Letters to the Editor

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Aspirin, Chance, and Results in Relation to Blood Pressure

To the Editor:

We read with great interest a recently published article entitled, "Administration Time-Dependent Effects of Aspirin on Blood Pressure in Untreated Hypertensive Patients."[1] However, we have serious concerns regarding it.

The objective of the study was to prove a relationship that was implicitly causal. Regrettably, the authors illustrated the results with some beautiful figure about circadian models, which distracts the attention of the reader from the main objective.

With respect to aspirin, the authors mixed results from in vitro studies with results obtained from the clinical practice (or clinical trials).[2,3] Such a procedure does not seem to be very orthodox.

The authors, to our surprise, did not offer information about the origin of the volunteers taking part in the study, training sessions for the investigators, homogeneity of the equipment used, and agreement among observers. They also did not provide data concerning other basic characteristics of the patients, such as comorbidity, any other treatment, etc. In addition, many records were taken out and omitted from the analysis, and information on 4 patients was missing. We wondered if the results would have been the same if all such incidences had occurred in the group of patients taking aspirin at night.

Unfortunately, no mention of the feasible placebo effect was shown in the study.[4,5] Since the authors did not make any adjustment of data by confounding variables, the reported effect over BP may not be attributable to aspirin.

Table 1 in the article does not add up. In that table, the first part is related to homogeneity between the 3 groups, and the second part of this table, which is just the result of the study, is where the authors should have made a comparison between the 3 groups.

The rest of the results seemed to be a series of "fishing" for differences in the level of significance. So, what were the rationale and the power for the analysis between the groups since there were no significant differences?

In summary, we are deeply concerned about the conclusions raised by the authors in this study. To confirm the results shown by the authors, a more suitable power and methodology should be required.

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1. Hermida RC, Ayala DE, Calvo C, Lopez JE, Fernandez JR, Mojon A, Domínguez MJ, Covelo M. Administration time-dependent effects of aspirin on blood pressure in untreated hypertensive patients. *Hypertension.* 2003;41:1259–1267.
2. Cornélissen G, Halberg F, Prikryl P, Dankova E, Siegelova J, Dusek J. Prophylactic aspirin treatment: the merits of timing. International Womb-to-Tomb Chronome Study Group. *JAMA.* 1991;266:3128–3129.
3. Grégoire C, Labrecque G. Chronopharmacology of increasing doses of collagen and aspirin on the in vitro platelet aggregation: biological rhythms and medications. Proc Sixth Int Conf Chronopharmacol Chronotherapeutics. Amelia Island, July 5–9.1994:Abstract XIV-1.
4. Suchman AL, Ader R. Classic conditioning and placebo effects in crossover studies. *Clin Pharmacol Ther.* 1992;52:372–377.
5. Preston RA, Materson BJ, Reda DJ, Williams DW. Placebo-associated blood pressure response and adverse effect in the treatment of hypertension: observations from a Department of Veterans Affairs Cooperative Study. *Arch Intern Med.* 2000;160:1449–1454.

Response: Aspirin Administered at Bedtime as Opposed to Upon Wakening Has an Effect on Ambulatory Blood Pressure: Further Evidence

In a recently published manuscript[1] we investigated the potential administration time-dependent effects of low-dose aspirin (ASA) on blood pressure (BP) in otherwise untreated patients with mild (grade 1) hypertension. The administration time-dependent influence of ASA on BP was previously demonstrated in a randomized trial on healthy women[2] and other independent double-blind, randomized, placebo-controlled clinical trials conducted first on clinically healthy subjects,[3] a second one on normotensive and hypertensive subjects,[4] and a third one on pregnant women at high risk for preeclampsia.[5] The findings of these BP studies, all of which used **a**mbulatory BP monitoring (ABPM) to derive primary outcome variables, are consistent; BP-lowering effect of low-dose ASA is achieved when administered at bedtime but not on awakening.

The advantages of ABPM over conventional BP values determined at the clinic have been previously established. Among others, ABPM it is particularly useful for defining the efficacy of antihypertensive medication in clinical trials.[6] While placebo control could be required in studies based on conventional BP, the need for a placebo group in clinical trials with ABPM is still under debate. The most commonly accepted position is that short-term trials on antihypertensive efficacy may be designed without a placebo arm.[7] Taking into account the advantages of ABPM, we decided to conduct a prospective, randomized, open-label, blinded endpoint (PROBE) trial.[1] As previously described,[8,9] this approach offers certain benefits, including a closer similarity between study design and daily clinical practice. Moreover, a recent meta-analysis has shown the validity of the PROBE design, compared with double-blind, placebo-controlled trials, in assessing antihypertensive efficacy based on blinded ABPM measurements.[9]

Our Figures 1 to 3[1] provide the information on BP averages throughout the day, as it is customary when the main outcome variable is ABPM. Figure 4 complements to the results of these figures by presenting the BP averages for the spans of diurnal activity, nocturnal rest, and the entire 24 hours. These figures represent the relevant results of the main outcome variables. The Table, as a complement, provides information to show, with the proper statistical testing, that (1) the 3 treatment groups were fully comparable at baseline in all potentially relevant confounding variables, including blood and urine ones; (2) the three groups were also comparable in all those variables after 3 months of intervention; and (3) all variables, except to some extent the conventional BP measurements of patients receiving the ASA at bedtime, remained unchanged after ASA treatment.

The relevant demographic, physical, and analytical characteristics of the previously untreated subjects with grade 1 hypertension who volunteered for this trial are fully described in page 1260 (left column, paragraph 2) and the Table. The use of antihypertensive and any other medication was forbidden during the trial. Accordingly, no patient had any other condition, apart from recently diagnosed mild hypertension, that would require drug treatment. Inclusion and exclusion criteria are clearly stated. The investigators who conducted this trial had been active in clinical research involving ABPM for over 18 years. No further training was considered necessary to conduct this trial. The

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description of the fully validated and regularly calibrated equipment for ABPM is also described. No observer bias or disagreement among investigators was detected that could possibly affect clinic BP measurements (a secondary endpoint) since only one investigator conducted all such measurements (page 1260, right column, paragraph 1, lines 8 to 11). Of course, observer bias or disagreement among investigators is not of concern with the objectively derived data from ABPM, the primary endpoint.

The manuscript also indicates clearly the requirements set a priori to define a valid ABPM profile. Based on such criteria or to a missing follow-up profile after the initiation of treatment, we excluded a total of 4 patients. We did not exclude any other ABPM profile from analysis, as clearly indicated in the manuscript. Three of the missing patients were originally assigned to the control group, and the fourth was assigned to take ASA on awakening. If these patients had been part of the group taking ASA before bedtime, they would need to show an increase of greater than 35 mm Hg in the 24-hour BP mean after treatment to render nonsignificant the results depicted in Figures 3 and 4. Finally, the results were tested for reproducibility. The significant BP lowering by ASA administered at bedtime as opposed to on wakening has been corroborated after doubling the required sample size[10] and again after triplicating the required sample size.[11] Our trial showed marked significant differences between treatment groups in the major outcome variable (ABPM).[1] The lack of among-groups differences in potentially confounding variables both at baseline and after 3 months of intervention as discussed in the paper and substantiated in the Table provides further evidence that the BP lowering effect shown in Figure 3 is due to administration time-dependent effect of ASA.

To this date, no clinical trial has provided contradictory evidence to the ABPM-determined reduction of BP with bedtime administration of ASA. Until such contradictory results are eventually provided, and the potential sources of disagreement with all previously reported information properly justified, the findings of properly designed and conducted peer-review research must be required valid. The scientific evidence published over the last 12 years corroborates that low-dose ASA at bedtime exerts BP lowering effects.

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1. Hermida RC, Ayala DE, Calvo C, López JE, Fernández JR, Mojón A, Domínguez MJ, Covelo M. Administration-time dependent effects of aspirin on blood pressure in untreated hypertensive patients. *Hypertension.* 2003;41:1259–1267.
2. Cornélissen G, Halberg F, Prikryl P, Dankova E, Siegelova J, Dusek J, International Womb-To-Tomb Chronome Study Group. Prophylactic aspirin treatment: The merits of timing. *JAMA.* 1991;266:3128–3129.
3. Hermida RC, Fernández JR, Ayala DE, Iglesias M, Halberg F. Time-dependent effects of ASA administration on blood pressure in healthy subjects. *Chronobiologia* 1994;21:201–213.
4. Hermida RC, Fernández JR, Ayala DE, Mojón A, Iglesias M. Influence of aspirin usage on blood pressure. Dose and administration-time dependencies. *Chronobiol Int.* 1997;14:619–637.
5. Hermida RC, Ayala DE, Iglesias M. Administration-time dependent influence of aspirin on blood pressure in pregnant women. *Hypertension.* 2003;41:651–656.
6. Coats AJ. Benefits of ambulatory blood pressure monitoring in the design of antihypertensive drug trials. *Blood Press Monit.* 1996;1:157–160.
7. Coca A. The placebo effect in ambulatory blood pressure monitoring. *Blood Press Monit.* 1998;3:195–199.
8. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Blood Press.* 1992;1:113–119.
9. Smith DH, Neutel JM, Lacourciere Y, Kempthorne-Rawson J. Prospective, randomized, open-label, blinded-endpoint (PROBE) designed trials yield the same results as double-blind, placebo-controlled trials with respect to ABPM measurements. *J Hypertens.* 2003;21:1291–1298.
10. Hermida RC, Ayala DE, Calvo C, López JE, Domínguez MJ, Covelo M, Mojón A, Fernández JR. Further evidence of the administration-time dependent effects of low-dose aspirin on blood pressure in hypertensive patients. *J Hypertens.* 2003;21:S269.
11. Hermida RC, Ayala DE, Calvo C, Domínguez MJ, Covelo M, Fernández JR, Mojón A, López JE. The effects of aspirin on blood pressure in untreated hypertensive patients are dependent on the time of drug administration. *J Am Coll Cardiol.* 2004;42: in press.

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