EVIDENCE BASED CASE REPORT

# Does paracetamol cause hypertension?

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We welcome contributions of evidence based case reports. These reports should describe a clinical dilemma raised by a real patient and show how evidence can be applied at all stages of patient care.

A newspaper article led this general practitioner and his patient to search for evidence and reach a decision on treatment

"Doc, I read in the paper that painkillers can give you high blood pressure. What do you think?" My patient was a 49 year old man with rheumatoid arthritis. His disease had previously been severe, but it had been improving in recent months with etanercept and intra-articular corticosteroids. In trying to answer his question, I began by explaining the cardiovascular risks of non-steroidal anti-inflammatory drugs.[1] However, the newspaper article he had read also linked paracetamol to the development of hypertension. I had not heard of this risk before.

Together, we retrieved the newspaper article from the internet.[2] It cited a recent American study which linked analgesic use to hypertension. I felt sceptical about this finding, but I needed to keep an open mind about this potentially common and important risk. I resolved to locate and appraise the study and to share my findings with my patient at a future consultation.

## Critically appraising the study

From clues in the newspaper article, I traced the study in question, which was by Forman and colleagues and had been published in *Archives of Internal Medicine*.[3] The paper began by explaining several possible mechanisms by which paracetamol may affect blood pressure, including inhibition of vasodilatory prostaglandins and effects on endothelial function. These "basic science" theories added plausibility to the possible association. The study was a prospective cohort study of 16 031 men followed for four years. The participants were male health professionals, aged on average in their mid-60s (older than my patient). The study aimed to measure the association between frequency of analgesic use and risk of new onset hypertension in men. The analgesic agents studied were paracetamol, non-steroidal anti-inflammatory drugs, and aspirin. The abstract stated that the risk of hypertension was 34% higher in frequent users of paracetamol than in the participants who did not use paracetamol.

A cohort study sounded like a feasible study design, allowing the authors to study a fairly common outcome in a large population of men. However, as with any observational study, I wondered how the authors had tried to avoid bias in their results. For example, were the frequent users of analgesics less active because of their pain and thus prone to hypertension because of inactivity? I was reassured to find that the authors used statistical techniques to adjust for many such potential confounders: age, body mass index, smoking, diet, physical activity, race, baseline blood pressure, and family history of hypertension.

I looked at the results. For paracetamol, the adjusted relative risk of hypertension was increased only in men taking paracetamol at least four days a week. The relative risk of hypertension was 1.59 for those taking paracetamol 4-5 days a week and 1.34 for those taking it 6-7 days a week. The former result was significant (95% confidence interval 1.13 to 2.24), but the latter was of borderline significance (1.00 to 1.79). After adjustment for baseline blood pressure, the latter risk became non-significant (relative risk 1.31; 0.96 to 1.80).

The study relied on men self reporting a diagnosis of hypertension; men who were hypertensive but unaware of their diagnosis would not have been counted. The authors considered whether men who took more analgesics were more likely to visit their doctors and therefore more likely to have hypertension incidentally detected. When they limited their analysis to men who had seen their doctors at least once during follow-up, the relative risk for men taking paracetamol 6-7 days a week lost significance (1.26; 0.94 to 1.70). Most men, however, had visited their physician at least once, and I was concerned that the authors seemed not to have adjusted for frequency of visits beyond a single visit. This seemed important, because the association between paracetamol and hypertension would likely be even less robust if this surveillance bias was controlled for.

Further, I wondered if the increase in blood pressure might be due to pain, rather than the paracetamol. This question had been raised previously in the literature.[4] I imagined that pain would be a difficult confounder to accurately measure and adjust for.

The paper left me unsure of what to tell my patient. It offered a tantalising suggestion of hypertensive harm from paracetamol, but this was of uncertain statistical

significance, and I detected a whiff of residual bias in the air. Would other papers answer our question?

## Other evidence

With the help of the "Asking focused clinical questions" tool on the University of Oxford's Centre for Evidence-Based Medicine's website (www.cebm.net/index.aspx?o=1036), I framed a clinical question using the PICO structure: in a man with rheumatoid arthritis (Patient), is paracetamol (Intervention) versus placebo (Comparison) associated with a different incidence of hypertension (Outcome)?

My initial search of PubMed was fruitless, so I left out "rheumatoid arthritis" and searched PubMed's Clinical Queries section for "paracetamol AND hypertension". This led me to three other relevant observational studies. One studied over 8000 male doctors[5] and had a prospective cohort design similar to the study by Forman et al.[3] It did not show a significant association between frequent paracetamol use and new onset hypertension (relative risk 1.08; 95% confidence interval 0.87 to 1.34). A subanalysis, looking only at the previous year's paracetamol use, teetered on significance (1.34; 1.00 to 1.80).

The two other observational studies looked at women so were less relevant to my patient but were still interesting. Again, these were prospective cohort studies relying on self reporting of hypertension. They were more consistent in their findings: after adjustment for most obvious confounders, significant associations remained between paracetamol use and hypertension.[6,7] Surprisingly, these associations held even among women taking paracetamol only 1-4 days a month. These studies adjusted for physician visits only in the crude manner of Forman et al[3] and also did not adjust for pain levels, and so were possibly biased.

Evidence from randomised controlled trials was limited. The two relevant trials I found that compared paracetamol to placebo were performed in people who already had hypertension. The trials were small, short term, and had inconsistent results.[8,9] One studied 20 patients over two treatment phases of four weeks each, crossing over between paracetamol and placebo. This found a significant 4 mm Hg increase in systolic blood pressure with paracetamol.[8] However, the other study, of 41 patients randomised to three weeks of ibuprofen, paracetamol, or placebo seemed to show no significant difference in blood pressure between the paracetamol and placebo arms.[9] Frustratingly, then, the experimental evidence was of little use to us.

A reviewer suggested that a better search strategy would have accommodated the US drug name "acetaminophen" and blood pressure end points other than hypertension, as follows: (acetaminophen OR paracetamol) AND (hypertension OR blood pressure). This advice seems wise, though when I later followed this search strategy, it was less specific than my search, yielding some extra articles but none of relevance to us.

## Sharing the evidence with my patient

I explained to my patient that the study had indeed shown a link between paracetamol use and hypertension. However, I emphasised that no such link was shown for men using paracetamol fewer than four days a week, so occasional use seemed safe. I also explained that the link might not be real, either because the blood pressure rise may have been due to pain rather than pills or because men taking more paracetamol may have gone to their doctor more often and so been more likely to have hypertension detected. Finally, even if the risk was real, it seemed fairly small in absolute terms. My patient's baseline four year risk of hypertension was about 7.5%; a 34% increase in relative risk with paracetamol would only raise this absolute risk to 10%. I could see him regularly and monitor his blood pressure, advising him to reduce or cease analgesics if needed.

My patient remained somewhat concerned about the risks of paracetamol and has minimised his use of analgesics. Thankfully, his arthritis has improved to a degree that this is feasible.

If a female patient had asked me the same question, the evidence would have painted a riskier picture for her.

In short, the answer to our question of whether paracetamol causes hypertension is "maybe." I remain curious about future research findings, and I hope that potential biases can be overcome with careful study design. Meanwhile, my patient is comfortable in his decision to minimise his use of simple analgesia, and I still take paracetamol when I get a headache.

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1 McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006;296:1633-44.
2 O'Leary C. Men warned over painkillers. *West Australian* 2007 Feb 28;15.
3 Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med* 2007;167:394-9.
4 Brotman DJ. Acetaminophen and hypertension: a causal association or pain mediated? *Arch Intern Med* 2003;163:1113-4.
5 Kurth T, Hennekens CH, Stürmer T, Sesso HD, Glynn RJ, Buring JE, et al. Analgesic use and risk of subsequent hypertension in apparently healthy men. *Arch Intern Med* 2005;165:1903-9.
6 Dedier J, Stampfer MJ, Hankinson SE, Willett WC, Speizer FE, Curhan GC. Non-narcotic analgesic use and the risk of hypertension in US women. *Hypertension* 2002;40:604-8.
7 Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. *Arch Intern Med* 2002;162:2204-8.
8 Chalmers JP, West MJ, Wing LM, Bune AJ, Graham JR. Effects of indomethacin, sulindac, naproxen, aspirin and paracetamol in treated hypertensive patients. *Clin Exp Hypertens A* 1984;6:1077-93.
9 Radack KL, Deck CC, Bloomfield SS. Ibuprofen interferes with the efficacy of antihypertensive drugs. A randomized, double-blind, placebo-controlled trial of ibuprofen compared with acetaminophen. *Ann Intern Med* 1987;107:628-35.

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