

Inhaled corticosteroids did not increase nonvertebral fractures in adults with asthma or chronic obstructive pulmonary disease

Johannes CB, Schneider GA, Dube TJ, et al. The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. *Chest*. 2005;127:89-97.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Pulmonology ★★★★★☆☆ Rheumatology ★★★★★☆☆

QUESTION

In adults with asthma, chronic obstructive pulmonary disease (COPD), or both, do inhaled corticosteroids (ICSs) increase the risk for nonvertebral fractures?

METHODS

Design: Nested case-control study within a cohort of 89 877 UnitedHealthcare members who were enrolled for ≥ 1 year from 1 January 1997 to 30 June 2001.

Setting: 17 states in the United States.

Patients: 1722 patients (mean age 53 y, 71% women) with a first-treated nonvertebral fracture constituted the cases. An index date corresponding to date of first claim for fracture treatment was assigned to cases. 17 220 control patients (mean age 52 y, 59% women) were randomly selected and assigned a random index date chosen from within the study interval. Additional selection criteria included age ≥ 40 years and ≥ 2 claims for a physician visit in an outpatient setting or 1 claim in an inpatient setting for asthma, COPD, or chronic airway obstruction.

Risk factors: ICS exposure (defined as ≥ 1 dispensing) was identified from pharmacy claims occurring in the year before the index date. All ICSs were grouped together as a class, but also evaluated separately or in combination with β -agonists. Covariates included

demographic variables and type of underlying respiratory disease. Potential confounders included such medical conditions as vertebral fracture and diabetes mellitus, medications (e.g., bisphosphonates and statins), and indicators of intensity of medical care use for underlying respiratory disease. Associations between the outcome and ICS exposure were assessed using multiple logistic regression.

Outcomes: Treated nonvertebral fractures.

MAIN RESULTS

About 40% of the cohort had COPD, 56% had asthma, and 4% had both at cohort entry. 35% of patients had exposure to ICSs (15% fluticasone propionate and 22% other

ICSs) and 27% had exposure to oral corticosteroids in the year before the index date. The risk for nonvertebral fractures did not differ between patients who were exposed to ICSs and those who were not (Table).

CONCLUSION

In adults with asthma, chronic obstructive pulmonary disease, or both, short-term use of inhaled corticosteroids at recommended doses did not increase the risk for nonvertebral fractures.

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Association between inhaled corticosteroids (ICSs) exposure over a 365-day period and risk for nonvertebral fractures in adults with asthma or chronic obstructive pulmonary disease (COPD)*

ICS class	Odds ratio (95% CI)		
	Full respiratory cohort (n = 18 942; 1722 cases)	COPD only (n = 6932; 609 cases)	Asthma only (n = 11 277; 1033 cases)
All ICSs	0.96 (0.85 to 1.08)	0.89 (0.69 to 1.15)	1.01 (0.87 to 1.17)
Fluticasone propionate	0.98 (0.84 to 1.34)	1.01 (0.73 to 1.39)	0.98 (0.82 to 1.17)
Other ICSs†	0.94 (0.82 to 1.07)	0.87 (0.64 to 1.16)	0.99 (0.85 to 1.16)

*Odds ratios were adjusted for patient demographics, medical conditions, medications (including oral corticosteroids), and health care use for underlying respiratory disease. CI defined in Glossary.

†Other ICSs included beclomethasone dipropionate, budesonide, flunisolide, and triamcinolone.

COMMENTARY

ICSs are commonly prescribed for chronic respiratory disease with air-flow obstruction. Although considerable interperson variability exists, ICS doses > 1.5 mg/d for budesonide/beclomethasone (equivalent to 0.75 mg/d of fluticasone) may be associated with dose-related adrenal suppression. Other side effects include increased risks for reduced bone mineral density; posterior subcapsular cataracts; and to a lesser extent, ocular hypertension and glaucoma. Hence, prescription and dosage of ICSs have to be carefully considered with this therapeutic risk-benefit ratio in mind.

The study by Johannes and colleagues showed that no significant relation exists between ICS exposure and fracture risk. The cohort was drawn from a large database, and adjustment was made for several potential confounders. However, the study is restricted in the question it is trying to address. First, the time frame of ICS exposure, as judged from pharmacy claims, is only within 1 year of index fracture date. The biological effect of prolonged ICS exposure leading to substantial bone demineralization and subsequent fracture is cumulative, and may be in the order of years. The endpoint of a nonvertebral fracture as a risk out-

come within this time frame is unrealistic. Second, several variables exist that determine the effective delivered dose as distinct from the prescribed dose. These include adherence to prescribed medication, type of inhaler device and delivery system (dry powder vs metered-dose inhaler, with or without spacer), and preparation of drug (dry powder vs aerosol). All these factors influence the effective delivered dose and potential systemic bioavailability. Also, it is noteworthy that industry-funded studies are likely to produce industry-favorable results (1). Realistic safety data require longer-term follow-up with accurate estimation of the effective delivered dose, as well as measurements of more subtle outcomes, such as adrenal suppression and bone mineral density.

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Reference

1. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ*. 2003; 326:1167-70.