Paracetamol: is all the concern valid?

Given the widespread use and availability of paracetamol, we appreciate the ongoing need to evaluate its safety. However the review by Roberts et al appears to be one in a string of recent articles drawing dubious or misleading conclusions regarding the safety of paracetamol. We question these conclusions about the safety of taking properly dosed paracetamol. The alternatives for chronic pain, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, carry risks of significant morbidity and mortality.

In the systematic review, the authors only included cohort studies. While cohorts can be valuable when studying the risk of long-term adverse events from an exposure, they can also introduce significant bias due to multiple other uncontrolled variables. While the included studies did attempt to adjust for confounders, half of the studies did not adjust for NSAIDs and what was adjusted for varied between studies. As such, paracetamol use may be a marker for other medical conditions, which caused the need for regular paracetamol use as well as complications such as cardiovascular, renal and gastrointestinal disease. The authors suggest a dose-response relationship between the amount of acetaminophen ingested and the adverse events as proof of a correlation between the two. An alternative interpretation is that sicker patients were more likely to use more paracetamol than NSAIDs or opioids. This association becomes even more dubious when included studies relied upon self-report to determine the amount of paracetamol ingested. In addition, the inclusion criteria widely varied between the different studies, including four that only included women, one that only included men, and one study that only included patients with chronic kidney disease. As such, the inclusion of all of the studies in a single meta-analysis may not be appropriate. The authors also intentionally left out case-control studies. We question their rationale for doing so as case-control studies may have been better suited to relate any adverse event to the use of acetaminophen, assuming the cases and controls were appropriately matched.

The quality of evidence included was also poor. We commend the authors for using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria to assess the quality of the outcomes of the included studies. Unfortunately, all of the studied outcomes were scored ‘very low,’ the lowest rating possible using GRADE. Even the best-conducted meta-analysis will suffer if the quality of data is poor as ‘garbage in equals garbage out.’ While the topic is worth studying and important, we wonder what, if any, useful conclusions these data provide.

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