

# Diuretics in proton pump inhibitor-associated hypomagnesemia

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Proton pump inhibitor (PPI) therapy is associated with hospitalization for hypomagnesemia, particularly among patients also receiving diuretics, according to research published this week in *PLOS Medicine*. The study, conducted by David Juurlink of the University of Toronto and colleagues, suggests that physicians reconsider long-term PPI therapy for patients with a diagnosis of hypomagnesemia or concurrent use of diuretics.

Roughly 145 million prescriptions for PPI are dispensed in the United States annually for acid-related disorders such as dyspepsia and gastroesophageal reflux, and these drugs are widely regarded as safe. However, adverse effects have been identified. Since 2006 thirty case studies have linked long-term use of PPIs to hypomagnesemia, possibly caused by impaired intestinal absorption of magnesium.

Hypomagnesemia is dangerous when severe; it can be associated with malignant cardiac arrhythmias, skeletal muscle dysfunction, and seizures. Thus, physicians require clear guidance for prescribing PPI in [patients](#) at risk for severe hypomagnesemia.

To probe the link between PPI therapy and severe hypomagnesemia, Juurlink and colleagues searched health care databases from Ontario, Canada between 2002-2012, including prescription records for individuals 65 years and older from the Ontario Drug Benefit Database, hospitalization data from the Canadian Institute for Health Information Discharge Abstract Database, and emergency department admissions from the National Ambulatory Care Report System. They identified PPI

prescription records from 366 patients (aged 66 and older) hospitalized with hypomagnesemia and 1464 matched controls. Based on these data, current PPI users have a 43% increased risk of hypomagnesemia over patients with no PPI prescription in the past year (adjusted odds ratio, 1.43; 95% CI 1.06 to 1.93). The risk was particularly increased among patients receiving diuretics, which may affect renal magnesium flux (adjusted odds ratio, 1.73; 95% CI 1.11 to 2.70), and not significant among patients not receiving diuretics (adjusted odds ratio, 1.25; 95% CI 0.81 to 1.91). To exclude the possibility that a medication with no causal link to hypomagnesemia shows a similar effect, Juurlink and colleagues performed the same analysis using exposure to histamine H2 receptor antagonists, and found no significant association (adjusted odds ratio 1.06; 95% CI 0.54 to 2.06).

Based on the authors' estimate, one excess hospitalization with hypomagnesemia will occur among 76,591 outpatients during the first three months of PPI treatment. While, as the authors note, the vast majority of PPI-users will not develop the condition, severe low magnesium may be "an underappreciated consequence of PPI use, particularly given the high background use of PPIs in the general population." Study limitations include a lack of access to participant blood magnesium levels, uncertainty regarding diagnostic coding of hypomagnesemia, and generalizability of the findings to younger patients. Study advantages include the availability of population-wide data and full coverage of PPI use from prescription data, as PPIs are not sold over the counter in Canada.

**More information:** Zipursky J, Macdonald EM, Hollands S, Gomes T, Mamdani MM, et al. (2014) Proton Pump Inhibitors and Hospitalization with Hypomagnesemia: A Population-Based Case-Control Study. *PLoS Med* 11(9): e1001736. [DOI: 10.1371/journal.pmed.1001736](https://doi.org/10.1371/journal.pmed.1001736)

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