direction shows an association while the other direction does not is highly questionable, since the two odds ratios are clearly highly compatible. What is more striking but was not noted by Blais et al. (1) is that, as in the New Zealand data (5), very few salbutamol patients were actually switched: Over a period of several years or more, only 5.7 percent of persons prescribed salbutamol were switched to fenoterol—a percentage that is too small to explain the increased risk of those on fenoterol, even if all of the switching was in one direction, since those who switched had illness only 1.6 times as severe as that of those who did not (on the other hand, 40.1 percent of those prescribed fenoterol were switched to salbutamol, a figure consistent with other evidence (7) of greater problems with severity and (lack of) control in patients prescribed fenoterol.

The claim of Blais et al. that “the comparison between inhaled fenoterol and salbutamol . . . may have been biased because of confounding by indication” (1, p. 1167) could have easily been checked, by conducting an analysis analogous to the “intention to treat” approach in which the 4,903 members of the new use subcohort (40 percent of the overall study cohort) were classified according to the β-agonist they were initially prescribed and subsequent “switches” of β-agonist were ignored. Such an analysis might suffer from nondifferential information bias (with regard to the regularly prescribed medication at the time of death), but it would indicate whether there was any possibility of such switches’ biasing the study results in the manner claimed by Blais et al. (1). It would be of great interest if such an analysis (using the same categories as those in our table 1) were carried out by Blais et al.

REFERENCES


THE AUTHORS REPLY

We thank Pearce et al. for their observations (1). Pearce et al. make three points. First, they state that there was no preferential prescribing of fenoterol to persons with more severe asthma in New Zealand from 1977 to 1987. Their conclusion appears to be based, at least in part, on an analysis showing that users of fenoterol, at one point in time, were consuming more antiasthma medications, particularly more oral corticosteroids, than were users of salbutamol (2). Pearce et al. offer two explanations, although they favor the second: Either 1) fenoterol was preferentially prescribed to the patients with more severe asthma or 2) patients using fenoterol regularly have a greater need for oral corticosteroids as a result of clinical deterioration. We do not believe that Pearce et al.’s design and analysis, which is cross-sectional in terms of exposure to β-agonists, can distinguish between these two possibilities, since the directionality between drug exposure and asthma severity is not known. Being able to establish this directionality is precisely why we undertook our study (3). In our study, the severity of illness in the patients was measured at the onset of the treatment with inhaled fenoterol or salbutamol and not at any point in time during the therapy. Differences in severity that may lead to confounding by indication need to be measured at the time at which the treatments being compared are initiated. If they are not, it becomes impossible to differentiate between the effects of the medication and the severity of the patient’s disease at baseline. Our results are thus not consistent with the conclusion of Pearce et al., since we found that new users of fenoterol who had been switched from inhaled salbutamol had more severe asthma than patients who were not switched and that approximately 70 percent of new users of fenoterol had used inhaled salbutamol in the past.

Second, Pearce et al. (1) state that our conclusion that the switch from inhaled fenoterol to salbutamol appeared less closely related to severity than the opposite switch was based on misuse of p values. We disagree, since we reached this conclusion on the basis of the statistical significance of the independent contributions of all variables included in the regression model, not just on the significance of the variable “asthma hospitalization.” In our model, only two (use of oral corticosteroids and use of oral bronchodilators) out of six markers of asthma severity and disease control had rate ratios that were statistically significant, despite the fact that the model had enough power to detect small differences. In the model investigating the switch from inhaled salbutamol to fenoterol, five out of six markers of asthma severity and disease control had statistically significant rate ratios. Moreover, the rate ratios associated with the markers of severity and disease control were all larger in the salbutamol-fenoterol switch model than in the fenoterol-salbutamol switch model. Thus, our conclusion was based on the statistical and clinical significance of all variables included in the models.

Third, Pearce et al. claim that the presence of confounding by indication could have been verified easily by carrying out an analysis analogous to the “intention to treat” approach (1). To perform this kind of analysis, it is essential to know which medication, either salbutamol or fenoterol, the patients were initially prescribed, implying that the complete history of β-agonist use is known for every subject. In our cohort, only a fraction of the subjects had been followed since their first prescription for asthma, and only a

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small fraction of the asthma deaths occurred among these subjects. Had we had a sufficient number of asthma deaths in the incident cohort, this analysis would have been performed in our initial study (4).

Nevertheless, our data showed that severe-asthma patients treated with salbutamol were preferentially switched to fenoterol. We believe that the presence of channeling is best investigated by measuring disease severity at the onset of the treatment and not at any point in time during therapy.

REFERENCES

RE: "HETEROREGENEITY OF HIP FRACTURE: AGE, RACE, SEX, AND GEOGRAPHIC PATTERNS OF FEMORAL NECK AND TROCHANTERIC FRACTURES AMONG THE US ELDERLY"

We have been following with interest the correspondence concerning the study by Karagas et al. (1) regarding the correct classification of unspecified fractures of the proximal femur. Both Levy et al. (2) and Karagas et al. (3) were able to show by validation studies that approximately 85 percent of unspecified fractures are transcervical. In a current analysis of routinely collected hospital discharge diagnoses for the year 1989 in the former German Democratic Republic, covering 17 million East Germans, we found further circumstantial evidence for a predominance of transcervical fractures among unspecified fractures. It is derived from similarities in in-hospital case fatality between classified transcervical fractures and unspecified fractures (table 1). Our analysis is restricted to closed fractures, which comprise over 97 percent of fractures in this anatomic region.

The case fatality rate for unspecified fractures in this region (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), code 820.0) is compatible with the figures for transcervical fractures (ICD-9-CM code 820.0) but not with those for pertrochanteric fractures (ICD-9-CM code 820.2). Overall case fatality appears high, which is partially attributable to the in-hospital rehabilitation of the East German health care system. The mean length of hospitalization, including transfers between wards and hospitals after closed fractures of the proximal femur, was 60 days.

Figure 1 puts the ratio of closed trochanteric fractures (ICD-9-CM code 820.2) to closed cervical fractures (ICD-9-CM code 820.0, including code 820.8) in perspective with regard to the reported figures from North America (1, 2).

Despite historically dissimilar political and social environments, similarities in the ratio of transcervical fractures to pertrochanteric fractures are striking. In accordance with Levy et al.'s suggestion of common etiologic processes for Canada and the United States (2), we presume that such processes are effective in Europe also and may be found at the biologic level, related to geographic latitude, or related to industrialization.

REFERENCES

TABLE 1. In-hospital case fatality for closed proximal femoral fractures in the German Democratic Republic, 1989

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>No. of cases</th>
<th>In-hospital case fatality (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All closed fractures</td>
<td>9,633</td>
<td>21.7</td>
<td>20.9–22.5</td>
</tr>
<tr>
<td>Pertrochanteric fractures (ICD-9-CM code 820.2)</td>
<td>4,087</td>
<td>25.1</td>
<td>23.8–26.4</td>
</tr>
<tr>
<td>Transcervical fractures (ICD-9-CM code 820.0)</td>
<td>5,011</td>
<td>19.3</td>
<td>18.3–20.5</td>
</tr>
<tr>
<td>Proximal femoral fractures of unspecified location (ICD-9-CM code 820.8)</td>
<td>535</td>
<td>17.6</td>
<td>14.6–21.3</td>
</tr>
</tbody>
</table>

* Persons aged ≥50 years only.
† CI, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

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