OBSERVATIONS

Vitamin B_{12} Deficiency Associated With Concomitant Metformin and Proton Pump Inhibitor Use

Metformin and proton pump inhibitors have been implicated in decreasing levels of vitamin B_{12} independently. The purpose of this study was to evaluate the effect of concomitant use of metformin and proton pump inhibitors on the incidence of vitamin B_{12} deficiency.

A retrospective chart review was done using the computerized patient record system at the Memphis VA Medical Center for 614 patients with type 2 diabetes and previously collected vitamin B_{12} levels. Patients were excluded if they were over the age of 60 years; on a vegetarian diet; had been diagnosed with pernicious anemia, documented by a positive Schilling test or anti-intrinsic factor antibody, or pancreatic exocrine insufficiency; had undergone a gastrectomy or bowel resection; or had been treated with supplemental calcium, H2 blocker, or B_{12} within 3 months of data collection. The vitamin B_{12} levels were assessed using a competitive immunoassay with direct chemiluminescent technology. Deficiency was defined as vitamin B_{12} levels <300 pg/mL. A χ^2 test was used to compare patients taking metformin or proton pump inhibitors alone and those taking both with a control population taking neither medication.

Mean ± SD age was 65.08 ± 9.23 years, with a majority of male patients (96.3%). African Americans comprised 40.07% of the study population and Caucasians 50.33%; 9.6% had "other" listed for race. The incidence of vitamin B_{12} deficiency was found in 48 (22.2%) of the 216 control subjects. This was not significantly different compared with 32 (21.91%) of the 146 metformin subjects or 33 (25.58%) of the 129 proton pump inhibitor alone subjects ($P = 0.9454$ and 0.4763). However, there was a significant difference found in 42 (34.15%) of the 123 concomitant metformin and proton pump inhibitor subjects compared with the control group ($P = 0.0096$).

Metformin is a first-line medication used in the treatment of type 2 diabetes but has also been shown in multiple studies to reduce serum B_{12} levels in 10–30% of patients (1). Proton pump inhibitors are also commonly used medications for the treatment of gastroesophageal reflux disease and peptic ulcer prevention and treatment and, short-term, have been shown to decrease B_{12} levels from 3.4 to 0.4% ($P < 0.05$) in a 2-week period (2). However, studies looking at long-term proton pump inhibitor use and vitamin B_{12} deficiency have yielded conflicting results (3,4). Ting et al. (5) found no significantly increased risk for concurrent use of histamine H2 receptor antagonist or proton pump inhibitor in the development of metformin-related B_{12} deficiency. However, they did not separate out the use of H2 blockers from proton pump inhibitors in calculating the risk of developing metformin-related B_{12} deficiency.

Proton pump inhibitors and metformin alone were not associated with a significant difference in vitamin B_{12} deficiency, but the combination was associated with a significant increase in vitamin B_{12} deficiency. More studies are needed to elucidate the exact mechanisms by which proton pump inhibitors and metformin affect vitamin B_{12} levels and relate these changes to clinical findings.

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