Acetaminophen Increases Blood Pressure in Patients With Coronary Artery Disease

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Background—Because traditional nonsteroidal antiinflammatory drugs are associated with increased risk for acute cardiovascular events, current guidelines recommend acetaminophen as the first-line analgesic of choice on the assumption of its greater cardiovascular safety. Data from randomized clinical trials prospectively addressing cardiovascular safety of acetaminophen, however, are still lacking, particularly in patients at increased cardiovascular risk. Hence, the aim of this study was to evaluate the safety of acetaminophen in patients with coronary artery disease.

Methods and Results—The 33 patients with coronary artery disease included in this randomized, double-blind, placebo-controlled, crossover study received acetaminophen (1 g TID) on top of standard cardiovascular therapy for 2 weeks. Ambulatory blood pressure, heart rate, endothelium-dependent and -independent vasodilatation, platelet function, endothelial progenitor cells, markers of the renin-angiotensin system, inflammation, and oxidative stress were determined at baseline and after each treatment period. Treatment with acetaminophen resulted in a significant increase in mean systolic (from 122.4±11.9 to 125.3±12.0 mm Hg $P=0.02$ versus placebo) and diastolic (from 73.2±6.9 to 75.4±7.9 mm Hg $P=0.02$ versus placebo) ambulatory blood pressures. On the other hand, heart rate, endothelial function, early endothelial progenitor cells, and platelet function did not change.

Conclusions—This study demonstrates for the first time that acetaminophen induces a significant increase in ambulatory blood pressure in patients with coronary artery disease. Thus, the use of acetaminophen should be evaluated as rigorously as traditional nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors, particularly in patients at increased cardiovascular risk.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00534651.

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Key Words: acetaminophen ■ blood pressure ■ coronary disease ■ endothelium

The Food and Drug Administration has mandated a "black-box warning" for cyclooxygenase-2 (COX-2) selective inhibitors and nonselective nonsteroidal antiinflammatory drugs (NSAIDs) in view of the potential of these agents to increase adverse cardiovascular outcomes.[1] Whereas hundreds of millions of patients worldwide continue to require pain-relieving therapy to maintain an acceptable quality of life, the uncertainty around the cardiovascular safety of NSAIDs and COX-2 inhibitors leaves practitioners and patients with difficult management decisions. Current guidelines recommend acetaminophen as the first-line analgesic of choice for the management of chronic pain despite weaker analgesic potency on the assumption of its greater cardiovascular safety, particularly in patients at high cardiovascular risk or with established cardiovascular disease.[1]

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One of the most commonly used drugs worldwide, a major ingredient in numerous cold and flu medications, and a drug commonly used even in children and pregnant women, acetaminophen (known as paracetamol outside the United

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States) was hitherto considered safe when taken in therapeutic doses.[1,2] It is of note, however, that sporadic studies linked acetaminophen with a higher incidence of hypertension[3,4] or even increased risk for cardiovascular events.[5] Only a few interventional studies assessing the effect of acetaminophen on hypertension are available, and all of them were performed either in hypertensive patients[6,7] or in patients who were hypertensive with osteoarthritis.[8] The results, however, are inconsistent. Nevertheless, the majority of data on the cardiovascular safety of acetaminophen are derived from observational studies, which are considered "hypothesis generating," and many examples exist where such findings were not confirmed in randomized trials.[6–8]

To date, no study has assessed the effect of acetaminophen on blood pressure (BP) in patients with coronary artery disease (CAD). Thus, we prospectively evaluated the potential impact of acetaminophen on ambulatory BP (ABP) and vascular function in patients with established CAD in whom traditional NSAIDs and COX-2 inhibitors are contraindicated and acetaminophen currently represents the treatment of choice.

Methods

Study Population

The patients were recruited at the Cardiovascular Center Cardiology, University Hospital Zurich, Zurich, Switzerland. Patients with CAD (documented by coronary angiography, nuclear imaging, or positive stress test) on stable cardiovascular medication for at least 1 month who were between 18 to 80 years of age and gave written informed consent were included in the study.

Exclusion criteria were acute myocardial infarction, unstable angina, stroke, or coronary intervention/revascularization procedure within 3 months before study entry; left ventricular ejection fraction <50%; use of other analgesics (platelet inhibition therapy with aspirin 100 mg/d was continued); chronic pain; smoking, alcohol, or substance abuse; uncontrolled BP despite adequate therapy (>160/100 mm Hg); renal failure (serum creatinine >200 μmol/L); liver disease (alanine aminotransferase or aspartate aminotransferase >100 IU); acute hepatitis; hyperbilirubinemia; concomitant therapy with oral anticoagulants, Phenobarbital, phenytoin, carbamazepine, isonicotinic acid, chloramphenicol, chlorzoxazone, zidovudine, and salicylamide; long-term use of nitrates; insulin-dependent diabetes mellitus; anemia (hemoglobin <10 g/dL); known allergies to acetaminophen; systemic inflammatory diseases (eg, rheumatoid arthritis, Crohn's Disease); and participation in another study within the last month. The patients were not allowed to take any drugs other than the background cardiovascular therapy (in particular, no anti-inflammatory and pain-relieving drugs) to secure the double-blind design.

Because patients included in the study did not present with pain and thus would potentially not benefit from the study drug, the number of patients investigated had to be limited to the minimal number determined by a preliminary power calculation. In addition, to limit the number of patients to exposure to a drug from which they potentially would not benefit, a "crossover" design was chosen.

Study Design and Protocol

In this prospective randomized, double-blind, investigator-initiated crossover study, we analyzed the impact of acetaminophen on ABP and endothelium-dependent and -independent vasodilatation in patients with stable CAD receiving optimal standard treatment. As secondary end points, platelet function, endothelial progenitor cells (EPCs), markers of the renin-angiotensin system, inflammation, and oxidative stress were assessed.

After screening and recruiting, the patients were randomly assigned to 2 groups. For randomization, an unpredictable allocation sequence was provided by external institutions (InterCorNet and Cantonal Pharmacy, both in Zurich, Switzerland), which were responsible for the blinding and labeling of the drugs. All investigators were unaware of the allocation procedure at any time. The patients were randomized to receive either acetaminophen 1 g TID, a typical dose for pain relief, or matching placebo for 2 weeks in the first part of the study or vice versa in the second part. Between the first and the second parts was a washout period of 2 weeks.

At each visit (baseline and after 2, 4, and 6 weeks), ABP and endothelial function were measured, blood samples were drawn, 24-hour urine was collected, clinical status was assessed, and adverse events were recorded. At each visit, a safety analysis was performed, including the assessment of electrolytes and of liver and kidney function, plus a white and red blood cell count. Pregnancy testing in women with child-bearing potential was performed only at the first visit. The patients were advised not to take their usual drugs in the morning of the examination day (all examinations and measurements were performed in the morning). Blood samples were taken and flow-mediated dilatation (FMD) was assessed before the patients took their medications. The regular medications and study drug were taken thereafter and before the 24-hour ABPM was placed.

The study drug and placebo were prepared in identical capsules to ensure uniform appearance of both formulations. The verum consisted of pure acetaminophen and did not contain sodium, with the exception of a 3% solution containing sodium lactate on the capsule surface. According to the manufacturer, this amount of sodium is not measurable in vivo. The placebo preparation contained D-mannitol only. The Ethics Committee of the Canton Zurich and the Swiss Agency for Therapeutic Products (Swissmedic) approved the study protocol. The study was registered at http://www.clinicaltrials.gov (identifier: NCT00534651).

ABP Measurement

ABP measurements were obtained over 24 hours with the Tracker NIBP 2 (Delmar, Del Mar Reynolds Medical, Hertford, UK) before and after the active treatment phase according to recent guidelines.[9] Patients were asked to keep their arm calm while the cuff was inflating and to avoid excessive physical exertion during monitoring. The monitors were programmed to take readings every 15 minutes during daytime and every 30 minutes during nighttime.

Endothelium-Dependent and -Independent Vasodilatation

FMD was performed according to current guidelines[10,11] as previously described.[12] In brief, a B-mode scan of the left brachial artery was obtained in a longitudinal section between 2 and 10 cm above the elbow with a high-resolution 10-MHz linear-array transducer and a high-resolution ultrasound system (Siemens X300, Siemens Switzerland AG, Zurich, Switzerland). The analog video signal was acquired with a video processing system that computed the artery diameter in real time (FMD Studio,[13,14] a system for real-time measurement, Institute of Clinical Physiology, Pisa, Italy). The reproducibility of the method has been demonstrated recently.[13,14] Baseline vessel size was considered to be the mean of the measures obtained during the first minute. FMD was calculated as the maximal percent increase in diameter above baseline. Endothelium-independent dilatation was measured after sublingual glycerol trinitrate (0.4 mg, Nitrolingual Spray, Pohl-Boskamp, Hohenlockstedt, Germany) application by recording arterial diameter continuously for at least 6 minutes. The response to glycerol trinitrate is calculated as the maximum percent increase in vessel size above the baseline.

The intraobserver mean of absolute difference in baseline diameter was 0.13±0.09 (I.S.) and 0.11±0.06 (P.K.), and the mean absolute difference in FMD was 0.61±0.19% (I.S.) and 0.62±0.46% (P.K.). The intraobserver coefficient of variation (CV) of the operators (defined as follows: SD of the paired differences/overall mean/$\sqrt{2}\times 100$) was 2.1% (I.S.) and 6.2% (P.K.).

Special Laboratory Analysis

Oxidative Stress Markers

8-Isoprostanes were measured in the plasma with an 8-isoprostane enzyme immunoassay (Cayman Chemicals, Ann Arbor, Mich; intra-assay CV, 7.2%; interassay CV, 15.5%).

Prostaglandins and Thromboxane

Prostaglandin E_2 was measured in plasma and urine with the prostaglandin E_2 enzyme immunoassay kit–monoclonal (Cayman Chemicals; intra-assay CV, 3.7%; interassay CV, 11.6%). Thromboxane B_2 was determined in plasma with the thromboxane B_2 enzyme immunoassay kit (Cayman Chemicals; intra-assay CV, 19.9%; interassay CV, 24.3%).

Assessment of Plasma Renin Activity and Aldosterone

Plasma renin activity was measured by trapping generated angiotensin I by high-affinity antibodies and subsequent radioimmunoassay.[15] Aldosterone was measured by a direct radioimmunoassay with high-affinity antibodies produced in New Zealand White rabbits.[16] For aldosterone, the intra-assay and interassay CVs were 5.3% and 9.4%. For plasma renin activity, the intra-assay and interassay CVs were 5% and 13%. The results were normalized to 24-hour sodium excretion.

Early EPCs

Isolation and Culturing of Early EPCs From Peripheral Blood

Blood (8 mL) was collected into BD Vacutainer Cell Preparation Tubes (BD, Franklin Lakes, NJ) and was centrifuged at 1800 *g* for 30 minutes at room temperature within 1 to 2 hours. The plasma layer was removed and stored at −80°C; the buffy layer was transferred to sterile 15-mL centrifuge tubes. Mononuclear cells were washed twice with PBS, first with 15 mL and spin at 900*g* for 15 minutes and then with 10 mL and spin at 900*g* for 10 minutes, and seeded on a fibronectin-coated Laboratory Tek Chamber Slide (BD) at a density of 8 000 000/mL in 20% FCS EGM-2. After 3 days, the medium was changed. The cultures were analyzed on the fifth day of plating.

Quantification and Characterization of Early EPCs in 5-Day Cultures

Early EPCs were quantified as described in detail previously.[17,18] In brief, the medium was removed with pipette, and EGM-2 with 5 μg/mL 1,1-dioctadecyl-3,3,3-tetramethylindocarbocyanine perchlorate low-density lipoprotein (DiI-LDL; Intracel, Frederick, MD) was added. The cells were incubated with DiI-LDL for 1 hour at 37°C. Then cells were washed with PBS and fixed with 4% paraformaldehyde in PBS for 10 minutes at room temperature. After removal of paraformaldehyde, cells were washed once with PBS and incubated with 10 μg/mL FITC-conjugated agglutinin lectin from *Ulex europaeus* (Sigma-Aldrich, Buchs, Switzerland) for 1 hour at room temperature. Then they were washed twice and covered by mounting medium with DAPI (1:1000). Using a fluorescent microscope (Olympus, Hamburg, Germany), we counted DiI-LDL/lectin double-positive cells in 3 different visual fields and considered them early EPCs. The CV was 6.3% (10 EPC cultures made twice). Furthermore, the number of CD34/KDR double-positive mononuclear cells was determined by fluorescence-activated cell sorting analysis.

Shear Stress–Dependent Platelet Function

Shear stress–dependent platelet function was assessed with a cone and platelet analyzer as described.[19]

Statistical Analysis

The primary end points were the changes in mean 24-hour systolic ABP (SBP) and diastolic ABP (DBP) and the change in FMD after 2 weeks of treatment with acetaminophen compared with placebo. After evaluation of the first 22 patients, the analysis demonstrated insufficient power for the results on BP measurements. Therefore, using the data obtained so far (SD of the difference, 4.9 mm Hg; minimal detectable difference in means, 2.5 mm Hg), we calculated the sample size needed (33 patients) for an 81% statistical power and a significance level of 0.05 (2 sided) for this crossover study. Analysis was performed with Wilcoxon-Mann-Whitney *U* tests (to account for possible nonnormality of the end points) using methods discussed by Senn.[20] That is, we considered 2 distinct groups of patients: group 1, who received acetaminophen followed by placebo, and group 2, who received placebo followed by acetaminophen. Within each group, data are summarized by examining within-patient changes between periods 1 and 2 (For both groups, this is a subject's respective change from baseline while on acetaminophen minus the change from baseline while on placebo). These unpaired change scores are then analyzed across groups 1 and 2 with the Wilcoxon rank-sum test (Mann-Whitney *U* test), as proposed by Hill and Armitage[21] and later discussed by Senn.[20] The effect of acetaminophen is estimated as the average of the 2 group-specific mean change scores. The period effect is estimated using the difference of the 2 group-specific mean change scores (divided by 2). The carryover effect was excluded through the use of an unpaired Wilcoxon test of within-patient change from baseline including only the first period of treatment. Because there were 3 end points of primary interest, a Bonferroni correction was made. Results are presented as mean±SD or SEM as described.

Analysis of the primary end point was performed in the R programming language (R Development Core Team, 2009). The statistical software package SPSS 17 (SPSS Inc, Chicago, Ill) was used to evaluate differences in the clinical characteristics. Statistical significance was accepted at $P<0.05$.

Results

Study Population

A total of 37 patients were enrolled; however, 4 patients withdrew their informed consent because of personal reasons after the first visit (Figure 1). Therefore, 33 patients (mean age, 60.5±8.5 years; 28 men; body mass index, 27.8±6.0 kg/m^2) were included in the analysis. Their clinical characteristics and baseline laboratory are presented in Tables 1 and 2.

Effects of Acetaminophen on 24-Hour BP

Acetaminophen (1 g TID) induced a significant increase in SBP (from 122.4±11.9 to 125.3±12.0 mm Hg; $P=0.021$ compared with placebo) and DBP (from 73.2±6.9 to 75.4±7.9 mm Hg; $P=0.024$ compared with placebo), whereas there was no change after placebo (SBP, from 122.7±11.6 to 122.2±10.5 mm Hg; DBP, from 74.4±6.9 to 74.6±7.2 mm Hg; Figure 2 and Table 1).

Heart rate in the 24-hour measurement increased with acetaminophen (from 68.2±10.2 to 70.8±10.1 bpm) and did not change with placebo (from 68.7±9.7 to 67.9±8.1 bpm). There was no significant difference between acetaminophen and placebo ($P=0.22$; Table 1).

A period effect was excluded for 24-hour SBP, DBP, and heart rate ($P=0.62$, 0.59, and 0.32, respectively). A carryover effect was excluded for 24-hour SBP, DBP, and heart rate ($P=0.67$, 0.53, and 0.41, respectively).

Effects of Acetaminophen on Endothelium-Dependent and -Independent Vasodilatation

After 2 weeks of treatment with acetaminophen, there was no change in FMD compared with placebo (from 4.73±2.3% to 4.53±2.22% and from 4.68±2.54% to 4.71±2.15%; $P=0.64$; Table 1). Endothelium-independent vasodilatation, as assessed with glycerol trinitrate, remained unaltered (from 13.9±6.0% to 13.4±5.1% with acetaminophen and from

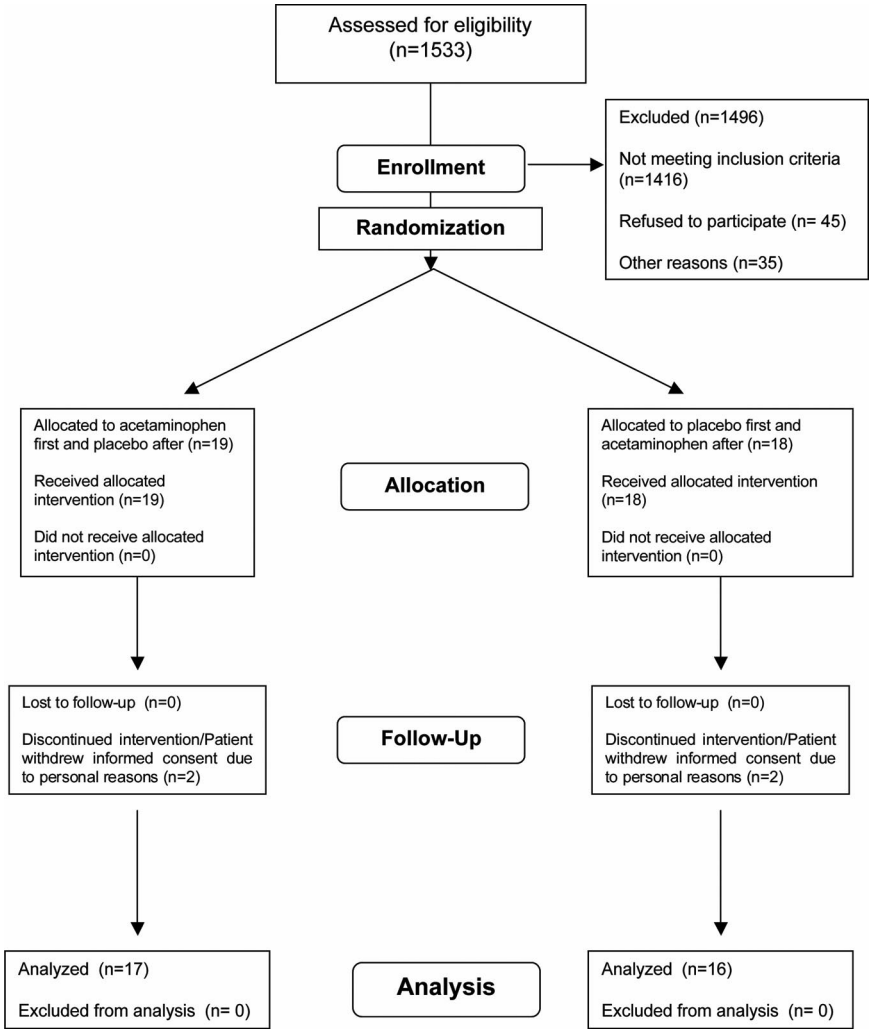

Figure 1. Flow chart of the study.

13.7±5.2% to 14.0±7.0% with placebo; $P=0.66$; Table 1). Baseline diameters (before acetaminophen, 4.45±0.65 mm; after acetaminophen, 4.46±0.58 mm; before placebo, 4.36±0.61 mm; and after placebo, 4.35±0.61 mm; $P=0.64$) and percent changes in flow velocity (before acetaminophen, 196.2%; after acetaminophen, 193.1%; before placebo, 203.1%; and after placebo, 201.5%; $P=0.92$) were similar in the 2 groups.

Effect of Acetaminophen on EPCs

The proportion of EPCs (percent double positive for both CD34 and CD309) was evaluated in 22 of the 33 patients and did not differ 2 weeks after treatment with acetaminophen or placebo (0.23% versus 0.34%, respectively; $P=0.11$).

Effect of Acetaminophen on Platelet Adhesion

Two weeks of treatment with acetaminophen 1 g TID or placebo did not change platelet adhesion significantly (area fraction, from 3.1±1.5% to 3.9±2.5% with acetaminophen and from 3.4±1.6% to 4.3±1.5% with placebo; $P=0.34$; Table 2).

Effect of Acetaminophen on Laboratory Parameters

Laboratory parameters before and after acetaminophen and placebo are shown in Table 2. No significant change in laboratory parameters was seen with the exception of γ-glutamyltransferase in the active treatment group. One patient showed a significant increase in γ-glutamyltransferase during acetaminophen therapy without any changes in alanine and aspartate aminotransferase; γ-glutamyltransferase normalized 2 weeks after cessation of the administration of acetaminophen. This patient denied recreational use of alcohol during the study time. The participant was included in the data analysis.

Discussion

This study demonstrates for the first time a significant increase in ABP in patients with CAD treated with acetaminophen but no significant effect on endothelial function, EPCs, or platelet function.

Selective and nonselective NSAIDs are associated with an increased risk for cardiovascular events.[22] Thus, current guidelines suggest avoiding NSAIDs and COX-2 inhibitors in patients with high cardiovascular risk or established CAD[1] and recommend acetaminophen as the first-line analgesic of choice, particularly in patients with high cardiovascular risk. The results of the present study, however, question the assumption of the cardiovascular safety of acetaminophen because they provide the first prospective evidence that

Table 1. Clinical Measures Before and After Acetaminophen, Placebo, and Concomitant Drug Therapies During the Whole Study

	Baseline for Treatment Period	Acetaminophen	Baseline for Control Period	Placebo
Clinical parameters				
FMD, %	4.73±2.30	4.53±2.22	4.68±2.54	4.71±2.15
GTN, %	13.9±6.0	13.4±5.1	13.7±5.2	14.0±7.0
24-h SBP, mm Hg	122.4±11.9	125.3±12.0*	122.7±11.6	122.2±10.5
Daytime SBP, mm Hg	124.5±12.2	127.3±12.5*	125.2±12.2	124.2±10.7
Nighttime SBP, mm Hg	115.7±12.4	117.7±12.4	114.1±1094	114.7±12.4
24-h DBP, mm Hg	73.2±6.9	75.4±7.9*	74.4±6.9	74.6±7.2
Daytime DBP, mm Hg	75.1±7.4	76.9±8.6*	76.2±7.7	76.1±7.7
Nighttime DBP, mm Hg	66.9±7.3	68.5±7.8	67.4±7.1	66.9.0±6.4
24-h HR, bpm	68.2±10.3	70.8±10.1*	68.7±9.7	67.9±8.1
Daytime HR, bpm	69.8±10.5	72.4±9.8*	70.9±9.5	70.9±9.0
Nighttime HR, bpm	62.1±8.4	64.6±10.2*	63.6±9.3	64.1±9.2
Office SBP, mm Hg	131.5±15.8	133.8±16.2	131.8±11.5	130.6±10.6
Office DBP, mm Hg	80.6±8.8	82.7±8.7	81.0±6.8	81.3±8.7
Office HR, bpm	58.6±7.5	60.2±7.5	59.9±10.2	60.0±8.0
Body weight, kg	84.3±17.3	84.4±17.6	84.4±17.3	84.7±17.5
Concomitant medication, n (%)				
ACE inhibitor	21/33 (64)			
ARB	7/33 (21)			
β-blocker	17/33 (52)			
Calcium antagonist	6/33 (18)			
Aspirin (100 mg)	31/33 (94)			
Clopidogrel	11/33 (33)			
Statin	30/33 (91)			
Ezetimibe	2/33 (6)			

GTN indicates glycerol trinitrate; HR, heart rate; ACE, angiotensin-converting enzyme; DBP, diastolic blood pressure; SBP, systolic blood pressure; and ARB, angiotensin receptor blocker. Data are shown as mean±SD.

*Statistically significant difference ($P<0.05$), acetaminophen versus placebo.

acetaminophen increases ambulatory BP in patients with CAD. Importantly, the observed increase in BP associated with the use of acetaminophen was within the range of the hypertensive effects of traditional NSAIDs, particularly diclofenac and ibuprofen.[3,23–30] Importantly, epidemiological studies such as that by Forman and coworkers[3] demonstrated that men who took acetaminophen 6 to 7 d/wk compared with nonusers demonstrated an increased relative risk for incident hypertension compared with those taking NSAIDs. Additionally, in the Nurses' Health Study I and II, the multivariable-adjusted relative risk of incident hypertension for women who took acetaminophen >500 mg/d was increased almost 2-fold compared with women who did not use acetaminophen.[25] Although the most rigorous way to examine an association between nonnarcotic analgesics and hypertension would be a randomized controlled trial,[31] such a trial randomizing patients with chronic pain to analgesics versus placebo is ethically questionable and unlikely to be performed.

Prospective controlled studies with acetaminophen are scarce, and the results inconsistent.[6–8] Indeed, 1 study showed a 4-mm Hg increase[6] and the remaining 2 showed no change in BP associated with the use of acetaminophen in patients with hypertension.[7,8] It is of note that these studies were performed in patients with hypertension, not in the high-risk group of patients with established CAD in whom the use of acetaminophen is recommended by current guidelines.[6–8]

Because the use of acetaminophen is prevalent, the pressor response found in our study is a major public health concern. Indeed, in view of the established continuous incremental risk of cardiovascular and cerebrovascular disease in relation to BP, an increase in BP associated with the use of acetaminophen could further substantially increase the risk of myocardial infarction and stroke in patients at high cardiovascular risk or, in particular, with established cardiovascular or cerebrovascular disease.[32,33] Importantly, more antihypertensive therapy may have to be prescribed to counter the rise in BP, leading to increased costs.[34]

NSAIDs most likely induce a rise in BP by blocking the synthesis of prostaglandins, which regulate vascular tone and sodium excretion. Acetaminophen is generally considered only a weak inhibitor of prostaglandin synthesis.[35,36] Indeed, and as expected in patients on a background therapy with aspirin,[37] plasma and urinary concentrations of prostacyclin and thromboxane remained unchanged, thus rendering a

Table 2. Laboratory Values Before and After Acetaminophen and Placebo

	Baseline for Treatment Period	Acetaminophen	Baseline for Control Period	Placebo
Hb, g/L	14.5±1.1	14.3±1.0	14.3±1.0	14.3±1.0
Ht, %	41.5±3.0	41.0±2.5	41.0±2.5	41.2±2.8
Sodium, mmol/L	140.4±2.2	140.6±1.9	140.8±1.8	140.4±2.3
Potassium, mmol/L	4.0±0.4	4.0±0.4	4.0±0.3	3.9±0.3
Creatinine, μmol/L	86.9±11.3	86.4±13.9	87.2±13.3	87.9±13.2
Glucose, mmol/L	5.7±1.0	5.6±1.0	5.8±1.3	5.7±1.1
TC, mmol/L	4.3±0.8	4.5±0.9	4.3±0.8	4.4±1.0
HDL-C, mmol/L	1.4±0.4	1.3±0.4	1.3±0.4	1.3±0.4
LDL-C, mmol/L	2.3±0.6	2.4±0.8	2.4±0.7	2.5±0.8
TG, mmol/L	1.4±0.7	1.7±0.9	1.3±0.6	1.3±0.6
ALT, U/L	29.9±8.04	35.1±12.4	28.8±17.0	31.3±10.6
AST, U/L	34.1±16.3	44.8±25.8	35.5±16.6	36.3±21
GGT, U/L	32.9±16.7	54.7±69.9*	37.2±23.2	33.5±17.4
Plasma PGE_2, ng/mL	45.1±18.2	45.3±18.2	47.1±19.8	45.6±21.5
Urinary PGE_2, ng/24 h	404.2±418.1	396.9±358.7	396.4±292.8	395.0±361.5
Plasma $TBXB_2$, ng/mL	34.2±21.4	32.1±24.3	33.2±23.9	34.1±23.9
hs-CRP, mg/L	1.5±1.8	1.5±1.5	1.4±1.3	3.6±6.1
Plasma 8-isoprostanes, pg/mL	1.6±0.9	1.6±0.6	1.5±0.7	1.7±1.1
PRA, $ng \cdot mL^{-1} \cdot /h^{-1}$	3.24±5.03	3.41±5.50	3.43±5.28	3.43±4.69
Aldosterone, pg/mL	72.5±28.7	69.3±23.8	67.5±24.1	74.2±24.8
Urinary sodium, mmol/L	108.0±43.4	105.1±38.8	116.8±39.4	103.5±40.8
Platelet adhesion, %	3.1±1.5	3.9±2.5	3.4±1.6	4.3±1.5

Hb indicates hemoglobin; Ht, hematocrit; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; hs-CRP, high-sensitivity C-reactive protein; PGE_2, prostaglandin E_2; $TBXB_2$, thromboxane B_2; and PRA, plasma renin activity. Data are shown as mean±SD.

*Statistically significant difference ($P<0.05$), acetaminophen versus placebo.

potential COX-2–inhibiting effect unlikely to fully explain the hypertensive effects of acetaminophen under the conditions of the present study.

Although the relative extent of COX-1 versus COX-2 inhibition has potential implications in determining drug safety in patients treated with NSAIDs,[38] concomitant COX-1 inhibition (and reduced thromboxane generation) with aspirin could have counterbalanced any potential COX-2–induced attenuation of prostacyclin release. However, in evaluations of drug safety, theoretical differences cannot serve as a substitute for well-designed randomized trials testing appropriate clinical outcomes. Furthermore, renal function, plasma renin activity, and plasma aldosterone remained unchanged and thus cannot account for the hypertensive effects of acetaminophen, particularly because the majority of patients were treated with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and β- adrenergic blockers.

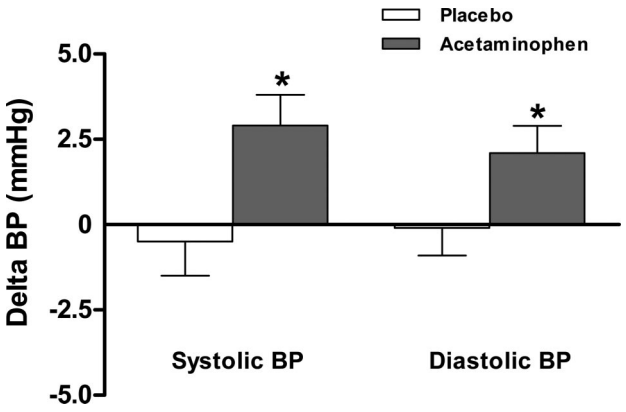

Figure 2. Difference in mean 24-hour ambulatory blood pressure (Delta BP, mm Hg) between baseline and treatment with acetaminophen (grey bars) and placebo (open bars). Data are presented as mean±SEM. Asterisks indicate a statistically significant difference ($P<0.05$) acetaminophen versus placebo.

Unexpectedly, the BP increase induced by acetaminophen was paralleled by a slight increase in rather than the expected baroreceptor-mediated decrease in heart rate. Even though this increase as such was not significant, it suggests a potential central effect of acetaminophen. A predominantly central mechanism of action involving central COX-2 inhibition or a COX variant has been proposed.[39,40] Of interest, a splice variant of COX-1 called COX-3, which is selectively inhibited by acetaminophen and is present mainly in the brain and spinal cord, has been reported.[41] The hypertensive effect of acetaminophen noted in the present study could be mediated by such central COX-3 activity or COX-2 inhibition by acetaminophen[42] or by an indirect activation of cannabinoid CB(1) receptors.[43]

In contrast to the observed effects on BP, the use of acetaminophen showed only a trend toward worsening of endothelial function, an important surrogate marker for vascular homeostasis. It is of note that any potential impairment of endothelial function after treatment with acetaminophen may be explained by a direct effect on the endothelium or secondary via the increase in BP. However, if endothelial function were affected by an increase in BP, 2 weeks of therapy would probably be too short to affect endothelial function. Moreover, a deleterious effect of acetaminophen could have been counterbalanced and masked by the concomitant angiotensin-converting enzyme inhibitors and statin therapy, all of which are known to beneficially affect EPCs and vascular function.[12,44] In contrast to acetaminophen, we demonstrated that celecoxib is able to improve endothelial function and to reduce low-grade chronic inflammation and oxidative stress in patients with CAD.[45]

Some limitations of our study should be taken into account. First, the study is relatively small. This could explain the lack of an effect of acetaminophen on FMD, particularly because the treatment period was short. However, because the patients included in this study did not present with pain and thus could not benefit from the study drug, the number of patients investigated was limited to the minimum required on the basis of sample size calculation. Although the capsules were identical in appearance and taste, a formal test of the adequacy of blinding was not performed. Although there may be a theoretical chance that the patients were able to determine their treatment arm, this appears to be relatively unlikely. Importantly, because of the crossover study design, all patients received both placebo and acetaminophen. Moreover, there was a predominance of men; therefore, the present results may not necessarily be extrapolated to women or to other patients with the exception of those with CAD under optimal pharmacological treatment.

Conclusions

Our study showed that acetaminophen at doses used in daily clinical practice may increase BP in patients with CAD and has no effect on vascular function. Unless the cardiovascular safety of acetaminophen has been cleared in randomized controlled clinical trials specifically addressing the safety of this agent, the use of acetaminophen should be as rigorously evaluated as all traditional antiinflammatory drugs, particularly in patients at increased cardiovascular risk.

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Disclosures

This study was investigator initiated and investigator driven. The authors report no actual or potential conflicts of interest in connection with this study.

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CLINICAL PERSPECTIVE

Nonsteroidal antiinflammatory drugs have been shown to increase the risk for cardiovascular events. In patients with coronary artery disease, current guidelines therefore suggest avoiding such drugs and recommend acetaminophen as the first-line analgesic of choice instead. However, the results of the present prospective study provide the first evidence of a blood pressure elevation in these patients, thus questioning the assumption of the cardiovascular safety of acetaminophen. In view of the established continuous incremental risk of cardiovascular and cerebrovascular disease in relation to blood pressure, an elevation associated with the use of acetaminophen could further increase the risk of myocardial infarction and stroke in patients at high cardiovascular risk or, in particular, in those with established cardiovascular disease. Because the use of acetaminophen is frequent, the blood pressure increase caused by this drug is a potential public health concern. Unless the cardiovascular safety of acetaminophen has been cleared in randomized controlled clinical trials specifically addressing the safety of this agent, the use of acetaminophen should be evaluated as rigorously as all traditional antiinflammatory drugs, particularly in patients at increased cardiovascular risk.