Analgesic Combination May Increase GI Bleeding

BY DOUG BRUNK

FROM ANNALS OF THE RHEUMATIC DISEASES

Combining ibuprofen and paracetamol at nonprescription doses conferred a modest improvement in pain relief in adults with knee pain/osteoarthritis. But this gain came at the expense of an increase in presumed gastrointestinal bleeding, results from a large randomized, controlled trial demonstrated.

The trial found that paracetamol 3 g per day may cause similar levels of blood loss as ibuprofen 1,200 mg per day, and that the combination of the two appears to be additive, or even synergistic in terms of the number of individuals with a decrease in hemoglobin greater than 2 g/dL.

"These results need to be confirmed, along with their clinical relevance and identification of the site of gastrointestinal bleeding," wrote the researchers, who were led by Dr. Michael Doherty of the Arthritis UK Pain Center at Nottingham (England) City Hospital. "If confirmed, this observation should lead to the re-consideration of current recommendations for oral analgesic use in osteoarthritis and in chronic pain in general, and to the consideration of strategies to reduce this side effect."

Over a period of 13 weeks, Dr. Doherty and his associates followed 892 adults with chronic knee pain who were randomized to one of four treatment regimens, each taken three times a day: ibuprofen (400 mg), paracetamol (1,000 mg), one fixed-dose combination tablet (ibuprofen 200 mg/paracetamol 500 mg), or two fixed-dose combination tablets (ibuprofen 400 mg/paracetamol 1,000 mg).

The primary short-term efficacy end point was the difference at 10 days between groups in the WOMAC (Western Ontario McMaster Universities) osteoarthritis index pain subscale, which was normalized to a 0- to 100-mm scale.

The primary long-term efficacy end point was the patient global assessment of study medication after 13 weeks. This was determined by asking patients, "Taking into account both how your medicine worked for you and any side effects you think it caused you, how would you rate your medication as a treatment for your painful knee?" Respondents used a 5-point scale for replies (1, excellent; 2, good; 3, fair; 4, poor; 5, unacceptable).

The primary safety end point was incidence of moderate and severe adverse events reported during the study period (Ann. Rheum. Dis. 2011;70:1534-41).

Criteria for inclusion were age of at least 40 years; knee pain for most of the past 3 months and on 4 of 7 preceding days; discontinuation of current analgesics; Steinbrocker functional capacity class I-III; and pain affecting the index knee (after a washout period if currently taking analgesics) of 30 mm or greater and 80 mm or less on a 100-mm visual analog scale over the previous 48 hours for one or more of the following: walking on a flat surface, going up/down stairs, at night, sitting, lying, or standing upright.

VITALS

Major Finding: Combining ibuprofen and paracetamol at nonprescription doses conferred a modest improvement in pain relief after 10 days in adults with knee pain/osteoarthritis (P less than .01), but at the expense of an increase in presumed GI bleeding at 13 weeks.

Data Source: A study of 892 adults with chronic knee pain who were randomized to one of four treatment regimens, each taken three times a day.

Disclosures: The study was sponsored by Reckitt Benckiser Healthcare International Ltd. Dr. Doherty disclosed that he has received honoraria for attending two advisory boards for Reckitt Benckiser. In addition, one of the study authors is currently employed by the company and two others are former employees.

The mean age of patients was 61 years and 51% were men. More than half of the study participants (63%) had radiographic osteoarthritis, and 85% fulfilled American College of Rheumatology criteria for the condition.

After measuring the mean change in WOMAC pain scores from baseline, the researchers found that at day 10, two combination tablets provided significantly more pain relief, compared with paracetamol alone (*P* less than .01). At 13 weeks, a significantly greater proportion of participants taking one or two combination tablets rated their treatment as excellent/good, compared with paracetamol alone ($P = .015$ and .0002, respectively).

The incidence of adverse events was comparable among groups and consisted mainly of dyspepsia, diarrhea, and nausea. However, at 13 weeks a decrease in hemoglobin level by at least 1 g/dL was observed among some participants in all treatment groups. More than two-thirds of patients taking two combination tablets experienced this decrease (38%), compared with 24% taking one combination tablet, 20% taking paracetamol monotherapy, and 20% taking ibuprofen monotherapy.

At 13 weeks, a significantly greater proportion of patients in the two combination tablet group experienced a decrease in hemoglobin level by 2 g/L or greater (6.9%), compared with their counterparts in the one combination tablet (1.8%), paracetamol (0.9%), and ibuprofen (0.9%) treatment groups. ■