

Beta-agonists - friends or foes?

We would like to respond to some comments about fenoterol in the editorial by C.G. Löfdahl and N. Svedmyr, "Beta-agonists-friends or foes?" [1].

The increase in asthma deaths in New Zealand began in 1975. It peaked in 1979 and, for unknown reasons, declined to near baseline by 1987. The "epidemic" of asthma deaths was temporarily related to a large per capita increase in the consumption of both inhaled salbutamol and fenoterol, and to the widespread introduction of regular β -agonist therapy. As the editorial points out, asthma mortality fell, while the consumption of fenoterol and salbutamol further increased. Simultaneously, parallel increases in beclomethasone use occurred (fig. 1). The argument that fenoterol caused the most recent New Zealand asthma mortality epidemic was based on selective presentation of data [2]. Fenoterol was never sold over the counter in New Zealand.

In the United States, where fenoterol has never been marketed, asthma mortality is rising. The asthma death rate in Australia, a country with a low fenoterol consumption, has also been increasing. Over the counter sale of β -agonists is common in Australia.

In Australia, analysis of the Victorian Mortality Study [3] data showed that at most 16 of the 163 asthma fatalities had ever used fenoterol during the study period. Many of these patients had also received other β -agonists. This study did not demonstrate an overrepresentation of fenoterol in fatal asthma cases. In Sweden, of the 110 asthma deaths between 1986 and 1990, only 3% used fenoterol [4], not more than expected with a market share between 1.7 and 3.4%.

There is now considerable evidence from The Netherlands, Germany and New Zealand that fenoterol was selectively prescribed to higher risk asthmatics [5-7]. This is not surprising, since the fenoterol metered dose inhaler (MDI) 200 μ g delivered

a higher dose of a β -agonist with higher intrinsic activity. In this situation, epidemiological studies can produce artificial, non-causal associations. None of the New Zealand Case Control Studies solved this problem. While, as Löfdahl and Svedmyr point out, the most recent New Zealand analysis [8] removed control selection bias, the unbiased control group revealed odds ratios not only for inhaled fenoterol, but also for oral salbutamol, nebulized salbutamol, theophylline and oral steroids. The odds ratio for salbutamol MDI is analytically linked to fenoterol, approximately the inverse. The design of the Saskatchewan Asthma Epidemiology Project permitted the odds ratios for fenoterol and salbutamol MDIs to be uncoupled. This showed use related increase in death rate not only for fenoterol but also for salbutamol MDI, as well as elevated odds ratios for nebulized and oral salbutamol.

Fenoterol has a higher intrinsic activity than salbutamol at the β_2 - as well as the β_1 -adrenoceptor. Salbutamol is a partial agonist at both receptor subtypes. According to binding studies (Birke F, Biochemical characterization of the new β -mimetic SOM 1122 MS in comparison with fenoterol and salbutamol: β_1/β_2 -adrenergic receptor affinities and selectivity, Boehringer Ingelheim KG 1989), there is no relevant difference between fenoterol and salbutamol in terms of β -selectivity. The pharmacological relevance in humans has been studied and results are expected soon.

Drugs with higher intrinsic activity, like fenoterol, have steeper dose response curves and have the potential for greater bronchodilatory and extrapulmonary effects (Kazim F, Statistical Report on: Cumulative Dose Response Curves to Nebulized Solutions of Fenoterol and Salbutamol in Stable Asthmatics; Investigators Newhouse M and Dolovich M, Data on File, Boehringer Ingelheim).

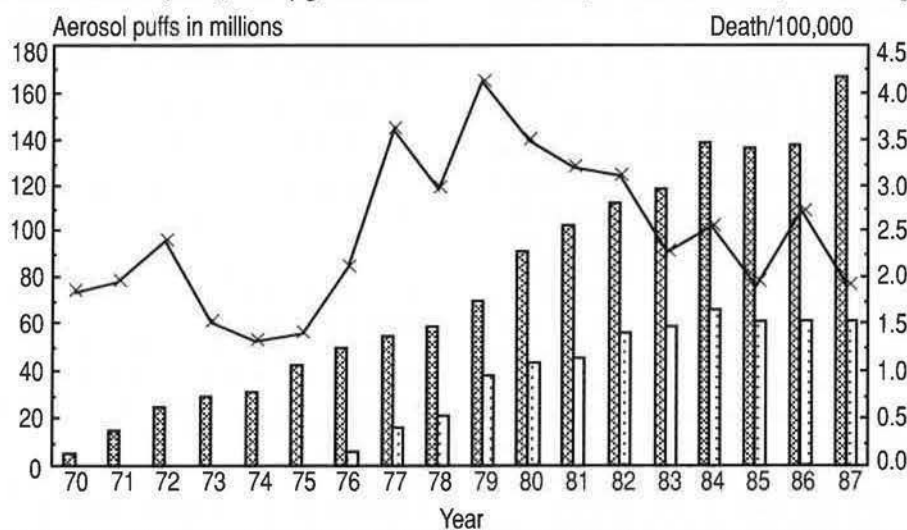


Fig. 1. - β -agonist inhalers in New Zealand (1970-1987): aerosol puffs vs mortality rate (age 5-34 yrs). \square : salbutamol; \square : fenoterol; \times : mortality rate.

For high and very high doses, a clinically relevant assessment of beneficial pulmonary *versus* unsought extrapulmonary effects can only be made under emergency room conditions. Two major emergency room studies comparing fenoterol and salbutamol are in progress. Since by far the majority of asthmatics die with evidence of suffocation, not with signs of cardiac toxicity such as rhythm disturbances, higher intrinsic activity could translate into additional therapeutic benefit in the severe acute attack.

The majority of the studies on extrapulmonary effects of fenoterol cited in the editorial have been performed by one group in New Zealand and suffer from a variety of methodological difficulties. For example, based on cumulative dose response data, BURGESS *et al.* [9] claim that the tachycardia produced by fenoterol is greater than that of isoprenaline. The study design ignored the much longer duration of action of fenoterol compared to isoprenaline. Such a design necessarily creates a bias unfavourable for any longer acting drug than isoprenaline, in this case fenoterol. Combined with the use of endpoints reflecting both β_1 - and β_2 -effects, like tachycardia, the study design does not allow valid conclusions about β -selectivity.

Findings consistent with some deterioration of asthma control on regular β -agonists have been reported for fenoterol, salbutamol and terbutaline. The observations are not consistent and the issue has to be regarded as still open.

The crossover study performed by SEARS *et al.* [10] was the most comprehensive study suggesting inferior asthma control with regular β -agonist treatment. Virtually all previous studies with other β -agonists, including long-acting drugs, have used parallel group designs. The Sear's study administered quantities of fenoterol in excess of that recommended as initial treatment for mild to moderate asthmatics in the company's basic product information. The question of whether similar findings would have occurred with customary doses remains open.

In pointing out that TREMBATH *et al.* [11] showed a reduction in airway calibre for fenoterol but not for terbutaline (used at about half the equivalent dose), the editorial seems to suggest that a better result with *p.r.n.* compared to regular therapy is specific to fenoterol. In fact, BESWICK *et al.* [12] showed a greater increase in morning peak expiratory flow (from a baseline of 320 to 352 $l \cdot min^{-1}$) after 10–12 months of on demand treatment with salbutamol compared to a minimal increase (from 293 to 301 $l \cdot min^{-1}$) with regular treatment. Increases in bronchial hyperreactivity have occasionally been observed with salbutamol, terbutaline and fenoterol.

In conclusion, the epidemiological evidence does not support a unique association between fenoterol and asthma mortality. Neither does the pharmacological or clinical evidence suggest that fenoterol is uniquely different from other β -agonists.

Nonetheless, based on the findings available,

especially the Saskatchewan Asthma Epidemiology Project, [13] it appears advisable to avoid chronic overuse of β -agonists. In addition to product information changes reflecting modern understanding of asthma therapy and recommending appropriate use of anti-inflammatory therapy, Boehringer Ingelheim has - in addition to the already lower dose fenoterol/ipratropium combinations - extended the availability of a lower dose fenoterol MDI (Berotec®100).

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