients in either group who needed only diuretics over the 12-week period for control. All patients had signed the written informed consent forms and the protocol was approved by the Research Ethics Committee of Jos University Teaching Hospital for the main study.

Data were analyzed with Microsoft Excel statistics software and the results expressed as means and standard deviations. The two-tailed Student's $t$ test was used to compare group means, while $\chi^2$ tests were used to determine the significance of associations when comparing categories or proportions, with statistical significance set at $p < 0.05$.

## Results

Of the 181 subjects who satisfied the inclusion criteria and were enrolled in the main study, 165 completed the trial, 81 in the morning dosing group and 84 in the night-time dosing group. Data for 35 patients in group A and 49 patients in group B who were controlled only with diuretics were extracted and analyzed. In group A there were 26 (74.3%) women and 9 (25.7%) men while in group B there were 33 (67.3%) women and 16 (32.7%) men. There was no statistically significant difference in proportion of men and women between the groups [$\chi^2 = 0.470$, degrees of freedom = 1, $p = 0.493$). The other indices of interest, measured on enrolment, were systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), interventricular septal thickness in diastole (IVSD), left ventricular posterior wall thickness in diastole (LVWD), E/A ratio (a measure of diastolic function), and left ventricular mass (LVM). These indices did not differ between groups as shown in Table 1. Any difference after 12 weeks of intervention could be largely ascribed to time of dosing effect.

**Table 1.** Anthropometric and echocardiographic indices in patients according to time of ingestion.

| | Group A | Group B | *p* |
|---|---|---|---|
| Age (years) | 47.11 (12.85) | 50.18 (13.4) | 0.297 |
| BMI (kg/$m_2$) | 28.29 (5.09) | 28.47 (4.69) | 0.864 |
| SBP1 (mmHg) | 148.97 (15.52) | 147.69 (14.00) | 0.695 |
| DBP1 (mmHg) | 94 (8.32) | 92.69 (9.27) | 0.509 |
| MAP1 (mmHg) | 112.9 (8.95) | 110.7 (8.66) | 0.273 |
| IVSD1 (mm) | 12.17 (3.43) | 12.59 (3.14) | 0.591 |
| LVPWD1 (mm) | 11.24 (2.23) | 10.98 (2.77) | 0.67 |
| E/A1 | 0.99 (0.29) | 1.05 (0.37) | 0.405 |
| LVM1 (g) | 197.6 (59.91) | 197.6 (65.78) | 0.996 |

All data are presented as mean (SD).
BMI, body mass index; DBP1, diastolic blood pressure at onset; E/A1, E to A ratio at onset; IVSD1, interventricular septal dimension at onset; LVM1, left ventricular mass at onset; LVPWD1, left ventricular wall dimension at onset; MAP1, mean arterial pressure at onset; SBP1, systolic blood pressure at onset.

**Table 2.** Differences in means of blood pressure and echocardiographic indices at onset (1) and end of study (2) according to ingestion time.

| | Group A | | Group B | |
|---|---|---|---|---|
| | *t* | *p* | *t* | *p* |
| SBP1 *versus* SBP2 | 4.756 | 0.000 | 9.458 | 0.000 |
| DBP1 *versus* DBP2 | 3.864 | 0.001 | 9.063 | 0.000 |
| MAP1 *versus* MAP2 | 4.905 | 0.000 | 10.26 | 0.000 |
| IVSD1 *versus* IVSD2 | 1.571 | 0.128 | 1.799 | 0.078 |
| LVPWD1 *versus* LVPWD2 | 1.248 | 0.222 | 3.113 | 0.003 |
| E/A1 *versus* E/A2 | –1.11 | 0.275 | –0.62 | 0.536 |
| LVM1 *versus* LVM2 | 0.596 | 0.556 | 2.381 | 0.021 |

DBP, diastolic blood pressure; E/A, E to A ratio; IVSD, interventricular septal dimension; LVM, left ventricular mass; LVPWD, left ventricular posterior wall dimension; MAP, mean arterial pressure; SBP, systolic blood pressure.

Mean values for all the above indices were compared for groups A and B on enrolment and after 12 weeks. SBP, DBP and MAP improved significantly in both groups. For LVWD and LVM, significant changes were recorded only for group B. For IVSD the improvement was better for group B than A but the difference did not attain statistical significance (see Table 2)

Morning dosing produced significant differences for SBP, DBP and MAP while night-time dosing produced significant differences for SBP, DBP, MAP, LVWD and LVM. Incidentally, when the changes from baseline in groups A and B were compared, the difference did not attain statistical significance (see Table 3). However, for MAP, the difference from baseline between the groups was evident but statistically significant levels were not attained. For a significant difference to emerge, a larger sample may be required. However, it may mean that although night-time dosing produced greater changes the difference is not sufficient to recommend it over morning dosing.

## Discussion

Clinical studies have documented morning–evening administration time differences of several different classes of blood-pressure-lowering drugs. The potential differential reduction of cardiovascular disease morbidity has been evaluated in the MAPEC study [Hermida *et al.* 2010]. Recently, our group demonstrated the same benefits in Nigerian Africans [Okeahialam *et al.* 2011]. In all of these studies, to the best of our knowledge, no study on Africans in the English medical

**Table 3.** Changes in blood pressure from baseline (onset to end) in different groups.

| Characteristic | Group A | Group B | p |
|---|---|---|---|
| SBP (mmHg) | 13.80 (15.89) | 18.81 (13.78) | 0.18 |
| DBP (mmHg) | 9.20 (13.04) | 14.33 (10.96) | 0.33 |
| MAP (mmHg) | 10.85 (12.12) | 14.80 (9.99) | 0.07 |
| IVSD (mm) | 0.62 (2.13) | 0.65 (2.49) | 0.97 |
| LVWD (mm) | 0.31 (2.26) | 0.84 (2.51) | 0.19 |
| E/A | −0.06(0.27) | −0.03 (0.35) | 0.76 |
| LVM (g) | 4.54 (41.02) | 21.41 (62.30) | 0.19 |

All data are presented as mean (SD).
DBP, diastolic blood pressure; E/A, E to A ratio; IVSD, interventricular septal dimension; LVM, left ventricular mass; LVWD, left ventricular posterior wall dimension; MAP, mean arterial pressure; SBP, systolic blood pressure.

literature used diuretics. Since black people are at significantly increased risk of hypertension and its sequelae [Sica, 2004], any potentially beneficial change in therapy would be of great positive impact.

This study has shown that African patients with hypertension treated with diuretics as monotherapy recorded an improvement in BP levels, LVWD, LVM and diastolic function. These effects are amplified by night-time chronotherapy. It is usual practice for healthcare givers to advise patients to use their antihypertensive drugs in the morning [Hermida *et al.* 2010]. However, with the outcome of chronotherapeutic studies in this area, there should be a change in this practice. Since most patients with hypertension require two or more drugs, at least one of them should be given in the evening. Our study showed that, even as monotherapy, night-time use of diuretics tended to result in improved reduction in BP and adverse left ventricular effects.

Related studies in other populations reported similar findings. One study that used ambulatory monitoring for 48 h before and 6 weeks after treatment recorded greater reduction in 24 h mean BP with night-time ingestion of torasemide, a high-ceiling diuretic [Hermida *et al.* 2008]. Again using hydrochlorothiazide as a combined pill with valsartan in patients whose condition was previously uncontrolled with valsartan monotherapy, 48 h mean ambulatory BP was similarly reduced but more so for the night-time ingestion group [Hermida *et al.* 2011]. This finding is consistent with our study results. As shown in Table 3, although the changes in indices for the night-time dosing group were greater than those for the morning dosing group, the differences did not attain statistical significance. However, our results also showed greater benefit of night-time ingestion on LVWD, MAP and diastolic function (Table 2).

Most physicians may be reluctant to give diuretics in the evening because of the consequent diuresis which may disturb sleep. As has been suggested, diuresis as the basis of BP reduction with diuretics is an acute phenomenon that occurs in the first 2 weeks of therapy. Subsequently, a vasodilatory effect is operational [Sica, 2008]. The findings of our study should encourage use of diuretics in the evening. However, we did not look at troublesome nocturnal diuresis and quality of sleep among the night-time group. This may have added to our findings. The reasons for better blood control with night-time chronotherapy are numerous. It normalizes an abnormal dipping pattern [Kario *et al.* 2000] and because nondipping is related to increased target organ damage [Brotman *et al.* 2008], correction of an abnormal pattern spares end organs like the left ventricle and the kidneys from damage. This was evident in the better BP and left ventricular anatomic and functional indices in the night-time group observed in our study. Circadian rhythms in gastric pH and emptying, gastric motility, biliary function and circulation to abdominal organs equally alter the pharmacokinetics of antihypertensives so that they are more effective given at night [Koopman *et al.* 1989]. In addition, the circadian pattern of the glomerular filtration rate that sees it highest during the day and lowest at night means that drugs ingested at night are retained in the system for longer to exert their antihypertensive effect [Morgan and Anderson, 2003].

Given the above findings and the fact that cardiac enlargement is determined more by the blood pressure during sleep, although only shown in rats so far [Morgan *et al.* 2000], our findings derive from logical sequence. In conclusion, night-time dosing of diuretics even for monotherapy provides better blood pressure lowering and amelioration of cardiovascular anatomical and functional consequences of hypertension. Whether for non-black or black patients (in whom its effects are greater) this chronothepeutic manipulation should become an option if not the preferred way to use diuretics to achieve better global morbidity and mortality statistics related to hypertension. The potential for troublesome night-time diuresis with poor quality sleep in some patients counter these benefits and should be borne in mind. For such patients, diuretics could still be used in the morning and any add-on drug given in the evening.

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## Conflict of interest statement

The authors declare that there are no conflicts of interest.

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