Administration Time–Dependent Influence of Aspirin on Blood Pressure in Pregnant Women

Ramón C. Hermida, Diana E. Ayala, Manuel Iglesias

Abstract—This study prospectively investigates the potential influence of low-dose aspirin on blood pressure in pregnant women who were at a higher risk of developing preeclampsia than that of the general obstetric population and who received aspirin at different times of the day according to their rest-activity cycle. A double-blind, randomized, controlled trial was conducted in 341 pregnant women (181 primipara) randomly assigned to 1 of 6 possible groups according to treatment (either placebo or aspirin, 100 mg/day, starting at 12 to 16 weeks of gestation) and the time of treatment: on awakening (time 1), 8 hours after awakening (time 2), or before bedtime (time 3). Blood pressure was automatically monitored for 48 consecutive hours every 4 weeks from the day of recruitment until delivery, as well as at puerperium. There was no effect of aspirin on blood pressure at time 1 (compared with placebo). A blood pressure reduction was highly statistically significant when aspirin was given at time 2 and, to a greater extent, at time 3 (mean reductions of 9.7/6.5 mm Hg in 24-hour mean for systolic/diastolic blood pressure at the time of delivery as compared with placebo given at bedtime). Differences in blood pressure among women receiving aspirin at different circadian times disappeared at puerperium ($P>0.096$). Results indicate a highly significant effect of aspirin on blood pressure that is markedly dependent on the time of aspirin administration with respect to the rest-activity cycle. Timed use of aspirin at low dose effectively contributes to blood pressure control in women at high risk for preeclampsia. (Hypertension. 2003;41[part 2]:651-656.)

Key Words: aspirin ■ blood pressure monitoring, ambulatory ■ pregnancy ■ hypertension, gestational ■ chronopharmacology ■ circadian

Several small studies aimed to test the effects of low-dose acetylsalicylic acid (ASA, aspirin) in the prevention of preeclampsia have concluded that beneficial effects of such treatment outweigh adverse ones. More recent, larger, randomized controlled trials, usually performed in the general obstetric population, have not corroborated the benefits of ASA in the prevention of preeclampsia. These studies concluded that the use of low-dose ASA during pregnancy was safe for the fetus, the newborn, and the mother, but the results did not support the routine prophylactic use of ASA for prevention of preeclampsia. Similar results were also found from a study involving women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestations, or a previous history of preeclampsia. However, a meta-analysis of low-dose ASA for prevention of intrauterine growth retardation (IUGR) indicated that the preventive effect was greater at higher doses (100 to 150 mg/day) compared with the lower doses most frequently used in those negative trials (50 to 80 mg/day). A recent retrospective study on women who received 100 mg/day ASA concluded that success (no preeclampsia) was associated with starting the use of medication before 17 weeks of gestation. Finally, little attention has been given so far to the timing of ASA administration, a relevant issue in keeping with the well known chronopharmacology effects of nonsteroidal antiinflammatory drugs. Thus, the potential role of low-dose ASA in pregnancy still seems to be an unresolved question.

Although some of all these previous studies of ASA effects in pregnancy reported average values of office blood pressure (BP) measurements for the pregnant women before and after long-term administration of ASA, the study of any possible influence of ASA on BP was never a primary objective. This seems at least partially surprising since an elevated BP is the hallmark for the diagnosis of gestational hypertension and preeclampsia. Along these lines, recent studies have shown no influence of ASA on BP in hypertensive patients under pharmacologic therapy who received ASA at an unspecified time of day, presumably in the morning with their antihypertensive medication. However, an administration time–dependent effect of low-dose ASA on BP has been docu-
mented in clinically healthy volunteers as well as in patients with untreated mild hypertension.\textsuperscript{13,16} Within the context of pregnancy, results from a previous double-blind, randomized, placebo-controlled trial on the effects of low-dose ASA (100 mg/day from 12 to 16 weeks of gestation until delivery) during gestation also indicated a highly significant administration time-dependent influence on BP by ASA, as well as statistically significant reductions in the incidence of gestational hypertension, preeclampsia, IUGR and preterm delivery when ASA, compared with placebo, was administered every 20 minutes during the day (7:00 AM to 11:00 PM) and every 30 minutes each woman were automatically measured on the nondominant arm at different times of the day according to their individual rest-activity cycle, and who were systematically studied by 48-hour ambulatory BP monitoring (ABPM) before entering the study.

**Methods**

**Subjects**

We report data on 341 white pregnant women (181 primipara) who fulfilled all required criteria for this trial (see below), who were at a higher risk for gestational hypertension or preeclampsia than that of the general obstetric population, and who were thus receiving medical care at the Obstetric Physiopathology Service (high-risk unit) of the Hospital Clínico Universitario, Santiago de Compostela, Spain. Reasons for receiving medical care at this unit include familial or personal history of gestational hypertension or preeclampsia; chronic hypertension; cardiovascular, endocrine, bleeding, or metabolic disease; a personal history of spontaneous abortion; multiple pregnancy; obesity; and adolescent or middle-aged nulliparous pregnancy (<18 or >35 years). The relative risk of gestational hypertension and preeclampsia in this unit is \( \sim 3.5 \) times that of the general obstetric population in our setting.\textsuperscript{17,18}

Additional inclusion criteria for this trial were the absence of any condition requiring the use on antihypertensive medication, maternal age (18 to 40 years) and gestational age (<17 weeks). Exclusion criteria were, among others, multiple pregnancy, chronic hypertension, chronic liver disease, any disease requiring the use of anti-inflammatory medication, diabetes or any other endocrine disease such as hyperthyroidism, and intolerance to ABPM device. Apart from the 341 women providing all required information, 12 subjects who provided <4 profiles of ABPM (5 who had spontaneous abortions and 7 who withdrew from the trial after the first visit) and 4 women who missed >6 tablets during any given month were eliminated from the study. The minimum sample size for this trial (55 women for each of the 6 treatment groups, see below) was calculated to show as statistically significant at the 95\% level with a 95\% power a BP difference between ASA and placebo \( \geq 4 \text{ mm Hg} \) in the 24-hour mean of BP at the time of delivery, according to the estimation of inter-individual variability provided by previous studies.\textsuperscript{17,18} The State Ethics Committee of Clinical Research and the Spanish Health Minister approved the study. All volunteers signed consent forms before entering the study.

**BP Assessment**

The systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) of each woman were automatically measured on the nondominant arm 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 an Space Labs 90207 (Space Labs Inc) device, validated for use in pregnancy,\textsuperscript{20} at the time of recruitment and then every 4 weeks until delivery. Additionally, BP and HR were also monitored following the same sampling scheme at puerperium (ie, 6 to 8 weeks after delivery). Women were assessed while adhering to their usual diurnal activity (9:00 AM to midnight 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 and to avoid the use of medications other than the assigned aspirin or placebo for the duration of the trial. A total of 106 BP series were eliminated from analysis because the women showed an irregular rest-activity schedule during the 7 days of sampling, an odd sampling with spans of >3 hours without BP measurement, or a night resting span <6 hours or >12 hours. The total number of valid BP series provided by the 341 women under investigation fulfilling all mentioned requirements set a priori was 2511.

**Medications**

The volunteers were randomly assigned (double-blind, randomized, placebo-controlled trial) at the time of their first visit to the hospital.

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**Table: Demographic and Baseline BP Characteristics of Pregnant Women**

<table>
<thead>
<tr>
<th>Group*</th>
<th>Subjects, n</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time 1</td>
<td>56</td>
<td>31.5±0.8</td>
<td>66.1±1.6</td>
<td>162.3±0.7</td>
<td>107.5±1.0</td>
<td>62.5±0.7</td>
</tr>
<tr>
<td>Time 2</td>
<td>55</td>
<td>32.0±0.6</td>
<td>67.3±1.6</td>
<td>162.6±0.8</td>
<td>108.8±1.2</td>
<td>64.3±0.8</td>
</tr>
<tr>
<td>Time 3</td>
<td>56</td>
<td>30.0±0.7</td>
<td>68.6±1.8</td>
<td>161.3±0.9</td>
<td>106.9±1.2</td>
<td>62.9±0.9</td>
</tr>
<tr>
<td>All</td>
<td>167</td>
<td>31.1±0.4</td>
<td>67.4±1.0</td>
<td>162.1±0.5</td>
<td>107.7±0.6</td>
<td>63.2±0.5</td>
</tr>
</tbody>
</table>

Aspirin (100 mg/day)

| Time 1 | 58          | 30.8±0.8| 69.4±2.0   | 162.2±0.9  | 106.3±1.1   | 62.1±0.8    |
| Time 2 | 57          | 30.6±0.7| 67.3±2.2   | 162.7±0.8  | 109.8±1.3   | 63.3±0.9    |
| Time 3 | 59          | 29.8±0.6| 67.8±1.7   | 162.4±0.8  | 108.5±1.1   | 63.1±0.8    |
| All    | 174         | 30.4±0.4| 68.1±1.1   | 162.4±0.5  | 108.1±0.7   | 63.0±0.5    |

Values are mean±SEM. Baseline BP values correspond to the average 24-hour mean of the BP series determined by 48-hour ambulatory monitoring before treatment started.

*Time 1 indicates women taking aspirin or placebo at awakening; Time 2, women taking aspirin or placebo 8 hours after awakening; and Time 3, women taking aspirin or placebo before bedtime.
to 1 of 6 groups, defined according to treatment (placebo or ASA, 100 mg/day; Table) and to the timing of daily administration of ASA and placebo: on awakening (time 1), 8 hours after awakening (time 2), or before bedtime (time 3). Baseline characteristics (given in the Table) related to age, weight, height, and 24-hour mean BP values obtained from the first profile of ABPM (sampled before treatment started) were similar for all 6 groups of treatment.

Oral ingestion of ASA or placebo started at 12 to 16 weeks of gestation and continued until the day of delivery. The dose of 100 mg used in this trial corresponds with the actual lower dose commercially available in Spain. The median numbers of tablets taken by the women investigated, to be compared with the maximum average expected number of 175 (medication for 25 weeks of gestation), were 171 in the ASA groups and 167 in the placebo groups. Compliance was measured on the basis of tablet count at the time of each visit. Because compliance was very high, we could not detect any difference in the number of missing tablets among groups of women assigned to take either ASA or placebo at different times of the day. Placebo (microcrystalline cellulose, corn starch, saccharin, and citric acid [included to simulate the flavor of ASA]) and ASA (100-mg uncoated tablets) were prepared in identical presentation and provided monthly to the volunteers in a box containing 3 blister packs, each with 10 tablets. The boxes, grouped in packs of 7 (to cover medication for the duration of pregnancy) and labeled with the randomization number, were assigned to each woman at the time of her recruitment.

Statistical Methods

Original data from each of the 2511 BP profiles were edited according to commonly used criteria for the removal of outliers and measurement errors.23 The remaining data were first analyzed by the use of Chronolab,22 a software package for biologic signal processing by linear and nonlinear least-squares estimation that, among other methods, includes the single and population multiple components analysis.23 In particular, each BP series was analyzed by the least-squares fit of a multiple component curve with periods of 24 and 12 hours to determine the rhythm-adjusted mean or midline estimating statistic of rhythm (MESOR; average value of rhythmic function fitted to data) and the amplitudes of both components. This model has been shown to describe sufficiently well the circadian pattern of BP variability both in pregnant24 and in nonpregnant subjects,24 even though other higher frequency rhythms, generally of low amplitude, can be demonstrated as statistically significant in some but not all individuals studied by 48-hour ABPM. Because the data were obtained at an unequidistant sampling rate covering 2 cycles (48 hours), the MESOR provides a better estimation of the true 24-hour mean than the average of all BP values (usually overestimating the true mean because of the denser sampling during the daytime activity compared with nighttime sleep span). The estimates of the 24-hour mean thus obtained for all BP series of each pregnant woman were expressed as percentage of the MESOR computed for that subject from the BP series sampled before treatment started (in order to avoid interindividual differences in BP along gestation). The time of sampling for each BP series was expressed in months from the pretreatment monitoring (as indication of duration of treatment). The values of 24-hour mean thus normalized were used to establish their pattern of variation along duration of treatment for each of the 6 groups of pregnant women by polynomial regression analysis. Effects of medication (placebo or ASA) and circadian time (time expressed by reference to individual rest-activity schedule instead of the most common clock hour) of treatment on BP along duration of treatment and at puerperium were evaluated by ANOVA.

Results

Placebo Administered at Different Times of the Day

Figure 1 shows the variation of the 24-hour mean (expressed as percentage of the value obtained for each subject before treatment started) for all groups of treatment (Table) of SBP (top) and DBP (bottom) along gestation (expressed in months from the pretreatment monitoring) in pregnant women who received placebo at different circadian times, starting at 12 to 16 weeks of pregnancy. This figure represents, first, the histograms with the average values of the 24-hour mean of BP with their SEM for each month of treatment along gestation; second, the figure also shows the best model of predictable BP variability along gestation for each group of women obtained by polynomial regression analysis.

Results in Figure 1 indicate that for all groups of pregnant women who received placebo, BP follows a predictable pattern of variation that can be approximated by a second order model in time (months of treatment). Figure 1 also shows nonsignificant changes in SBP and DBP up to the 20th week of pregnancy (=1.5 months of treatment), followed by an increase in BP up to the day of delivery (≈6.5 months after treatment started). Figure 1 also indicates that the model of variation of the 24-hour mean of BP along gestation is similar for all 3 groups of pregnant women receiving placebo at different circadian times. Results from ANOVA further indicate the lack of differences among groups of women under placebo treatment in the average value of 24-hour mean of BP at all times along gestation (P>0.256 in all cases), including the pretreatment BP values (Table). There was no different on HR at any gestational age among groups of women taken placebo at different circadian times (data not shown).
ASA Administered at Different Times of the Day

Figure 2 compares the predictable variation in BP along time of treatment in pregnant women receiving 100 mg/day of ASA at different times of the day. This predictable pattern follows again a second-order model for both SBP and DBP in all groups of women. In opposition to the results shown in Figure 1 for pregnant women receiving placebo, the models of BP variation along gestation obtained for women receiving ASA at different circadian times are not similar (P<0.001 in a test for comparison of second-order coefficients from the regression models, for both SBP and DBP). Results from Figure 2 indicate a highly statistically significant administration time–dependent effect of low-dose ASA on BP. There is no effect when ASA, compared with placebo, is administered on awakening; the BP reduction is, however, statistically significant when ASA is given 8 hours after awakening and, to a greater extent, when ASA is administered before bedtime. Results from ANOVA indicate that the differences between treatment groups in the 24-hour mean value of BP are statistically significant as soon as on the first month of treatment for SBP and DBP (P<0.001). Results further indicate that at the time of delivery, the use of 100 mg/day of ASA before bedtime can decrease SBP in an average of 12.4 mm Hg and DBP in 8.1 mm Hg compared with the use of the same dose of ASA on awakening. Despite the highly statistically significant administration time–dependent effect of ASA on BP, there was no difference in HR among the 3 groups of pregnant women (data not shown).

Comparison of BP at Puerperium

The comparison of the histograms represented in Figures 1 and 2 for women receiving either ASA or placebo on awakening indicates that the model of variation of the 24-hour mean of BP along gestation is similar for both groups of pregnant women. Moreover, there is no statistically significant difference among groups of women in the average value of 24-hour mean at any time along gestation (P>0.110 in all cases). At the time of delivery, the predictable average difference in 24-hour mean between women receiving either placebo or ASA on awakening is not statistically significant (P=0.719 for SBP and 0.726 for DBP). A further comparison of histograms represented in Figures 1 and 2 indicates that the models obtained for women receiving placebo or ASA 8 hours after awakening are not similar (P<0.001 in a test for comparison of second-order coefficients from the regression models, for both SBP and DBP). Results indicate that the differences in the average value of the 24-hour mean of BP between women receiving placebo or ASA at time 2 are already statistically significant after the first month of treatment (P<0.001). At the time of delivery, the statistically significant difference (P<0.001) in the 24-hour mean value of BP between women receiving placebo and those receiving ASA at time 2 is 4.4 mm Hg for SBP and 3.5 mm Hg for DBP. Results also indicate statistically significant differences in BP between placebo and ASA given at bedtime after the first month of treatment (P<0.001). Moreover, at the time of delivery, there is a reduction of 9.7 and 6.5 mm Hg in the 24-hour mean of SBP and DBP, respectively, for those women receiving 100 mg/day of ASA at bedtime compared with women receiving placebo at the same circadian time.
who received ASA before bedtime), the differences among groups are not longer significant.

**Discussion**

The major conclusion from this prospective study is that ASA selectively decreases BP as a function of the time of its administration in relation to the rest-activity cycle of each individual pregnant woman. Results indicate that (1) there is no statistically significant difference in BP (\(P>0.256\)) between women receiving placebo at different circadian times; (2) there is a highly statistically significant BP reduction consistently increased along gestation in women receiving 100 mg/day of ASA (\(P<0.001\) from a comparison of ASA versus placebo without taking into account circadian time of medication); and (3) the effect of ASA on BP is markedly dependent on the time of its administration. There is no effect when ASA is taken on awakening, but the BP reduction is highly statistically significant when ASA is ingested 8 hours after awakening and, to a larger extent, before bedtime (Figure 2). Despite the highly statistically significant administration–dependent changes that have been described when the pharmacokinetics of nonsteroidal antiinflammatory drugs were investigated in humans,10 Thus, effects of ASA on lipoperoxides and \(\beta\)-adrenergic receptors in healthy women have been shown to be dependent of the circadian time of ASA administration.28 On the other hand, ASA has also been shown not only to restore vascular reactivity to angiotensin II29 but also to produce a time- and dose-dependent BP reduction, as well as >30% inhibition of angiotensin II.30 Along these lines, previous results have demonstrated a predictable circadian variation in plasma renin activity, angiotensin II, catecholamines, atrial natriuretic peptides, aldosterone, and ACE.31,32 These results may be relevant inasmuch as ASA given at the end of the activity cycle could thus much as ASA given at the end of the activity cycle could thus more properly target the peak of plasma renin activity, while enhancing the nocturnal through in the production of NO,33 and inhibition of platelet aggregation produced by ASA.25,26 Another relevant factor to be taken into consideration is the pharmacokinetic observation that ASA exhibits a faster rate of clearance when administered during the morning compared with the evening.27 These results complement administration time–dependent changes that have been described when the pharmacokinetics of nonsteroidal antiinflammatory drugs were investigated in humans.10 Thus, effects of ASA on lipid peroxides and \(\beta\)-adrenergic receptors in healthy women have been shown to be dependent of the circadian time of ASA administration.28 On the other hand, ASA has also been shown not only to restore vascular reactivity to angiotensin II29 but also to produce a time- and dose-dependent BP reduction, as well as >30% inhibition of angiotensin II.30 Although secondary to the main objective of this report on the influence of ASA on BP, it seems to be worthwhile to summarize results on the outcome of the women investigated. There was no difference between ASA given at awakening and any of the 3 groups of placebo in any outcome variable (incidence of 15.5%, 25.9%, 15.5%, and 12.1% for pre-eclampsia, gestational hypertension, IUGR, and preterm delivery, respectively, for the composite of the 4 treatment groups). When ASA was given before bedtime, the incidence of those complications was 1.7%, 6.8%, 3.4%, and 0%, compared with values of 14.3%, 30.4%, 16.1%, and 17.9% for placebo at the same time (\(P<0.001\) for all variables). When ASA was given at time 2 or time 3, there were significant increases in newborn’s weight and gestational age at delivery (\(P=0.011\)) compared with values obtained for ASA on awakening or placebo at any time. Finally, there were no differences between ASA and placebo in maternal bleeding during the third trimester, placental abruption or any other maternal or fetal complication. Thus, BP regulation by timed use of low-dose ASA seems to have also contributed efficiently to improve maternal and perinatal outcome.

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.

Perspectives

Results, in full agreement with previous reports on smaller groups of women,17,18 indicate a statistically significant ad-
ministration time–dependent effect of low-dose ASA on BP in women with high risk of developing hypertension in pregnancy. The use of ASA in doses >80 mg/day that do not affect placental thromboxane, starting the use of ASA after 16 weeks of gestation when differences in BP between healthy and complicated pregnancies are already highly statistically significant, and the lack of circadian timing for ASA administration, could explain the lack of positive results in many previous clinical trials for the prevention of pre-eclampsia and its complications by the use of ASA. Finally, results from this trial indicate that timed use of ASA at low dose not only effectively contributes to BP control in high-risk pregnant women but also significantly reduces the incidence of hypertensive complications in pregnancy and improves relevant perinatal outcome variables.

References

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