A childhood asthma death in a clinical trial: potential indicators of risk


ABSTRACT: A 9 yr old girl with a history of eczema and asthma was admitted to our specialist asthma service and recruited into a trial designed to investigate systemic as well as therapeutic benefits of inhaled corticosteroids. Eight months after referral the patient died from an acute asthma attack. This childhood asthma death during an inhaled steroid trial has facilitated identification of risk factors.

Death from asthma is rare in childhood although its existence has been recognized for decades [1]. In the USA, even in 1967 it was calculated that between 4 and 10% of children have asthma, of whom 1–2% will die of the disease [2]. A study from Australia in 1987 reported the clinical and pathological features of five children who died from asthma [3]. The authors of this study calculated that 20% of children have asthma, of whom 5% have significant disease and 0.5%, chronic severe disease. The mortality rate in the severe group was 1–2% with the 10–14 yr old age group being particularly at risk. Since the above figures were generated, there has been a considerable increase in the prevalence of asthma [4]. However, mortality rates in childhood asthma have remained relatively stable in the same populations which suggests that the risk of dying from asthma amongst asthmatics has diminished.

In the 15–64 yr old age group, mortality rates for asthma are very much higher and most of the attempts to identify risk factors for death have concentrated on this age group. These have taken the form of retrospective surveys of patients dying from asthma and have suggested that there are potentially avoidable factors which appear to have contributed to this demise [5]. The characteristics of patients who have died have included: inappropriate treatment with over reliance on bronchodilators and under-use of systemic steroids, poor perception of airflow limitation; and an underestimate of severity of the chronic asthma and acute exacerbation. The latter has often led to a delay in obtaining appropriate medical help [6]. Similar features have been identified in rather more limited surveys of childhood asthma deaths. Thus, one survey identified the deaths as occurring in chronic asthma sufferers, usually at night after a lengthy period of deterioration with inadequate management and deficiencies in corticosteroid treatment. A greater proportion of girls died than would have been predicted from the proportion attending hospital [7]. A survey of asthma deaths in the age group 1–16 yrs in the Northern Health Region of England identified 35 cases over a 15 yr period. There was an excess in the number of girls who died and two thirds of the total were teenagers. It was suggested in this study that 28 of the 35 deaths were potentially preventable with both long-term under-treatment and suboptimal management of the final illness [8].

Inevitably, there are problems in interpreting the data from retrospective surveys because there are no adequate controls. It is difficult to know whether the features identified truly distinguish those at risk of death from those who do not die. There are virtually no studies which have derived information prospectively in individuals who have subsequently died. However, one publication on two girls who died from asthma has perhaps highlighted potential physiological factors which might be associated with an increased risk of demise. These two girls had undergone detailed lung function studies within a few months of their demise and in comparison to a reference group of asthmatic children, had an extreme degree of bronchial hyper-reactivity on cold air challenge and incomplete recovery of lung function after bronchodilator administration. They also had an appreciably reduced perception of severe lung function impairment [9].

A recent tragic experience in our group, was that of a girl who died of asthma while being closely supervised during an inhaled steroid trial [10]. This has provided an opportunity to evaluate risk factors by comparison with equivalent patients who were also involved with the study.
and did not die. The data accumulated identify factors influencing the risk of death and also indicates possible mechanisms.

**Case report**

We report the case of a 9 yr old girl with a history of eczema and asthma since the age of 8 months. Symptoms of cough and wheeze were triggered by infections, change in weather, exercise and emotional stress. The asthma symptoms were perennial and always worse at night. She had had one hospital admission for a severe asthma attack at 6 yrs of age and had missed an average of 3 weeks’ schooling per year due to asthma. She had been treated with regular cromolyn sodium, slow release theophylline and β-agonists, but despite this, required several courses of oral corticosteroid each year. Her referral to our specialist asthma service was very delayed and only occurred 8 months before her death.

At the point of referral, she had recently completed a short course of oral corticosteroid but was still requiring 20 doses of salbutamol/albuterol per day for relief of acute symptoms. She was recruited into a trial designed to investigate the systemic effects as well as therapeutic benefits of inhaled corticosteroids (ICS). Although at the severe end of the spectrum of patients enrolled in the study, she was not dissimilar to any others in clinical characteristics. The key criterion for enrolment was that she should not have received any ICS in the past but had disease sufficiently severe to justify their use. Clearly, in fact, based on current guidelines [11], she should have been on inhaled steroids for many years.

Together with 13 other children, 11 boys and two girls aged 8–14 yrs, she agreed to take part in the prospective study testing the effects of two ICSs, beclomethasone dipropionate (BDP) and budesonide (BUD) on endocrine and lung function. She was subsequently followed-up with all the other patients with the intention of maintaining surveillance for a full year. During that time, she was taking inhaled BUD 200 µg b.i.d. as a replacement for the cromolyn sodium while continuing slow release theophylline with the use of inhaled β-agonists (terbutaline) 500 µg b.i.d. and extra doses as necessary.

She responded extremely well to treatment and within 1 week, had few symptomatic days and rarely required additional doses of β-agonist. She remained well, having occasional mild to moderate asthmatic symptoms responding well to bronchodilators. In March after 6 months of therapy, asthma symptoms increased prior to the onset of the tree pollen season and her requirement for inhaled corticosteroids increased. There was some evidence of intercurrent infection with shadowing in the right mid-zone on chest radiograph and she improved after a course of antibiotics. At this stage, she also commenced on an antihistamine (terfenadine 60 mg b.i.d.), because of a previous history of seasonal exacerbation of rhinoconjunctivitis and also, indeed, asthma. She improved on treatment and asthma symptoms declined.

At the end of May, 8 months after commencing BUD, on a humid, warm day, when the pollen count was high, she went out to a park in the early evening. She became wheezy and having not responded to four puffs of terbutaline, her father took her home by car. At home, she tried to use nebulized salbutamol/albuterol but again there was no response and she became cyanosed. An ambulance was called and oxygen was supplied with an additional nebulizer treatment being administered. However on arrival at hospital, the patient was apnoeic, cyanosed and pulseless. Extensive and prolonged resuscitation attempts were unsuccessful.

At necropsy, she had ballooned lungs with moderately severe peripheral congestion and mucus plugging of all airways from main bronchi down to the bronchioles. The postmortem theophylline level was 7 mg.L⁻¹. Adrenal glands were of normal size.

**Comparison of index case with the other study patients**

At the beginning of the trial, the index patient was randomized as patient No. 8. One additional child, a 10 yr old boy, patient No. 13, had been dropped from the 1 yr follow-up study as his asthma could not be controlled on increasing doses of BUD and frequently resorted to oral corticosteroid. These two dropouts were replaced by two other children, maintaining 12 follow-ups who are reported in an accompanying paper [12]. Thus in all the data presented in this paper, patient No. 8 who died and patient No. 13 who was only controlled on very much higher doses of inhaled and oral corticosteroids, are distinguished from the other 12.

Ten patients had immunoglobulin (Ig)E levels raised above 100 IU·mL⁻¹. Patient No. 8 had an IgE of 323 IU·mL⁻¹, as compared with a mean of 533±472 IU·mL⁻¹ for the other 12 patients and 858 IU·mL⁻¹ for patient No. 13. Patient No. 8 had positive skin-prick tests to cat dander, dog dander, house-dust mite and grass pollen with weak reactions to milk and egg. All the study patients had positive skin-prick tests.

Day and night asthma symptoms recorded on a 0–3 scale on diary cards revealed that our index patient had scored well within the 95% range calculated for the other 12 patients. During her exacerbation in March, the asthma symptom score increased for 2 months but was back to her previous steady state for a whole month before the fatal attack. In contrast, patient No. 13 had continuously increasing symptoms for 4 months until he was admitted and commenced on oral corticosteroid in month 6. The use of β-agonists showed a similar profile (fig. 1).

At the beginning of the study, the flow-volume profiles in our index patient revealed severe obstructive disease with particularly marked flow limitation at low lung volume. However, these results were still within the 95% confidence intervals for the other 12 study patients, as indeed were: the total lung capacity (TLC) 100% of predicted value; residual volume (RV) 157% pred; functional residual capacity (FRC) 154% pred; and airways resistance 99% pred.

Having started topical corticosteroids, flow-volume curves of the index patient showed gradual but continuous improvement up to 4 months of treatment. The 6 month values showed a slight deterioration but were still appreciably better than they had been at enrolment. In contrast to the improvement in interval clinic lung function, the regular peak flow readings at home remained unstable. The variability of both morning and evening peak flows shown
in figures 2 and 3 amplify the difference between the index patient and also, indeed, patient No. 13 compared with the remaining 12 patients who completed 1 yr of follow-up. Variabilities of peak flow were expressed as a coefficient of variance (CV) which was SD divided by the mean expressed as a percentage.

A histamine challenge test was performed on the majority of patients at enrolment and after 2 and 4 weeks on ICS. Our index patient could not participate in the enrolment challenge because of low baseline lung function. At 2 weeks, the baseline lung function had improved but there was a 25% fall after inhalation of saline. It is, however, relevant to note that patient No. 10 had an even greater drop in lung function after inhalation of saline at the same time-point. After 2 months of treatment, a repeat challenge resulted in a 72% drop in forced expiratory volume in one second (FEV1) after inhalation of isotonic saline and complete recovery on a single dose of inhaled β-agonist. No other patient reacted to saline at this time-point. After 4 months, patient No. 8 tolerated a challenge up to a histamine dose of 0.5 mg·mL⁻¹ (modified Cockcroft method). After 1 mg·mL⁻¹, there was a 66% drop in FEV1 from the baseline value. No other patient had such a steep FEV1 decline.

Soluble interleukin-2 receptor (sIL-2R) levels were measured in the sera from each of the patients at 4 time-points and were compared with age-matched controls. The controls were 18 healthy nonatopic children with no recent infections aged 8–14 yrs, who had blood sampling prior to routine day-surgical procedures such as dental extractions, hernia repairs, circumcision, etc. (fig. 4). In the group as a whole, the asthmatic children had significantly higher sIL-2R levels at all time-points compared with controls. There was no appreciable change throughout the observation period and no apparent effect of treatment with ICS despite the considerable clinical and lung function improvements. Our index patient had the highest sIL-2R at enrolment but only marginally above the rest. At the 2 and 4 week measurements after commencing ICS, the sIL-2R levels climbed very steeply. In our experience, we have never seen this dramatic and remarkable increase in a marker of T-cell activation after commencing ICS in a situation where there was an apparently very good clinical and lung function response.
Discussion

Childhood asthma deaths are fortunately very rare and most publications on the subject involve very small numbers [13–15]. Much of the knowledge about factors predicting risk of death come from retrospective surveys in adults. However, the smaller surveys conducted in the paediatric age range have tended to reveal similar results. The range of factors associated with increased risk of death include poor socioeconomic circumstances [15], delay in diagnosis and under-treatment of disease, both long-term [8] and in the final acute event [7]. Such factors as poor perception of airflow limitation and inadequate use of oral corticosteroid are also highlighted [3, 7, 13, 14]. However, no studies have been able to satisfactorily compare and contrast the factors in the patients who have died with those of individuals with severe asthma who have not died. Indeed, this has become a major issue in interpreting the data relating to fenoterol usage in the New Zealand studies of asthma deaths during the 1970s [16–18], and a subsequent study from Saskatchewan, Canada [19]. There is much dispute about the selection of appropriate comparator populations and the use of statistical adjustment for confounder factors [18].

Attempts to identify the fatality prone asthmatic patients has been limited by the very few published studies which have any objective measurements prior to the final attack [20]. Our observations are unique in that the index patient was enrolled into a clinical trial at a time when she was indistinguishable in the majority of her clinical features from the others who completed the study. This has offered the opportunity to detect the features which distinguished her from the others and which might be indicators of risk of death. Usually asthma deaths are reported to occur in the early hours of the morning [5, 7, 13, 14, 21, 22]. However, deaths have also been reported in the afternoon and evenings as in our patient [13, 15]. Our patient had no asthma symptoms in the 8 days prior to the fatal event, with relatively good evening peak flow measurements, though still a very striking and large variation in peak flow readings between the morning and the evenings. However, patient No. 13 had even greater variability of peak flows. The other patients in the study had relatively low variability with no particular change after the introduction of the ICS. This feature of variability is one that was highlighted in a previous serendipitous observation of two children who subsequently died of asthma [9].

One feature of risk of death highlighted in a number of studies, including one in children [9, 13, 21–23], is a lack of perception of severe airflow limitation. Patient No. 13 in our study continually recorded a wide variability of peak flows but his subjective diary card ratings of symptoms were initially very low. Once he had been on inhaled steroids for a time, his recording of symptoms increased. However, our index patient had symptom scores well within the range recorded for all the other patients other than a transient increase during an intercurrent infection. This increase in symptoms was associated with an increased use of β-agonists. Nevertheless, for a period of at least 2 weeks before her fatal attack, she had few symptoms, reasonable peak flows and low bronchodilator usage. Thus, it cannot be attributed that her demise was due to a lack of perception of severe airflow limitation.

Another striking feature in the index patient was the steep slope of the histamine response curve. This represents histamine reactivity rather than sensitivity. Indeed, on the one occasion it was possible to do the challenge, the concentration of histamine causing FEV1 to fall 20% from baseline (PC20,mas) was very similar to that of the other patients in the trial. This is a feature that was noted in the one other investigation of children prior to demise [9]. It is very likely that these children fall into the category which has sometimes been described as brittle asthma [24]. We suggest that increased histamine reactivity may well be an important feature of the fatality prone patient.

Perhaps the most unexpected abnormality in the index patient was the high and dramatically rising level of sIL-2R. She commenced with a rather high level and the remarkable increase over a very short 4 week period when her clinical features had all improved is uniquely different from any of the other patients in the trial. The detection of increased sIL-2R in the sera suggests increasing T-lymphocyte activation which one might expect to have diminished in response to the ICS. The fact that there was a paradoxical response could be of major significance in distinguishing the fatality prone individual.

Recent insights into the induction of corticosteroid resistance may well be highly relevant to our observation. Airway cells from patients with steroid resistance express higher levels of interleukin (IL)-2 messenger ribonucleic acid (mRNA) than those from steroid-sensitive individuals [25]. It has been shown that the combined effects of IL-2 and IL-4 alter the binding affinity of the glucocorticoid receptor [26]. Thus, one could hypothesize that this girl's dramatically rising sIL-2R levels, which reflect a rise in IL-2 due to T-lymphocyte activation, would have had the potential to affect corticosteroid responsiveness and thereby render her more prone to acute severe problems. However, it is rather odd that she should at least in the first instance have had a very favourable clinical response to the ICS. This suggests some dissociation between the effect of the corticosteroid on some aspects of asthma symptoms compared with the effect on immune responses.

We believe that there is every indication from our anecdotal observation to embark on prospective studies utilizing markers of T-cell activation to identify whether this will truly distinguish the fatality prone asthmatic. Certainly the immunohistochemical studies on postmortem specimens from asthma deaths have indicated a gross exaggeration of the inflammatory response which, in turn, may impair subsequent efficacy of corticosteroids [27].

References

5. British Thoracic Association. Death from asthma in two


