

ALTERNATIVE VIEWPOINTS

Effect of Intravenous Propacetamol on Blood Pressure in Febrile Critically Ill Patients – An Alternative Viewpoint

Aimée C. LeClaire, Pharm.D., and Lawrence J. Caruso, M.D.

Key Words: Acetaminophen, Propacetamol, Hypotension
(*Pharmacotherapy* 2009;29(3):140e–141e)

Propacetamol is the water-soluble, parenteral prodrug of acetaminophen, which is classified as a para-aminophenol analgesic and antipyretic known to inhibit central prostaglandin synthesis. In a recent article, Dr. Hersch and colleagues describe propacetamol-induced hypotension.¹ Of note, hypotension has been previously reported following the administration of acetaminophen.²⁻³ Dr. Hersch and colleagues suggest that defervescence with propacetamol should produce vasoconstriction and that hypotension may actually be related to decreased cardiac output. However, thermoregulatory mechanisms involved in the homeostasis of body temperature can explain the documented hypotension following propacetamol and acetaminophen administration in febrile patients.

The hypothalamus regulates body temperature through a complex feedback loop. During fever of infection or malignancy, the thermal set point is elevated in response to endogenous pyrogens.⁴⁻⁶ Certain prostaglandins are known to be pyrogenic.^{2,7} Perhaps via prostaglandin synthesis inhibition, drugs like aspirin, propacetamol, and acetaminophen alter the hypothalamic reaction to endogenous pyrogens.^{4,5} In result, the thermal set point decreases, which stimulates physiologic heat loss mechanisms.^{4,5} To dissipate heat, actions of the hypothalamus on the autonomic nervous system produce vasodilation and facilitate sweating. We propose it is this vasodilation that is responsible

for the observed blood pressure decrease after administering propacetamol and acetaminophen to febrile patients. When using either agent for antipyresis, vasodilation can be expected, and in the absence of a compensatory increase in cardiac output, would be expected to cause hypotension.

Anecdotally, we have also observed hypotension following the administration of acetaminophen in our febrile, critically ill surgical population. Because the thermal set point is not elevated in the afebrile patient, we postulate that hypotension with propacetamol or acetaminophen occurs only when these agents are used as antipyretics, not as analgesics in afebrile patients. More research is necessary to confirm our hypothesis.

References

1. Hersch M, Raveh D, Izbicki G. Effect of intravenous propacetamol on blood pressure in febrile critically ill patients. *Pharmacotherapy* 2008;28:1205–10.
2. Mackenzie I, Forrest K, Thompson, Marsh R. Effects of acetaminophen administration to patients in intensive care. *Intensive Care Med* 2000;26:1408.
3. Brown G. Acetaminophen-induced hypotension. *Heart Lung* 1996;25:137–40.
4. Atkins E, Bodel P. Fever. *NEJM* 1972;286:27–34.
5. Lovejoy FH. Aspirin and acetaminophen: a comparative view of their antipyretic and analgesic activity. *Pediatrics* 1978;62(suppl):904–9.
6. Stern RC. Pathophysiologic basis for symptomatic treatment of fever. *Pediatrics* 1977;59:92–7.
7. Dascombe MJ. The pharmacology of fever. *Prog Neurobiol* 1985;25:327–73.

Authors' reply

We appreciate the comments by Drs. LeClaire and Caruso and their anecdotal observation which is similar to ours.

As we stated in our article,¹ our explanation regarding the possible pathophysiologic mechanism behind the propacetamol induced

From the Department of Pharmacy Services, Shands at the University of Florida, Gainesville, Florida (Dr. LeClaire) and the Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida (Dr. Caruso).

Please address correspondence to: Aimee C. LeClaire, Pharm.D., Shands at the University of Florida - Pharmacy Services, P.O. Box 100316, Gainesville, FL 32610-0316; email: leclaa@shands.ufl.edu.

hypotension is only theoretical. As we know, the blood pressure is a product of cardiac output and peripheral resistance. When it drops, it might occur either because of decreased cardiac output, or because of dropping peripheral resistance, or both. They both interact in order to maintain the blood pressure such that if cardiac output decreases, peripheral resistance increases to maintain the pressure and vice versa.

In these patients, where vasodilation is usually maximized as of the well-recognized "vasoplegia" of sepsis,² the compensatory mechanism of vasoconstriction to maintain blood pressure is not effective. Although Le Claire's hypothesis is theoretically possible, we do not believe that the inhibition of prostaglandin synthesis and its effect on hypothalamus can cause further vasodilation in these already maximally vasodilated septic patients.

We do agree with the authors' final comment

concerning the possibility that propacetamol may cause hypotension only when used as antipyretic (in septic patients) and not as analgesic (in afebrile patients). This observation is in concert with our preliminary observation in afebrile post-operative patients, where propacetamol, used as an analgesic agent, did not cause any decrease in the blood pressure (unpublished data). We strongly agree that more research is necessary to confirm these suggested mechanisms.

References

1. Hersch M, Raveh D, Izbicki G. Effect of intravenous propacetamol on blood pressure in febrile critically ill patients. *Pharmacotherapy* 2008;28:1205-10
2. Parratt JR. Nitric oxide in sepsis and endotoxemia. *J Antimicrob Chemother* 1998;41(suppl A):31-9

Moshe Hersch, M.D., M.Sc.
David Raveh, M.D.
Gabriel Izbicki, M.D.