A RANDOMISED CROSS-OVER TRIAL OF THE IMPACT OF MORNING OR EVENING DOSING OF ANTIHYPERTENSIVE AGENTS ON 24 HOUR AMBULATORY BLOOD PRESSURE:

The HARMONY Trial

Short title: Impact of AM or PM dosing on 24-hour BP levels

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Abstract

Some data suggest that nocturnal dosing of antihypertensive agents may reduce cardiovascular outcomes more than daytime dosing. This trial was designed to evaluate whether ambulatory blood pressure monitoring levels differ by timing of drug dosing.

Patients aged 18-80 years with reasonably controlled hypertension ($\leq$150/$\leq$90 mmHg) on stable therapy of $\geq$1 antihypertensive agent were recruited from two centres in London and Thessaloniki. Patients were randomised to receive usual therapy either in the morning (6am – 11am) or evening (6pm – 11pm) for 12 weeks when participants crossed-over to the alternative timing for a further 12 weeks.

Clinic blood pressures and a 24-hour recording were taken at baseline, 12 and 24 weeks and routine blood tests were taken at baseline. The study had 80% power to detect 3mmHg difference in mean 24-hour systolic blood pressure (α=0.05) by time of dosing. A 2-level hierarchical regression model adjusted for centre, period and sequence was used.

Of 103 recruited patients (mean age 52: 44% female), 95 patients (92%) completed all three 24-hour recordings. Mean 24-hour systolic and diastolic blood pressures did not differ between daytime and evening dosing. Similarly, morning and evening dosing had no differential impact on mean daytime (7am – 10pm) and night-time (10pm – 7am) blood pressure levels nor on clinic levels.

Stratification by age ($\leq$65/$\geq$ 65 years) or gender did not affect results.

In summary, among hypertensive patients with reasonably well-controlled blood pressure, the timing of antihypertensive drug administration (morning or evening) did not affect mean 24-hour or clinic blood pressure levels.

Key words

Randomised, cross-over trial, antihypertensive therapy, dosing time, 24-hour blood pressure levels.

Introduction

Observational data show a strong linear relationship between clinic blood pressure levels and subsequent major adverse cardiovascular events[1]. However, ambulatory blood pressure monitoring has shown that night-time blood pressure levels are more strongly predictive of major adverse cardiovascular events than 24-hour or daytime levels[2,3]. Furthermore, night-to-day blood pressure ratio and dipping status are also significant independent predictors of cardiovascular outcomes[4]. These findings may have implications for optimal dosing times for antihypertensive medications.

In the MonitorizaciÓn Ambulatoria de la PresiÓn arterial y Eventos Cardiovasculares (MAPEC) Study[5], bedtime dosing of at least one blood pressure-lowering agent compared with only morning dosing was associated with better blood pressure control, reduced prevalence of non-dipping patterns and reduced morbidity and mortality from cardiovascular events. The results of the placebo-controlled HOPE trial in which the protocol specified that the antihypertensive agent (Ramipril) should be given at bedtime, showed that active therapy was associated with greater benefits in terms of cardiovascular outcome that would be expected from the small reduction in daytime clinic blood pressure observed[6].

The Treatment In the Morning versus Evening (TIME) Study[7] is designed to compare the impact on major cardiovascular outcomes of evening dosing of antihypertensive agents than morning dosing. In April 2017 after 25 months of recruitment, the TIME trial completed

randomisation of 21,113 patients who are currently being followed up for a mean period of 4 years. Meanwhile the Hellenic-Anglo Research into Morning or Night Antihypertensive Drug Delivery (HARMONY) trial was designed to evaluate any differential effects of morning versus evening dosing on mean 24-hour ambulatory blood pressure levels.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. [if author providing data is not the corresponding author, please provide contact information for that author].

This study was a two-centre (London and Thessaloniki), prospective randomised cross-over trial of hypertensive men and women who were aged 18-80 years. Eligibility was dependent on patients having hypertension diagnosed at least one year ago and being on stable antihypertensive medication (at least one agent with no change for at least three months) with reasonably controlled blood pressure levels (systolic $\leq$ 150 mmHg and $\geq$ 115 mmHg and diastolic $\leq$ 90 mmHg) and the patients' physician did not feel further antihypertensive therapy was necessary). Patients with atrial fibrillation and night shift workers were excluded. Eligible patients were randomised to receive their usual medications in the morning (6am to 11am) or in the evening (6pm – 11pm) for 12 weeks at which point they crossed over to evening and morning dosing respectively, for a further 12 weeks. Compliance was assessed at 12 and 24 weeks by self-reporting the number of tablets taken and at what time in the previous 2 weeks. Participants were advised to make no changes to their usual diets and lifestyles and other drug therapy, which were in place before entry to the trial, unless advised to do so by a physician.

Written informed consent was obtained from all participants and at baseline three sitting blood pressure recordings were taken in the clinic (mean of the last two were used for analyses) using standardised methods and machines[8,9]. In addition, a 24-hour ambulatory blood pressure recording was taken prior to baseline using the Spacelabs 90207 and 90217 machines in London and the TM-2430 (A&D Company Limited) or the BPOne 2.03a (H and C Medical Devices Spa) machines in Thessaloniki. Cuff sizes for ambulatory and clinic blood pressure recordings were adjusted according to current UK recommendations [10] and manufacturers instructions. Routine blood samples were taken and an ECG recorded during screening to ensure eligibility and at baseline, a quality of life (QoL) questionnaire (EQ-5D-5L)[11] was administered. At 12 weeks and at the end of the trial any changes in lifestyle, medical procedures, visits to a doctor and self-reported serious adverse events were recorded. In addition, at the same time points, the QoL questionnaire was completed and clinic blood pressures plus a 24-hour ambulatory blood pressure recording was taken and body weight measured.

The primary end point was change in 24-hour mean systolic blood pressure and secondary end points were changes in mean daytime and night-time systolic and diastolic pressures and mean sitting clinic systolic and diastolic pressures. Change in self-reported QoL was also pre-specified as a secondary endpoint.

Statistical Methods

The study was designed to include 100 patients (approximately 50 at each site) in order that it would have 80% power (2-sided) at the 5% α level, to detect a 3mmHg difference in mean 24-hour systolic blood pressure between those taking medication in the morning compared

with the evening. Assumptions included a drop-out rate of 10% and an estimated standard deviation (SD) in mean 24-hour systolic blood pressure of 10 mmHg.

Patient characteristics were summarised as means with SDs for continuous variables and frequencies and percentages for categorical variables and data on all patients completing both limbs of the trial were included in an intention to treat analyses.

A 2-level hierarchical regression adjusted for centre, carry over and period effect was used to compare the impact of drug dosing time on blood pressure.

Pre-specified subgroup analyses were carried out by centre (London and Thessaloniki) and also post-hoc sensitivity analyses were carried out stratifying by sex, age (<65 years/≥65 years), alternate daytime and night-time windows (9am to 9pm and midnight to 6am), and excluding non-white participants and extreme outliers in terms of differences in 24-hour systolic blood pressure (those which were greater than 20mmHg when medications were taken in the morning compared with the evening).

Results

Between July 2013 and January 2015, 103 eligible patients (mean age 62 years, 56% male) were randomised (53 in London, 50 in Thessaloniki) in the trial. At baseline, those randomised were taking a mean of 1.9 antihypertensive agents per day (range 1-4). All patients were receiving at least one agent which is recommended for once-daily dosing and 80% were receiving at least one agent which provides good 24-hour blood pressure control. Only eight patients were receiving an agent which should ideally be prescribed on a twice daily basis. One patient reported any significant lack of compliance prior to their 12-week assessment and 3 patients reported incorrect timing of drug dosing on more than 15% of days, one before

their 12 week visit and two at their 24 week visit. Baseline mean clinic blood pressure readings of participants showed good control (systolic 128.0 mmHg, SD=8.8; diastolic 76.4 mmHg, SD=6.1) with a mean body mass index of 29.1Kg/m², SD=5.2, fasting plasma glucose of 5.6 mmol/L, SD=0.9 and a non-HDL cholesterol of 3.5 mmol/L, SD=1.0 (Table 1). There were no important or significant differences in baseline variables between the two randomised groups (Table 1). Of those randomised, 95 (92%) completed all three 24-hour ambulatory blood pressure recordings.

Mean 24-hour ambulatory systolic blood pressure did not differ after taking tablets in the morning or evening compared with baseline (Table 2). Similarly, there were no significant differences between the two groups in mean 24-hour diastolic blood pressure, mean daytime or night-time systolic or diastolic blood pressure, nor in clinic systolic or diastolic blood pressure (Table 2).

There were no changes in QoL score recorded, body weight or heart rates between groups and no changes with baseline (data not shown).

Results were unaffected in sensitivity analyses when data were stratified by centre, age, sex and using restricted time windows for day and night-time blood pressures, and excluding one South Asian and one black patient or seven extreme outliners (>20 mmHg difference in mean 24-hour systolic blood pressure recorded after daytime compared with night-time dosing).

Discussion

Results of the HARMONY trial suggest that the dosing of routine antihypertensive medication in the morning or evening does not affect ambulatory blood pressure levels – whether 24-hour, daytime or night-time, nor clinic blood pressure levels. This is, as far as we are aware,

the only trial to have evaluated a comparison of the timing of all antihypertensive agents currently in use, on 24-hour ABPM levels and conflicts with results of the MAPEC study[5]. The MAPEC study included patients whose blood pressures were uncontrolled whilst receiving three antihypertensive agents taken in the morning. They were randomised to continue to receive all three drugs in the morning or to take one of the agents in the evening and two in the morning. After three months, the latter regimen produced significantly lower 24-hour mean systolic and diastolic pressures, and reduced major cardiovascular events.

The large beneficial effects on cardiovascular outcomes observed in the HOPE[6] and SYST-EUR[12] trials have been considered by some to be attributable to the nocturnal dosing used preferentially in these trials but no randomised evaluation of day versus night dosing was incorporated into these trials. In a trial of 41 patients with obstructive sleep apnoea and newly diagnosed hypertension, patients received one or two agents as a morning dose for eight weeks, followed by the same treatment as an evening dose, for a further eight weeks[13]. The second eight-week period was associated with significantly lower clinic and 24-hour blood pressures but the non-randomised design precludes the definitive conclusion that the benefits accrued from the dosing time, rather than an order effect.

There were only two non-Caucasian patients (one black and one South Asian) among the HARMONY participants and particularly in view of the known lower rates of nocturnal dipping among black patients[14], the results of this trial may not be generalisable to ethnic groups other than Caucasian.

This trial was relatively small, with 80% power to detect a 3mmHg difference in 24-hour systolic blood pressure between morning and evening dosing. Furthermore, it is possible that if the 1.62 mmHg lower night-time systolic blood pressure associated with evening dosing

(Table 2) reflects a real difference, this could translate into lower rates of cardiovascular outcomes, as suggested by epidemiological observations[2,3]. However, all analyses with or without adjustment and among subgroups were consistent in suggesting limited, if any, differences in blood pressures related to dosing time.

This apparently neutral effect could reflect the small average number of agents being used (<2) by the HARMONY patients and their good blood pressure control at baseline. Furthermore, since participants were recruited from two specialist hypertension centres, the drugs routinely prescribed were, in keeping with currently recommended best practice[8,9,15], very largely long-acting agents providing good 24-hour control. This in turn might minimise any 24-hour blood pressure difference based on dosing times. By contrast, in settings in which agents with shorter durations of action are more commonly used, dosing times may more likely affect 24-hour blood pressure control (assuming differential effects of such agents when given at day or night time).

It remains to be seen whether these possible limitations of the HARMONY trial will be reflected in the results of the TIME trial [7] in which large numbers of patients recruited from more population-based settings throughout the UK have been randomised.

Meanwhile, it seems reasonable to conclude that the timing of dosing of antihypertensive medications should be primarily based on whichever time suits the patient best whilst using as simple a regimen as possible, and long acting agents.

Perspectives

The results of the HARMONY trial suggest that the impact of antihypertensive medications on 24-hour ambulatory blood pressure levels is unaffected by whether medications are taken in

the morning or evening. In light of the trial inclusion criteria and demography of participants these findings maybe only applicable to white Caucasian patients with reasonably well controlled blood pressure levels.

These results may be in-part dependant on the predominant use of long-acting formulations of agents. Nevertheless, these findings appear reasonably robust given the trial had 80% power to detect a 3mmHg difference in 24-hour systolic blood pressure between randomised groups, high rates of adherence (albeit self-reported) and 92% of participants completing all three 24-hour blood pressure recordings. Furthermore, the lack of impact of morning versus evening dosing was consistent across all types of blood pressure measurements and in all sensitivity analyses.

By contrast, extensive epidemiological data suggest that night-time blood pressure levels predict cardiovascular outcomes better than daytime or 24-hour levels and therefore a link between night-time drug dosing levels and preferential cardiovascular outcomes has been made. The results of the large TIME trial which is evaluating the impact of daytime versus night-time dosing on major cardiovascular events are required to see definitively whether night-time dosing does impart important benefits. Meanwhile there is no reason to expect specific drug timing to improve blood pressure control, except presumably if the timing adversely affects drug compliance at the individual level.

Therefore, pending further evidence patients should be advised to take their antihypertensive medications when it best suits them.

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Conflicts of Interest/Disclosures

All authors report no conflicts of interests or disclosures in relationship to this publication.

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Novelty and significance

1. What is new? This is the first randomised trial to evaluate and to show that taking usual blood pressure-lowering medications either all in the evening or in the morning did not impact on 24-hour ambulatory blood pressure levels or clinic blood pressure levels.
2. What is relevant? Epidemiological data suggest that nocturnal blood pressure levels predict adverse cardiovascular outcomes better than daytime levels and hence the possible preferential use of night-time drug dosing has been suggested.
3. Summary. Pending further definitive evidence (particularly the results of the TIME trial) patients should take their antihypertensive medications at a time which optimises adherence.

Table 1 Baseline characteristics by order of dosing schedule

Variable*	Evening / Morning	Morning / Evening	Total
Number (N)	52	51	103
Age	62.8 (9.7)	61.8 (11.0)	61.8 (10.3)
Female, N (%)	21 (40)	24 (47)	45 (44)
BMI	29.1 (5.6)	29.1 (4.7)	29.1 (5.2)
Heart rate	72.8 (10.3)	72.7 (9.6)	72.7 (9.9)
Systolic BP	127.1 (8.7)	129.0 (8.8)	128.0 (8.8)
Diastolic BP	76.6 (6.1)	76.3 (6.2)	76.4 (6.1)
Current smoker, N (%)	4 (8)	8 (8)	12 (12)
Alcohol units per week	16.7 (17.2)	11.8 (11.9)	14.6 (15.2)
Fasting plasma glucose	5.6 (0.9)	5.5 (1.0)	5.6 (0.9)
Non-HDL cholesterol	3.4 (1.0)	3.5 (1.0)	3.5 (1.0)

*Mean (Standard Denation) except where specified

Table 2 Blood pressure levels (mmHg) by timing of dosing schedules

Outcome mmHg (N=95)	Baseline	Drug taken		Observed difference (Evening - Morning)	*Adjusted difference (95%CI)
		Morning	Evening		
24h Systolic BP	128.64	129.65	129.75	**0.10**	**0.11 (-3.20, 3.42)**
24h Diastolic BP	76.92	77.24	77.99	**0.75**	**0.77 (-1.38, 2.91)**
Daytime SBP	131.16	132.24	132.77	**0.53**	**0.54 (-2.82, 3.89)**
Daytime DBP	79.14	79.27	80.55	**1.28**	**1.30 (-0.96, 3.56)**
Night-time SBP	120.89	122.76	121.08	**-1.68**	**-1.62 (-5.38, 2.15)**
Night-time DBP	69.83	70.92	70.57	**-0.35**	**-0.32 (2.81, 2.17)**
Clinic SBP	128.07	129.37	129.81	**0.44**	**0.39 (-2.91, 3.69)**
Clinic DBP	76.54	77.26	77.41	**0.15**	**0.14 (-2.03, 2.32)**
QoL Score	82.8	84.14	84.04	**-0.10**	**-0.12 (-3.12, 2.89)**

*Site, period (visit) and sequence (group)