

Aspirin: A Novel Antihypertensive Drug? Or Two Birds With One Stone?*

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Ever since its synthesis by Felix Hoffmann in 1897 and registration by the Imperial Patent Office in Berlin in 1899, the list of diseases and disorders for which aspirin was found to be beneficial continues to grow. Today, about 50,000 tons of acetylsalicylic acid are produced every year across the globe. If this entire output were pressed into 500-mg tablets, it would amount to 100 billion tablets every year.

Clearly, aspirin has become a widely used, efficacious drug with numerous effects and side effects. Such are its pleiotropic effects that most physicians would select aspirin as the quintessential drug for a survival kit. However, these pleiotropic and adverse effects are also such that were aspirin discovered today, it would probably not pass muster at the Food and Drug Administration for any indication without a black box warning.

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In this issue of the *Journal*, Hermida and et al. (1) report yet another rather unexpected pleiotropic effect of aspirin; namely, antihypertensive activity. The authors showed that aspirin at a dose of 100 mg lowered blood pressure (BP) by 7/5 mm Hg when given at bedtime, but not when given in the morning. The authors, using 48-h ambulatory BP monitoring, studied more than 300 untreated patients with grade 1 hypertension, randomly divided into three groups: 1) lifestyle modification; 2) lifestyle modification plus aspirin in the morning, and; 3) lifestyle modification plus aspirin at bedtime. Whereas aspirin given on awakening increased BP slightly (2.6/1.6 mm Hg, $p < 0.002$), there was a robust and highly significant BP reduction in patients who received aspirin at bedtime, lasting throughout the 24-h period. The reduction of BP seen with bedtime aspirin was impressive and compared favorably with commonly used antihypertensive drug classes. According to the largest meta-analysis ever done, such an antihypertensive effect could reduce stroke mortality by more than 30% and ischemic heart disease mortality by almost 20% (2).

Given that aspirin is a nonsteroidal anti-inflammatory drug with inhibitory effects on cyclooxygenases (COX), these findings are surprising and thought provoking; COX

inhibition has vasoconstrictive and antinatriuretic effects, which are mediated by inhibition of prostaglandin E-2 and prostacyclin. Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors have been well documented to elevate BP and to possibly increase the risk of heart attack and stroke (3–8). The mechanism that the authors put forward to explain the antihypertensive effect of aspirin is based on the nocturnal rise of the activity of the renin-angiotensin-aldosterone system (RAAS) (9). Because BP falls during the night, renal perfusion pressure decreases resulting in a surge of RAAS activity by as much as 200%. Conceivably, aspirin given at bedtime could abolish or at least mitigate this surge and concomitantly diminish the nocturnal trough of nitric oxide production (10), thereby providing a mechanism by which BP is lowered. We should also remember there is a link between inflammation and hypertension (11) and that the prolonged use of any anti-inflammatory drug is prone to affect the cardiovascular system. Thus, aspirin could possibly lower BP by its anti-inflammatory properties. Finally, aspirin could possibly also lower BP by its central nervous (i.e., hypothalamic) effect (12). Although all three of these hypothetical mechanisms appear plausible, they are fraught with a common drawback: the half-life of aspirin is merely 15 min; that of salicylate about 3 h. Why would aspirin, when given at bedtime, have an effect on BP lasting a whole 24-h period and why would it when given in the same dose in the morning, if anything, cause an increase in BP?

The potential implications for antihypertensive therapy of the findings by Hermida et al. (1) are most important. If one assumes—and there is some controversy to this—that the antihypertensive efficacy of RAAS blockers is at least to some extent dependent on the circulating angiotensin levels, low-dose aspirin at bedtime will abolish or at least mitigate the effect of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on BP. Indeed, nonsteroidal anti-inflammatory drugs and COX-2 inhibitors have been shown to antagonize the antihypertensive effect of RAAS blockers but not of calcium antagonists (13,14). Also, in a meta-analysis of more than 20,000 patients, most of whom had congestive heart failure or coronary artery disease, a small reduction in benefits of angiotensin-converting enzyme inhibitors was documented when aspirin was added (15). Thus, when aspirin is taken at bedtime, calcium antagonists or possibly diuretics would become more efficacious antihypertensive drug classes than RAAS blockers or beta-blockers. Also, the findings of Hermida et al. (1) do

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not provide any data on a dose-response curve, if any, pertaining to aspirin and BP. One would perhaps expect to see a U-shaped relationship, because at higher doses the COX inhibitory effect of aspirin may well abolish its antihypertensive effect and lead to an increase in BP.

These and many other questions will have to be clarified before low-dose bedtime aspirin can be recommended routinely for its antihypertensive efficacy. As provocative as these findings are, they originate from a single source only. As such, however thorough, they should be interpreted with extreme caution. The present study showing a BP-lowering effect of aspirin is somewhat reminiscent of the various small reports purporting to document that statins had antihypertensive effects. These findings were recently laid to rest by a thorough, large factorial design study showing not a shred of evidence that atorvastatin, when added to amlodipine, had any effect on BP. I wholeheartedly agree with the authors that prospective investigation should address whether or not aspirin given at bedtime will be able to provide incremental cardiovascular protection, particularly in hypertensive patients.

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REFERENCES

1. Hermida RC, Ayala DE, Calvo C, López JE. Aspirin administered at bedtime, but not on awakening, has an effect on ambulatory blood pressure in hypertensive patients. *J Am Coll Cardiol* 2005;46:975-83.
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective studies collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
3. Solomon DH, Schneeweiss S, Levin R, Avorn J. Relationship between COX-2 specific inhibitors and hypertension. *Hypertension* 2004;44:140-5.
4. White WB. Hypertension associated with therapies to treat arthritis and pain. *Hypertension* 2004;44:123-4.
5. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993;153:477-84.
6. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994;121:289-300.
7. Topol EJ, Falk GW. A coxib a day won't keep the doctor away. *Lancet* 2004;364:639-40.
8. Topol EJ. Good riddance to a bad drug. *New York Times*. October 2, 2004, A15.
9. Gordon RD, Wolfe LK, Island DP, Liddle GW. A diurnal rhythm in plasma renin activity in man. *J Clin Invest* 1966;45:1587-92.
10. Kanabrocki EL, Third JL, Ryan MD, et al. Circadian relationship of serum uric acid and nitric oxide. *JAMA* 2000;283:2240-1.
11. Bautista LE, Lopez-Jaramillo P, Vera LM, Casas JP, Otero AP, Guaracao AI. Is C-reactive protein an independent risk factor for essential hypertension? *J Hypertens* 2001;19:857-61.
12. Nye EJ, Hockings GI, Grice JE, et al. Aspirin inhibits vasopressin-induced hypothalamic-pituitary-adrenal activity in normal humans. *J Clin Endocrinol Metab* 1997;82:812-7.
13. Morgan TO, Anderson A, Bertram D. Effect of indomethacin on blood pressure in elderly people with essential hypertension well controlled on amlodipine or enalapril. *Am J Hypertens* 2000;13:1161-7.
14. Polonia J, Boaventura I, Gama G, et al. Influence of non-steroidal anti-inflammatory drugs on renal function and 24h ambulatory blood pressure-reducing effects of enalapril and nifedipine gastrointestinal therapeutic system in hypertensive patients. *J Hypertens* 1995;13:925-31.
15. Teo KK, Yusuf S, Pfeffer M, et al. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002;360:1037-43.