Ibuprofen-Induced Renal Tubular Acidosis

To the Editor: Patil *et al.*[1] recently reported in this journal a patient with mixed renal tubular acidosis (RTA) after ibuprofen abuse. They suggested that carbonic anhydrase (CA) II inhibition by ibuprofen overdose may have led to RTA in this patient.[1] More than 16 patients with ibuprofen-induced RTA have been reported[1,2]; however, these reports did not discuss the possible mechanisms of CA II inhibition by ibuprofen overdose. Greene *et al.*[3] reported that ibuprofen can inhibit human erythrocyte CA II at more than several times to dozens of times higher concentrations than the concentrations at which ibuprofen is typically used as an analgesic. Timotheatou *et al.*[4] previously proposed that ibuprofen, a carboxylate, directly binds to zinc through the negatively charged oxygen atoms of the carboxylate moieties, leading to CA inhibition. A recent review of CA inhibition mechanisms by Supuran[5] showed that carboxylate compounds inhibit CA through direct binding to the catalytic zinc and displacing the bound water/hydroxide ion, anchoring to the zinc-coordinated water molecular/hydroxide ion, or occlusion of the entrance to the active site cavity. Thus, ibuprofen overdose may cause RTA due to CA inhibition through one of these mechanisms.

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4. Timotheatou D, Ioannou PV, Scozzafava A, et al. Carbonic anhydrase interaction with lipothioars enites: a novel class of isozymes I and II inhibitors. *Met Based Drugs*. 1996;3:263–268.
5. Supuran CT. How many carbonic anhydrase inhibition mechanisms exist? *J Enzyme Inhib Med Chem*. 2016;31:345–360.

Toru Watanabe[1]

[1]Department of Pediatrics, Niigata City General Hospital, Niigata City, Japan

Correspondence: Toru Watanabe, Department of Pediatrics, Niigata City General Hospital, 463-7 Shumoku, Chuo-ku, Niigata City 950-1197, Japan. E-mail: twata@hosp.niigata.niigata.jp

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The Authors Reply: We appreciate the comment by Watanabe[1] regarding possible mechanisms that could be associated with ibuprofen-induced renal tubular acidosis. We reviewed the suggested articles and are in agreement that these articles do point to mechanisms of action for carbonic anhydrase inhibition. Watanabe adds to our article[2] by providing valuable insight into possible mechanisms at play. We also opine that based off this information, it is possible that naproxen, indomethacin, phenylbutazone, and aspirin also could behave in a similar manner, as they too have a similar chemical structure with similar carboxylate moieties.[3]

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Manisha Singh[1] and Michele Krause[1]

[1]Department of Nephrology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Correspondence: Manisha Singh, Department of Nephrology, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205, USA. E-mail: msingh@uams.edu

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