

# Asthma and the $\beta$ agonist debate

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## Introductory articles

### A cohort analysis of excess mortality in asthma and the use of inhaled $\beta$ agonists

S Suissa, P Ernst, J-F Boivin, RI Horwitz, B Habbick, D Cockcroft, L Blais, M McNutt, AS Buist, WO Spitzer

*The association between the use of inhaled  $\beta$  agonists and the risk of death and near death from asthma has previously been reported. It was based on a nested case-control study of 129 cases and 655 control subjects selected from a cohort of 12 301 users of asthma drugs followed during the period 1980 through 1987. In this paper, we examine the question of asthma and non-asthma mortality using data from the entire cohort of 12 301 asthmatics. There were 46 asthma and 134 non-asthma deaths in this cohort, for which there were 47 842 person-years of follow-up. The overall rate of asthma death was 9.6 per 10 000 asthmatics per year. This rate varied significantly according to the use of fenoterol, albuterol, or oral corticosteroids in the prior 12 months and the number of hospitalisations in the prior 2 years. The rate decreased significantly, by 0.6 asthma deaths per 10 000 asthmatics per year over the study period, after controlling for the effect of the four other risk factors. It also increased significantly with the use of all  $\beta$  agonists, and more so for fenoterol than for albuterol, although this difference was partly explained by the dose inequivalence of the two drugs. Change-point dose-response curves showed that the risk of asthma death began to escalate drastically at about 1.4 canisters (of 20 000  $\mu$ g each) per month of inhaled  $\beta$  agonist, the recommended limit. For non-asthma death, the overall rate of 28 deaths per 10 000 asthmatics per year was not related to the use of inhaled  $\beta$  agonists. We conclude that the strong association between the use of inhaled  $\beta$  agonists and asthma mortality is confined primarily to the use of these drugs in excess of recommended limits. Non-asthma mortality, including that from cardiovascular causes, is not associated with the use of inhaled  $\beta$  agonists.*

(*Am J Respir Crit Care Med* 1994;149:604–10)

### Regular v as-needed inhaled salbutamol in asthma control

KR Chapman, S Kesten, JP Szalai

*Recent studies have suggested that regular use of inhaled beta<sub>2</sub> agonists causes loss of control as measured by worsening peak-flow rates, increased asthma symptoms, and more frequent need for supplementary bronchodilators. However, the magnitude of this effect and the reliability of investigator-originated definitions of control is unknown. We studied 341 people with asthma in a four-week, randomised, crossover trial of regular salbutamol (2 puffs – 200  $\mu$ g – four times daily) for two weeks and as needed for two weeks. There were no significant differences in morning and evening peak-flow rates between treatments but asthma symptoms and supplementary bronchodilator use were significantly less frequent when salbutamol was given regularly. Asthma episodes occurred 1.39 (1.52) times per day during regular treatment and 2.44 (1.75) times per day during as-needed treatment ( $p < 0.0001$ ) and 0.50 (0.56) v 0.65 (0.66) times per night ( $p < 0.0001$ ). Daytime use of supplementary salbutamol was 1.14 (1.40) v 2.35 (1.71) puffs per day ( $p < 0.0001$ ); night-time use was 0.45 (0.55) v 0.64 (0.66) puffs per night ( $p < 0.0001$ ). When control endpoints were compared between treatment periods for each individual by two blinded investigators and control judged by six different sets of criteria, in*

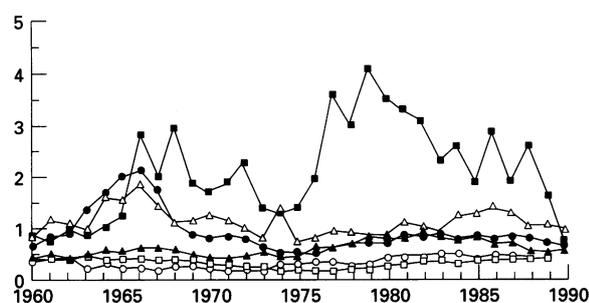
70 asthmatics there was no difference in symptom control between periods but in the remainder, control was achieved more often by regular than by as-needed salbutamol (166 v 69,  $p < 0.0001$ ). In asthma of moderate severity, regularly administered salbutamol does not produce lower peak flow rates than as-needed salbutamol and is associated with less frequent asthma symptoms.

(Lancet 1994;343:1379–82)

The two recently published studies by Suissa *et al*<sup>1</sup> and Chapman *et al*<sup>2</sup> provide the latest instalments in the long running controversy of  $\beta$  agonists and asthma deaths – a debate which stretches back to the 1960s and which has had renewed vigour since 1989.<sup>3</sup> A casual observer could be excused for concluding that recent debate has generated more heat than light, and that the epidemiological and clinical evidence is uncertain and contradictory. However, this impression arises from the confusion of several issues that should be kept separate. In particular, it is essential to distinguish between the causes of epidemics of asthma deaths and the causes of the gradual non-epidemic increases in asthma deaths that have occurred in many countries over the past few decades; related issues include the safety of fenoterol compared with the safety of  $\beta$  agonists as a class, and the relevance to mortality of the acute and chronic side effects of  $\beta$  agonists. When these various issues are considered separately, the two papers considered here, together with the other recent evidence,<sup>4,5</sup> contribute to an increasingly coherent body of evidence.

### Epidemic increases in asthma deaths: the relevance of the Saskatchewan study

This paper by Suissa *et al*<sup>1</sup> is most relevant to the issues relating to the asthma mortality epidemics, and is the latest publication from the Saskatchewan study of asthma deaths. This continues a long debate which was generated initially in the 1960s when epidemics of asthma mortality occurred in six countries (figure).<sup>6,7</sup> The epidemics of the 1960s were eventually linked to sales of the high-dose formulation of the non-selective  $\beta$  agonist isoprenaline forte.<sup>8</sup> Isoprenaline forte was never formally restricted, partly because the association of the epidemics with this high-dose formulation (five times the regular dose) was only discovered in retrospect.<sup>8</sup> However, the death rate fell immediately after



Trends in asthma mortality (per 100 000) in 5–34 year olds in a number of different countries during the past 30 years. ■—■, New Zealand; ●—●, England and Wales; △—△, Australia; ▲—▲, West Germany; ○—○, Canada; □—□, USA.

general warnings about the safety of inhaled  $\beta$  agonists were issued, and they were withdrawn from over the counter sale in the United Kingdom.<sup>3</sup>

A second epidemic occurred only in New Zealand, commencing in 1976 (figure), and was eventually linked to fenoterol in a case-control study published in 1989.<sup>9</sup> The initial case-control study findings were the subject of considerable controversy and criticism, but they have now been confirmed by two further New Zealand case-control studies,<sup>10,11</sup> and a recent small cohort study of patients with chronic obstructive pulmonary disease in Germany also found an increased death rate in those prescribed fenoterol compared with those prescribed other  $\beta$  agonists.<sup>12</sup> Fenoterol was marketed in a high-dose 200  $\mu\text{g}/\text{puff}$  preparation, compared with salbutamol at 100  $\mu\text{g}/\text{puff}$ ; there is some evidence that fenoterol is twice as potent as salbutamol, and that the 200  $\mu\text{g}/\text{puff}$  preparation is effectively a forte preparation at four times the strength of salbutamol.<sup>13</sup> When taken repeatedly, fenoterol has similar adverse cardiac side effects to those observed with isoprenaline forte.<sup>14</sup> The highest per capita sales of fenoterol in the world were in New Zealand; sales in most other countries were very low and it was not licensed in the USA.<sup>15</sup> A dramatic fall in the death rate was observed in New Zealand immediately after the restriction of fenoterol in mid 1989.<sup>5</sup>

As a result of these New Zealand findings, the manufacturer of fenoterol funded the study of asthma deaths in the Canadian province of Saskatchewan (table 1).<sup>16</sup> The authors began by examining the computerised files of the Saskatchewan Prescription Drug Plan which held prescriptions for drugs for asthma listed in the Saskatchewan formulary that had been dispensed to eligible residents of the province aged 5–54 years during 1980–7. They identified 12 301 patients who had received at least 10 such prescriptions over the period 1978–87, and these patients were then followed (retrospectively) over the period 1980–7. The Saskatchewan group then nested a case-control study<sup>16</sup> within this cohort study; this involved 44 asthma deaths and 233 controls drawn from other members of the cohort who did not die or experience a near-fatal asthma attack during the follow up period. For both groups the computerised prescription records were used to ascertain prescriptions for asthma medicines in the 12 month period prior to the index date (the date of death for the cases and the corresponding date for the controls). When the data were analysed using the same methods as were used in the New Zealand studies the fenoterol relative risk was 5.3, whereas the salbutamol relative risk was 1.0. The authors also investigated the possibility that the association of fenoterol with asthma death was due to confounding by severity – that is, by selective prescribing of fenoterol to patients with more severe asthma; however, as in the New Zealand studies,<sup>17</sup> it was found that

Table 1 Studies of prescribed  $\beta$  agonist therapy and asthma deaths

	1st NZ Study <sup>9</sup>	2nd NZ Study <sup>10</sup>	3rd NZ Study <sup>11</sup>	Saskatchewan study <sup>16</sup> (Case-control study)	Saskatchewan study <sup>2</sup> (Cohort study)
Study period	1981-3	1977-81	1981-7	1980-7	1980-7
Study base	All asthmatics	Patients with a hospital admission for asthma in previous year	Patients with a hospital admission for asthma in previous year	Patients with 10 different asthma prescriptions during 1978-87	Patients with 10 different asthma prescriptions during 1978-87
Study design	Case-control	Nested case-control	Nested case-control	Nested case-control	Cohort
Matching for severity?	Yes (hospital admission controls)	Yes (hospital admission controls)	Yes (hospital admission controls)	No	No
Source of drug information	Family doctor and routine hospital records	Routine hospital records	Routine hospital records	Routine prescription records	Routine prescription records
Main exposure information	Prescribed medication†	Prescribed medication†	Prescribed medication†	Dispensed medication	Dispensed medication
Additional information	Nil	Nil	Nil	Number of units/month	Number of units/month
Information on use?	No	No	No	No	No
Severity markers	Hospital admissions, oral steroids, 3+ categories of drugs	Hospital admissions, oral steroids, 3+ categories of drugs	Hospital admissions, oral steroids, 3+ categories of drugs, peak flows, Pao <sub>2</sub> , psychotropic drugs	Hospital admissions, oral steroids	Hospital admissions, oral steroids
Odds ratio					
Fenoterol	1.6	2.0	2.1	5.3	11.8
Salbutamol	0.7	0.7	0.6	1.0	1.1
Both drugs	2.0	3.2	4.5	4.4	8.7
Fenoterol only	1.6	1.9	2.0	3.7	8.1
Salbutamol only†	1.0	1.0	1.0	1.0	1.0
Neither	1.0	1.1	1.2	0.3	0.2

\* Findings using control group A.

† Reference category.

‡ Prescribed medication is synonymous with dispensed medication since prescribed  $\beta$  agonists were free during the study period.

there was little evidence of selective prescribing and that this hypothesis did not appear to explain the association of fenoterol with asthma deaths.<sup>18</sup>

As noted above, these initial findings of the Saskatchewan study were based on a nested case-control analysis. It is well known that a nested case-control study will produce very similar findings to those of a full cohort study analysis,<sup>19</sup> and the Saskatchewan case-control findings have now been confirmed by the publication of the full cohort analysis by Suissa *et al.*<sup>1</sup> This was based on the same patient population as the nested case-control study, but involved two further asthma deaths that were identified after the publication of the case-control study. As expected, the findings are very similar to those of the case-control analysis although the fenoterol findings are somewhat stronger in the full cohort analysis. The death rate in those prescribed fenoterol alone (in the dose in which it was marketed) was about eight times that in those prescribed salbutamol alone, and half of the patients who died had been prescribed fenoterol (compared with less than 10% of the total cohort). These findings are even stronger than those in New Zealand when the studies were analysed in an identical manner.<sup>20</sup>

#### A FENOTEROL EFFECT OR A CLASS EFFECT OF $\beta$ AGONISTS?

Although epidemics of deaths from asthma have only occurred with isoprenaline forte and fenoterol, it is natural to ask whether similar problems could be occurring to a lesser extent with other  $\beta$  agonists. In fact, salbutamol has never been associated with an epidemic of asthma deaths, despite the very high sales in many countries.<sup>21</sup>

Nevertheless, the Saskatchewan group<sup>16</sup> has suggested a more general association between inhaled  $\beta$  agonists and asthma mortality, and this claim has now been repeated with the publication of the full cohort analysis.<sup>1</sup> However, it has been argued that these conclusions should be considered with caution because they did not involve the primary hypothesis of the study (which centred on fenoterol<sup>22,23</sup>), because of the inclusion of some non-asthmatics in the control group,<sup>24</sup> and because they were not apparent in the initial analyses but only emerged in complex multivariate analyses involving questionable assumptions.<sup>25</sup> Furthermore, these conclusions of Suissa *et al.*<sup>1</sup> are not consistent with other studies that have attempted to assess the association between  $\beta$  agonists (as a class) and asthma deaths; in fact, all other studies have found no evidence of such an association.<sup>4</sup>

The strong conclusions of Suissa *et al.* were based on the questionable comparison of the "fenoterol only" and "salbutamol only" groups with the very small group who were not prescribed either drug; some of these had been prescribed other  $\beta$  agonists (two deaths in this subgroup) but most of them had not (no deaths in this subgroup). The claim for a class effect of  $\beta$  agonists therefore rests on the strong (and unlikely) assumption that there were no significant differences in asthma severity between patients who were and were not prescribed  $\beta$  agonists. The latter group included some patients who were not prescribed any asthma drugs in the 12 months before the index date and may have had very mild asthma or even not had asthma at all during this period; furthermore, some patients may not have had asthma at any time but may have been prescribed asthma drugs for other conditions. It is therefore not surprising that this group had a very low risk of asthma

death. This is illustrated by the findings of the full cohort analysis in which the asthma death rate was 64.3 per 10 000 asthmatics per year in those prescribed both fenoterol and salbutamol, 60.2 in those prescribed fenoterol only, 7.4 in those prescribed salbutamol only, and 1.3 in those prescribed neither drug.

A further questionable feature of the Saskatchewan study analysis has been the "dose adjustment" in which the authors compared the fitted mortality dose-response curves of the fenoterol and salbutamol data. The authors concluded that the fenoterol curve would have been similar to the salbutamol curve if fenoterol had been marketed in 100 µg doses (half of the dose actually marketed). However, assuming a linear dose-response relationship (which is the more orthodox approach) would have resulted in comparability of the curves at about 50 µg per puff (one quarter of the marketed dose), a dose level which is more compatible with the findings of experimental studies.<sup>14</sup> Furthermore, the full cohort analysis now shows that the fenoterol dose-response curve was stronger than that of salbutamol even after the dose adjustment.<sup>1</sup> However, the most important issue is that the dose adjustment is entirely hypothetical since fenoterol was almost exclusively marketed in a high-dose formulation. Thus, the dose adjustment is not relevant to the fundamental question (addressed in the New Zealand studies) of whether fenoterol caused asthma deaths in the dose in which it was marketed; it is only relevant to the mechanism by which these deaths occurred – that is, whether it was just a dose problem or whether it was due to different pharmacological properties of the drug.

#### ACUTE EFFECTS OF $\beta$ AGONISTS AND THEIR RELEVANCE TO MORTALITY

So what mechanisms could be involved in the causation of epidemics of asthma deaths by isoprenaline forte and fenoterol? The high-dose formulation must have been important as there were no epidemics in countries in which isoprenaline forte was not marketed, even when there were high sales of the regular dose formulation of isoprenaline. However, it is probably also significant that these  $\beta$  agonists have considerably greater cardiac side effects than other commonly available  $\beta$  agonists even when used in equivalent bronchodilator doses.<sup>14</sup> In particular, isoprenaline forte and fenoterol are both full agonists at the  $\beta_1$  receptor, and not only have greater cardiac side effects when administered on an equal weight basis, but also appear to have greater maximal cardiac side effects when taken repeatedly.<sup>26</sup>

This evidence has been strikingly ignored by most commentators on the safety of  $\beta$  agonists. For example, Taylor and Sears,<sup>27</sup> in an otherwise excellent review, are dismissive of the cardiac side effects of  $\beta$  agonists, merely noting that respiratory and not cardiac events appear to cause the fatal outcome and that death in asthma is due to asphyxia not arrhythmia. However, this stance ignores the important cardiovascular interactions between hypoxaemia and  $\beta$  agonists.<sup>14,17,28</sup> Collins *et al*<sup>29</sup> showed that it was possible to administer large doses of isoprenaline intravenously to anaesthetised dogs with normal blood gas tensions without producing serious arrhythmias, whereas much smaller doses caused fatal cardiac depression during hypoxaemia. In this situation

death occurred through cardiac depression, with bradycardia followed by asystole, which was similar to that observed with more severe degrees of hypoxaemia alone. Pathological studies suggested that isoprenaline could cause ischaemia and subendocardial infarction, and that the pathological appearance of the lesions is similar to those described in some children dying of asthma.<sup>30</sup> Similar pathological findings have now been observed in sheep with fenoterol and, to a lesser extent, with isoprenaline and salbutamol.<sup>31</sup> Lockett<sup>32</sup> showed in the cat isolated heart-lung preparation that, in the presence of a high workload, small doses of isoprenaline or orciprenaline produced heart failure and death, whereas this did not occur when the workload was normal.

These studies suggest why, during the epidemics, most asthma deaths occurred outside hospital under conditions of hypoxaemia, whereas the administration of high doses of  $\beta$  agonists in hospital may be safe if oxygen is also administered. They also suggest that acute toxicity is unlikely to occur unless there have also been delays, causing asthma to deteriorate and hypoxaemia to occur. As pointed out by Tattersfield,<sup>33</sup> the problem with  $\beta$  agonists is that it is difficult to distinguish a drug-induced death from the underlying disease, and such hypoxaemic drug-induced deaths would be clinically and pathologically indistinguishable from other hypoxaemia-induced asthma deaths. Thus, the cardiac side effects of  $\beta$  agonists are likely to increase the risk of "asthma death", not of "cardiac death". It is therefore not surprising that the Saskatchewan group<sup>1</sup> reports that fenoterol was associated with an increased risk of asthma deaths, but was not associated with cardiac deaths or other non-asthma deaths.

#### Non-epidemic increases in asthma deaths: the relevance of the study of Chapman *et al*<sup>2</sup>

Although the evidence regarding the mortality epidemics is relatively clear, the picture is more murky when one considers the more gradual increase in asthma mortality and the associated increase in asthma morbidity that has occurred in most western countries since the 1940s. This includes countries in which isoprenaline forte and fenoterol were not marketed. There are a number of possible explanations for this gradual increase, including increases in the prevalence of asthma and increases in exposure to factors that trigger asthma attacks.<sup>6</sup> However, it has been noted that the increase has been particularly marked since the late 1970s, when many physicians started recommending the use of  $\beta$  agonists on a regular basis (usually four times per day) rather than just for symptomatic relief. This has given rise to much speculation regarding the possible mechanisms by which regular use of  $\beta$  agonists might increase asthma severity including increased allergen load, tachyphylaxis, and increased airways hyperresponsiveness.<sup>27</sup> These mechanisms would probably apply to all  $\beta$  agonists (since in most instances they involve  $\beta_2$  effects rather than the cardiac side effects), but they would be most relevant to high-dose formulations such as isoprenaline forte and fenoterol.

Interest in these issues has heightened since Sears *et al*<sup>34</sup> reported an increase in the severity of clinical asthma when fenoterol was added regularly to an on-demand  $\beta$  agonist drug regimen. There has been considerable

**Table 2** Regimen of  $\beta$  agonist providing overall better control of asthma\*

	Percentage of subjects with better control			p value
	Regular	As required	Indeterminate or no difference	
Fenoterol <sup>34</sup>	26.5%	62.5%	10.9%	0.003
Salbutamol <sup>1</sup>	53.0%	22.0%	24.9%	<0.00001

\* Assessment of "overall better control" according to criteria developed by Sears *et al*<sup>24</sup> in which symptoms and PEFr recordings were ranked according to their perceived relative importance.

debate as to whether this phenomenon is specific to fenoterol or whether it is a class effect of  $\beta$  agonists, and the extent to which it may be dose-dependent.

This brings us to the issue addressed in the recent paper of Chapman *et al*.<sup>2</sup> They studied 341 people with asthma in a four week randomised crossover trial of regular salbutamol (two puffs four times daily) for two weeks and salbutamol as needed for two weeks. When control end points were compared between treatment periods for each individual by two blinded investigators, there was no difference in symptom control between the periods in 70 asthmatics but in the remainder control was achieved more often by regular than by as needed salbutamol (166 *v* 69,  $p < 0.0001$ ). However, the authors noted that the improvement was small and was achieved at the cost of approximately six puffs/day; furthermore, they noted that a decrease in symptoms may itself be hazardous when there is unwitting exposure to an asthma inducer.

One must wonder why the findings of Chapman *et al*<sup>2</sup> are so strikingly different from those of Sears *et al* (table 2).<sup>34</sup> The study by Chapman *et al* was shorter, but the authors argue that the duration was still sufficient to detect a significant deterioration in asthma control. The authors themselves identify two key differences between the studies. The first is that Chapman *et al* used salbutamol rather than fenoterol. If this accounts

for the different findings, it raises the question as to whether the explanation is merely a dose effect or whether it is due to pharmacological differences between the two drugs. Although there is substantial evidence of differences in acute side effects between fenoterol and other commonly used  $\beta$  agonists,<sup>14</sup> their relative chronic side effects at equivalent bronchodilator doses have not been systematically studied. One study<sup>35</sup> did, however, report that regular treatment with fenoterol led to a significant reduction in lung function, whereas terbutaline did not cause this effect.

The second difference between the studies lies with the patient populations involved. Both studies were of adult asthmatic patients, but the study by Sears *et al* involved mild to moderate asthmatics whereas the study by Chapman *et al* involved patients with more severe disease. This difference may be crucial in that regular use may in practice be the same as "as required" use in moderate and severe asthmatics, whereas it may involve considerably greater medication use in mild asthmatics.

#### Implications of these studies for asthma management

The evidence incriminating isoprenaline forte and fenoterol as the major causes of the asthma mortality epidemics is compelling. As Tattersfield notes,<sup>33</sup> both epidemics "have been associated with use of a high dose drug with less  $\beta_2$  selectivity, and both have improved once the drug was withdrawn". Although it is possible that chronic side effects may have been involved, it appears most likely that the epidemics of asthma deaths were due to the acute cardiac side effects of the self-administration of high doses of isoprenaline forte and fenoterol under conditions of hypoxaemia and hypercapnia associated with life threatening attacks of asthma. The therapeutic implication is that these drugs should no longer be used, and that newer  $\beta$  agonists should also be examined for acute cardiac side effects under conditions of hypoxaemia and repeated administration.

## LEARNING POINTS

- \* Asthma mortality epidemics occurred in six countries in the 1960s following the introduction of isoprenaline forte.
- \* A second epidemic occurred in New Zealand with the introduction of fenoterol in 1976.
- \* No other  $\beta$  agonists have been implicated in asthma mortality epidemics.
- \* Laboratory studies have shown that isoprenaline forte and fenoterol are high-dose, poorly selective  $\beta$  agonists and have cardiac side effects that may be hazardous in high doses under conditions of hypoxaemia.
- \* Many countries have experienced a gradual (non-epidemic) increase in asthma mortality since the late 1970s.
- \* One possible explanation for the gradual increase in asthma mortality is that the regular use of  $\beta$  agonists may lead to worsening asthma.
- \* This effect has only been demonstrated with fenoterol in mild to moderate asthmatics; it has not been found with salbutamol in a study in severely asthmatic subjects.

The evidence is more equivocal regarding the non-epidemic increases in asthma mortality (and morbidity) and the possible role of the regular use of  $\beta$  agonists. There is evidence that regular use of fenoterol increases asthma severity in mild asthmatics, but there is also now evidence that regular use of salbutamol is not hazardous in moderately severe asthmatics. Clearly, further long term studies in different patient populations are needed to test the whole range of currently available  $\beta$  agonists, particularly the new long acting  $\beta$  agonists salmeterol and formoterol. In the interim, the preferred regimen is to use inhaled  $\beta$  agonists "as required", as currently recommended in the various national and international guidelines.<sup>36 37</sup>

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