Administration Time–Dependent Effects of Aspirin on Blood Pressure in Untreated Hypertensive Patients

Ramón C. Hermida, Diana E. Ayala, Carlos Calvo, José E. López, José R. Fernández, Artemio Mojón, María J. Domínguez, Manuel Covelo

Abstract—Previous studies on the potential influence of aspirin on blood pressure have not taken into consideration the chronopharmacological effects of nonsteroidal anti-inflammatory drugs. This pilot study investigates the effects of aspirin on blood pressure in untreated hypertensive patients who received aspirin at different times of the day according to their rest-activity cycle. We studied 100 untreated patients with mild hypertension (34 men and 66 women), 42.5±11.6 (mean±SD) years of age, randomly divided into 3 groups: nonpharmacological hygienic-dietary recommendations; the same recommendations and aspirin (100 mg/d) on awakening; or the same recommendations and aspirin before bedtime. Blood pressure was measured every 20 minutes during the day and every 30 minutes at night for 48 consecutive hours before and after 3 months of intervention. The circadian pattern of blood pressure in each group was established by population multiple-component analysis. After 3 months of nonpharmacological intervention, there was a small, nonsignificant reduction of blood pressure (<1.1 mm Hg; P>0.341). There was no change in blood pressure when aspirin was given on awakening (P=0.229). A highly significant blood pressure reduction was, however, observed in the patients who received aspirin before bedtime (decrease of 6 and 4 mm Hg in systolic and diastolic blood pressure, respectively; P<0.001). Results indicate a statistically significant administration time–dependent effect of low-dose aspirin on blood pressure in untreated patients with mild hypertension. The influence of aspirin on blood pressure demonstrated in this study indicates the need to quantify and control for aspirin effects in patients using this drug in combination with antihypertensive medication. (Hypertension. 2003;41:***-***.)

Key Words: antihypertensive agents • blood pressure monitoring, ambulatory • heart rate • hypertension, mild • drug therapy • circadian rhythm

There is an extensive literature on the effects of acetylsalicylic acid (ASA, or aspirin), one of the most commonly consumed nonsteroidal anti-inflammatory drugs (NSAID), mainly in the prevention of cardiovascular events.1–3 Although some of these studies reported average values of office blood pressure (BP) measurements for the patients before and after long-term administration of ASA or placebo, the study of a possible effect from ASA on BP was not a primary objective. In fact, the effect of ASA on BP was evaluated only in a few small studies.4–6 It has been reported that NSAID may increase BP both in normotensive and hypertensive subjects.4,7–9 The effects appear more marked in hypertensive subjects under treatment.4,7,10 The mechanisms whereby NSAID may increase BP are not fully understood, nor it is known whether the increase in BP is a long-term effect. In any event, the dose of ASA regularly used to show anti-inflammatory effects is markedly larger than the dose used as anticoagulant10 and recommended for prevention of cardiovascular events.1–3

ASA use in hypertensive patients is expected to increase after the publication of the results from the Hypertension Optimal Treatment (HOT) study, which documented the efficacy of low-dose ASA in preventing major cardiovascular events in hypertensive subjects.11 Recent studies have shown no influence of low-dose ASA on BP in hypertensive patients under pharmacological therapy,12–13 yet little if any attention has been paid thus far in clinical trials to potential circadian rhythm dependencies in effects.

Previous results suggest that effects of ASA on lipoperoxides, β-adrenergic receptors, and BP in clinically healthy subjects depend on the circadian timing of ASA administration.14 Moreover, the inhibition of collagen-induced platelet aggregation produced by ASA is circadian time–dependent.15 Another factor to be taken into consideration is the pharmacokinetic observation that ASA has a faster rate of clearance when administered during the morning as compared with the evening.16 These results complement time-dependent changes that have been described when the pharmacokinetics of NSAID were investigated in humans.17,18

Along these lines, an effect of ASA on BP dependent both on the dose as well as on the time of administration has been
documented in clinically healthy volunteers as well as in a small group of patients with untreated mild hypertension. In both groups, results indicated a small but statistically significant BP reduction when ASA (100 mg/d for 1 week) was administered in the evening and, to a larger extent, at bedtime, such effects could not be demonstrated when the same dose of ASA was administered on awakening. A higher dose of ASA (500 mg/d), however, showed a pressor effect, even when administered before bedtime, although results are somehow limited by the lack of follow-up of the volunteers beyond 1 week. Finally, results from a double-blind, randomized, placebo-controlled trial on the influence of low-dose ASA (100 mg/d from 12 to 16 weeks of gestation until delivery) on BP in pregnant women at high risk for pre-eclampsia also showed a highly significant administration time–dependent effect on BP by ASA. In keeping with these chronopharmacological effects and the previous findings suggesting that ASA at low doses may have a potential beneficial effect on BP, the current study investigated the influence of ASA on BP in previously untreated hypertensive patients who received low-dose ASA at different times of the day according to their rest-activity cycle and who were evaluated by 48-hour ambulatory BP monitoring (ABPM) before and after 3 months of pharmacological intervention.

Methods

Subjects

We studied 100 untreated volunteers (34 men and 66 women), 42.5±11.6 years of age (range, 23 to 79), with diagnosis of mild (grade 1) essential hypertension, according to the recent World Health Organization–International Society of Hypertension classification, based on conventional BP measurements and corroborated by the results of an ABPM profile at the time of recruitment. All patients received medical care at the Hypertension and Vascular Risk Unit, Hospital Clínico Universitario, Santiago de Compostela, Spain. Shift workers and patients with either moderate or severe arterial hypertension, according to the definitions provided by the VI Joint National Committee and the World Health Organization–International Society of Hypertension, secondary arterial hypertension, cardiovascular disorders other than essential hypertension, obstructive sleep apnea, or contraindications to the use of ASA were excluded from this trial. In all cases, a complete clinical evaluation was performed following the standardized protocol at the unit, including blood sampling and 24-hour urine collection. Blood samples were obtained from an antecubital vein in the early morning hours (8:00 AM to 9:00 AM) after nocturnal fasting, on the same day before starting ABPM, both before and after 3 months of intervention (see below).

Patients were randomly assigned to 1 of 3 possible groups, keeping a priori a proportion of 2:1:1 among groups to increase power for comparisons between treated and untreated patients: group 1, nonpharmacological hygienic-dietary recommendations (HDR) according to the recent guidelines for the management of mild hypertension; group 2, the same HDR and ASA (100 mg/d) on awakening; and group 3, the same HDR and ASA (100 mg/d) before bedtime. The dose of 100 mg used in this trial corresponds with the actual lower dose commercially available in Spain within the accepted range of low dosing (75 to 150 mg). Compliance was measured on the basis of tablet count and a personal interview with each volunteer. HDR included sodium restriction, information on the Dietary Approach to Stop Hypertension Diet, limit alcohol intake, and regular aerobic exercise. Results from blood and urine sampling were further used to evaluate adherence with HDR. The demographic characteristics of the patients participating in this trial are included in the Table.

All issues related to ABPM, including handling and preparation of the monitors, individualized explanation about their use to each patient, and processing of the data provided by any patient after monitoring, were always carried out by the same member of the research group in one room of the unit. Conventional clinical examinations, usually done on the same day just after finishing ABPM, were carried out by other members of the research group in different rooms of the unit. Conventional office BP measurements (6 at each study visit after 48 consecutive hours with a validated 5 minutes, on the same day just before starting ABPM) were always obtained by the same investigator to avoid observer’s bias. Assignment of volunteers to each of the 3 groups was done by one member of the research team, according to the order of recruitment, by following an allocation table constructed with the use of a computerized random-number generator. The assignment of patients to each intervention group was always blinded to the investigator obtaining the BP measurements as well as to those who performed the statistical analysis of the data. The minimum sample size for this trial (22 patients for each treatment group) was calculated to show as significant at the 95% level with a power of 95% changes in the 24-hour mean of BP >5 mm Hg, according to the estimation of interindividual variability provided by previous studies. The center Ethics Committee of Clinical Research approved the study. All patients provided informed consent before entering the study.

BP Assessment

The systolic BP (SBP), mean arterial BP (MAP), diastolic BP (DBP), and heart rate (HR) of each patient were automatically measured every 20 minutes during the day (7:00 AM to 11:00 PM) and every 30 minutes during the night for 48 consecutive hours with a validated SpaceLab 92027 (SpaceLabs Inc) device before and after 3 months of intervention with either ASA or HDR alone. To keep a possible “white-coat” effect to a minimum, only the first BP measurement was performed at the medical setting to validate the proper functioning of the ABPM device and to check accuracy by comparison of BP readings with those obtained conventionally. Patients were assessed while adhering to their usual diurnal activity (8:00 AM to 11:00 PM for most)–nocturnal sleep routine. They were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 days of ABPM. No person was hospitalized during monitoring. BP series were eliminated from analysis when they did not contain at least 70% of valid measurements and when the subjects showed an irregular rest-activity schedule during the 2 days of sampling, an odd sampling with spans of >3 hours without BP measurement or a night resting span >6 hours or >12 hours. Apart from the 100 patients provided all required information, 4 subjects were eliminated from the trial because of invalid ABPM measurements.

Actigraphy

Actigraphic evaluation of this oscillometric monitor according to the standards published by the Association for Advancement of Medical Instrumentation and the British Hypertension Society has been previously established. The BP cuff was worn on the nondominant arm, with cuff size determined by upper arm circumference at each study visit. The monitor was always set to the so-called “blind function.” Accordingly, the display never shows the actual BP readings after measurement, keeping the information blind to the patient. To ensure accuracy of BP measurement for the whole 48 hours, we used nickel metal hydride rechargeable batteries. Since they have no memory effect, the batteries always can be recharged to their maximum capacity. The SpaceLab 92027 can run up to 21 consecutive days with these batteries. ABPM always began between 10:00 AM and noon. During monitoring, each subject maintained a diary listing the times they went to bed at night, woke in the morning, ate meals; exercise and unusual physical activity; and events and mood/emotional states that might affect BP.

Actigraphy

The patients wore a MiniMotionLogger actigraph (Ambulatory Monitoring Inc) on the dominant wrist to monitor physical activity every minute at the time of ABPM. This compact device (about half the size of a wristwatch) functions as an accelerometer. The clock
Demographic and Analytical Characteristics of Subjects Investigated

<table>
<thead>
<tr>
<th>Variable</th>
<th>HDR</th>
<th>ASA-1</th>
<th>ASA-2</th>
<th>P for Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>50</td>
<td>24</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>43.7±12.4</td>
<td>40.0±6.3</td>
<td>45.2±12.7</td>
<td>0.172</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.1±10.1</td>
<td>164.1±10.9</td>
<td>160.2±11.6</td>
<td>0.394</td>
</tr>
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</table>

Before intervention

<table>
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<tr>
<th>Weight, kg</th>
<th>74.2±14.7</th>
<th>76.1±14.9</th>
<th>74.4±14.2</th>
<th>0.866</th>
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</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>27.9±5.1</td>
<td>28.2±4.9</td>
<td>28.9±5.2</td>
<td>0.677</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>88.8±12.4</td>
<td>91.0±13.5</td>
<td>91.3±11.9</td>
<td>0.630</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>104.4±9.1</td>
<td>105.6±9.9</td>
<td>105.8±10.4</td>
<td>0.788</td>
</tr>
<tr>
<td>SBP, mm Hg*</td>
<td>143.1±14.0</td>
<td>144.2±11.9</td>
<td>146.6±10.1</td>
<td>0.442</td>
</tr>
<tr>
<td>DBP, mm Hg*</td>
<td>84.2±8.5</td>
<td>86.0±8.0</td>
<td>85.5±6.3</td>
<td>0.388</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.1±1.3</td>
<td>14.4±1.5</td>
<td>14.3±1.2</td>
<td>0.909</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>93.6±10.7</td>
<td>100.6±28.8</td>
<td>99.3±13.6</td>
<td>0.268</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.86±0.13</td>
<td>0.82±0.10</td>
<td>0.85±0.14</td>
<td>0.448</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>217.6±47.3</td>
<td>202.6±44.8</td>
<td>224.91±46.3</td>
<td>0.289</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>114.2±80.9</td>
<td>98.15±57.8</td>
<td>103.0±52.8</td>
<td>0.659</td>
</tr>
<tr>
<td>Sodium (serum), mmol/L</td>
<td>139.6±0.2</td>
<td>139.9±0.4</td>
<td>139.7±0.4</td>
<td>0.233</td>
</tr>
<tr>
<td>Potassium (serum), mmol/L</td>
<td>4.41±0.03</td>
<td>4.40±0.06</td>
<td>4.39±0.07</td>
<td>0.757</td>
</tr>
<tr>
<td>Sodium (urine), mEq/L</td>
<td>106.7±5.8</td>
<td>119.7±20.4</td>
<td>98.3±18.7</td>
<td>0.265</td>
</tr>
<tr>
<td>Potassium (urine), mEq/L</td>
<td>55.2±3.4</td>
<td>60.3±7.4</td>
<td>48.1±8.6</td>
<td>0.252</td>
</tr>
</tbody>
</table>

After intervention (P value from comparison with values before intervention)

<table>
<thead>
<tr>
<th>Weight, kg</th>
<th>73.6±14.4 (0.283)</th>
<th>76.0±15.2 (0.679)</th>
<th>74.4±14.5 (0.962)</th>
<th>0.801</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>27.6±4.8 (0.181)</td>
<td>28.2±5.0 (0.672)</td>
<td>29.0±5.7 (0.863)</td>
<td>0.534</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>87.0±13.2 (0.104)</td>
<td>91.0±14.2 (0.964)</td>
<td>91.9±12.0 (0.481)</td>
<td>0.232</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>103.8±8.0 (0.308)</td>
<td>106.0±10.3 (0.613)</td>
<td>105.4±10.4 (0.514)</td>
<td>0.585</td>
</tr>
<tr>
<td>SBP, mm Hg*</td>
<td>141.4±12.6 (0.143)</td>
<td>142.3±10.8 (0.357)</td>
<td>141.7±11.7 (0.008)</td>
<td>0.620</td>
</tr>
<tr>
<td>DBP, mm Hg*</td>
<td>81.9±8.0 (0.125)</td>
<td>83.8±6.6 (0.144)</td>
<td>82.0±6.9 (0.007)</td>
<td>0.583</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.1±1.3 (0.872)</td>
<td>14.2±1.7 (0.229)</td>
<td>14.0±1.1 (0.447)</td>
<td>0.582</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>93.5±9.0 (0.296)</td>
<td>100.7±27.3 (0.423)</td>
<td>102.7±13.6 (0.684)</td>
<td>0.247</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.87±0.13 (0.494)</td>
<td>0.85±0.11 (0.321)</td>
<td>0.87±0.16 (0.833)</td>
<td>0.852</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>214.5±40.0 (0.508)</td>
<td>198.3±36.0 (0.382)</td>
<td>197.3±29.0 (0.027)</td>
<td>0.179</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>112.8±69.5 (0.724)</td>
<td>97.1±57.9 (0.377)</td>
<td>100.0±66.0 (0.881)</td>
<td>0.654</td>
</tr>
<tr>
<td>Sodium (serum), mmol/L</td>
<td>139.2±0.3 (0.339)</td>
<td>139.3±0.5 (0.282)</td>
<td>139.4±0.4 (0.501)</td>
<td>0.237</td>
</tr>
<tr>
<td>Potassium (serum), mmol/L</td>
<td>4.39±0.03 (0.573)</td>
<td>4.35±0.07 (0.268)</td>
<td>4.36±0.05 (0.629)</td>
<td>0.435</td>
</tr>
<tr>
<td>Sodium (urine), mEq/L</td>
<td>90.5±8.4 (0.104)</td>
<td>106.0±26.8 (0.740)</td>
<td>89.5±21.2 (0.632)</td>
<td>0.622</td>
</tr>
<tr>
<td>Potassium (urine), mEq/L</td>
<td>51.3±3.4 (0.319)</td>
<td>54.0±8.2 (0.220)</td>
<td>44.8±7.3 (0.187)</td>
<td>0.472</td>
</tr>
</tbody>
</table>

All values are mean±SD. HDR indicates hygienic-dietary recommendations; ASA-1, aspirin (100 mg/day) on awakening; ASA-2, aspirin (100 mg/day) before bedtime.

Values provided correspond to the average of 6 conventional BP measurements obtained for each patient before starting ABPM.

Statistical Methods

Each individual’s clock hour BP and HR values were first referred from clock time to hours after awakening from nocturnal sleep, according to the information obtained from wrist actigraphy. This transformation avoided the introduction of bias caused by differences among subjects in their sleep/activity routine.27 BP and HR time series were then edited according to conventional criteria to remove measurement errors and outliers.28 The circadian rhythm of BP and HR before and after 3 months of intervention was objectively assessed by population multiple-component analysis,29 a method applicable to nonsinusoidal-shaped hybrid time series data (time series of data collected from a group of subjects) consisting of values distributed at equal or unequal intervals. Circadian parameters obtained for each group of patients before and after intervention were compared with a paired parametric test developed to assess differences in parameters derived from population multiple-components analysis.29 Additionally, the demographic and clinical characteristics in the Table were compared among groups by ANOVA and before and after 3 months of intervention within each group by paired t test.
Results

Demographic Characteristics and Serum Parameters

The baseline characteristics of the 3 groups of previously untreated hypertensive patients investigated in this trial were similar in age, height, weight, body mass index (BMI), and waist and hip perimeters, as well as in the average of 6 conventional measurements of SBP and DBP obtained on the same morning just before starting ABPM (Table). Results further indicated the lack of statistically significant changes after 3 months of intervention in weight, BMI, or waist and hip perimeters in any of the 3 groups of hypertensive patients. Conventional BP measurements were unchanged after 3 months of intervention with either HDR alone or in combination with ASA given on awakening. There was, however, a statistically significant reduction of 4.9 and 3.5 mm Hg in office values of SBP and DBP, respectively, after 3 months of ASA given before bedtime ($P=0.008$ and $0.007$ for SBP and DBP, respectively). Serum values of glucose, cholesterol, and triglycerides remained unchanged after HDR or ASA on awakening. Cholesterol was slightly reduced after ASA before bedtime, although the difference would not be statistically significant if corrected for multiple testing. Only 38% of the patients in this group showed a reduction in cholesterol after intervention. Moreover, the average values of cholesterol at baseline and after intervention were not different among groups of patients. The use of the low-dose of 100 mg/d of ASA did not modify the baseline values of hemoglobin at any time of administration here tested (Table). Sodium and potassium (both serum and 24-hour urine samples) were not significantly modified in any group, although they show a slight tendency to decrease after 3 months of intervention.

Hygienic-Dietary Recommendations

The circadian rhythm of SBP, MAP, DBP, and HR, in untreated mild hypertensive patients measured by 48-hour ABPM before and after 3 months of nonpharmacological HDR, is depicted in Figure 1. Hours of nocturnal rest (average across all patients) are indicated by the dark bar on the lower horizontal axis of each graph. Results indicate a small and not statistically significant reduction in BP and HR after 3 months of nonpharmacological intervention. Most of the apparent reduction in BP was found in the few hours of daily activity soon after starting ABPM. This difference could thus just be explained by the significant pressor effect that characterizes mostly the first but in a much lower degree successive profiles of ABPM in hypertensive patients (the recently described “ABPM effect”$^{30,31}$).

ASA on Awakening

There was no statistically significantly change in the 24-hour, daily, or nocturnal means of BP and HR after 3 months of 100 mg/d of ASA given on awakening (Figure 2). The small increase in BP, mainly during nocturnal resting hours, was very small and not statistically significant ($P>0.279$).

ASA Before Bedtime

Figure 3 shows the BP changes after 3 months of ASA given before bedtime. The administration of low-dose ASA at this circadian time resulted in a significant reduction of 6.2 and 4.1 mm Hg in the 24-hour mean of SBP and DBP, respectively ($P<0.001$). A reduction in BP was observed in 85% of the patients in this group. Despite the significant effect on BP, HR remained unchanged after 3 months of intervention (Figure 3). BP reduction was slightly higher during daytime activity as compared with nocturnal resting hours. The BP reduction, however, was statistically significant for both the diurnal as well as for the nocturnal means of BP ($P<0.01$ in all cases).

Comparison Among Groups

The comparison of results provided in Figures 1 through 3 indicates the lack of statistically significant differences in BP at baseline among the 3 intervention groups ($P=0.393$ for comparison of 24-hour mean of SBP among groups; $P=0.283$ for DBP). The 24-hour mean of HR was also equivalent at baseline among groups ($P=0.335$). After intervention, results indicate a highly significant reduction in the 24-hour mean of BP after ASA given before bedtime in comparison to the other 2 groups ($P<0.001$ for SBP; $P=0.002$ for DBP). Figure 4 provides further information on the comparison among groups of the changes in diurnal, nocturnal, and 24-hour mean BP values after 3 months of intervention. Results, as a complement to those shown in Figures 1 through 3, indicate highly significant differences when comparing the BP changes among the 3 groups of patients.

Discussion

The major result of this study is that ASA selectively decreases BP as a function of the timing of its administration in relation to the rest-activity cycle of each individual subject. The administration time-dependent effects of ASA on BP shown in Figure 3 are fully in agreement with conclusions found earlier in clinically healthy normotensive subjects using the same low dose of ASA but for the much shorter time of 1 week.$^6$ Similar conclusions regarding the time-dependent influence of ASA on BP was also corroborated in pregnant women who used 100 mg/d of ASA for most of the duration of their pregnancy.$^{19–21}$ In the current study, low-dose ASA given before bedtime not only significantly reduced the mean BP from ABPM but also the average of conventional BP measurements. Further results from the Table indicate the poor compliance of HDR among all 3 groups of patients, inasmuch as there was no significant change in weight, waist and hip perimeters, serum glucose, cholesterol, or triglycerides after 3 months of intervention. Although there was a tendency to lower values of sodium in urine after intervention, the change was not statistically significant. Hemoglobin levels also remained unchanged after ASA administration.

The mechanism(s) involved in the responsiveness of BP to ASA administered at different times according to the rest-activity cycle is still unknown and awaits further investigation. The hypothesis that a time-dependent effect of ASA on thromboxane production could also be at least partly responsible for the time-dependent effects of ASA on BP gains some relevancy given the lack of any effect of ASA on HR (Figure 3). Taking into account the administration time-dependent BP lowering by ASA, relevant studies have also
shown statistically significant circadian rhythms in thromboxane and prostacyclin production, circulating platelets, platelet aggregation, clotting and fibrinolytic inhibitors, and in the inhibition of platelet aggregation produced by ASA. On the other hand, ASA has also been shown not only to restore vascular refractoriness to angiotensin II but also to produce a dose-dependent BP reduction and >30% inhibition of angiotensin II. Along these lines, previous results have demonstrated a predictable circadian variation in plasma renin activity, angiotensin II, catechol-
amines, atrial natriuretic peptides, aldosterone, and angiotensin-converting enzyme. These results may be relevant inasmuch as ASA given at the end of the activity cycle could thus target the nocturnal peak of plasma renin activity while enhancing the nocturnal through in the production of nitric oxide, hypotheses that deserve further investigation.

From the clinical point of view, the effects of ASA on BP demonstrated in this study indicate the need to identify...
patients using both ASA and antihypertensive medication, as well as the time of ingestion of ASA, due to the possible confounding effects of ASA on BP that could result from its use in conjunction with other drugs. Whether or not ASA enhances the effects of antihypertensive medication or if such a possible influence is circadian time–dependent are further issues of clinical interest that should be addressed in future research.

Figure 3. Changes in circadian pattern of BP and HR after aspirin (100 mg/d) administered before bedtime in patients with mild hypertension sampled by 48-hour ambulatory monitoring. Each graph shows 2-hourly means and standard errors of data collected before (continuous line) and after (dashed line) 3 months of aspirin administration. Nonsinusoidal-shaped curves correspond to the best-fitted waveform model determined by population–multiple component analysis. Arrows descending from upper horizontal axis point to circadian orthophase (rhythm crest time).
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morning administration.47

ASA would be generally associated to lower potential risks as

effects among the 3 groups of patients by ANOVA.

tory monitoring. Probability values are shown for comparison of

in patients with mild hypertension sampled by 48-hour ambula-
ted before bedtime (ASA-2), or after nonpharmacological HDR

SBP (top) and DBP (bottom) after aspirin (100 mg/d) adminis-
tion time-dependent influence of low-dose ASA on BP.

Figure 4. Changes in diurnal, nocturnal, and 24-hour mean of

SBP (top) and DBP (bottom) after aspirin (100 mg/d) adminis-
tered after awakening (ASA-1), after aspirin (100 mg/d) adminis-
tered before bedtime (ASA-2), or after nonpharmacological HDR

patients with mild hypertension sampled by 48-hour ambula-
tory monitoring. Probability values are shown for comparison of

effects among the 3 groups of patients by ANOVA.

Apart from these limitations, one could also discuss the

ten potential risks of ASA administered at different times of the
day. Compliance is not different between morning and night
dose because those two times are mainly equally remembered
by the patient, as previously demonstrated.6,19,20 With respect
to tolerability and potential side effects, a previous endo-
scopic trial on volunteers who took high-dose ASA (1300
mg) at different times on separate study days have shown that
even the evening dose, in comparison to the morning, produced
37% fewer gastric hemorrhagic lesions.46 Although low-dose
ASA would be generally associated to lower potential risks as
compared with higher doses, a conclusion has been made that
nighttime administration of ASA is better tolerated than
morning administration.37

Perspectives

The results from this trial in untreated patients with mild
hypertension corroborate earlier findings on the administr-
tion time-dependent influence of low-dose ASA on BP. Results
indicate that the timed administration of low-dose ASA with respect to the rest-activity cycle of each individual
patient could provide a valuable approach not just for the
secondary prevention of cardiovascular disease but also in
the added BP control of patients with mild essential hypertension
and poor compliance with hygienic and/or dietary
recommendations.

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