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EDITORIAL

Acetaminophen-Induced Hypertension: Where Have All the "Safe" Analgesics Gone?

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The prevalence of hypertension continues to rise, but despite improved treatment rates, blood pressure (BP) control remains elusive in most populations and fewer than half of patients treated achieve BP <140/90 mm Hg.[1,2] An important but often underappreciated contributor to stagnant BP control rates is drug-induced hypertension. At least 40 to 50 drugs currently in use have been implicated in raising BP, through activation of sympathetic (eg, pseudoephedrine, venlafaxine) or renin–angiotensin systems (estrogen-based oral contraceptives), promotion of sodium/volume retention (corticosteroids, calcineurin inhibitors), or other mechanisms.[3,4] Some drugs—for example, nonsteroidal anti-inflammatory drugs (NSAIDs)—also blunt the effectiveness of many first-line antihypertensives.[4,5] However, the evidence base supporting these associations varies widely and many drugs have been implicated from adverse event reporting, case series, or, at best, underpowered trials or secondary analyses from randomized trials not explicitly focused on BP/hypertension. It is striking that few have been subjected to rigorous investigations confirming causal effects or determining incidence.

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Judging by the lay health literature, and much of the scientific literature currently available, one could easily conclude that acetaminophen has never been implicated in elevating BP. One might even conclude that it has been proven to have no effect on BP. Acetaminophen is, after all, almost universally recommended as a "safe" alternative to NSAIDs, which are well known to increase BP. However, evidence to the contrary dates back more than half a century, when acetaminophen was first shown to increase systolic BP by 4 mm Hg on average, relative to placebo in patients with hypertension.[6] Since then, numerous observational studies have generally supported a positive dose–response relationship, with greater acetaminophen exposure associated with highest risk of incident hypertension. Clinical trials have been few and somewhat more inconsistent, but several have shown a hypertensive effect. Nevertheless, some had important limitations including small sample sizes, lack of blinding, or study designs that did not precisely address the causal contrast of interest (eg, by comparing fixed-dose combination products in which nonacetaminophen drugs may have had differential BP effects). Furthermore, all observational studies and many clinical trials have focused on populations with pain, creating challenges in interpreting results when pain- and acetaminophen-related BP effects are not easily disentangled.

In this issue of *Circulation*, MacIntyre et al report on an important addition to this body of literature with results from the PATH-BP trial (Paracetamol in Hypertension–Blood Pressure).[7] The authors enrolled 110 adult patients with hypertension (one-third untreated) but with neither chronic pain nor present acetaminophen or NSAID use. Participants were randomly assigned to 2 weeks of treatment with acetaminophen (4 g/day) or placebo, with subsequent crossover to the other arm. The primary outcome was daytime ambulatory BP. Most patients (94%) completed the trial and acetaminophen adherence appeared to be high, with 87% of patients having a detectable drug in serum at the end of the acetaminophen treatment

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Nonstandard Abbreviations and Acronyms

BP	blood pressure
NSAID	nonsteroidal anti-inflammatory drug
PATH-BP	Paracetamol in Hypertension–Blood Pressure trial

phase. Relative to placebo, acetaminophen increased mean daytime ambulatory systolic BP by 5 mm Hg (95% CI, 3–7) and mean 24-hour ambulatory systolic BP by 4 mm Hg (95% CI, 2–6); mean daytime and 24-hour diastolic BP also were greater after acetaminophen treatment. Close to one-third of patients had a ≥10 mm Hg placebo-corrected daytime systolic BP response to acetaminophen, and several patients had substantial increases (ie, ≥25 mm Hg). One patient was withdrawn because of severely elevated BP (clinic BP, 185/76 mm Hg) at day 14 of acetaminophen treatment, which remitted after discontinuation. Findings were essentially unchanged when analyzing acetaminophen-adherent patients only and acetaminophen increased clinic BP by a similar magnitude as daytime ambulatory BP.

Overall, PATH-BP overcomes several limitations of previous studies and provides strong additional evidence in support of a clinically important BP-elevating effect of acetaminophen in patients with preexisting hypertension. Yet, there are some important questions that neither PATH-BP nor previous trials of similar rigor[8] have answered. Perhaps the most important is whether these BP effects translate to increased cardiovascular risk. At the population level, a persistent increase of 5 mm Hg in 24-hour ambulatory systolic BP is expected to increase stroke mortality by ≈15%, coronary heart disease mortality by 9%, and total mortality by ≥7%.[9] Previous observational studies that have sought to address this question suggest modestly elevated risk (ie, ≈17% to 44%) with acetaminophen; however, these studies include no active comparator group, making interpretation of the associations somewhat difficult.[10,11]

Additional questions remain regarding generalizability of the results. To date, trials have been short term (≤4 weeks), and it remains unclear whether these effects persist with chronic treatment. Second, the extent to which acetaminophen increases BP in individuals with lower baseline BP, including those with normal or elevated BP, or even stage 1 hypertension (per newer classifications), is not well understood. Third, it is plausible that acetaminophen may have differential effects in antihypertensive-treated versus untreated patients. The exact mechanism through which acetaminophen may increase BP is unknown, but previous research suggests that it may have pharmacological effects similar to those of NSAIDs—namely, the inhibition of COX-2 (cyclooxygenase-2) isoenzymes that results in decreased prostaglandin production. If this mechanism is responsible for the effect of acetaminophen on BP, then it seems reasonable to assume that, like NSAIDs, acetaminophen may blunt antihypertensive efficacy of some antihypertensive classes. Stratified analyses were performed in PATH-BP for untreated versus treated patients, and although the interaction term was not significant (P=0.13), it is entirely possible this secondary analysis was underpowered. Unfortunately, the trial was likewise underpowered to examine differences in acetaminophen-induced BP response across baseline antihypertensive regimens, although such information may be helpful in understanding how best to use acetaminophen and antihypertensives together, should both be necessary. Last, the dosing strategy used in PATH-BP (4 g/day) is consistent with typical UK dosing strategies, whereas doses >3 g/day have largely fallen out of favor in the United States, particularly with over-the-counter preparations, because of concerns with acetaminophen overdose and acute toxicity. As previously noted, the hypertensive effect of acetaminophen seems to be dose dependent; whether lower doses of acetaminophen have clinically important effects on BP is an important question.

Findings from the PATH-BP trial are also concerning given the frequency with which acetaminophen continues to be used by patients with hypertension. Previous research shows that >8% of patients being newly treated for hypertension are coprescribed ≥1 acetaminophen-containing product and many continue to fill acetaminophen prescriptions for up to 6 months thereafter.[12] Nearly 6% of those initiating a fourth antihypertensive drug (ie, meeting treatment-resistant hypertension criteria) were also prescribed acetaminophen.[12] It is important to note that these numbers represent only prescribed acetaminophen; over-the-counter acetaminophen is reportedly used by as much as one-third of the noninstitutionalized US population ≥1 day/month, and ≈5% of patients report use ≥15 days/month.[13] It seems entirely plausible also that heightened awareness around opioids may drive up nonnarcotic analgesic use further.

A survey commissioned by the American Heart Association reported in November 2021 that "39% of US adults with high blood pressure report acetaminophen is the over-the-counter medication they take most often for pain," and that "only 21% of US adults know that *acetaminophen does not raise blood pressure*, and those with high blood pressure are only slightly more aware of *this fact* (28%)"[14] [emphasis ours]. These observations illustrate an important problem: despite mounting evidence to the contrary, there seems to be a pervasive belief that acetaminophen is innocuous in terms of cardiovascular effects. These beliefs are likewise being conferred, if imperfectly, to a significant proportion of individuals with hypertension. The results of PATH-BP may not defini-

tively dispel these beliefs, but they should at least give us pause in routinely recommending acetaminophen as a "safe" alternative to chronic NSAID use, especially in patients with, or at risk of developing, hypertension.

ARTICLE INFORMATION

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