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| GSK Medicine: Fluticasone propionate, beclomethasone, salmeterol |
| Study No.: WWE113665/EPI40206 |
| Title: Inhaled corticosteroid use in COPD and the risk of fracture |
| <p>Rationale: Inhaled corticosteroids are effective drugs for the treatment of asthma, improving symptoms and reducing morbidity and mortality, even at low doses. They are now also being used to treat chronic obstructive pulmonary disease (COPD). Safety concerns, including osteoporosis and fractures, have been expressed in relation to long-term use of corticosteroids. Clinical studies have shown accelerated bone resorption occurs at all doses. However, whether this actually translates to fractures is unknown but of great consequence as people age. To date, the epidemiological studies assessing the risk of fracture associated with inhaled corticosteroids are inconclusive and none have evaluated the effect of longer term use of these drugs.</p> |
| <p>Objectives: The objective of the study was to assess whether and at what dose long-term inhaled and nasal corticosteroid use increases the risk of fracture among elderly patients with COPD.</p> |
| Indication: COPD |
| <p>Study Investigators/Centers: McGill University Royal Victoria Hospital 687 Pine Avenue West, Ross 4.29 Montréal, Québec, CANADA</p> |
| Research Methods: |
| <p>Data Source: The health databases of the Régie de l'assurance maladie du Québec (RAMQ), the agency responsible for administering the universal health insurance program of the province of Québec, Canada, was used as the data source. The databases contain information on demographics, all medical services rendered, along with the diagnostic code of the service (ICD-9 code), and, for people aged 65 years or older, all out-patient prescription medications dispensed. Information obtained from the Quebec prescription claims databases has been previously validated.</p> |
| <p>Study Design: A population-based cohort design with a nested case-control analysis was used.</p> |
| <p>Study Population: The source population consisted of all subjects who, between January 1, 1988 and December 31, 2001, were 65 years of age or older and were dispensed at least one of the following respiratory medications during this period: any form of β-agonist, theophylline, ipratropium bromide, sodium cromoglycate, nedocromil, ketotifen, leukotriene antagonist, or inhaled corticosteroids. All subjects with three or more prescriptions for these medications in any one-year period and on at least two different dates were included in the cohort. Cohort entry was taken as the date of the third prescription. Patients were excluded if there was a mention of asthma in any hospitalization or physician visit (ICD9 code 493), or a prescription of an anti-asthma drug (leukotriene antagonist, cromolyn, nedocromil, ketotifen) prior to cohort entry. Subjects with a previous such fracture, at anytime prior to cohort entry, as well as subjects with a prior reported vertebral fracture (ICD9 code 805), were also excluded.</p> |
| <p>Study Exposures, Outcomes: A case was defined as the first fracture of the hip or upper extremities that required medical attention reported in the RAMQ databases during cohort follow-up. The date of the case defining fracture was called the index date. Only cases occurring after four years of follow-up were considered, to ensure sufficient time to assess exposure information. For each case, up to twenty age-matched controls were selected at random from all subjects who entered the cohort on the same year as the case and who were born within six months of the birth date of the case. Controls also had to be at risk on the date of their corresponding case event. This date was taken as the index date for the controls.</p> <p>All prescriptions of corticosteroid medications dispensed during the entire period prior to the index date were obtained for all cases and controls and classified according to their formulation, dose, quantity, duration, and date of dispensing. To combine the different corticosteroids, dose equivalencies were established. For oral corticosteroids, the dose equivalencies were taken directly from Goodman and Gilman. The equivalent doses for inhaled and nasal corticosteroids are beclomethasone 100 mcg, budesonide 80 mcg, triamcinolone 200 mcg, fluticasone 50 mcg and flunisolide 200 mcg.</p> <p>Covariates included age, gender and the severity of COPD, as well as other conditions associated with the risk of fracture. We quantified the severity of COPD, independently of inhaled corticosteroid use, by counting the number of dispensed prescriptions of β-agonists, ipratropium bromide and theophylline, and measuring the concurrent use of oral</p> |

corticosteroids use by the cumulative prednisone equivalent dose dispensed during the 4-year period prior to the index date. In addition, we adjusted for other drugs that affect osteoporosis or falls including central nervous system acting drugs as well as rheumatic drugs. For adjustment purposes, exposure to these drugs was considered at any time during the 4-year period prior to the index date.

Data Analysis Methods:

All analyses were based on techniques for matched data and performed separately for inhaled and nasal formulations. The primary analysis was based on the corticosteroid exposure during the four-year period prior to the index date. Crude and adjusted rate ratios of fracture for inhaled and nasal corticosteroid use were estimated by conditional logistic regression, with non-use during the 4-year period as the reference. Subjects were considered as current users if the last prescription was dispensed within 90 days of the index date. All analyses were repeated for the subset of subjects who had 8 years or more of cohort follow-up and considered the 8-year exposure window prior to the index date.

Effect measure modification for the use of oral corticosteroids was assessed in the year prior to the index date. As this interaction was not found to be significant, users and non-users of oral corticosteroids were combined in the analyses, after adjustment for the cumulative dose of oral corticosteroids. The number of cases and controls was determined so as to provide over 95% power to detect a rate ratio of 1.2 or higher for high-dose inhaled corticosteroid use.

Limitations: Limitations of this study were as follows: 1) fractures occurring outside the Province are not always included in the RAMQ database, possibly inducing selection bias 2) fracture of the hip and upper extremities were selected as the outcome, and not vertebral fractures, to avoid underestimating the risk estimate since the latter do not always result in a medical intervention and would thus not be systematically recorded in the databases 3) the measure of exposure, based on dispensed inhaled corticosteroids, is a common limitation of databases studies as it may not represent actual intake or even actual use. 4) the exposure period was restricted to the 4-year span prior to the index date. This was necessary as prescription drug data were only available starting at 65 years of age. Thus oral corticosteroids prior to age 65 that may have affected bone mass could not be adjusted for. 5) we did not have access to potential confounding factors such as smoking, physical activity or obesity.

Study Results:

The respiratory cohort, defined by three or more prescriptions for respiratory drugs in any one year period, contained 202,007 people. Of those subjects, 61,208 with less than 4 years of follow-up and 7,773 with a previous fracture of the hip or upper extremities were excluded. After excluding subjects with a prior asthma diagnosis or treatment or a vertebral fracture, the cohort comprised 100,709 subjects with COPD.

We identified 8,044 new cases of fracture of the hip or upper extremities that occurred during follow-up and selected 138,102 age-matched controls from the risk sets. Cases and controls were 81 years of age at the index date. The cases were more likely to be women and had experienced more other types of fracture during the prior 4 years than controls. They were also more likely to use CNS drugs at the time of the index date, that is dispensed within 90 days of the index date.

The rate of fracture for current use of inhaled and nasal corticosteroids, as well as for use at any time during the four-year time window, is no different than for non use during this period. The rate ratios were also similar for the individual corticosteroids. After adjustment for the covariates, a log-linear dose-response model showed the rate of fracture increases by 5% (rate ratio 1.05; 95% CI: 0.99-1.12) for every 1000 mcg increase in the daily dose of inhaled corticosteroids. For doses of inhaled corticosteroids above 2000 mcg per day, the adjusted rate ratio of fracture is 1.17 (95% CI: 0.87-1.57). For nasal corticosteroids, no increase with increasing doses is observed. The rate ratios for hip fracture are similar to the overall rate ratios. For fractures of the upper extremities, the rate ratios are slightly higher. The rate of these fractures increases significantly by 11% (rate ratio 1.11; 95% CI: 1.02-1.20) for every 1000 mcg increase in the daily dose of inhaled corticosteroids. To assess effect modification by concurrent oral corticosteroid use the dose-response rate ratios for inhaled corticosteroid similar rate ratios between users and non-users of oral corticosteroids.

In an analysis based on an 8-year exposure period, most rate ratios were no different than unity. Only the use of more than 2000 mcg of inhaled corticosteroids per day was associated with an elevated risk (rate ratio 1.60; 95% CI: 1.00-2.56). The log-linear continuous dose-response analysis showed no increase (rate ratio 1.00; 95% CI: 0.89-1.11).

CHARACTERISTICS OF CASES AND CONTROLS

| | Cases (n=8044) | Controls (n=138102) |
|--|-------------------|------------------------|
| Age (mean ± std) | 81.1 ± 6.14 | 81.4 ± 6.02 |
| Female sex (%) | 67.8 | 51.3 |
| Hospitalized during follow-up (%) | 79.4 | 69.8 |
| Other fracture* in the four years prior index date | 37.7 | 5.8 |
| Use of medications possibly associated with hip fracture risk during the four years prior to index date | | |
| Estrogens (%) | 9.4 | 7.8 |
| Diuretics | 57.6 | 54.9 |
| Benzodiazepines (%) | 69.8 | 63.9 |
| Other central nervous system drugs (%) | 37.3 | 26.1 |
| NSAIDs (%) | 59.4 | 57.2 |
| Tamoxifene | 2.0 | 1.3 |
| Heparine | 0.2 | 0.1 |
| Opiates | 11.7 | 7.1 |
| Anticonvulsants | 6.0 | 4.0 |
| Uses of central nervous system medication within 90 days of index date: | | |
| Benzodiazepines (%) | 45.6 | 41.9 |
| Other central nervous system drugs (%) | 20.5 | 12.5 |
| Opiates | 4.4 | 1.4 |
| Anticonvulsants | 3.5 | 2.0 |
| Use of oral corticosteroids in the 4 years prior index date | | |
| Any use (%) | 35.3 | 30.9 |
| Cumulative dose** in all subjects in mg (mean ± std) | 783 ± 2316 | 581 ± 1956 |
| Cumulative dose** in users in mg (mean ± std) | 2222 ± 3467 | 1880 ± 3151 |
| <p>* ICD9 805 (Fracture of the vertebral column), 808 (Fracture of pelvis) 809 (ill-defined fractures of trunk), 810 (Fracture of clavicle), 811 (Fracture of scapula), 814 (Fracture of carpal bone), 818 (ill-defined fractures of upper limb), 819 (Multiple fractures involving both upper limbs, and upper limb with rib and sternum), 821 (Fracture of other and unspecified parts of femur), 822 (Fracture of patella), 823 (Fracture of tibia and fibula) 824 (Fracture of ankle), 825 (Fracture of tarsal and metatarsal bone), 828 (Multiple fractures involving both lower limbs, lower with upper limb, and lower limb with rib and sternum), 829 (Fracture of unspecified bones).</p> <p>** Cumulative dose computed in prednisone equivalent units</p> | | |

CRUDE AND ADJUSTED RATE RATIOS OF FRACTURE OF THE HIP OR UPPER EXTREMITY FOR INHALED AND NASAL CORTICOSTEROID USE DURING THE FOUR-YEAR PERIOD PRIOR TO INDEX DATE

| | Cases | Controls | Crude RR | Adjusted RR | 95% Confidence Interval | | |
|--------------------------------|-------|----------|----------|-------------|-------------------------|---|------|
| Number of Subjects | 8044 | 138102 | | | | | |
| Inhaled corticosteroids | | | | | | | |
| None (%) | 44.3 | 45.7 | 1.00 | 1.00 | Reference | | |
| Any use (%) | 55.7 | 54.3 | 1.05 | 0.95 | 0.90 | - | 1.00 |
| Beclomethasone (%) | 41.8 | 39.7 | 1.10 | 1.04 | 0.99 | - | 1.10 |
| Budesonide (%) | 16.6 | 16.9 | 0.97 | 0.91 | 0.85 | - | 0.97 |
| Fluticasone (%) | 15.5 | 14.0 | 1.04 | 0.93 | 0.86 | - | 1.01 |
| Current use** (%) | 29.7 | 28.9 | 1.06 | 0.96 | 0.90 | - | 1.02 |
| Beclomethasone (%) | 15.4 | 15.1 | 1.08 | 1.01 | 0.94 | - | 1.10 |
| Budesonide (%) | 5.5 | 6.0 | 0.93 | 0.88 | 0.78 | - | 0.98 |
| Fluticasone (%) | 9.6 | 8.5 | 1.10 | 0.95 | 0.86 | - | 1.05 |
| Nasal corticosteroids | | | | | | | |
| None (%) | 82.2 | 82.0 | 1.00 | 1.00 | Reference | | |
| Any use (%) | 17.8 | 18.0 | 0.98 | 0.96 | 0.90 | - | 1.02 |
| Current use** (%) | 3.8 | 4.2 | 0.91 | 0.88 | 0.78 | - | 1.00 |

* Adjusted for one another, age, gender, the number of prescriptions of β -agonists, ipratropium bromide and theophylline, the cumulative dose of oral corticosteroids, as well as the use of diuretics, NSAIDs, estrogens, thyroid hormones, cardiovascular drugs, rheumatic drugs, and drugs for osteoporosis, all during the 4-year period prior to the index date, and central nervous acting drugs, during the 90-day period prior to the index date.

** Current use defined by a prescription within 90 days of the index date

Crude and adjusted rate ratios of fracture of the hip or upper extremity for the mean daily dose of inhaled and nasal corticosteroid use during the four-year period prior index date

| | Cases | Controls | Crude RR | Adjusted RR | 95% Confidence Interval | | |
|---|-------|----------|----------|-------------|-------------------------|--|--|
| Number of Subjects | 8044 | 138102 | | | | | |
| Inhaled corticosteroids | | | | | | | |
| Mean daily dose** (in mcg) used during four years prior to index date | | | | | | | |
| None | 3564 | 63096 | 1.00 | 1.00 | Reference | | |

| | | | | | | | |
|--|---------------|---------------|----------|--------|-------------------------|---|------|
| >0 to 500 mcg | 2613 | 45667 | 1.01 | 0.93 | 0.88 | - | 0.99 |
| >500 to 1000 mcg | 1108 | 18125 | 1.08 | 0.97 | 0.89 | - | 1.05 |
| >1000 to 1500 mcg | 501 | 7678 | 1.15 | 1.03 | 0.92 | - | 1.15 |
| >1500 to 2000 mcg | 199 | 2796 | 1.25 | 1.04 | 0.88 | - | 1.23 |
| >2000 mcg | 59 | 740 | 1.40 | 1.17 | 0.87 | - | 1.57 |
| | | | | | | | |
| Mean ± SD | 300.8 ± 464.8 | 274.4 ± 436.1 | 1.14 | 1.05 | 0.99 | - | 1.12 |
| Nasal corticosteroids | | | | | | | |
| Mean daily dose** (in mcg) used during four years prior to index date | | | | | | | |
| None | 6615 | 113234 | 1.00 | 1.00 | Reference | | |
| >0 to 100 mcg | 1095 | 19529 | 0.95 | 0.93 | 0.86 | - | 0.99 |
| >100 to 200 mg | 201 | 3200 | 1.06 | 1.03 | 0.89 | - | 1.21 |
| >200 mg | 133 | 2139 | 1.05 | 1.01 | 0.83 | - | 1.22 |
| | | | | | | | |
| Mean ± SD | 12.8 ± 47.4 | 12.8 ± 48.3 | 1.00 _ | 0.99 _ | 0.94 | - | 1.04 |
| <p>* Adjusted for one another, age, gender, the number of prescriptions of β-agonists, ipratropium bromide and theophylline, the cumulative dose of oral corticosteroids, as well as the use of diuretics, NSAIDs, estrogens, thyroid hormones, cardiovascular drugs, rheumatic drugs, and drugs for osteoporosis, all during the 4-year period prior to the index date, and central nervous acting drugs, during the 90-day period prior to the index date.</p> <p>** Mean daily dose (in mcg of beclomethasone-equivalent units) estimated by the cumulative dose divided by the treatment period.</p> <p>_ Rate ratio per additional 1000 mcg (beclomethasone-equivalent units) of mean daily dose of inhaled corticosteroids or 100 mcg of nasal corticosteroids</p> | | | | | | | |
| Rate ratios of fracture separately for hip and upper extremities according to the mean daily dose of inhaled corticosteroids used during the four-year period prior to index date | | | | | | | |
| | | | | | Adjusted | | |
| | Cases | Controls | Crude RR | RR | 95% Confidence Interval | | |
| Hip fracture | | | | | | | |
| Number of subjects | 2951 | 50652 | | | | | |
| Mean daily dose** (mcg) | | | | | | | |
| None | 1356 | 23303 | 1.00 | 1.00 | Reference | | |
| >0 to 500 mcg | 951 | 17037 | 0.95 | 0.88 | 0.80 | | 0.96 |
| >500 to 1000 mcg | 384 | 6375 | 1.02 | 0.85 | 0.74 | | 0.97 |

| | | | | | | | |
|--|-----------|-----------|----------|-------|-------------------------|--|------|
| >1000 to 1500 mcg | 171 | 2693 | 1.07 | 0.89 | 0.73 | | 1.07 |
| >1500 mcg | 66 | 986 | 1.14 | 0.82 | 0.62 | | 1.10 |
| >2000 mcg | 23 | 258 | 1.53 | 1.14 | 0.71 | | 1.83 |
| | | | | | | | |
| Mean ± std | 286 ± 456 | 265 ± 428 | 1.11_ | 0.94_ | 0.85 | | 1.05 |
| Upper extremity fracture | | | | | | | |
| Number of subjects | 5093 | 87450 | | | | | |
| Mean daily dose** (mcg) | | | | | | | |
| None | 2208 | 39793 | 1.00 | 1.00 | Reference | | |
| >0 to 500 mcg | 1662 | 28630 | 1.04 | 0.97 | 0.90 | | 1.04 |
| >500 to 1000 mcg | 724 | 11750 | 1.11 | 1.05 | 0.95 | | 1.16 |
| >1000 to 1500 mcg | 330 | 4985 | 1.19 | 1.13 | 0.98 | | 1.30 |
| >1500 to 2000 mcg | 133 | 1810 | 1.31 | 1.15 | 0.93 | | 1.42 |
| >2000 mcg | 36 | 482 | 1.33 | 1.16 | 0.79 | | 1.69 |
| | | | | | | | |
| Mean ± std | 309 ± 470 | 280 ± 440 | 1.15_ | 1.11_ | 1.02 | | 1.20 |
| <p>* Adjusted for age, gender, the number of prescriptions of β-agonists, ipratropium bromide and theophylline, the cumulative dose of oral corticosteroids, as well as the use of diuretics, NSAIDs, estrogens, thyroid hormones, cardiovascular drugs, rheumatic drugs, and drugs for osteoporosis, all during the 4-year period prior to the index date, and central nervous acting drugs, during the 90-day period prior to the index date.</p> <p>** Mean daily dose (in mcg of beclomethasone-equivalent units) estimated by the cumulative dose divided by the treatment period.</p> <p>_ Rate ratio per additional 1000 mcg (beclomethasone-equivalent units) of mean daily dose of inhaled corticosteroids.</p> | | | | | | | |
| Crude and adjusted rate ratios of fracture of the hip or upper extremities for the mean daily dose of inhaled and nasal corticosteroid use during the eight-year period prior to index date among subjects with at least 8 years of follow up | | | | | | | |
| | | | | | Adjusted | | |
| | Cases | Controls | Crude RR | RR | 95% Confidence Interval | | |
| Number of subjects | 3218 | 64198 | | | | | |
| Inhaled corticosteroids | | | | | | | |
| Mean daily dose** (in mcg) used during eight years prior to index date | | | | | | | |

| | | | | | | | |
|--|-------------|-------------|-------|-------|-----------|--|------|
| None | 1039 | 21384 | 1.00 | 1.00 | Reference | | |
| >0 to 500 mcg | 1392 | 27757 | 1.04 | 0.95 | 0.86 | | 1.03 |
| >500 to 1000 mcg | 524 | 10101 | 1.08 | 0.94 | 0.83 | | 1.07 |
| >1000 to 1500 mcg | 183 | 3667 | 1.04 | 0.85 | 0.71 | | 1.03 |
| >1500 to 2000 mcg | 57 | 1029 | 1.15 | 1.05 | 0.78 | | 1.41 |
| >2000 mcg | 23 | 260 | 1.84 | 1.60 | 1.00 | | 2.56 |
| | | | | | | | |
| Mean ± std | 311 ± 432 | 297 ± 417 | 1.09_ | 1.00_ | 0.89 | | 1.11 |
| Nasal corticosteroids | | | | | | | |
| Mean daily dose** (in mcg) used during eight years prior to index date | | | | | | | |
| None | 2376 | 45848 | 1.00 | 1.00 | Reference | | |
| >0 to 100 mcg | 696 | 15703 | 0.86 | 0.81 | 0.74 | | 0.89 |
| >100 to 200 mg | 93 | 1709 | 1.05 | 1.02 | 0.82 | | 1.28 |
| >200 mg | 53 | 938 | 1.09 | 1.03 | 0.76 | | 1.39 |
| | | | | | | | |
| Mean ± std | 14.4 ± 46.8 | 14.6 ± 46.4 | 0.99_ | 0.97_ | 0.89 | | 1.05 |
| * Adjusted for one another, age, gender, the number of prescriptions of β-agonists, ipratropium bromide and theophylline, the cumulative dose of oral corticosteroids, as well as the use of diuretics, NSAIDs, estrogens, thyroid hormones, cardiovascular drugs, rheumatic drugs, and drugs for osteoporosis, all during the 4-year period prior to the index date, and central nervous acting drugs, during the 90-day period prior to the index date | | | | | | | |
| Conclusion: See publication below | | | | | | | |
| Publications: Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. Am J Respir Crit Care Med 2004;169:83-88. | | | | | | | |

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