

Original Investigation

Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Use and Vitamin B₁₂ Deficiency

Jameson R. Lam, MPH; Jennifer L. Schneider, MPH; Wei Zhao, MPH; Douglas A. Corley, MD, PhD

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IMPORTANCE Proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H₂RAs) suppress the production of gastric acid and thus may lead to malabsorption of vitamin B₁₂. However, few data exist regarding the associations between long-term exposure to these medications and vitamin B₁₂ deficiency in large population-based studies.

OBJECTIVE To study the association between use of PPIs and H₂RAs and vitamin B₁₂ deficiency in a community-based setting in the United States.

DESIGN, SETTING, AND PATIENTS We evaluated the association between vitamin B₁₂ deficiency and prior use of acid-suppressing medication using a case-control study within the Kaiser Permanente Northern California population. We compared 25 956 patients having incident diagnoses of vitamin B₁₂ deficiency between January 1997 and June 2011 with 184 199 patients without B₁₂ deficiency. Exposures and outcomes were ascertained via electronic pharmacy, laboratory, and diagnostic databases.

MAIN OUTCOMES AND MEASURES Risk of vitamin B₁₂ deficiency was estimated using odds ratios (ORs) from conditional logistic regression.

RESULTS Among patients with incident diagnoses of vitamin B₁₂ deficiency, 3120 (12.0%) were dispensed a 2 or more years' supply of PPIs, 1087 (4.2%) were dispensed a 2 or more years' supply of H₂RAs (without any PPI use), and 21 749 (83.8%) had not received prescriptions for either PPIs or H₂RAs. Among patients without vitamin B₁₂ deficiency, 13 210 (7.2%) were dispensed a 2 or more years' supply of PPIs, 5897 (3.2%) were dispensed a 2 or more years' supply of H₂RAs (without any PPI use), and 165 092 (89.6%) had not received prescriptions for either PPIs or H₂RAs. Both a 2 or more years' supply of PPIs (OR, 1.65 [95% CI, 1.58-1.73]) and a 2 or more years' supply of H₂RAs (OR, 1.25 [95% CI, 1.17-1.34]) were associated with an increased risk for vitamin B₁₂ deficiency. Doses more than 1.5 PPI pills/d were more strongly associated with vitamin B₁₂ deficiency (OR, 1.95 [95% CI, 1.77-2.15]) than were doses less than 0.75 pills/d (OR, 1.63 [95% CI, 1.48-1.78]; *P* = .007 for interaction).

CONCLUSIONS AND RELEVANCE Previous and current gastric acid inhibitor use was significantly associated with the presence of vitamin B₁₂ deficiency. These findings should be considered when balancing the risks and benefits of using these medications.

Author Affiliations: Division of Research, Kaiser Permanente, Oakland, California.

Corresponding Author: Douglas A. Corley, MD, PhD, Division of Research, Kaiser Permanente, 2000 Broadway, Oakland, CA 94612 (douglas.corley@kp.org).

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Conclusion

This study found an association between the use of PPIs and H₂RAs for 2 or more years and a subsequent diagnosis of vitamin B₁₂ deficiency. We cannot completely exclude residual confound-

ing as an explanation for these findings, but, at minimum, the use of these medications identifies a population at higher risk of B₁₂ deficiency, independent of additional risk factors. These findings do not recommend against acid suppression for persons with clear indications for treatment, but clinicians should exercise appropriate vigilance when prescribing these medications and use the lowest possible effective dose. These findings should inform discussions contrasting the known benefits with the possible risks of using these medications.