Drug Monitor

ACE-Inhibitor Cough Highly Underreported

Many more patients may experience the irritating dry cough associated with angiotensin-converting enzyme (ACE) inhibitors than is reported in the *Physicians' Desk Reference* (*PDR*) or on drug labels, say researchers from Brigham and Women's Hospital, Boston, Massachusetts, and St. Luke's Roosevelt Hospital, New York, New York. In most cases, the rates not only are "grossly underreported," they say, but—as with the 1.3% rate reported in the *PDR* for enalapril—so low as to be "laughable to practicing physicians." Getting the number right matters: The cough is one reason patients might stop using their medication.

The researchers conducted searches on PUBMED, EMBASE, and CENTRAL using the search terms "angiotensin-converting enzyme inhibitors" and the names of individual ACE inhibitors (eg, enalapril, lisinopril, perindopril). The search was restricted to randomized, clinical trials conducted from 1990 to February 2010, which enrolled at least 100 patients in the ACE-inhibitor arm, had a follow-up of at least 3 months, and reported the rate of cough. They found 125 studies enrolling 198,130 patients that reported the incidence or withdrawal rates due to cough.

Researchers also searched the *PDR* from 1990 to 2009 and extracted the reported incidence of cough and withdrawal of the drug due to cough for individual ACE inhibitors. They also searched the Food and Drug Administration (FDA) Web site for approval letters, final approved drug labels, number of labeling revisions, and the change in reported rates of cough with the revision. "Not surprisingly," the researchers say, "the reported rates of cough in the product label were the same as the reported rates in the *PDR*." (If the *PDR* reported a range of rates, they took the greater of the 2 rates.)

Analysis of the clinical trials revealed the pooled weighted incidence of cough for all ACE inhibitors to be 10.60% (range, 9.14% to 12.07%), and the pooled weighted withdrawal rate due to cough to be 2.54% (range, 2.10% to 2.99%). Both of these rates were significantly higher than the rates associated with placebo, beta-blockers, diuretics, calcium antagonists, and angiotensin-receptor blockers. The results of the analysis suggest that the rate of cough with ACE inhibitors is grossly underreported in the *PDR* and on drug labels.

The incidence rates for cough vary in the literature, the researchers acknowledge. The variations can be attributed to, for instance, the sample size, duration of follow-up, and metric used to assess symptoms. Rates of cough and withdrawal were lower in studies where ACE inhibitors were used in combination with non–angiotensin-receptor blockers. Rates were higher among patients with heart failure, in whom, cough can be multifactorial and may be misdiagnosed as cough due to ACE inhibitors, say the researchers. Furthermore, rates were higher when cough was evaluated using a questionnaire.

Discontinuation rates were similar in the literature, which suggests that those rates might be a more objective measure of adverse events than reported incidence rates. Moreover, placebo-adjusted rates from the meta-analysis were greater than the corresponding adjusted rates from the *PDR*/drug label, suggesting that, regardless of how the data are viewed, the rates are substantially less in the *PDR*/drug label.

What are the consequences of underreporting? The researchers say there are several: (1) The reported low rates can create a false sense of security for physician and patient; (2) the reported low rate of adverse events may result in evaluation for other causes of cough, leading to misdiagnosis and mistreatment; and (3) underreported rates may cause one drug to be promoted over another—to the detriment of treatment. For example, the researchers point out, a lower reported incidence of cough with enalapril (1.3%), compared with that of ramipril (12%), may lead to a false conclusion that enalapril is better tolerated. The researchers' analysis "clearly" suggests, however, that cough is a class effect, with an incidence similar among all ACE inhibitors.

One way to bring everything into alignment, the researchers advise, is to mandate drug companies to systematically update the FDA on accumulating safety and efficacy data. Data on drug safety and medication-specific adverse effects should be updated regularly on the label as well.

Source: *Am J Med.* 2010;123(11):1016–1030. doi:10.1016/j.amjmed.2010.06.014.

DHA for Better Memory

A 6-month course of supplementation with docosahexaenoic acid (DHA) improved learning and memory function in healthy older adults with age-related cognitive decline, according to a recent multicenter study.

Four hundred eighty-five men and women aged ≥ 55 years with a Mini-Mental State Examination score > 26 and a Logical Memory (Wechsler

Memory Scale III) baseline score ≥ 1 SD below younger adults were included in the study. Participants were randomly assigned either to the treatment group (242 participants; 900 mg/day DHA in 3 capsules), or to the control group (243 participants; placebo). The primary outcome was a change from baseline in the Cambridge Neuropsychological Test Automated Battery (CANTAB) Paired Associate Learning (PAL), a computer-based visuospatial learning and episodic memory test.

The groups did not differ significantly on the PAL and other CANTAB tests at week 12. After 24 weeks, however, the DHA group had a 2-fold reduction in the number of visuospatial learning and episodic memory errors on the PAL test (6 pattern errors), compared with the placebo group. The treatment group also showed significant increases in Verbal Recognition Memory. DHA supplementation did not change working memory or executive function—cognitive functions typically impaired in multidomain mild cognitive impairment and later stages of Alzheimer disease—the researchers say. They suggest that a longer course of supplementation might produce changes in those domains. DHA was well tolerated, with no reported serious treatment-related adverse events.

Mean PAL errors at baseline in the DHA group corresponded to a cognitive age of 72.6 years. After 24 weeks of DHA supplementation, the cognitive age represented by the PAL scores was 65.6 years (a 7-year improvement). By comparison, the PAL error performance scores for the placebo group corresponded to 70.6 years at baseline and 66.9 years at week 24 (a 3.6-year improvement).

The researchers note that cardiovascular disease is considered by some to be a potential risk factor for cognitive disorders, such as dementia. Within their study population, 68% had a history of cardiovascular disease, 36% were taking statins, and 50% were on antihypertensives, suggesting comorbidity of cognitive and cardiovascular problems that might be ameliorated with additional DHA supplementation. The study revealed a significant reduction in heart rate associated with DHA supplementation, which could help reduce the risk of fatal cardiovascular events.

Studies have shown that changes in episodic memory may predict preclinical Alzheimer disease. This study's positive findings—which might be seen as moderate—nonetheless, have important implications, the researchers conclude, indicating that 900 mg/day of DHA may be neuroprotective. This hypothesis will need to be confirmed with long-term prevention trials.

Source: *Alzheimers Dement.* 2010;6(6):456–464. doi:10.1016/j.alz.2010.01.013.

Nutrition for Hip-Surgery Recovery

Oral nutritional supplements (ONS) may help geriatric patients with hip fracture recuperate better from surgery by boosting the proteins diminished through blood loss, according to researchers from Spain. Serum albumin is an independent prognostic factor for rehabilitation outcomes after hip fracture surgery not only preoperatively, but also at discharge.

In the randomized, controlled, open, paralleled study, 60 patients (aged > 65 years) with mild or no malnutrition were divided into 2 groups: the ONS (intervention) group, which received energy and protein supplements via commercial enteral nutrition, started at admission and maintained until hospital discharge; and the control group, which received no ONS but were given a standard or texture-adapted diet to meet their calculated metabolic rate.

Patients in the intervention group ingested approximately half of the prescribed supplements per day for 6 days prior to surgery and until discharge. Recent guidelines suggest that geriatric patients need 1.0 g/Kg/day to 1.2 g/Kg/day or more for muscle mass restoration; this intervention achieved its effects with an increase of 0.97 g/Kg/day to 1.37 g/Kg/day of protein intake.

At follow-up, serum albumin and serum prealbumin were significantly higher in the intervention group, in spite of their lack of high adherence to ONS.

Only supplemented proteins per day were associated with fewer postoperative complications, though the difference was not significant. Twelve control patients had complications, compared with 6 ONS patients. Control patients were more likely to experience vomiting or diarrhea or develop an infection. The results of this study suggest that fewer patients in the ONS group needed to continue rehabilitation after discharge, though long-term effects were not assessed in the study. Postoperative stay and total hospital stay were similar in both groups.

Source: *Clin Nutr.* 2010;29(5):574–579. doi:10.1016/j.clnu.2010.01.012.