Opioids Riskier Than Other Agents in Elderly

BY MARY ANN MOON

FROM ARCHIVES OF INTERNAL MEDICINE

Opioids were associated with more risks than were other analgesics in elderly patients taking the drugs for arthritis pain, according to a report in the Archives of Internal Medicine.

Although NSAIDs are known to pose certain risks, the results of the study "support the safety of [NSAIDs] compared with other analgesics," said Dr. Daniel H. Solomon and his associates at Brigham and Women's Hospital, Boston.

Few studies have examined the relative risks of the three major analgesic groups: NSAIDs, opioids, and coxibs (selective cyclooxygenase-2 inhibitors). "Postmarketing surveillance data from usual care cohorts provide an opportunity to examine comparative safety across a wide range of events and can complement safety data from randomized controlled trials. However, imbalance in baseline population characteristics confounds many postmarketing surveillance studies," Dr. Solomon and his colleagues noted (Arch. Intern. Med. 2010;170:1968-78). "Propensity score-matched analyses may provide better balance of confounders and facilitate relatively straightforward comparative safety analyses," they added.

To compare safety, the researchers performed a propensity-matched cohort analysis using information from a Medicare database of pharmaceutical coverage for low-income elderly residents of Pennsylvania and New Jersey in 1999-2005. The study population included 12,840 adults with rheumatoid arthritis or osteoarthritis who began using one of the three types of analgesics during the study period and were followed for at least 1 year.

Overall, adverse safety event rates were high for all three groups, with the rate of adverse-event hospitalization being greater than 100 per 1,000 person-years for all three types of analgesics.

Opioid users had the highest rates of serious adverse events. Their rate of hip, pelvis, wrist, or humerus fractures was 101 per 1,000 person-years, compared with 19 per 1,000 person-years in the coxib group and 26 per 1,000 person-years in the NSAID group. Even though a link between opioids and fractures has been reported previously, "the strength of the association we observed is larger than in previous reports," the researchers said.

Compared with NSAIDs, opioids (hazard ratio, 1.77) and coxibs (HR, 1.28) were associated with elevated risk for cardiovascular events such as MI, stroke, heart failure, revascularization, and cardiac death. That "unexpected" finding regarding such severe events warrants further study, the investigators noted.

Compared with NSAIDs, risk for upper GI bleeding, lower GI bleeding, or bowel obstruction was similarly high for opioid users (HR, 1.07) but was lower for coxib users (HR, 0.60).

In general, opioid users experienced the most adverse events over time, and NSAID users experienced the fewest. In addition, "opioid users experienced moderate risk early in treatment," the researchers noted, whereas the other groups did not. Opioid users had significantly higher all-cause mortality (75 deaths per 1,000 person-years) than did either NSAID users (48 deaths per 1,000 person-years) or coxib users (47 deaths per 1,000 person-years).

The study findings indicate that recent concerns that have been raised regarding the use of opioids for nonmalignant pain are warranted, the researchers said.

The study was supported by the Agency for Healthcare Research and Quality. Dr. Solomon reported being an unpaid member of a celecoxib trial executive committee sponsored by Pfizer and an unpaid member of the data safety monitoring board for an analgesic trial sponsored by Pfizer. ■

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The propensity matching was meticulous in this study, leading to well-balanced baseline characteristics among the three treatment groups. This reassures readers that the observational study design is as robust as possible, and that treatment effects alone account for the observed differences among opioid, NSAID, and coxib users.

However, there is a single unmeasured confounder that calls into question the validity of some of the study findings: the use of over-the-counter NSAIDs, noted Dr. William C. Becker and Dr. Patrick G. O'Connor.

It is likely that "a significant proportion" of patients in the opioid group were also taking NSAIDs, because "physicians routinely recommend antiinflammatory medication in addition to opioids to achieve therapeutic synergy in the treatment of arthritis," they noted.

"It seems implausible that a group of 'opioid-only' elderly patients" who were actually taking supplemental NSAIDs would have a higher risk of adverse cardiovascular events, GI bleeding, and acute kidney injury than would a group taking NSAIDs alone, because these are all known effects of NSAID therapy.

Despite this limitation, "the data on falls and fracture from this ... study are nonetheless compelling and carry important clinical implications," Dr. Becker and Dr. O'Connor said.

DR. BECKER *and* DR. O'CONNOR *are in general internal medicine at Yale University, New Haven, Conn. They reported no financial disclosures.*

These comments were taken from their invited commentary accompanying Dr. Solomon's report (Arch. Intern. Med. 2010;170:1986-8).

Short-Acting Opioids Up Fracture Risk in Arthritic Elderly

BY BRUCE JANCIN

FROM THE ANNUAL MEETING OF THE AMERICAN PUBLIC HEALTH ASSOCIATION

DENVER – Elderly patients who are placed on a short-acting opioid analgesic for treatment of arthritis pain are twice as likely to experience a fracture during the subsequent year, compared with those on a long-acting opioid, according to a large cohort study.

Long-acting opioids provide adequate relief in a time scale that's similar to that for short-acting drugs.

DR. MILLER

The increased fracture risk was particularly strong during the first 2 weeks after initiation of therapy, when the relative risk was almost sevenfold higher in patients on a short-acting opioid, such as propoxyphene or oxycodone, than in those who were started on an NSAID or long-acting opioid, including fentanyl or sustained-release hydrocodone. After that initial 2-week period, the fracture risk dropped off but remained about threefold greater than with NSAID therapy, Dr. Matthew Miller reported at the meeting.

The fracture risk during the first 2 weeks on a long-acting opioid didn't differ significantly from that in patients on an NSAID. Over the course of 1 year, however, the difference grew such that the cumulative fracture risk was 2.6-fold greater in the group on a long-acting opioid than in those on an NSAID.

In contrast, the relative risk of fracture at 1 year was increased 5.1-fold in elderly arthritis patients on a short-acting opioid, added Dr. Miller of the Harvard Injury Control Research Center, Boston.

"Our findings ... suggest that clinicians should be alert to the possibility that short-acting opioids pose a significantly greater risk of fractures among older adults than do equianalgesic doses of long-acting opioids, especially during the first 2 weeks after initiating therapy," he observed. These results have the potential to change clinical practice by shifting prescribing in the direction of greater use of long-acting opioids in the elderly. At present, short-acting opioids are prescribed far more often than long-acting ones.

His study involved 12,436 Medicare beneficiaries with arthritis who initiated monotherapy with an opioid analgesic, and 4,874 who started on an NSAID. Participants averaged 81 years of age, and 85% were women. Osteoarthritis was the diagnosis in 90%; the rest had rheumatoid arthritis. None of the subjects had been on an opioid within the previous 6 months. Not surprisingly, patients who were started on an opioid tended to be somewhat sicker, with a mean baseline Charlson comorbidity index score of 2.2 in the short-acting opioid group, 2.1 in those on a long-acting opioid, and 1.6 in the NSAID group.

The primary study end point was the 1-year incidence of fractures of the hip, radius, ulna, or wrist. The incidence rate was 25 fractures per 1,000 person-years in the NSAID group, 128 per 1,000 person-years in those on short-acting opioids, and 53 per 1,000 person-years in the group on long-acting opioids.

A dose effect was evident. Patients on a low-dose opioid had a 2.2-fold greater fracture risk than did those on an NSAID, after adjustment for comorbid conditions and other potential confounding variables. Patients on a moderate-dose opioid had a 4.6-fold increased risk. And those on high-dose opioid therapy had a 5.1-fold increased risk.

Asked why he thought short-acting opioids were prescribed 13 times more frequently than long-acting ones in the study population, Dr. Miller replied that although the study didn't address this question, it's his impression that many physicians believe that if they place a patient on a long-acting opioid, the patient may not get pain relief quickly enough. Hence, the patient might take another dose, and then another, perhaps getting into the overdose range. This belief about long-acting opioids' sluggish onset of action, he added, is erroneous.

"It's important to recognize that the modern formulations of these long-acting drugs can actually provide adequate analgesia in a time scale that's similar to that for short-acting drugs, because of the long-acting agents' biphasic distribution in the blood stream," Dr. Miller said.

The Food and Drug Administration recently removed from the U.S. market one of the short-acting opioids in this study – propoxyphene – because of an increased risk for fatal heart rhythm abnormalities associated with its use.

Dr. Miller declared having no relevant financial interests. ■