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Q/ How often does long-term PPI therapy cause clinically significant hypomagnesemia?

EVIDENCE-BASED ANSWER

A/ **Rarely.** Proton pump inhibitors (PPIs) may be associated with decreases in serum magnesium laboratory values to below 1.6 to 1.8 mg/dL, especially when used concurrently with diuretics and loop diuretics (strength of recommendation [SOR]: **C**, disease-oriented outcomes based on cohort, case-control, and cross-sectional studies). Clinically significant or symptomatic hypomagnesemia (below 1.2 mg/dL) appears to be quite rare, however.

Evidence summary

A systematic review and meta-analysis of observational studies examined the risk of hypomagnesemia, defined in various studies as serum magnesium levels of 1.6, 1.7, or 1.8 mg/dL.[1] Two cohort studies, one case-control study, and 6 cross-sectional studies met inclusion criteria; 115,455 patients were enrolled. The studies were significantly heterogeneous (I^2=89.1%), because of varying study designs, population sizes, and population characteristics.

PPI use increased the risk of hypomagnesemia (pooled odds ratio [OR]=1.5; 95% confidence interval [CI], 1.1-2.0) after adjustment for possible confounders such as use of diuretics.

Risk rises with long-term use, but severe hypomagnesemia is rare

Two more recent cohort studies produced conflicting results. Of 414 patients in a managed care cohort who received long-term PPIs, only 8 had mild hypomagnesemia (1.2-1.5 mg/dL) on nearly 14% of their combined 289 measurements. At final measurement, all patients had normal serum magnesium levels.[2]

A cross-sectional analysis of data from a retrospective cohort analysis of 9818 patients in the Netherlands found that any PPI use during the previous year was associated with an increased risk of hypomagnesemia (serum magnesium <1.73 mg/dL) compared with no use (adjusted OR=2; 95% CI, 1.4-2.9).[3] The risk was greatest with use longer than 182 days (OR=3.0; 95% CI, 1.7-5.2). As with studies included in the meta-analysis, this study examined laboratory values exclusively. Only 3 of 724 PPI users had a serum magnesium level below 1.2 mg/dL, the point at which symptoms usually occur.

Case-control studies produce conflicting results

Two recent case-control studies also produced conflicting results. The first compared 154 outpatients who used PPIs for at least 6 months (mean, 27.5 months) with 84 non-users.[4] No association was found with hypomagnesemia (2.17 mg/dL vs 2.19 mg/dL), and none of the patients had a serum magnesium level below 1.7 mg/dL. The control group was poorly defined, however, and the study excluded patients taking diuretics.

Conversely, a study that compared 366 patients hospitalized with a primary or secondary diagnosis of hypomagnesemia (determined from an insurance claims data-

base and defined as the presence of ICD-10 codes for hypomagnesemia or magnesium deficiency) with 1464 matched controls found that hospitalized patients with hypomagnesemia were more likely than controls to be current PPI users (adjusted OR=1.4; 95% CI, 1.1-1.9).[5] Whether hypomagnesemia was the cause of the hospitalizations or an incidental finding wasn't clear.

Concurrent use of diuretics and loop diuretics can increase risk

In a subgroup analysis of the second case-control study, PPI users who also used diuretics had an increased risk of hypomagnesemia (adjusted OR=1.7; 95% CI, 1.1-2.7) compared with patients who weren't taking diuretics (adjusted OR=1.3; 95% CI, 0.8-1.9).[5]

A comparison of the use of loop diuretics and thiazides by patients taking PPIs found that concurrent use of loop diuretics increased serum magnesium reduction (–0.08 mg/dL; 95% CI, –0.14 to –0.02), but thiazides didn't. Numbers were small: Of the 45 participants taking both a PPI and a loop diuretic, only 5 had hypomagnesemia (OR=7.2; 95% CI, 1.7-30.8).[3]

Recommendations

In 2011, the US Food and Drug Administration (FDA) warned of a possible increased risk of hypomagnesemia in patients taking PPIs long-term. The FDA advisory panel recommended evaluating serum magnesium before beginning long-term PPI therapy and in patients concurrently taking diuretics, digoxin, or other medications associated with hypomagnesemia.[6] JFP

References

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