Risk of severe life threatening asthma

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There have been many components to the debate on the safety of β_2 agonists but one of the most important has been the interpretation of the New Zealand studies investigating associations between asthma death and the use of the inhaled β_2 agonist fenoterol. In 1976 a striking rise in the death rate from asthma occurred in New Zealand[1] and many studies have been performed to try and unravel the causes of this epidemic. In a case control study the Wellington group reported an association between the use of fenoterol and death from asthma.[2] This study was heavily criticised and, in the light of these criticisms, a second case control study using improved methodology and a longer time period was performed.[3] This again showed an association between prescribed fenoterol and asthma deaths. Further criticism led to another study, again using a different time period, and the same conclusion was reached.[4] The major problem in interpreting the results of these three studies was whether the relationship between fenoterol usage and death was causal or whether fenoterol was selectively prescribed to more severe asthmatics who were at greater risk of dying. This explanation is termed "confounding by severity". To answer the criticism that their results could be due to confounding by severity the Wellington group reanalysed the data and argued that it was extremely difficult to explain their results on this basis.[6] In this issue of *Thorax* Garrett *et al*[7] have performed a retrospective cohort study of patients presenting with asthma to a single Auckland hospital during 1986 and 1987. They followed this cohort until the occurrence of death, admission to an intensive care unit for asthma, or until 31 May 1989. Patients using inhaled fenoterol had a greater incidence of severe life threatening asthma than patients using the other most commonly prescribed β_2 agonist, salbutamol. The relative risk at 2·1 is similar to the previous case control studies from Wellington. By controlling for two markers of asthma severity (a recent hospital admission and prescribed oral steroids) the relative risk fell to 1·5. By controlling for other markers of asthma severity such as the number of hospital admissions, continuous use of oral steroids, the severity of the previous attack, and race, no association remained between fenoterol use and severe life threatening asthma. They go on to argue that the results of the three case control studies were due to confounding by severity and that no causal relationship between fenoterol use and asthma death is proven. The paper does indicate that confounding by severity can suggest an association between fenoterol use and asthma death. However, the study period is towards the end of the New Zealand epidemic, it is different in design from the previous studies, and may have lacked power in some areas.

It was undoubtedly the case that other factors apart from fenoterol were of importance in the epidemiology of death from asthma in New Zealand. Deficiencies in asthma management were identified and, in particular, the death rate was high in ethnic minorities with poorer access to health care and potential cultural barriers to taking regular preventive treatment. However, the increase in asthma mortality in the mid 1970s which continued until the sharp decline in 1989[8] is difficult to explain on the basis of management deficiencies and ethnicity, factors which would be expected to cause a slower change in death rate. Furthermore, these factors were present in New Zealand before 1976 and in other countries without causing a dramatic increase in asthma deaths. It is, however, noteworthy that the death rate began to fall before the withdrawal of fenoterol, which suggests that other factors were having an effect. Even after the withdrawal of fenoterol[8] it took some further time before the death rate from asthma in New Zealand fell to levels found in other countries. These features of the epidemic suggest that the observed rise in asthma deaths was due to a combination of factors and that fenoterol use could not be the sole explanation of the problem.

Pharmacological explanations as to why fenoterol might have caused particular problems exist. Fenoterol is a full agonist at the β_2 receptor[9] as was isoprenaline and unlike the other commonly used β_2 agonists such as salbutamol and terbutaline. There is also evidence of greater β_1 activity and greater potency on a microgram for microgram basis than salbutamol in terms of extrapulmonary effects.[10]

It is difficult for epidemiological studies to answer conclusively clinical questions on their own; however, an overview of the studies to date would suggest that the epidemic of asthma deaths in New Zealand was due to an interaction of factors, one of the most important of which was the use of fenoterol.

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