EpiPen epidemic: Suggestions for rational prescribing in childhood food allergy

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Abstract: There has been a marked increase in community concerns of the risk of food induced anaphylaxis in children and a consequent increase in the provision of the self or carer injectable epinephrine (EpiPen) (CSL Ltd, Parkville, Victoria, Australia). The Australian use of EpiPens in children under 10 years has increased by 300% over 5 years with a crude rate of EpiPen provision of 1 per 544 Australian children aged under 10 years. However, the risk of a fatal reaction to food, particularly in preschool children, is remote (in Australia, an estimated one fatality in 30 years in the under 5-year-old population and two deaths in 10 years in the entire child population). It is therefore important to provide a perspective on the risk of death from food induced anaphylactic to parents and carers in view of the anxiety generated on this issue. The indications for provision of an EpiPen to children are not well defined. Six risk factors, which can be considered in evaluating the risk of a life-threatening reaction (age over 5 years; a history of respiratory tract involvement with the initial or subsequent reactions; a history of asthma requiring preventer medication; peanut or tree nut sensitivity; reactions induced by traces or small amounts of allergen; a strongly positive skin prick test) are proposed. It is suggested that the greater the number that are positive, the lower the threshold for provision of an EpiPen. In addition, instruction in EpiPen administration and the provision of both a clear and simple anaphylaxis action plan and a rational perspective on the remote risk of death is just as important as the provision of the device itself.

Key words: anaphylaxis; epinephrine; EpiPen; food.

INTRODUCTION

Community concerns concerning the risk of food-induced anaphylaxis and death in children have multiplied in recent years. Statements by lay and consumer groups, such as the following ‘thousands of families with young children are forced to live with the possibility that everyday foods may be contaminated by a known allergen which could kill in minutes’ reflect the anxiety which parents feel. This anxiety, together with the incorrect perception that allergic reactions invariably increase in severity, which is common among both lay people and the medical profession, has generated a potent pressure for action by the medical profession to avert these perceived threats. A combination of increased community concern and an increase in awareness of anaphylaxis is the likely cause of the rapid increase of prescriptions for self or carer administered epinephrine EpiPen (EpiPen; CSL Ltd, Parkville, Victoria, Australia) in recent years (Table 1). In Australia, all EpiPens are supplied by CSL Ltd. and, thus their sales figures reflect the Australian usage. Over 5 years, the total number of units provided to retail pharmacies and hospitals has increased by 193% and the provision of EpiPen junior (EpiPen Jr.), which is recommended for children under 30 kg (i.e. under about 10 years of age), a dramatic 300%. Although allergic diseases are increasing, it does not appear that the rapid increase in EpiPen usage is primarily due to this factor. Sampson observed in his patients that peanut sensitization (a positive skin prick test) had increased by 55% over a 10-year period and Hourihane et al. found peanut allergy increased four-fold between generations. Allowing a time span of 30 years between generations this would indicate a 66% increase over 5 years while EpiPen Jr. usage has increased by 300% over the same time period. In Australia, in 2000, there were approximately 2.6 million children under 10 years of age. Assuming all EpiPen Jr. were prescribed for children under 10 years of age, this gives a crude rate of EpiPen provision of 1 per 544 children, which is in excess of estimates for children in some other countries: 1/1600 in UK, and 1/5800 in France but less than a remarkable 1/84 of a population of 280 000 children in the province of Manitoba, Canada. While the rate refers to the number of units per child in the community and not the number of children with EpiPens, which may be less if the practice of prescription of more than one unit per child is widespread, it does accord with the population survey of provision of some form of adrenaline of 1/417 in a sample of 4173 South Australian children. The appropriate rate of provision of EpiPens in a given population is yet to be determined. In these calculations, it has been assumed that all EpiPens are provided for food anaphylaxis. While personal experience indicates that the majority of EpiPens in children (> 95%) are provided for food allergy, these figures will overestimate the rate to the extent that EpiPens are also prescribed for other conditions such as bee sting anaphylaxis.

Concurrent with the marked increase in prescriptions in Western communities has been controversy in the medical literature concerning benefits and risks with some authorities...
expressing the opinion that EpiPens are over prescribed and challenge to this by others. The response to the remote risk of death in a child from food anaphylaxis is essentially about risk management. A perspective on this issue is needed for paediatricians to inform their patients, and indications for rational prescribing are urgently required. This paper will attempt to provide both.

THE RISK OF DEATH IS LESS IN CHILDREN UNDER 5 YEARS

A study in the UK identified eight deaths in children (population of 13 million children) over a period of 10 years from food anaphylaxis. Another survey in the USA, between 1994 and 1999, identified 32 fatalities, of which nine were under 16 years of age, due to food-induced anaphylaxis from a national registry. If one extrapolated the UK figures to the Australian childhood population, there would be one death in 30 years in the under 5-year-old population and two deaths in 10 years in the entire child population. The great majority of deaths occur in children aged 5 years and older and adults, 7/8 (88%) in the UK study and 30/32 (94%) in the USA. In contrast, food-induced immediate hypersensitivity reactions occur most commonly in preschool children to milk, egg and peanuts; frequently, in the case of egg and milk, and less commonly with peanut they resolve by 5 years of age. However, as it is those children with food allergy who are the ones at risk, it is necessary to consider the risk of death from food anaphylaxis in this subpopulation. Up to 5% of the childhood population may have food allergies. Assuming all the deaths occurred in this group, there would be 0.3 deaths in Australia in 10 years in the estimated 65 000 food allergic children under 5 years of age. This may be compared with the death rate from vaccine preventable meningococcal infection in the same 65 000 children of 1.2 deaths in 10 years (15 deaths/year from meningococcal disease in Australian children, half occur in under 5-year-old age group and one-third preventable by immunization). Thus, a food allergic child aged under 5 years may be four times more likely to die from a preventable meningococcal infection than from food anaphylaxis. This example does not suggest that appropriate emergency measures should not be prescribed where indicated but does indicate that perspective needs to be applied in the assessment of risks to health and choices concerning expenditures.

GUIDELINES FOR EPIPEN PRESCRIPTION ARE UNCLEAR

Currently there are no clear guidelines on which children should be prescribed an EpiPen. In 1994, the American Academy of Allergy and Immunology stated ‘If there is a history of anaphylaxis or serious reaction and the risk of another reaction is substantial in the judgment of the clinician, an epinephrine kit should be prescribed with clear instructions regarding its use’. This recommendation invites the clinician to consider what is a substantial risk and, in addition, implies that adrenaline is not necessarily prescribed for any level of risk. A recent review of deaths in the USA concluded, ‘patients at risk for food-induced anaphylaxis (i.e. those with previous reactions involving the airway or those with asthma and food allergies) must be educated to recognize the early signs of anaphylaxis and be given and trained in the use of self-injectable epinephrine’. This conclusion reflects the fact that the greater majority of deaths occur in patients with significant asthma and also suggests that the severity of the presenting reaction (i.e. previous reaction involving the airway) might be utilized as an indicator of the risk of a subsequent severe reaction. However, in another publication, these authors expand the potential population by stating ‘young children with peanut and/or tree nut reactions should be considered at risk for more severe reactions and should be provided with emergency medications (epinephrine)’. In a recent review, Sampson stated ‘All patients with peanut allergy should be given a written emergency plan and adequate doses of liquid diphenhydramine and self-injectable epinephrine for use in case they accidentally ingest peanuts’.

ESTIMATE OF COST TO AUSTRALIAN COMMUNITY

It is possible to make some estimate of the potential cost to the Australian community for the provision of EpiPens to children under 16 years with peanut or tree-nut allergy if the recommendations of Sampson that all such patients should be provided with an EpiPen are followed. Adopting the US estimate that 1.1% of the population has peanut or tree-nut allergy, which is likely to be an underestimate for the under 16 year age group (peanut allergy is more common in children than adults) there would be 46 200 children under 16 years with peanut or tree-nut allergy in Australia. The current recommended retail cost for an EpiPen is $A140.00. To ensure appropriate 24 h coverage, many children are prescribed two units, one for home and one for kindergarten/school. With a shelf life of 15 months, this provides an annual cost of $10.35 million dollars if each child has two units. From the figures provided above, the estimated death rate for children under 16 years in Australia is one child every 5 years, and assuming all deaths in childhood were due to peanut allergy and were preventable by provision of an EpiPen this gives a cost of $51.7 million dollars per life saved. In attempting to evaluate the costs and benefits of EpiPen usage, there may be other benefits unrelated to prevention of death such as a reduction in morbidity and increased quality of life, however, there is insufficient data to enable a cost analysis to be made.

INDICATIONS FOR PRESCRIPTION OF EPIPEN

As the prescription of an EpiPen is primarily concerned with risk management in attempting to develop some rational guidelines, it seems appropriate to ask whether there are factors which might point to the likelihood of developing a severe life-threatening reaction. I suggest that there are six, which may be considered.

1. Age over 5 years.
2. A history of respiratory tract involvement with the initial or subsequent reactions.
3. A history of asthma requiring preventer medication.

Table 1 Number of EpiPen units provided to Australian retail pharmacies and hospitals (annual totals to March each year are shown)

<table>
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<th>Year</th>
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<td>2002</td>
<td>9265</td>
<td>4685</td>
<td>13 950</td>
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4. Peanut or tree-nut sensitivity.
5. Reactions induced by traces or small amounts of allergen.
6. A strongly positive skin prick test.

Few would disagree to provision of an EpiPen to a child, of any age with peanut sensitivity, who has developed a previous reaction involving the respiratory tract. In contrast, the indications are less clear for a preschool child with a generalized urticarial reaction, without respiratory tract involvement, following ingestion of 50 mL of cow’s milk and a 5-mm skin prick test wheal to milk extract.

The great majority of fatalities are recorded in children are over 5 years of age, despite the fact that food allergic reactions are more common in preschool children and frequently lessen with time. In the survey of deaths in the USA over 6 years, there were two deaths in children less than 5 years; one to Brazil nut, which occurred on the first exposure and thus would not have been preventable, and a second to cows milk. In Sweden, a prospective survey conducted over 4 years identified six fatal reactions in children, two to peanut and four to soy, all of whom were older than 8 years. In the UK, the single fatality in a child under 5 years was due to egg white. Thus, in a total of 14 years observation, in three countries, of the 46 fatal reactions recorded, only three (7%) occurred in children less than 5 years.

It has been suggested that the severity of the initial reaction be taken into account when prescribing an EpiPen. Bock et al. stated that a previous history of airway reactions was an indication for prescription of EpiPen. An unresolved issue is how predictive of subsequent severity is the initial reaction. Whilst it appears clear that a severe reaction can follow a mild reaction there is evidence to indicate that the severity of the initial reaction provides some prediction of the nature of a subsequent reaction. Hourihane et al. surveyed over 600 allergic reactions in adults and children to peanuts. Of the patients whose first reaction was severe (wheeze, cyanosis, collapse or faint), the most recent reaction was also severe in 78% of cases (173/223) whilst in those cases with a mild reaction the most recent reaction was severe in 32% of cases (34/107). Ewan and Clark found that of 15 patients with a mild initial reaction who had a further reaction, three (20%) had a more severe reaction in which some form of adrenaline (inhaled 2, injected 1) was used. Sicherer et al., in a study of peanut allergic reactions in children, found ‘On average, symptoms after accidental exposure were generally similar to those at initial exposure’. In this study, approximately half the reactions involved the respiratory tract.

The presence of asthma increases the risk of death or a severe reaction. This observation has lead to the recommendation that those subjects with both asthma and a food allergy should be prescribed an EpiPen. In the paediatric context, it seems reasonable to apply this to those children with asthma of sufficient severity to require preventer medication.

It is clear that the great majority of deaths are associated with nut, and, in particular, peanut sensitivity. Combining the mortality results from USA, UK and Sweden, 34/46 deaths were associated with peanut or tree-nut reactions. Deaths from egg and cows milk sensitivity are much less common despite being among the most common food allergies detected. Of the three deaths in the under 5 years age group, one occurred to milk and one to egg. In Sweden, there were four deaths due to soy anaphylaxis in peanut sensitive subjects. There are immunological cross reactivities between soy and peanut, and both are members of the same botanical family. The specific properties of peanuts that lead to severe reactions are unknown; however, they may relate to properties of the three major allergenic proteins in peanuts Ara h 1, 2, 3. Another factor, which may help, is an assessment of the amount of food allergen ingested and the severity of reaction induced. Although this has not been studied in detail, many authorities believe that the severity of an adverse reaction bears some relationship to the amount of allergen ingested, as evidenced by recommendations to avoid challenges or commence with lower doses in severely food allergic subjects. That the amount of allergen ingested is related to the severity of a reaction is also evidenced by the common practice of performing food challenges with gradually increasing doses of food in order to reduce the risk of a severe reaction. In adults, repeat challenges of peanut protein on two occasions have been remarkably consistent in the threshold doses required to elicit clinical reactions in peanut sensitive subjects. Moneret-Vautrin et al. utilized the dose eliciting symptoms as one factor in the decision to prescribe an EpiPen. Thus, a child who develops mild generalized urticaria following ingestion of half an egg is likely to be in a different risk category to one with a respiratory reaction following exposure to a small amount of egg protein in a cake or biscuit.

An important and unresolved issue is whether the size of the skin prick test bears a relation to the likelihood of a severe reaction, and should be taken into account when deciding to prescribe an EpiPen. In a large group of both adults and children, overall skin prick test size did correlate with severity (P = 0.04); however, the substantial overlap between groups lessens the predictive power in any individual case. In children, the size of the skin prick test was related to the occurrence of a clinical reaction on formal food challenge. An Australian study of Sporik et al. demonstrated that a wheal size 8 mm or greater was associated with a 100% (28/28) reactivity on peanut challenge while a wheal of 2–4 mm was associated with only 47% (8/17) reactivity. Pucar et al. performed a peanut challenge in children with a positive skin prick test and 46% (13/28) of those with a skin prick test wheal 7 mm or greater reacted clinically, while only 14% (5/36) of those with a wheal size less than 7 mm reacted. Two of the 18 children with a positive challenge developed wheeze. However, children with a definite history and a 5 mm or greater skin prick test reaction were not challenged. As food challenges are generally performed with a progressive increase in dose of food and cease once minor symptoms develop, the results obtained by a controlled challenge may not reflect the severity of the reaction on exposure to larger amounts of allergen. From this data it is difficult to make recommendations, some may choose to ignore the size of the skin prick test, however, as challenge studies indicate that clinical reactivity bears some relationship to the skin prick test wheal size, it seems reasonable to factor this into the decision to prescribe.

**SENSITIZATION WITHOUT PRIOR FOOD INGESTION**

A common issue in preschool children is the identification of peanut sensitivity by skin prick testing in children who have never knowingly ingested peanut but have reacted to another food (usually milk or egg). In this situation, the risk of a severe anaphylactic reaction on exposure to peanut is unknown. Pucar et al. found that, in those who have never knowingly been exposed to peanut but had a positive skin prick test, there was a 31% (5/16) prevalence of clinical reaction to peanut challenge and 50% (4/8) in those with a wheal size greater than 7 mm. In view of this, a case can be made for formal peanut challenge in this group to determine the clinical features of a reaction just prior to school entry, and provision of an EpiPen to those with
a generalized cutaneous or more severe reactions following challenge. An alternative policy would be to provide EpiPens to all children with a prick test wheal size greater than a predetermined size (e.g. > 7 mm); however, on the evidence of Pucar et al.,21 this would be unnecessary in 50% of cases and, in addition, perpetuate a significant amount of unwarranted parental anxiety. It has been suggested that ‘no allergist would prescribe an epinephrine kit on the basis of a positive skin prick test in the absence of a significant history or formal challenge’.9

CONCLUSIONS

It can be seen that there are no clear-cut guidelines for the provision of an EpiPen to a child with food allergy. This, in part, reflects the difficulty in predicting those children most likely to be at risk and in deciding the limits of an acceptable risk. I have listed six factors that can be taken into consideration. It would be generally agreed that a child over 5 years of age, with a history of respiratory involvement following exposure to peanut, should be provided with an EpiPen; however, many cases are not as clear-cut. I suggest that each factor be considered and, the greater the number that are positive, the lower the threshold for prescribing an EpiPen. Each of these factors will need to be assessed by the practitioner and weighed in the light of the parental wishes and environmental circumstances. It must be emphasized that the prescription of an EpiPen alone is not a satisfactory response to the risk of food anaphylaxis. This is highlighted by the Australian evidence that only 29% of EpiPens prescribed were used appropriately in a subsequent anaphylactic reaction.24 Thus, instruction in EpiPen administration and the provision of both a clear and simple anaphylaxis action plan and a rational perspective on the remote risk of death is just as important as the provision of the device itself.

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REFERENCES