ISOPRENALINE, FENOTEROL AND ASTHMA DEATHS IN JAPAN

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ABSTRACT

Asthma mortality rates were very stable, and very low, in Western countries during the first half of this century. However, there were asthma mortality epidemics in six Western countries in the 1960s. These were linked with the introduction of isoprenaline forte which was only marketed in the six epidemic countries (England and Wales, Scotland, Ireland, Norway, Australia and New Zealand), and in two other countries for whom sales were low (The Netherlands and Belgium). Although the high-dose (forte) formulation of isoprenaline was not marketed in Japan, and the country showed only a modest increase in asthma mortality in the 5-34 years age-group, there was a more marked increase in mortality in the 10-14 years age-group which paralleled the increase in total sales of beta-agonist aerosols. A second mortality epidemic occurred in New Zealand in the 1970s. This was linked with the introduction of fenoterol, which was not licensed in the USA and had a low market share in most other countries. Japan experienced a doubling in asthma deaths in the 5-34 years age-group following the introduction of fenoterol in 1985, and there was a parallel between the increase in fenoterol sales and the increase in mortality. Furthermore, a recent study found that a high proportion of asthma deaths were in persons prescribed fenoterol (53% compared with a market share of 18%). Thus, the available data for Japan is consistent with the studies in Western countries that have indicated an increase in the risk of asthma death in patients prescribed isoprenaline or fenoterol, which are both poorly selective full agonists that were marketed in high dose preparations. These findings have policy implications for Japan and the Asia Pacific region, as well as for the rest of the world.

INTRODUCTION

Asthma mortality rates were very stable, and very low, in Western countries during the first half of this century¹⁾. However, there were asthma mortality epidemics in six Western countries in the 1960s, and again in New Zealand in the 1970s, associated with the use of two specific beta agonist drugs, isoprenaline and fenoterol. In this paper, we briefly review asthma mortality studies in Western countries, particularly those which have investigated the role of beta agonist therapy, and compare them with data from Japan, the only Asian country for which comparable information is available in English-language publications. As with pre-

vious reviews of these issues, we focus on studies of the 5-34 years age-group because the diagnosis of asthma mortality is more firmly established in this group²⁾.

ISOPRENALINE

The 1960s epidemics

In contrast to the relatively stable asthma death rates during the first half of this century, asthma mortality increased dramatically in at least six developed countries in the 1960s: England and Wales, Scotland, Ireland, New Zealand, Australia and Norway. Speizer et al.³⁾ conducted a detailed examination of the mortality trends in the

5-34 age-group in England and Wales. They concluded that the epidemic was real and was not due to changes in death certification, disease classification, or diagnostic practice. They also considered that it was unlikely to be due to a sudden increase in asthma prevalence, but was rather due to an increase in case-fatality due to new methods of treatment. In particular, they found that the sudden increase in asthma deaths followed the introduction of pressurized beta agonist aerosols in 1961 (including isoprenaline), and paralleled the subsequent increase in sales. They also noted that the increase in mortality was greatest in the 10-19 year age-group and that "at these ages children have begun to act independently and may be particularly prone to misuse a self-administered form of treatment". Inman and Adelstein⁴⁾ subsequently concluded that "the excess deaths... were likely to have been the result of overuse of pressurized aerosols and that the subsequent decline in mortality has resulted from a greater awareness by doctors and patients of the dangers of overuse".

These deaths were often sudden and unexplained, most occurred outside hospital⁵⁾, direct information on drug usage was scanty, and the likely mechanism of death was unknown. However, it was noted that the relief of symptoms could enable a patient to tolerate worsening hypoxia and to unduly delay seeking medical help⁶⁾. It was also argued that both chronic and acute side effects could occur⁷⁾, and that direct toxicity could occur in certain circumstances since isoprenaline is a non-selective beta-agonist⁸⁾. Collins et al⁹⁾ showed that it was possible to administer large doses of isoprenaline intravenously to anaesthetized dogs with normal blood gas tensions without producing serious arrhythmias, whereas much smaller doses caused fatal cardiac depression during hypoxaemia. These studies suggested a reason why most 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 suggested that acute toxicity was unlikely to occur unless there had also been delays causing asthma to deteriorate and hypoxaemia to be present.

The isoprenaline forte hypothesis

Despite these striking findings, there were a number of anomalies in the epidemiological data. In particular, there had also been high sales of aerosols in the United States and several other countries which did not experience mortality epidemics. This confusing situation was clarified by Stolley¹⁰⁾ who noted that a high dose formulation of isoprenaline (isoprenaline forte), which contained five times the dose per administration of other isoprenaline aerosols, had only been licensed in eight countries. Six of these (England and Wales, Ireland, Scotland, Australia, New Zealand, and Norway) had mortality epidemics which coincided with the introduction of the drug, and in the other two countries (the Netherlands and Belgium) the preparation was introduced relatively late and sales volumes were low. Overall, there was a strong positive correlation internationally between the asthma mortality rate and isoprenaline forte sales in these eight countries, whereas no mortality epidemics occurred in countries in which isoprenaline forte was not licensed, such as Sweden, Canada, West Germany and the United States^{10,11)}. Formal epidemiological studies (e.g. case-control studies¹²⁾) were never mounted because the epidemics declined before there was time to conduct them. Nevertheless, the weight of evidence was highly consistent with the hypothesis that isoprenaline forte was the main cause of the mortality epidemics. Thus, death from bronchodilator aerosols was designated one of the most important adverse drug reactions since thalidomide¹³⁾, and an editorial in the *British Medical Journal*⁵⁾ entitled "Asthma deaths: a question answered" concluded that "[Stolley's work] strengthens still further the case for relating the increase in asthma deaths to aerosols and the sympathomimetic drugs they contain...".

Figure 1. Asthma mortality per 100,000 in persons aged 5-34 years and 10-14 years and sales of pressurized bronchodilators in Japan, 1950-1980

Isoprenaline in Japan

The 1960s epidemics occurred in Western countries, and the only Asian country for which comparable mortality and drug sales data appears to be available, at least in English-language publications, is Japan. In Japan the death rate in the 5-34 age-group decreased during the 1950s (Figure 1). Pressurized bronchodilators went on sale in 1957; sales began to increase rapidly from 1960 (Figure 1), and mortality began to gradually increase from about the same time¹⁰. However, the forte formulation of isoprenaline was not marketed in Japan, and the country showed only a modest increase in asthma mortality in the 5-34 years age-group (Figure 1). This is the age group of prime interest and has been the focus of all previous analyses of mortality time trends; in this age group the Japanese data are consistent with the data from other countries^{10,11} that shows that no mortality epidemics occurred in countries in which isoprenaline forte was not marketed. Nevertheless, it is of interest that there was a marked increase in mortality in the 10-14 years age-group which

paralleled the increase in total sales of beta-agonist aerosols¹⁰. There were reports of patients who died with nebulisers in their mouths, or surrounded by empty pressurized aerosol containers¹⁰. In 1972 the Japan Ministry of Public Welfare made beta agonist aerosols a prescription drug, sales decreased rapidly, and the death rate fell in both the 5-34 and 10-14 years age-group (Figure 1). Sales began to increase again after 1975, but the death rate did not increase during 1975-1980, possibly due to more prudent patient management¹⁴.

FENOTEROL

In 1976 a second asthma mortality epidemic began in New Zealand, but not in other countries. As for the 1960s epidemic, initial investigations identified that it was real, and could not be explained by changes in the classification of asthma deaths, inaccuracies in death certification, or changes in diagnostic fashions^{15,16}. It was also concluded that it was very unlikely that the epidemic could be due to changes in the incidence or preva-

lence of asthma in New Zealand, and that the most likely explanation, as for the 1960s epidemics, appeared to be due to an increased case fatality rate related to changes in the management of asthma in New Zealand¹⁶.

The New Zealand asthma mortality survey

A national asthma mortality survey was subsequently undertaken by the Asthma Task Force.^{17,18} This was a comprehensive survey of asthma deaths in persons under 70 years between 1981 and 1983. A number of factors were identified that contributed to asthma deaths including inadequate functional assessment of the severity of asthma, inappropriate drug therapy with over-reliance on beta agonists and under-use of corticosteroids, delay in seeking and in some cases providing medical care, inadequate emergency care, and lack of follow-up after treatment of acute attacks. However, there was no evidence that any of these factors had suddenly increased in 1976 in New Zealand, but not in other countries. It was evident that although many of these factors may have contributed to the "background" causes of asthma deaths, it is very unlikely that they could have caused the New Zealand epidemic.

The fenoterol hypothesis

The role of the beta agonist fenoterol in the second New Zealand mortality epidemic was subsequently investigated by Crane et al.¹⁹ The fenoterol hypothesis stemmed initially from two published studies indicating that fenoterol was used by a relatively high proportion of asthmatics who died^{15,20}. These observations prompted an examination of the time trend data¹⁹ which revealed that fenoterol was introduced to New Zealand in 1976 and that the epidemic began in the same year, with a close parallel between fenoterol sales and asthma deaths in the early years of the epidemic, whereas total beta agonist sales only began to increase three years after the epidemic had started²¹. It was also observed that fenoterol represented less than 5% of the market in most other

countries and had not been licensed in the United States. Although fenoterol had a 50% market share in West Germany, the per capita sales of fenoterol were only one-third of those in New Zealand²² and although there was no sudden mortality epidemic in West Germany, mortality nearly doubled in the 5 years following the introduction of fenoterol²².

A further observation was that fenoterol was dispensed by aerosol as a 200 μ g/puff preparation, compared with salbutamol at 100 μ g¹⁹. In fact, fenoterol is twice as potent as salbutamol, and the 200 μ g/puff preparation is a forte preparation with effectively four times the strength of salbutamol²³. Finally, a series of laboratory studies found that repeated inhalation of fenoterol resulted in greater inotropic and chronotropic effects than those of salbutamol, but similar to those of isoprenaline^{8,24,25}.

Case-control studies of fenoterol and asthma deaths

New Zealand studies

In response to these observations, a series of case-control studies were conducted to investigate the possible role of fenoterol in the second New Zealand asthma mortality epidemic. In the first study¹⁹ cases were obtained from the previous New Zealand asthma mortality survey, and included all asthma deaths in New Zealand in the 5-45 year age-group during 1981-1983. The only anti-asthma drug that was associated with a significantly increased risk of death was fenoterol (Table 1). The possibility that the increased risk of death observed with fenoterol could have been due to selective prescribing of fenoterol to more severe asthmatics (i.e. confounding by severity), was assessed by examining subgroups defined by markers of chronic asthma severity. In these subgroups the fenoterol relative risk was markedly increased, with the relative risk ranging from 2.2 to 13.3 in the most severe subgroup²⁶. These find-

Table 1. Findings from studies of fenoterol and asthma deaths

	First New Zealand study	Second New Zealand study	Third New Zealand study	Saskatchewan study	
			Group A	Group B	
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Fenoterol	1.6 (1.0-2.3)	2.0 (1.1-3.6)	2.1 (1.4-3.2)	2.7 (1.7-4.1)	4.8 (2.5-9.3)
Salbutamol	0.7(0.5-1.1)	0.7 (0.4-1.2)	0.6 (0.4-1.0)	0.5 (0.4-0.8)	0.9 (0.4-1.7)
Fenoterol only	1.6 (1.0-2.5)	1.9 (1.0-3.7)	2.0 (1.3-3.2)	2.5 (1.6-3.9)	3.7 (1.7-8.0)
Salbutamol only@	1.0	1.0	1.0	1.0	1.0

@Reference category

ings strongly indicated that the overall association between fenoterol and asthma deaths was not due to confounding by severity, since in this situation the fenoterol relative risk would have decreased as the analysis was increasingly restricted to the most severe subgroup^{27),28)}. No other anti-asthma drug-examined increased the risk of death disproportionately in severe asthmatics. Furthermore, there is little evidence of selective prescribing of fenoterol in the population on which the case-control study was based²⁹⁾.

The second New Zealand case-control study³⁰⁾ of asthma deaths also examined the 5-45 year old age group, but during the first five years of the epidemic(1977-1981). By obtaining prescribing information for all cases and controls from routine hospital records, the potential problem of information bias was overcome. The overall relative risk of asthma death in patients prescribed inhaled fenoterol was 2.0 (Table 1), and as before, the relative risk again increased markedly when the analysis was restricted to subgroups defined by markers of asthma severity. A third national case-control

study examined the same hypothesis in the same age-group during the period 1981-1987³¹⁾. For both control groups used, fenoterol but not other drug therapy was associated with an increased risk of asthma death (Table 1).

A final piece of evidence concerning the role of fenoterol in the second New Zealand epidemic is that, following the Government warnings about the use of fenoterol, the mortality rate fell significantly³²⁾. During 1983-1988 the New Zealand mortality rate in the 5-34 year age-group had averaged 2.3 per 100,000, the highest in the world. The death rate was 2.2 per 100,000 in the first half of 1989. In mid-1989, the New Zealand Department of Health issued warnings that fenoterol should not be used in severe asthmatics. Sales of the drug fell markedly and death rate fell by one-half to 1.1 per 100,000 in the second half of 1989. In December 1989 the Department of Health announced that Government subsidies for fenoterol would be withdrawn, leading to the virtual elimination of the drug from the New Zealand market. Mortality fell further to 0.8 in 1990 and by

1993 New Zealand mortality rate of 0.5 per 100,000 in the 5–34 age-group was the lowest for 50 years and was lower than in many other countries including Japan.

The Saskatchewan Study

The strongest evidence in support of the New Zealand findings has come from a Canadian case-control analysis³⁹, and a cohort analysis of the same data base⁴⁰ funded by Boehringer Ingelheim, the manufacturer of fenoterol. The case-control study examined 44 asthma deaths in the province of Saskatchewan during 1980–1987 and 233 controls. The Saskatchewan study was similar in many respects to the New Zealand studies, and used the same severity markers. The unadjusted fenoterol relative risk was 4.8 (Table 1), with nearly one half of the deaths having been prescribed fenoterol compared with 16% of the controls. Thus the findings were even stronger than those in New Zealand when the studies were analysed in an identical manner. The authors interpreted the findings as reflecting a class effect of beta agonists but conceded that the study showed that fenoterol was more hazardous than other beta agonists in the dose in which it was marketed. The accompanying editorial in the *New England Journal of Medicine* concluded that there was enough doubt about the safety of fenoterol to avoid it altogether⁴¹. Hensley³⁰ (a member of the Scientific Advisory Board of the study) also noted that the Saskatchewan findings supported the New Zealand findings and that “the weight of evidence and availability of alternative medication should lead to a recommendation that fenoterol not be used to treat asthma.”

Other relevant studies

There have been no other formal case-control studies of asthma deaths in Western countries, but relevant information is provided from a recent small cohort study of patients with chronic obstructive pul-

monary disease in Germany which found a ten-fold increased death rate in those prescribed fenoterol compared with prescribed other beta agonists³⁷.

Fenoterol in Japan

Although the asthma death rate in Japan had been declining during the late 1970s, the death rate began to increase again after 1980 doubling within the subsequent 10 year period (Figure 2)³⁹. Concern about these mortality trends led to the formation of the Committee on Asthma Death of the Japanese Society of Pediatric Allergy and Clinical Immunology, which sent investigation forms to physicians attending asthma deaths from 1990^{39,40}. The 1995 Report stated that there was a relationship between asthma death and over-reliance or excessive dependence on beta₂-agonists³⁹. In the analysis of 51 asthma deaths during the period 1990–1993, it was reported that in 45.1% of deaths there was excessive reliance on beta₂-agonist inhalers or nebulisers³⁹. This was particularly noted in males and in those aged 13 years or more. These findings are of particular interest because the increase in asthma deaths was particularly notable in adolescent and young adult males, as had been the case in the 1960s epidemics and in the second New Zealand epidemic^{41,42}. The reasons for these patterns are not clear, but it is possible that teenagers and males are particularly likely to misuse a self-administered form of treatment and to fail to seek medical help³.

In a subsequent report from the Committee on Asthma Death, including 124 cases that had been registered and analysed by July 1996, excessive dependence on β_2 agonists was again identified as a common factor contributing to a fatal outcome⁴³. This report also made the important point that this excessive dependence on β_2 agonists contributed to other factors associated with the fatal outcome, such as delay in seeking emergency hospital treatment. It is also interesting to note that a recent Japanese case-control study identified that

Table 2. Proportion of cases (asthma deaths) and controls prescribed fenoterol in studies in New Zealand, Saskatchewan and Japan

	Total deaths	% cases on fenoterol	% controls on fenoterol	Odds ratio	95% CI
First New Zealand study	117	51.3%	40.4%	1.6	1.0-2.3
Second New Zealand study	58	51.7%	35.7%	1.9	1.1-3.4
Third New Zealand study	112	59.8%	45.9%	1.8	1.2-2.7
Saskatchewan study	44	47.7%	15.9%	4.8	2.5-9.3
Japan	30	53.4%	18.3%*	5.1	2.6-9.9

*Market share (this study did not include a formal control group)

excessive dependence on β_2 agonists was more than twice as common in asthmatic patients who died, compared with those experiencing a near-fatal attack⁽⁴⁾.

A review was also conducted of the 30 asthma deaths in Japan included in this investigation in which the beta agonist used in the one month period before death was known⁽³⁰⁾. This analysis identified that fenoterole was used by just over half (53.4%) of the asthmatic patients who died at a time when it had only a 18.3% market share in Japan (Figure 3). In contrast, procaterol and salbutamol were used by 30% and 10% of the asthmatic patients who died, despite greater market shares than fenoterol (procaterol 27.6%, salbutamol 20.1%). These figures yield a relative risk of asthma death of five-fold in persons prescribed fenoterol, an estimate consistent with those from New Zealand and Saskatchewan (Table 2).

It should be emphasised that the interpretation of these findings in relation to fenoterol is limited as this study did not include a control group and no information is available on the market share of fenoterol in the different age groups or amongst asthmatics of different severity in Japan. Thus, a prospective case-control study using a similar de-

Figure 2. Fenoterol market share (%) and asthma mortality per 100,000 in persons aged 5-34 years in Japan, 1980-1993

sign to that employed in New Zealand, with appropriate controls and a detailed analysis of each death, would be valuable to further clarify the role of fenoterol in asthma deaths in Japan.

Nevertheless, the Japanese data currently available is consistent with that from other countries, that the use of fenoterol is associated with an increased risk of death from asthma. Further support comes from analysis of time trends in Japan which show a parallel between the increase in

Figure 3. Types of beta₂-agonist MDI used in asthma deaths compared with market share in Japan

fenoterol market share since its introduction in 1985 and asthma mortality in persons aged 5–34 years (Figure 2). This increase in fenoterol market share occurred on a background of increasing overall sales of inhaled beta agonist drugs.

DISCUSSION

Asthma mortality rates were very stable, and very low, in Western countries during the first half of this century, but there were asthma mortality epidemics in six countries in the 1960s. The 1960s epidemics only occurred in countries in which the high dose formulation of isoprenaline (isoprenaline forte) was marketed. However, although only the regular dose formulation was available in Japan, and there was only a modest change in mortality in the 5–34 years age-group, there was a striking increase in mortality in the 10–14 years age-group which paralleled sales of isoprenaline aerosols.

A second epidemic of asthma deaths occurred in New Zealand in the 1970s following the introduction of fenoterol. This epidemic was apparent in New Zealand because of the very high market share and per capita use of fenoterol, and perhaps also because of local prescribing patterns (e.g. asthma medications were free but there was a charge for family doctor consultations, thus encouraging reliance on medication in asthma at-

tacks). However, other countries for which statistics are available, including Germany and Japan, also show (non-epidemic) increases in asthma deaths following the introduction of fenoterol.

Furthermore, a recent Japanese study found that a high proportion of asthma deaths were in persons prescribed fenoterol (53% compared with a market share of 18%), and there was a parallel between the increase in fenoterol sales and the increase in the asthma mortality rate in Japan.

As a result of these concerns, the Japanese Ministry of Health and Welfare recently cautioned that "the use of fenoterol MDI should be avoided in children as possible". This makes Japan the fourth country to adopt restrictions or recommendations against the use of fenoterol, after the USA (which declined to license the medication), New Zealand (which issued warnings and removed government subsidies for the medication) and Australia (which recommended that the medication not be used in severe asthmatics). Other countries have not taken formal action to date, although the dose of fenoterol has been reduced to 100 μ g/puff in most other countries in which it is available. Japan is one of the few countries still using the 200 μ g formulation.

Thus, the data for Japan (apparently the only Asian country for which the relevant data is available in English-language publications) is consistent with the studies in Western countries indicating that isoprenaline and fenoterol have been associated with increases in asthma deaths. These medications have the distinction of being high dose, poorly selective, full agonists⁸. The evidence relating isoprenaline and fenoterol to asthma deaths in Japan, as well as in the West, is of considerable policy importance for Japan and for other countries in the Asia Pacific region, as they increasingly adopt "Western" practices of asthma management. In particular, they not only demonstrate the hazards of isoprenaline forte and fenoterol, which should no longer be available for the treatment of asthma, but also emphasize the

dangers of even-reliance on beta agonist therapy in general.

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