Regular acetaminophen use and blood pressure in people with hypertension The PATH-BP Trial

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Regular Acetaminophen Use and Blood Pressure in People With Hypertension: The PATH-BP Trial

Iain M. MacIntyre, PhD; Emma J. Turtle, MD; Tariq E. Farrah, MBChB; Catriona Graham, MSc; James W. Dear, PhD; David J. Webb, DSc; for the PATH-BP (Paracetamol in Hypertension–Blood Pressure) Investigators*

BACKGROUND: Acetaminophen is widely used as first-line therapy for chronic pain because of its perceived safety and the assumption that, unlike nonsteroidal anti-inflammatory drugs, it has little or no effect on blood pressure (BP). Although observational studies suggest that acetaminophen may increase BP, clinical trials are lacking. We, therefore, studied the effects of regular acetaminophen dosing on BP in individuals with hypertension.

METHODS: In this double-blind, placebo-controlled, crossover study, 110 individuals were randomized to receive 1 g acetaminophen 4× daily or matched placebo for 2 weeks followed by a 2-week washout period before crossing over to the alternate treatment. At the beginning and end of each treatment period, 24-hour ambulatory BPs were measured. The primary outcome was a comparison of the change in mean daytime systolic BP from baseline to end of treatment between the placebo and acetaminophen arms.

RESULTS: One-hundred three patients completed both arms of the study. Regular acetaminophen, compared with placebo, resulted in a significant increase in mean daytime systolic BP (132.8±10.5 to 136.5±10.1 mm Hg [acetaminophen] vs 133.9±10.3 to 132.5±9.9 mm Hg [placebo]; $P<0.0001$) with a placebo-corrected increase of 4.7 mm Hg (95% CI, 2.9–6.6) and mean daytime diastolic BP (81.2±8.0 to 82.1±7.8 mm Hg [acetaminophen] vs 81.7±7.9 to 80.9±7.8 mm Hg [placebo]; $P=0.005$) with a placebo-corrected increase of 1.6 mm Hg (95% CI, 0.5–2.7). Similar findings were seen for 24-hour ambulatory and clinic BPs.

CONCLUSIONS: Regular daily intake of 4 g acetaminophen increases systolic BP in individuals with hypertension by ≈5 mm Hg when compared with placebo; this increases cardiovascular risk and calls into question the safety of regular acetaminophen use in this situation.

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Key Words: acetaminophen ■ blood pressure ■ cardiovascular disease ■ chronic pain ■ hypertension

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Acetaminophen (paracetamol in the United Kingdom) is the most widely used analgesic globally, and is generally the initial drug of choice for the treatment of chronic pain.[1] Recent evidence, however, suggests that its role in the management of chronic pain has probably been overstated.[2–5] As evidence grows to suggest regular acetaminophen use has, at best, limited benefit for chronic pain, greater emphasis on determining the harms of acetaminophen will allow more informed decision-making by clinicians and patients. The significant risks of acetaminophen in overdose are well-known.[6] However, considerable uncertainty remains

Correspondence to: David J. Webb, DSc, The Queen's Medical Research Institute, 3rd Floor East, Room E3.22, 47 Little France Crescent, Edinburgh EH16 4TJ, UK. Email D.J.Webb@ed.ac.uk

*A list of investigators in the PATH-BP (Paracetamol Treatment in Hypertension–Blood Pressure) trial is given in the Appendix.

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Clinical Perspective

What Is New?

- Regular acetaminophen use increases both systolic and diastolic blood pressure in individuals with hypertension, with an effect similar to that of nonsteroidal anti-inflammatories.
- This rise in blood pressure is seen both in those taking and not taking antihypertensive therapy.

What Are the Clinical Implications?

- Acetaminophen is widely prescribed for the management of chronic pain but has limited evidence of efficacy.
- Because of the established continuous relationship between blood pressure and cardiovascular and cerebrovascular diseases, as well as the widespread use of acetaminophen, this rise in blood pressure may contribute to an increase in cardiovascular morbidity and mortality.
- Caution should be taken when prescribing acetaminophen, particularly in those with increased cardiovascular risk, and opportunities to stop acetaminophen or reduce the dose should be considered.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitor
ALT	alanine aminotransferase
BP	blood pressure
NHS	National Health Service
NSAID	nonsteroidal anti-inflammatory drug

regarding the safety of chronic acetaminophen use at therapeutic doses because of reliance on observational data and cohort studies[1] that often have conflicting results. One key area of study has been on the effect of acetaminophen on blood pressure (BP). Many observational studies suggest that acetaminophen increases BP. However, interventional data remain limited to smaller, largely underpowered trials that have not affected clinical practice.[7] To address this knowledge gap, we performed a randomized, double-blind, crossover study comparing the effects of regular acetaminophen and matched placebo on BP in individuals with hypertension: the PATH-BP (Paracetamol Treatment in Hypertension–Blood Pressure) trial.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This single-center, randomized, double-blind, placebo-controlled, investigator-initiated crossover study funded by the British Heart Foundation analyzed the impact of regular acetaminophen treatment on BP in individuals with treated and untreated hypertension during a 2-week period. The study was performed in the University of Edinburgh's Clinical Research Center (Western General Hospital, Edinburgh, UK) and was overseen by the Academic and Clinical Central Office for Research Development, a partnership between the University of Edinburgh and National Health Services (NHS) Lothian Health Board. The study protocol was approved by the East of Scotland Research Ethics Service (13/ES/0087) and the Medicines and Healthcare products Regulatory Agency (2013-003204-40). It was registered with the US National Institutes of Health (URL: https://clinicaltrials.gov; Unique identifier: NCT01997112) and European Union Drug Regulating Authorities Clinical Trials Database (URI: https://www.clinicaltrialsregister.eu; Unique identifier: 2013-003204-40).

Study Population

To meet inclusion criteria for enrollment, individuals had to be aged ≥18 years of age and hypertensive. They had to either be: (1) treated for hypertension with an average daytime ambulatory BP of <150/95 mm Hg on stable doses of ≥1 antihypertensive medication; or (2) untreated with an average daytime ambulatory BP ≥135/85 mm Hg but <150/95 mm Hg. Individuals were excluded if they had a history of ischemic heart disease, heart failure, cerebrovascular disease, liver impairment (ALT [alanine aminotransferase] >50 IU/L), chronic kidney disease staged III to V, or suicidal ideation. Individuals were also excluded if they weighed <55 kg or were regularly taking acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or oral anticoagulants. Participants were recruited from local ambulatory BP clinics, general practices (with support from NHS Research Scotland Primary Care Network), and the Scottish Health Research Register (an NHS Research Scotland register of people interested in participating in health research). All study participants provided written informed consent before participation.

Protocol

After screening and recruitment, participants were randomly assigned to receive either 1 g acetaminophen 4× daily (the maximum recommended daily dose and a commonly prescribed dose for chronic pain in the UK[8]) or matched placebo for 2 weeks. After a 2-week washout, patients crossed over to the other treatment arm for an additional 2 weeks of treatment (Figure S1). Treatment order was randomized, with concealed allocation, using a random block design, and participants were assigned to receive drug then placebo, or placebo then drug, in a 1:1 ratio. All researchers and participants were blinded to treatment throughout the study.

Participants attended 4 visits during each arm of the study: 2 long visits at Days 0 (pretreatment) and 14; and 2 short visits at Days 4 and 7. During the long visits, clinic BP was recorded, a 24-hour ambulatory BP monitor (ABPM) fitted, and blood samples taken. On short visits, only clinic BP and blood samples were taken. Blood samples were taken for measurement

of urea and electrolytes, liver function tests (bilirubin, alkaline phosphatase, and ALT), and acetaminophen concentration.

The study drug and placebo were both prepared in identical hard gelatin capsules (Swedish Orange, size 00; Capsugel) by the Investigational Supplies Group (University of Edinburgh) to ensure identical appearance of both formulations for blinding purposes. The study drug contained 500 mg acetaminophen (product license No. PL17907/0057; Bristol Laboratories Ltd., Berkhamsted, UK) and had negligible sodium content (0.04 mg sodium per capsule). Placebo contained maize starch. No changes to background antihypertensive therapy were allowed during the study.

BP Monitoring

During each visit clinic BP measurements were taken after subjects had been sitting for a minimum of 10 minutes. Three serial clinic BP measurements were taken in the nondominant arm using a calibrated Microlife Watch BP recorder (Microlife AG Swiss Corporation, Switzerland).[9] The average of the second and third readings was recorded.

At the beginning and end of each phase of the study, ABPM was obtained during a 24-hour period using the Spacelabs Healthcare 90207 Ambulatory BP recorder (Spacelabs, WA). This was done in accordance with current UK guidelines.[10] The monitors were set to record BP every 30 minutes during the day and hourly at night.

Laboratory Analysis

Urea and electrolytes, liver function tests, and serum acetaminophen were analyzed by NHS Lothian laboratories (UK Accreditation Service Laboratory No. 8699) in accordance with International Standard ISO 15189:2012 using Abbott Architect c16000 and ci16200 analyzers.

Study Outcomes

The primary outcome was defined as the change in mean daytime systolic ambulatory BP after 2 weeks of treatment with acetaminophen compared to placebo. The prespecified secondary end points were changes in mean daytime diastolic, systolic 24-hour, diastolic 24-hour, and clinic BPs after 2 weeks of treatment with acetaminophen compared with placebo.

Sample Size and Statistical Analysis

We estimated that a total of 110 patients would need to be recruited to detect a 1.6-mm Hg difference in the change in systolic BP between acetaminophen and placebo arms using a 2-sided, paired Student *t* test with 5% level of significance and 90% power, assuming a 4.9-mm Hg[11] SD of the difference and a dropout rate of 10%.

The statistical analysis was predefined in the statistical analysis plan which was finalized and signed before the data were unblinded. The ABPM analyses were based on a modified intention-to-treat population, consisting of all randomized participants who had valid ABPM data at all time points, thus excluding participants with missing ABPM data. To account for the potential impact of treatment order, the primary and secondary BP data were analyzed using a mixed model where treatment, period and baseline BP were fitted as fixed effects and the participant as a random effect with results presented in the form of least square means. Each of the comparisons was considered significant if $P < 0.05$. In addition, a per-protocol analysis was performed based on compliance with treatment, where compliance was based on serum acetaminophen levels. Compliance was defined as an undetected acetaminophen level (<3 mg/L) throughout the placebo phase and at baseline of the acetaminophen phase, as well as a detectable acetaminophen level at the final measurement (when ABPM was assessed) and at least 1 of the other 2 time points during the treatment period. Blood results were analyzed using paired Student *t*-tests. Each of the comparisons was considered significant if $P < 0.05$.

RESULTS

Study Population

A total of 204 local participants were screened; 110 White participants were randomized onto the study between September 2014 and June 2019 (Figure). Seven participants did not complete both arms of the study (drop-out rate < 10%), so 103 participants were included in the modified intention-to-treat analysis. The study group was balanced on all baseline characteristics (Table 1; Table S1). Based on acetaminophen assays, 90 participants were included in the per-protocol analysis (Figure).

Primary End Point

Using a mixed model to account for period effect, an increase in mean daytime systolic ambulatory BP of 4.7 mm Hg (95% CI, 2.9–6.6; $P<0.0001$) with acetaminophen compared with placebo was observed (Table 2).

Secondary End Points

Ambulatory BP

Compared to placebo treatment, acetaminophen treatment was associated with a 4.2-mm Hg increase in mean 24-hour systolic BP (95% CI, 2.4–6.0; $P<0.0001$); 1.6-mm Hg increase in mean daytime diastolic BP (95% CI, 0.5–2.7; $P=0.005$); and a 1.4-mm Hg increase in mean 24-hour diastolic BP (95% CI, 0.3–2.5; $P=0.017$; Table 2). Similar findings were seen in the per-protocol analysis with increases in mean daytime systolic BP of 4.5 mm Hg (95% CI, 2.5–6.5; $P<0.0001$), mean 24-hour systolic BP of 4.2 mm Hg (95% CI, 2.3–6.1; $P<0.0001$), mean daytime diastolic BP of 1.5 mm Hg (95% CI, 0.3–2.7; $P=0.015$), and mean 24-hour diastolic BP of 1.3 mm Hg (95% CI, 0.2–2.5; $P=0.021$; Table 3). Post hoc analysis showed no evidence of a statistical difference in the change in daytime systolic BP between participants with treated or untreated hypertension (Figure S2).

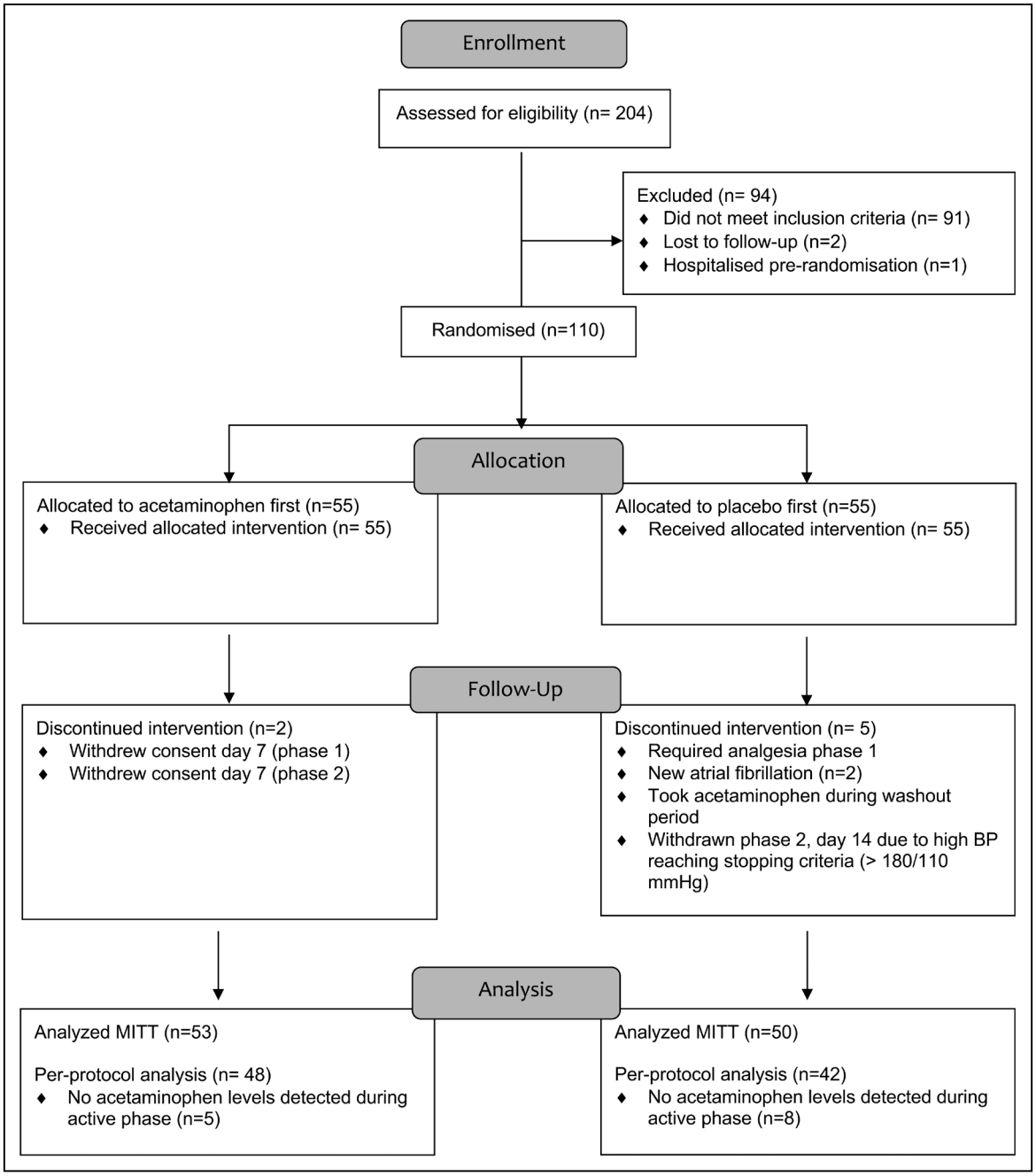

Figure. Flow diagram of study.
BP indicates blood pressure; and MITT, modified intention-to-treat.

Clinic BP

An increase in clinic BP was seen in the acetaminophen arm when compared with placebo, with a systolic BP change of 4.6 mm Hg (95% CI, 2.4–6.7; $P<0.0001$) and diastolic BP change of 1.6 mm Hg (95% CI, 0.1–3.0; $P=0.031$; Table 2). In the per-protocol analysis, there was an increase in systolic BP of 4.4 mm Hg (95% CI, 2.1–6.7; $P<0.001$) with no significant change in diastolic BP ([1.5 mm Hg] 95% CI, −0.1 to 3.0; $P=0.059$; Table 3). The rise in BP was seen by Day 4 and sustained at Day 14 (Figure S3).

Biochemical Parameters

Biochemical parameters are shown in Table 4. No significant changes were seen except for a modest but statistically significant rise in ALT activity with acetaminophen therapy, which normalized within 2 weeks of stopping acetaminophen.

Serious Adverse Events

Two serious adverse events were recorded during the study. The first was a case of atrial fibrillation requiring

Table 1. Baseline Characteristics

	Acetaminophen first (n = 55)	Placebo first (n = 55)
Age, y (mean ± SD)	60.9±7.8	62.5±7.8
Male sex, No. (%)	40 (73)	44 (80)
Smoking status, No. (%)		
Current	2 (4)	2 (4)
Ex-smoker	17 (31)	22 (40)
Never smoked	36 (65)	31 (56)
Receiving treatment for hypertension, No. (%)	39 (71)	35 (64)
Antihypertensive treatment, No. (%)		
Angiotensin-converting enzyme inhibitor	19 (35)	15 (27)
Angiotensin receptor blocker	18 (33)	16 (29)
Calcium channel blocker	10 (18)	14 (25)
Diuretic	13 (24)	17 (31)
β-blocker	4 (7)	4 (7)
Number of antihypertensives, No. (%)		
0	16 (29)	19 (35)
1	21 (38)	14 (25)
2	11 (20)	14 (25)
3	7 (11)	8 (15)
Statin therapy, No. (%)	15 (27)	13 (24)

Data for the patients in the modified intention-to-treat group are shown in Table S1.

the participant to be admitted to hospital. This occurred during the active phase of the study but was not considered to be related to acetaminophen. The second serious adverse event, a myocardial infarction, occurred before dosing of any study medications and was, therefore, not related to either acetaminophen or placebo.

One participant had to be withdrawn from the study after exceeding the predefined safety stopping criteria for BP (defined as having a clinic BP >180/110 mm Hg). This occurred on Day 14 of acetaminophen treatment. The participant's clinic BP measured 185/76 mm Hg and after a further 10-minute rest period, it remained elevated at 183/85 mm Hg. After discontinuation of acetaminophen, the participant's BP normalized. As this patient did not complete all 4 ABPM recordings, their data were not included in the modified intention-to-treat or per-protocol analysis.

DISCUSSION

This randomized, placebo-controlled, crossover study provides clear evidence that acetaminophen raised BP during a 2-week period when compared to placebo in people with hypertension. The effects are robust for systolic BP measured by ABPM (the "gold standard" for BP measurement[10]) and in the clinic. When compared with placebo, the increases in systolic and diastolic BPs were ≈4.7 mm Hg and ≈1.6 mm Hg, respectively, both significant when compared with placebo. This effect on BP was similar in those with treated or untreated hypertension. Because of the established continuous relationship between BP and cardiovascular and cerebrovascular diseases, even a small change in BP can have important effects on clinical outcomes. Indeed, the 4.7-mm Hg difference in BP, greater than the study was powered to detect, might be expected to translate to ≈20% more cardiovascular events during any period of chronic treatment.[12,13]

Acetaminophen is the most widely used over-the-counter and prescription analgesic worldwide.[1] In Scotland alone, >500 000 patients (from a total population of 5.4 million) received ≥3 prescriptions for acetaminophen-containing medications in 2018, consistent with regular use; it is the predominant treatment of chronic pain (National Health Service's National Services Scotland prescribing data, 2018). In the United States it is estimated that between 3% to 5% of the adult population regularly take acetaminophen,[14] increasing to ≈8% in those newly diagnosed with hypertension.[15] Given the large number of people taking acetaminophen regularly in the United States and worldwide, the 4.7-mm Hg pla-

Table 2. Change in BP After Acetaminophen and Placebo: Modified Intention-to-Treat Analysis

	Acetaminophen			Placebo			Estimate of difference in change from mixed model	*P* value
	Baseline	Day 14	Mean change in baseline to Day 14	Baseline	Day 14	Mean change in baseline to Day 14		
Daytime systolic BP, mm Hg	132.8±10.5	136.5±10.1	3.7±7.4	133.9 ± 10.3	132.5±9.9	−1.4±7.6	4.7 (2.9–6.6)	<0.0001
24-h systolic BP, mm Hg	126.5±9.8	130.0±9.9	3.5±7.1	127.4±9.6	126.4±9.9	−1.0±7.3	4.2 (2.4–6.0)	<0.0001
Daytime diastolic BP, mm Hg	81.2±8.0	82.1±7.8	0.9±4.2	81.7±7.9	80.9±7.8	−0.8±4.4	1.6 (0.5–2.7)	0.005
24-h diastolic BP, mm Hg	76.8±7.5	77.8±7.3	0.9±4.2	77.3±7.0	76.7±7.0	−0.5±4.3	1.4 (0.2–2.5)	0.017
Clinic systolic BP, mm Hg	137.4±11.0	140.5±12.2	3.15±10.3	136.6±10.3	135.6±10.9	−1.1±9.2	4.6 (2.4–6.7)	<0.0001
Clinic diastolic BP, mm Hg	85.9±8.5	86.5±9.1	0.6±6.6	85.7±8.8	84.8±8.9	−0.9±6.1	1.6 (0.1–3.1)	0.031

The modified intention-to-treat analysis included all subjects with valid ambulatory BP recordings for each time period and included the primary end point: placebo-corrected change in daytime systolic BP. *P* values were derived from a mixed model with treatment, period, and baseline BP as fixed effects and participant as a random effect. Data are mean±SD. Estimate (95% CI) of difference in change from the mixed model is presented as least square means. N=103. BP indicates blood pressure.

Table 3. Change in BP After Acetaminophen and Placebo: Per-Protocol Analysis

	Acetaminophen			Placebo			Estimate of difference in change from mixed model	*P* value
	Baseline	Day 14	Mean change in baseline to Day 14	Baseline	Day 14	Mean change in baseline to Day 14		
Daytime systolic BP, mm Hg	133.1±10.6	136.7±10.2	3.6±6.9	134.1±10.5	132.9±10.2	−1.2±7.6	4.5 (2.5–6.5)	<0.0001
24-h systolic BP, mm Hg	126.7±9.9	130.3±9.9	3.6±6.6	127.5±9.7	126.7±9.3	−0.9±7.0	4.2 (2.3–6.1)	<0.0001
Daytime diastolic BP, mm Hg	80.8±7.8	81.8±7.7	1.0±3.9	81.4±7.7	80.8±7.9	−0.5±4.4	1.5 (0.3–2.7)	0.015
24-h diastolic BP, mm Hg	76.5±7.5	77.5±7.4	1.0±4.0	77.0±7.0	76.5±7.1	−0.4±4.1	1.4 (0.2–2.5)	0.021
Clinic systolic BP, mm Hg	137.4±11.0	140.1±11.8	2.7±10.2	137.0±10.3	135.5±10.4	−1.5±9.0	4.4 (2.1–6.7)	0.0002
Clinic diastolic BP, mm Hg	85.6±8.6	85.9±8.9	0.3±6.3	85.3 ± 8.4	84.3±8.6	−1.0±6.2	1.5 (−0.1 to 3.0)	0.059

Per-protocol analysis included all patients with appropriately detectable acetaminophen during the study. *P* values were derived from a mixed model with treatment, period, and baseline BP as fixed effects and participant as a random effect. Data are shown as mean±SD. Estimate (95% CI) of difference in change from the mixed model is presented as least square means. N=90. BP indicates blood pressure.

cebo-corrected rise in systolic BP, as seen in our study, could have considerable consequences on the population as a whole.

Many observational studies have suggested that long-term acetaminophen use is associated with an increased risk of developing hypertension.[7] The prospective Nurses' Health Study II, which included 80 030 participants, found an association between regular acetaminophen use and hypertension with a relative risk of developing hypertension of 2 (95% CI, 1.5–2.6). This was near identical to that of NSAIDs, which had a relative risk of 1.9 (95% CI, 1.5–2.3).[16] Further analysis of the Nurses' Health Studies I and II also suggested a possible dose–response relationship with increasing doses of acetaminophen independently increasing the risk of hypertension in women.[17] In contrast, however, a recent retrospective, observational, propensity-matched study of 2754 participants showed no association between regular acetaminophen use and hypertension.[18] With many possible confounders, not all of which are likely to be identified, drawing any reliable conclusions from these observational studies is difficult; prospective interventional trials, however, have generally been limited by small size and poor design.[7] Previously, the largest and best designed study involved 33 participants with known coronary artery disease. The results showed that 3 g acetaminophen per day significantly increased BP after 2 weeks, with a rise in systolic BP of ≈3 mm Hg compared with placebo.[11] These results are in keeping with the present study. Unfortunately, the study's relatively small sample size and its very specific patient population limits its generalizability.

The findings of our study further call into question current guidelines suggesting that acetaminophen is a safe alternative to NSAIDs. Indeed, the rise in BP seen in this study matches that seen with NSAIDs,[19–22] and may well explain the finding that self-reported frequent acetaminophen use in women is associated with an increase in cardiovascular events similar to that seen with frequent NSAID use.[23] While the precise mechanism of actions of acetaminophen remain unclear, it is believed to involve COX2 (cyclooxygenase-2) inhibition which may, at least in part, explain the these similarities.[1] These findings suggest that caution should be used when encouraging or prescribing regular use of acetaminophen, particularly in those with hypertension and are otherwise at risk of ischemic heart disease and stroke. Additionally, acetaminophen should no longer be

Table 4. Laboratory Values Before and After Acetaminophen and Placebo

	Acetaminophen		Placebo	
	Baseline	Week 2	Baseline	Week 2
Urea, mmol/L (n=103)	5.6 ± 1.4	5.7±1.6	5.7 ± 1.4	5.6±1.6
Sodium, mmol/L (n=103)	139.8±2.0	139.7±2.5	140.0±1.8	139.9±2.1
Potassium, mmol/L (n=103)	4.3±0.3	4.4±0.4	4.3±0.3	4.4 ± 0.3*
Creatinine, µmol/L (n=103)	77.2 ± 12.0*	76.3±11.9	77.2±11.9	77.6±12.3
Serum bicarbonate, mmol/L (n=103)	25.7±2.0	25.4±2.0	25.5 ± 1.9*	25.6±2.1
Alkaline phosphatase, U/L (n=100)	74.2±18.4	70.9±16.2	73.1±16.6	72.2±15.4
Alanine aminotransferase, U/L (n=100)	24.3±18.7	36.2±20.7†	23.5±10.5	22.4±9.6
Bilirubin, µmol/L (n=100)	10.4±4.3	9.8±4.1	10.3±4.8	9.8±4.4

Data are mean±SD.
*Single data point missing (n=102).
†Statistically-significant difference (*P*<0.0001), acetaminophen vs placebo.

thought of as a "safe" alternative analgesic to NSAIDs, at least with respect to hypertension.

Some limitations of our study should be taken into account. Firstly, the study was performed in individuals who had diagnoses of hypertension. Therefore, it is not clear whether findings can be extrapolated to individuals who are not hypertensive. In general, however, rates of chronic pain increase with age—similar to rates of hypertension—so it is expected that a substantial proportion of patients with chronic pain will also have a diagnosis of hypertension. The second limitation is study duration; it is unclear whether the increase in BP with acetaminophen use during 2 weeks is sustained in people taking longer-term acetaminophen therapy. However, the clinic BP data shows that BP rises by Day 4 and remains stably elevated at Day 14 (Figure S3), making the effect likely to be long term, in keeping with the findings of the largest observational study[16] and other studies examining the effects of NSAIDs on BP.[19,20] A third limitation of the study was that it was performed in a group of individuals who did not suffer from chronic pain and would not normally be taking regular acetaminophen. The study was designed in this way to remove pain as a possible confounder because of its known effects on BP. With increasing evidence that acetaminophen has limited, if any, effect on chronic pain,[2–5] it is likely, that in many patients, reducing the dose or even stopping acetaminophen would reduce BP, as well as its associated cardiovascular risk, without worsening chronic pain. Finally, the study was only performed in a White population and it is therefore unclear whether these differences would be observed in other populations.

Conclusion

The present study shows that acetaminophen increases BP in people with hypertension and adds to concerns regarding the safety of regular acetaminophen treatment, particularly in those at risk of developing ischemic heart disease and stroke.

ARTICLE INFORMATION

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Affiliations

Department of Renal Medicine, Royal Infirmary of Edinburgh, National Health Service Lothian, UK (I.M.M., T.E.F.). University/British Heart Foundation Center of Research Excellence, Center for Cardiovascular Science, Queen's Medical Research Institute (I.M.M., E.J.T., T.E.F., J.W.D., D.J.W.), and Edinburgh Clinical Research Facility (C.G.), University of Edinburgh, UK.

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Disclosures

None.

Supplemental Material

Figures S1–S3
Table S1

APPENDIX: PATH-BP (PARACETAMOL TREATMENT IN HYPERTENSION–BLOOD PRESSURE) STUDY INVESTIGATORS

Morag McCallum, RN, University/British Heart Foundation Center of Research Excellence, Center for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Little France Crescent, Edinburgh, UK

Vanessa Melville, RN, University/British Heart Foundation Center of Research Excellence, Center for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

Henry Fok, PhD, University/British Heart Foundation Center of Research Excellence, Center for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

Jame C. McCrae, PhD, University/British Heart Foundation Center of Research Excellence, Center for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

Ashish Sule, MD, University/British Heart Foundation Center of Research Excellence, Center for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

Thomas M. Caparrotta, MBBCh, University/British Heart Foundation Center of Research Excellence, Center for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

Nicholas S. Kirkby, PhD, Cardiothoracic Pharmacology, National Heart and Lung Institute, Imperial College London, UK

Jane A. Mitchell, PhD, Cardiothoracic Pharmacology, National Heart and Lung Institute, Imperial College London, UK

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