

## Paracetamol for dengue fever: no benefit and potential harm?



See [Articles](#) page e664

Dengue fever is a mosquito-borne illness that is highly endemic in tropical areas of Asia and Latin America. An estimated 58·4 million (23·6–121·9) symptomatic dengue infections occur annually, resulting in about 10 000 deaths per year.<sup>1</sup> These estimates show a dramatic increase in dengue incidence during the past two decades, with the number of symptomatic dengue infections more than doubling every 10 years between 1990 and 2013.<sup>1</sup>

There are four dengue virus serotypes and individuals living in dengue endemic areas can experience repeat dengue infections.<sup>2</sup> The virus causes a wide spectrum of manifestations, from asymptomatic infection to a mild febrile illness to severe dengue.<sup>3</sup> The criteria for severe dengue include severe plasma leakage leading to shock or respiratory distress from fluid accumulation, severe bleeding, or severe organ failure.<sup>4</sup> In the absence of specific antiviral treatment, the management of dengue fever involves supportive care, close monitoring, and prompt and judicious intravenous fluid management, when needed. Dengue fever has been named break-bone fever because of the excruciating body pain that it typically causes, together with high-grade fever. Paracetamol (known as acetaminophen in the USA) is recommended in the WHO dengue treatment guidelines for patients with high fever who are uncomfortable,<sup>4</sup> but this advice is based on expert opinion and not from randomised controlled trials. In *The Lancet Global Health*, Vasin Vasikasin and colleagues<sup>5</sup> report their double-blind, randomised placebo-controlled trial in Thai adults hospitalised with dengue fever comparing 500 mg of paracetamol versus placebo, given every 4 h for fever of 38°C and higher. For pain relief, patients were given an analgesic, tramadol, every 8 h for a pain score of 6 out of 10 or higher. The trial had to be stopped early after an interim analysis found that patients allocated to paracetamol had significantly higher transaminase elevation than did those receiving placebo. Daily mean and maximum body temperatures, analgesic intake, pain score, duration of fever, or length of hospital stay did not differ between the paracetamol and placebo groups.

Elevated transaminases, commonly alanine transaminase (ALT) and aspartate transaminase (AST), are a non-specific indicator of hepatocellular damage. ALT is

specific to the liver, while AST is released following liver, cardiac, or skeletal muscle injury.<sup>6</sup> Hepatic dysfunction, manifested as elevation of liver transaminases, is well recognised during dengue infections and might be due to viral-induced liver cell apoptosis, immune-mediated damage, and hypoxic injury from reduced hepatic perfusion.<sup>7</sup> In this study, the elevation of transaminases associated with paracetamol use in dengue patients was asymptomatic and resolved spontaneously. Yet, it is unclear whether, in a subset of patients, the damage to liver cells would not be self-limiting and could contribute to severity and mortality in dengue fever. Paracetamol is hepatotoxic at high doses but not at therapeutic doses. The situation might be different when hepatocytes already stressed by dengue virus infection are further challenged by paracetamol.

The results of this study lead to the question of whether paracetamol, which is widely used in the management of dengue fever, causes more liver injury than previously recognised? Before considering this question, the limitations of the study must be considered. First, the 4-h dosing of paracetamol in the trial (resulting in a median daily paracetamol dosage of 1·5 g and a median total dosage of 2·5 g) might not reflect actual practice. Paracetamol is recommended for dengue fever at dosing intervals of no less than 6 h.<sup>4</sup> Second, just like paracetamol, tramadol is also metabolised in the liver.<sup>8</sup> Although the amount of tramadol given in the study was low (a mean 0·5 capsule in both groups), could an interaction between paracetamol and tramadol have produced an additive hepatotoxic effect? Third, in many dengue endemic countries, the burden of disease is greatest in children and it is unclear whether these findings are generalisable to children. Despite these limitations, the findings of this rigorous study are quite persuasive, particularly the association of cumulative paracetamol dosage with the level of transaminase elevation.

The absence of a convincing defervescent or analgesic benefit from paracetamol in adults with dengue fever is disappointing. In this study, not only does paracetamol appear to be useless in dengue fever, it might also be unsafe. What are health-care providers looking after febrile dengue patients in pain supposed to do? The intuitive next choice for many practitioners could be ibuprofen. However, ibuprofen, acetylsalicylic acid

(aspirin), and other non-steroidal anti-inflammatory agents are contraindicated in dengue fever because they can aggravate gastritis or bleeding.<sup>4</sup> Tramadol and other stronger analgesics might not be available, and practitioners could be reluctant to describe potentially addictive analgesics. Practitioners in dengue endemic countries are therefore left in the dark about which analgesics and antipyretics they should prescribe for their dengue patients. Safe and effective drugs that can ameliorate fever and pain, reduce the duration of illness, and decrease the risk for progression to severe dengue are urgently needed.

This study highlights the need for randomised controlled trials of drugs used in the management of dengue fever. An objective evaluation of adverse events that could be dengue manifestations or drug-related events, or both, requires meticulous study designs that incorporate masking and control groups, careful baseline measurements, and close follow up.<sup>9</sup>

Jacqueline Deen, \*Lorenz von Seidlein

University of the Philippines, Manila, Philippines (JD); Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (LvS); and Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK (LvS)  
lorenz@tropmedres.ac

We declare no competing interests.

Copyright © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY NC-ND 4.0 license.

- 1 Stanaway JD, Shepard DS, Undurraga EA, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. *Lancet Infect Dis* 2016; **16**: 712–23.
- 2 Simmons CP, Farrar JJ, Nguyen vV, Wills B. Dengue. *N Engl J Med* 2012; **366**: 1423–32.
- 3 Yacoub S, Mongkolsapaya J, Screaton G. Recent advances in understanding dengue. *F1000Res* 2016; **5**: 78.
- 4 WHO/TDR. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition. 2009. <https://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf> (accessed March 13, 2019)
- 5 Vasikasin V, Rojduongrattana T, Chuerboonchai W, et al. Effect of standard dose paracetamol versus placebo as antipyretic therapy on liver injury in adult dengue infection: a multicentre randomised controlled trial. *Lancet Global Health* 2019; **7**: e664–70.
- 6 Ozer J, Ratner M, Shaw M, Bailey W, Schomaker S. The current state of serum biomarkers of hepatotoxicity. *Toxicology* 2008; **245**: 194–205.
- 7 Fernando S, Wijewickrama A, Gomes L, et al. Patterns and causes of liver involvement in acute dengue infection. *BMC Infect Dis* 2016; **16**: 319.
- 8 Bravo L, Mico JA, Berrocoso E. Discovery and development of tramadol for the treatment of pain. *Expert Opin Drug Discov* 2017; **12**: 1281–91.
- 9 Simmons CP, Wolbers M, Nguyen MN, et al. Therapeutics for dengue: recommendations for design and conduct of early-phase clinical trials. *PLoS Negl Trop Dis* 2012; **6**: e1752.