Kidney Medicine

Acetaminophen Exacerbates Hypertension: A #NephJC Editorial on PATH-BP

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#NephJC is a recurring twitter-based journal club. #NephJC editorials highlight the discussed article and summarize key points from the NephJC TweetChat.

Pain is very common, and therefore so is the use of analgesics. If analgesics in widespread use even slightly increase cardiovascular risk, the knock-on effects can be huge; if the single most common analgesic worldwide were to cause a significant increase in blood pressure, this would be a public health disaster.

Acetaminophen (also known as paracetamol) is one of the options on the first rung of the World Health Organization analgesic ladder for treatment of cancer pain,[1] and it is the most commonly used analgesic worldwide.[2] Recently, acetaminophen's efficacy as an analgesic for chronic pain has been questioned.[3,4] Nevertheless, it is the perceived safety of acetaminophen that reassures doctors and patients regarding continuous long-term use. This remains true when compared with alternative over-the-counter analgesics such as nonsteroidal anti-inflammatory drugs, whose side effects are well known and include increased cardiovascular risk, hypertension, gastrointestinal ulceration, and acute kidney injury.[5]

The safety profile of acetaminophen has now been called into question. Previous observational studies have reported associations with increased cardiovascular, kidney, and gastrointestinal adverse events.[6] The Nurses Health Study II reported an association between regular acetaminophen use and hypertension, with a relative risk of developing hypertension of 2.00 (compared to an relative risk of 1.86 with nonsteroidal anti-inflammatory drugs),[7] with a dose-dependent relationship (relative risk 1.38 in those who used 100 to 500 mg daily and relative risk 2.38 in those who used >500 mg daily).[8] However, these observational studies are subject to selection bias and confounding. The largest previous randomized, placebo-controlled crossover trial included only 33 patients with coronary artery disease, and reported a statistically significant increase in ambulatory blood pressure monitoring (ABPM) of 2.9 mm Hg systolic blood pressure (BP) while on 1 g acetaminophen 3 times daily.[9]

Due to decreasing confidence in acetaminophen's analgesic benefit and increasing concerns about it exacerbating hypertension, there was a need for high-quality data to address this safety concern. Therefore, the Paracetamol Treatment in Hypertension-Blood Pressure (PATH-BP) trial was designed to compare the effect of acetaminophen versus placebo on BP in individuals with hypertension.[10]

THE STUDY

PATH-BP was a randomized, double-blinded, placebo-controlled, crossover trial performed at a single center in Edinburgh. It was funded by the British Heart Foundation. Participants were aged ≥18 years and hypertensive, defined as either treated for hypertension with an average daytime ABPM <150/95 mm Hg on stable doses of antihypertensive medications, or untreated with an average daytime ABPM between ≥135/85 and 150/95 mm Hg. Notable among exclusion criteria were history of ischemic heart disease or heart failure, cerebrovascular disease, liver impairment, chronic kidney disease stages 3-5, weight <55 kg, or regular treatment with acetaminophen, nonsteroidal anti-inflammatory drugs, steroids, or oral anticoagulants.

Participants were randomized to receive 2 weeks of 1 g acetaminophen 4 times daily (note this dose exceeds the package insert for acetaminophen in the United States) or a matched placebo. This was then followed by a 2-week washout period, after which participants crossed to the opposite treatment arm for a further 2 weeks. During each of the 2 weeks of intervention, participants attended 4 follow-up visits, with clinic BP checked at each and 24-hour ABPM undertaken twice. Adherence was assessed by checking acetaminophen blood levels. The primary outcome was change in mean daytime systolic ABPM after 2 weeks of treatment with acetaminophen versus placebo.

The trial was conducted between September 2014 and June 2019, with 110 participants randomized into the study and 103 participants included in the intention to treat analysis. All participants were White, the mean age was 62 years, 24% were women, and 68% were on at least one antihypertensive medication.

Being in the acetaminophen arm, compared to placebo, resulted in a significant increase in mean daytime systolic ABPM of 4.7 mm Hg (95% CI, 2.9-6.6; $P < 0.0001$). There was also a significant increase in mean daytime diastolic ABPM of 1.6 mm Hg, and consistent systolic and diastolic BP results noted in 24-hour ABPM and clinic BP measurements. This change was apparent as early as day 4 and had peaked by about day 7 based on clinic BP measurements. One participant on acetaminophen did develop accelerated hypertension, leading to exclusion from the study.

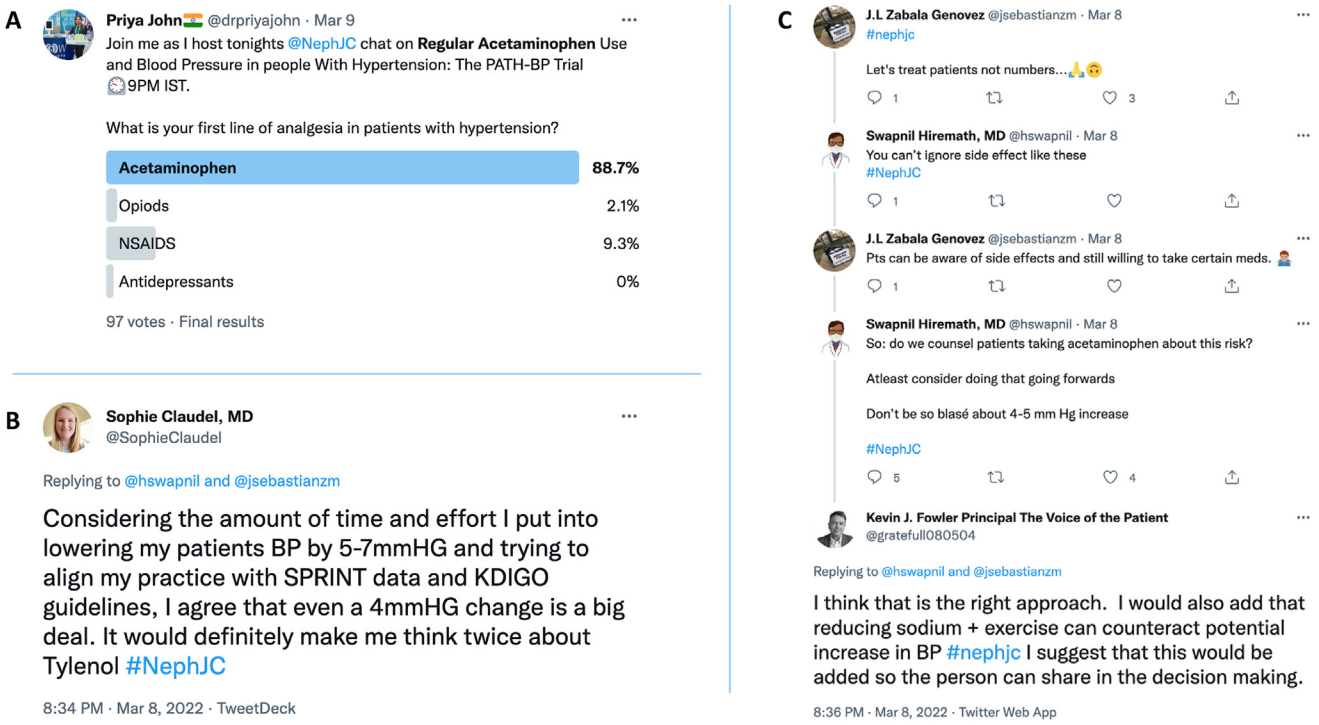

Figure 1. (A) A pre-chat Twitter poll was utilized to gauge analgesic practice patterns for patients with hypertension. From https://twitter.com/drpriyajohn/status/1501472376919568387?s=20&t=vrpU3OTTIT_7W8wCcBKSQQ. (B) A Twitter comment from an internal medicine resident physician about the magnitude of blood pressure increase. From https://twitter.com/SophieClaudel/status/1501385910553878529?s=20. (C) A Twitter discussion on having adverse effect discussions with patients and response providing a patient perspective. From https://twitter.com/gratefull080504/status/1501386378260664325?s=20.

THE TWEETCHAT

The 2 NephJC twitter discussions on PATH-BP on March 8 and 9, 2021 included 205 participants—nephrologists, internists, trainees, and patients. These participants tweeted a total of 841 times. In a poll at the outset, 88% of the participants' first choice analgesic for patients with hypertension was acetaminophen (Fig 1A), with lack of kidney side effects being voted as the most appealing feature by a large majority of respondents (who, admittedly, were largely nephrologists).

Overall, chat participants agreed this was a well-conducted trial but with concerning results. One cannot ignore a 4.7 mm Hg increase in systolic BP after only 2 weeks of acetaminophen therapy in an already hypertensive population (Fig 1B and 1C). If the 4.7 mm Hg difference in BP was sustained with chronic treatment, this would be expected to translate into increased cardiovascular events, given the linear relationship between BP and outcomes such as stroke, heart failure, and all-cause mortality.[11]

However, the validity of the study results in populations outside of the United Kingdom was questioned. Only White Europeans were recruited, restricting extrapolation of the results to other populations. In the United States, women are more likely to use analgesics than men,[12] but the study population was predominantly male. The acetaminophen dose of 1 g 4 times daily is commonly used in the UK but is often considered excessive worldwide, meaning that the lower doses used in other countries may be less likely to increase BP to the same extent, if this relationship is dose-dependent. It is unclear why this reasonably brief trail with only 110 participants took almost 5 years to perform.

Prolonged courses of acetaminophen are sometimes used for chronic pain, but in this study, patients only took active drug for 2 weeks. Although we would have liked to know the effects of long-term acetaminophen use on hypertension, it would have been hard to justify giving longer courses of analgesics to study participants without pain. From that ethical viewpoint, it was felt this study got the duration right, clearly establishing the effect of acetaminophen on BP.

This was not a mechanistic study, and the discussion speculated on whether the mechanism driving the observed BP increase could be decreased natriuresis, aldosterone upregulation, or some other mechanism. This study used an oral acetaminophen formulation with negligible sodium content, and there was concern that different (especially effervescent) preparations with very high sodium content may result in a greater hypertensive effect. Without knowing the mechanism driving the increased BP, we do not know whether patients with chronic kidney disease are

likely to have an attenuated or exacerbated BP response to acetaminophen, but given the lack of other safe options in this population, there was palpable disappointment as participants reflected on the results.

Examination of the side effect profile was of great interest. There was a statistically significant alanine aminotransferase increase in the acetaminophen group, but it remained in the "normal range" and settled after drug cessation. The second side effect mentioned was accelerated hypertension in one in 110 patients while on acetaminophen, which improved after drug cessation and led to their exclusion from the study results. This could have been due to chance, with the acetaminophen playing no causative role, but given the millions of people worldwide who use acetaminophen over the counter, it was certainly thought to be a scary observation.

Ultimately, as healthcare practitioners we have to decide whether a trial will change our practice, and it is useful in any journal club to get a sense of how other doctors are reacting to new data. It was agreed that there is unfortunately no such thing as an entirely "safe" analgesic, and we should continue to pursue nonpharmacological methods of pain relief where appropriate. However, we must also not be defeatist and just accept that our patients must suffer with pain. It was observed in the chat that our alternative options to acetaminophen, such as nonsteroidal anti-inflammatory drugs or opiates, are also fraught with side effects. The use of this study was to give us information about what to tell our patients with hypertension about the risks of acetaminophen so that we can come to a shared decision while acknowledging the importance of analgesics in improving quality of life for some of our patients.

CONCLUSION

Acetaminophen has long been considered a safe option for acute and chronic pain. Unfortunately for patients, PATH-BP was a well-executed trial that showed a 4.7 mm Hg increase in systolic BP when acetaminophen is used at a dose of 4 g per day for 2 weeks in patients with hypertension. This should lead us to be more cautious when recommending it, especially for patients with hypertension or increased cardiovascular risk.

ARTICLE INFORMATION

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