

Short-Acting Opioids Up Fracture Risk in 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.

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 a non-steroidal anti-inflammatory drug (NSAID) or long-acting opioid, including fentanyl or sustained-release hydrocodone. After that initial 2-week period, the fracture risk associated with short-acting opioid therapy 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 did not dif-

fer significantly from that in patients who were placed 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, associate director of the Harvard Injury Control Research Center, Boston.

“Our findings indicate that opioids increase the risk of fractures among older patients with arthritis, and 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.

“Our findings, if borne out in other databases, could help inform safer prescribing practices consonant with the latest American Geriatrics Society guidelines on the pharmacological management of pain in older persons, which recommend that all patients with

moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy,” the physician continued.

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,

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Indication and Important Limitations of Use

KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

KOMBIGLYZE XR has not been studied in combination with insulin.

Important Safety Information

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately.

[See Warnings and Precautions]

Contraindications

- Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or abnormal creatinine clearance)
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- KOMBIGLYZE XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function.

Warnings and Precautions

- The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years). When it occurs, it is fatal in approximately 50% of cases. Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency.
- Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis.
- Lactic acidosis risk increases with the degree of renal dysfunction and patient age. The risk may be significantly decreased by use of minimum effective dose of metformin and regular monitoring of renal function. Careful renal monitoring is particularly important in the elderly. KOMBIGLYZE XR should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- Withhold KOMBIGLYZE XR in the presence of any condition associated with hypoxemia, dehydration, or sepsis.
- Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal.
- KOMBIGLYZE XR is not recommended in patients with hepatic impairment.
- Metformin may lower vitamin B12 levels. Measure hematological parameters annually.
- Warn patients against excessive alcohol intake.
- KOMBIGLYZE XR should be suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until patient's oral intake has resumed and renal function is normal.
- Use of saxagliptin or metformin with medications known to cause hypoglycemia
 - Saxagliptin: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if used in combination with KOMBIGLYZE XR.

Please see adjacent Brief Summary of US Full Prescribing Information including Boxed WARNING about lactic acidosis.



When 90% of opioids prescribed to the elderly are short-acting, we may be putting people at unnecessary risk.

DR. MILLER

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.

Among high-dose opioid users, patients who were placed on a short-acting opioid had an adjusted 2.1-fold greater risk of a fracture than did those on a high-dose, long-acting opioid.

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

The cumulative relative risk of fracture at 1 year was 5.1-fold higher in elderly arthritis patients on a short-acting opioid, such as propoxyphene or oxycodone, than in those on an NSAID.

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. Yet 90% of the drugs that we're prescribing when we're prescribing opioids in an elderly population are short-acting drugs, raising the question of whether we're putting people at unnecessary risk," 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. ■

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- Adverse reactions reported in $\geq 5\%$ of patients treated with saxagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (7.7% vs 7.6%), urinary tract infection (6.8% vs 6.1%), and headache (6.5% vs 5.9%).
- Adverse reactions reported in $\geq 5\%$ of treatment-naïve patients treated with coadministered saxagliptin and metformin immediate-release (IR) and more commonly than in patients treated with metformin IR alone were: headache (7.5% vs 5.2%) and nasopharyngitis (6.9% vs 4.0%).

Drug Interactions: Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, limit KOMBIGLYZE XR to 2.5 mg/1000 mg once daily when coadministered with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

Use in Specific Populations

- **Pregnant and Nursing Women:** There are no adequate and well-controlled studies in pregnant women. KOMBIGLYZE XR should be used during pregnancy only if clearly needed. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE XR is administered to a nursing woman.
- **Pediatric Patients:** Safety and effectiveness of KOMBIGLYZE XR in pediatric patients have not been established.

- Metformin: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, during concomitant use with other glucose-lowering agents (such as sulfonylureas or insulin), or with use of ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.
- Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. KOMBIGLYZE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours after the procedure and reinstituted only after renal function is normal.
 - There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other anti-diabetic drug.

Adverse Reactions

- Adverse reactions reported in $>5\%$ of patients treated with metformin extended-release and more commonly than in patients treated with placebo were: diarrhea (9.6% vs 2.6%) and nausea/vomiting (6.5% vs 1.5%).

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