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Withdrawal of Fenoterol and the End of the New Zealand Asthma Mortality Epidemic

Key Words
Asthma mortality
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Abstract
In response to the evidence that fenoterol was a major cause for the second epidemic of asthma deaths in New Zealand, the Department of Health severely restricted its availability, thereby allowing an 'experiment in prevention' to be undertaken. These regulatory actions, which effectively removed fenoterol from the market in New Zealand, were associated with a sudden and marked reduction in asthma mortality, providing further evidence for a causative role of fenoterol in the epidemic of asthma deaths in New Zealand.

Introduction

Following publication of the initial epidemiological [1, 2] and experimental [3] evidence implicating fenoterol as a major factor in the second New Zealand asthma mortality epidemic, the New Zealand Department of Health severely restricted the availability of fenoterol [4], firstly by advising against its use in severe asthma (mid 1989), and then by withdrawing it from the Drug Tariff (mid 1990). These regulatory actions effectively removed fenoterol from the market in New Zealand and allowed an 'experiment in prevention' to be undertaken. There has been considerable interest in the time trends in asthma medicine sales and asthma deaths in New Zealand since these regulatory steps were taken, and these trends are considered in this paper.

Fenoterol

The times trends shown in figure 1 are consistent with other evidence [1–3, 5–8] that prescribed fenoterol is associated with an increased risk of asthma death and was the major factor in the New Zealand asthma mortality epidemic. The New Zealand mortality epidemic commenced when fenoterol was introduced in 1976, and the death rate remained high for more than a decade. The death rate fell somewhat after media publicity following the publication of the first report on the epidemic in 1981 which suggested that beta agonists may be involved in the increase in deaths [9]. However, the New Zealand asthma death rate in the 5 to 34-year-old age group was still the highest in the world during 1983–1988, and in the first half of 1989 the mortality rate remained relatively high at 2.2 per 100,000.

When the first fenoterol case-control study was published in mid 1989 [1] and safety warnings were issued [4], the

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fenoterol market share fell sharply (fig. 1). This was accompanied by an immediate sharp (and statistically significant) fall in the asthma death rate to 1.1 per 100,000 in the second half of 1989 (fig. 1) [10]. Since then, asthma mortality has fallen even further to 0.8 per 100,000 in 1990, and 0.73 in 1991. These are the lowest death rates from asthma in New Zealand for more than 30 years.

Total Beta Agonists

The authors of the Saskatchewan study [6] also suggested a more general association between inhaled beta agonists and asthma mortality, although other studies which have attempted to assess the association between beta agonists (as a class) and asthma deaths have found little evidence of such an association [11, 12].

The hypothesis of a class effect of beta agonists is also inconsistent with the New Zealand time trend data. The switch to regular use of beta agonists (and the sharp rise in sales) commenced in 1979, whereas the epidemic commenced in 1976 [13] (fig. 1). Furthermore, total sales of beta agonists actually increased slightly during 1989–1990, whereas fenoterol sales and asthma deaths both fell dramatically during this period.

Inhaled Steroids

The time trend data are also inconsistent with the hypothesis that the epidemic may have occurred because of underprescribing of inhaled steroids, since there was little change in prescribing patterns at the time the epidemic commenced and the epidemic only occurred in New Zealand, and not in other countries, most of which had lower prescribing of inhaled steroids than in New Zealand [13]. Similarly, the time trend data are not consistent with the hypothesis [14] that the epidemic ended because of increased precribing of inhaled steroids. Sales of inhaled steroids in New Zealand did increase markedly during the 1980s, and it is therefore possible that this may have made some contribution to the reduction in asthma deaths during this period. However, as noted above, the death rate was in fact reasonably constant during 1983–1988 and was considerably higher than in other countries, despite a marked increase in prescribing of inhaled corticosteroids. Furthermore, the end of the epidemic occurred very suddenly in 1989, and during 1990–1992 the death rate has remained uniformly low, with little apparent benefit from the continuing increases in inhaled steroid sales.

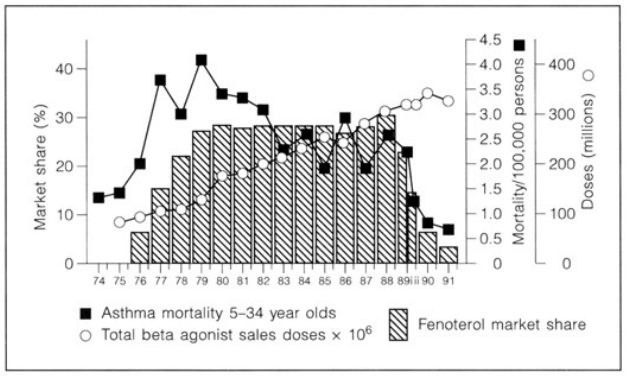

Fig. 1. Inhaled fenoterol market share, total inhaled beta agonist sales, and annual mortality from asthma per 100,000 persons aged 5–34 years in New Zealand.

Conclusion

Data on time trends should be assessed with considerable caution, because time trends in asthma deaths can be affected by many different factors. Nevertheless, it is interesting to note that the New Zealand time trends are consistent with other epidemiological evidence indicating a major role of fenoterol in the second New Zealand mortality epidemic. In contrast, the time trends are not consistent with alternative hypotheses relating to total beta-agonist sales or inhaled steroid sales.

References

1 Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, et al: Prescribed fenoterol and death from asthma in New Zealand, 1981–1983: A case-control study. Lancet 1989;i:917–922.

2 Pearce NE, Grainger J, Atkinson M, Crane J, Burgess C, Culling C, et al: Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977–1981, Thorax 1990;45:170–175.

3 Beasley R, Pearce NE, Crane J, Windom H, Burgess C: Asthma mortality and inhaled beta agonist therapy. Aust NZ J Med 1991;21:753–763.

4 Bernier R: Asthma drug controversy climaxes with government decision to restrict use. Epidemiol Monitor 1990;11:1–5.

5 Grainger J, Woodman K, Pearce NE, Crane J, Burgess C, Keane A, et al: Prescribed fenoterol and death from asthma in New Zealand 1981–1987: A further case-control study. Thorax 1991;46:105–111.

6 Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al: The use of beta-agonists and the risk of death and near death from asthma. N Engl J Med 1992;326:501–506.

7 Suissa S, Ernst P, Bonvin J-F, Horwitz RI, Habbick B, Cockroft D, Blais L, McNutt M, Buist AS, Spitzer WO: A cohort analysis of excess mortality in asthma and the use of inhaled β-agonists. Am J Respir Crit Care Med 1994;149:604–610.

8 Hensley MJ: Fenoterol and death from asthma (letter). Med J Aust 1992;156:882.

9 Wilson JD, Sutherland DC, Thomas AC: Has the change to beta-agonists combined with oral theophyllines increased cases of fatal asthma? Lancet 1981;i:1235–1237.

10 Crane J, Pearce NE, Burgess C, Beasley R, Jackson R: Asthma deaths in New Zealand (letter). BMJ 1992;304:1307.

11 Pearce N, Crane J, Burgess C, Beasley R: The association between beta agonist use and death from asthma (letter). JAMA 1994;271:822–823.

12 Mullen M, Mullen B, Carey M: The association between beta-agonist use and death from asthma. JAMA 1993;270:1842–1845.

13 Keating G, Mitchell EA, Jackson R, Beaglehole R, Rea H: Trends in sales of drugs for asthma in New Zealand, Australia, and the United Kingdom, 1975–1981. Br Med J 1984;289:348–351.

14 Garrett J: Positive Directions in New Zealand Asthma Management: Shift in Asthma Control Gives Exciting Results. 3M Pharmaceuticals New Zealand, May 1992.

15 Pearce N, Beasley R, Crane J, Burgness C, Jackson R: End of the New Zealand asthma mortality epidemic. Lancet 1995;345:41–44.