Clinical and Experimental Allergy, 2000, Volume 30, pages 1144–1150

Lessons for management of anaphylaxis from a study of fatal reactions

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Summary

Background The unpredictability of anaphylactic reactions and the need for immediate, often improvised treatment will make controlled trials impracticable; other means must therefore be used to determine optimal management.
Objectives This study aimed to investigate the circumstances leading to fatal anaphylaxis.
Methods A register was established including all fatal anaphylactic reactions in the UK since 1992 that could be traced from the certified cause of death. Data obtained from other sources suggested that deaths certified as due to anaphylaxis underestimate the true incidence. Details of the previous medical history, the reaction and necropsy were sought for all cases.
Results Approximately half the 20 fatal reactions recorded each year in the UK were iatrogenic, and a quarter each due to food or insect venom. All fatal reactions thought to have been due to food caused difficulty breathing that in 86% led to respiratory arrest; shock was more common in iatrogenic and venom reactions. The median time to respiratory or cardiac arrest was 30 min for foods, 15 min for venom and 5 min for iatrogenic reactions. Twenty-eight per cent of fatal cases were resuscitated but died 3 h–30 days later, mostly from hypoxic brain damage. Adrenaline (epinephrine) was used in treatment of 62% of fatal reactions but before arrest in only 14%.
Conclusions Immediate recognition of anaphylaxis, early use of adrenaline, inhaled beta agonists and other measures are crucial for successful treatment. Nevertheless, a few reactions will be fatal whatever treatment is given; optimal management of anaphylaxis is therefore avoidance of the cause whenever this is possible. Predictable cross-reactivity between the cause of the fatal reaction and that of previous reactions had been overlooked. Adrenaline overdose caused at least three deaths and must be avoided. Kit for self-treatment had proved unhelpful for a variety of reasons; its success depends on selection of appropriate medication, ease of use and good training.

Keywords: anaphylaxis, management

Clinical and Experimental Allergy, Vol. 30, pp. 1144–1150. Submitted 8 July 1999; revised 8 November 1999; accepted 27 December 1999.

Introduction

Anaphylaxis is difficult to manage. Severe reactions are unexpected and may progress so fast that no treatment can be given before respiratory or cardiac arrest. Iatrogenic reactions must first be treated by the doctor at hand who has rarely seen one before. Non-iatrogenic reactions are medical emergencies that occur away from immediate access to medical care.

Most experts consider that adrenaline is the first priority for treatment of reactions but there is discussion about route and dose [1]. Guidelines are based on theory and anecdote; there has never been a controlled trial to determine the best practice. Because reactions are uncommon, unpredictable and may be fatal even if optimal treatment is given immediately, a prospective randomized controlled trial would be difficult.

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Some other approach was needed and it seemed that study of a large number of fatal reactions might give insight into why prevention and treatment had failed. With this in mind, a register was established of all fatal anaphylactic reactions in the UK since 1992. This has provided a wealth of data, some of which is reported here because there are important lessons for the management of anaphylaxis.

Methods

The Office of National Statistics (ONS) keeps records of death certificates, which since 1993, have been coded allowing searches for anaphylaxis as a cause of death. Before this date, searches are possible by looking for text strings that may indicate anaphylaxis contributed to the cause of death. Within limitations imposed by the local Medical Ethical Committee and approved by the ONS, it was possible to retrieve detailed information about the fatal reactions from Her Majesty's Coroners and medical staff involved in the care of individuals on the register.

Requests for measurement of mast cell tryptase in serum following reactions had been sent to a number of UK laboratories; these were used to identify further fatal reactions. Other notifications came from the Anaphylaxis Campaign, the police, pathologists and others.

Anonymous accounts were prepared to permit confidential independent expert review for cases where there was suspicion that the treatment might have been a contributory factor or the sole cause of death.

Results

The register holds details of 164 fatalities during 1992–98 for which dates of birth and death, sex, putative allergen and location of death are known. Further details are known for 148; Tables 1–4 summarize these data. An arithmetic mean of 20.4 probable anaphylactic deaths each year was recorded.

The 25 'excluded' cases in Table 1 comprise two fatalities that following independent expert review proved due to adrenaline overdose in the absence of anaphylaxis; two fatal myocardial infarctions following adrenaline treatment for mild iatrogenic reactions (a third similar infarction is included in the figures for contrast media); a case certified as anaphylaxis to chlorpromazine that was more likely due to direct cardiac effects of the drug, and 14 other cases where the circumstances around the time of death were complicated, and although anaphylaxis was listed on the death certificate, other factors seemed more likely to have been fatal. Six reactions were attributed to bone cement; the mechanism is unclear [2] but in these cases serum mast cell tryptase or urinary methyl histamine were raised and no embolic cause could be found at necropsy. All six came from one centre; this cause of death is more common than indicated by the numbers reported here.

Two fatalities certified as due to anaphylaxis had collapsed about 30 min after a sting in the mouth, from asphyxia that may have been due to local swelling rather than anaphylaxis [3]. These two are included in the figures for wasp reactions in the tables. Myocardial infarction was not found at necropsy in any of the venom-related deaths. Previous hypertension was recorded for three who died following stings but only one was known to be taking a beta-adrenoceptor blocking drug.

Two patients on the register had systemic mastocytosis that was thought to have contributed to the fatal reaction: one died following a bee sting, the other during an anaesthetic [4].

Thirty-five cases referred to the register with a clear history of fatal anaphylaxis did not have this as the certified cause of death. In some cases, this was because the necropsy revealed no evidence of upper or lower airways obstruction [5]. Other deaths were certified as due to asthma.

Table 1. Categories of fatalities on the register. Individual anaesthetic drugs had commonly been identified but never with good evidence that they had been the allergen. Antibiotics reactions had been caused by cephalosporins (8), penicillins (5), ciprofloxacin, amphotericin and vancomycin. Other iatrogenic reactions were thought to have been due to modified gelatins (4), vitamin K in cremophore (2), protamine (2), kabikinase, ibuprofen, acetazolamide, pethidine and perindopril. Contrast reactions were caused by iodine-containing media (Hexabrix and Optiray) (7) and technetium. 'Excluded' reactions are explained in the text.

Cause	Numbers Male	Female	Age Median (range)	Further details
Anaesthetic	10	17	62 (19–88)	22/27
Antibiotic	5	11	60 (5–86)	16/16
Contrast	7	1	56 (26–73)	6/8
Other iatrogenic	7	6	67 (53–88)	11/13
Venom	23	12	54 (9–85)	32/35
Nuts	7	18	22 (13–67)	24/25
Other food	5	9	24 (8–53)	12/14
Hydatid cyst rupture	1	0	36	1/1
Excluded	9	16	69 (0–89)	24/25

	Cause	Location	Mode
55 iatrogenic	anaesthetic 22	theatre 31	shock 19
	antibiotic 16	ward/X-ray/A & E 16	respiratory 5 + 5 + 3
	other 17	home 8	combined 23
37 food	peanut 10	restaurant/bar 13	shock 0
	walnut 5	take-away 6	respiratory 4 + 14 + 14
	nuts 10	party food 2	combined 5
	chickpea 1	school 2	
	seafood 3	canteen 3	
	milk 2	home 6	
	banana 1	other 5	
	nectarine 1		
	uncertain 4		
32 venom	bee 4	house 9	shock 15
	wasp 18	garden 11	respiratory 6 + 3 + 4
	unidentified 10	fruit picking 2	combined 4
		bee-keeping 1	
		out and about 9	
1 hydatid	spontaneous		
	rupture of cyst	?house	combined

Table 2. Registered fatalities for which further details are known. The mode of reaction is based on a combination of clinical observation at the time of the reaction and on necropsy findings. Shock is recorded as the cause where there was no marked difficulty breathing reported. The figures for respiratory difficulty are split into upper + lower + remainder who had undefined difficulty breathing or both upper and lower airways obstruction. 'Combined' indicates a combination of shock and respiratory difficulty. Foods and insects are those thought most likely from the available information but the identification was often uncertain.

It was in some cases impossible to determine whether a fatal reaction had been anaphylactic (due to IgE-sensitized mast cells triggered by allergen) or anaphylactoid. Probable anaphylactoid reactions include the reactions to vitamin K (possibly due to complement activation by the polyethoxylated castor oil used as an excipient [6]). A case of fatal angioedema due to perindopril was probably due to raised tissue bradykinin concentration [7]. The fraction of anaesthetic reactions due to anaphylaxis to muscle relaxants is unknown; it seems likely that the majority were of this type [8]. Reactions to protamine [9], ibuprofen [10], vancomycin [11] and contrast media may have been anaphylactoid or IgE mediated anaphylactic reactions [12].

Whether arrest was initially respiratory or circulatory depended on the cause of the reaction: all food-allergic fatal reactions caused difficulty breathing that in 86% led to respiratory arrest. Shock was more common in venom and iatrogenic reactions (Table 3). Although there was a difference in median age between these groups, the different mode of reaction was not related simply to age.

Discussion

This is the first study to report an unselected series of fatal anaphylactic reactions from all causes. Approximately half the reactions were due to medical interventions, quarter each to insect venom and food. It is not clear what fraction of the total number of fatal reactions have been identified; unidentified cases will include those dying from acute asthma due to unrecognized food allergy [13], sudden death from unrecognized insect stings [14] and elderly bronchitics dying at home from unrecognized antibiotic

Table 3. 124 fatalities showing timing of first adrenaline (none, before or after arrest), compared with rate of arrest and numbers resuscitated. '$n + b + a$' indicates 'none + before + after' − the numbers resuscitated in each group. Those resuscitated lived between 3 h and 30 days (median 3 days) and died most commonly due to the effects of anoxic brain damage sustained during the reaction

	Minutes to arrest		First adrenaline			Resuscitated	
	Median	Range	None	Before	After	$n + b + a$	%
55 iatrogenic	5	1–80	6	9	40	0 + 3 + 16	35
37 food	30	6–360	13	8	16	0 + 2 + 9	30
32 venom	15	4–120	29	0	4	2 + 0 + 3	16

Table 4 Nine patients who had been given adrenaline self-treatment kit. Eight of the 37 food-allergic patients and 6 of the venom-allergic patients had had previous severe generalized reactions. Four further venom allergic patients had had previous generalized allergic reactions that had not been severe and all the remaining food-allergic patients had some previous reaction although this had been mild.

Unused	nut	F37	Used kit for another person; had not replaced it
	nut	F24	Had not taken kit to restaurant
	nut	F38	Found kit was out of date; subsequent treatment unsuccessful
	wasp	M79	May have collapsed too quickly to use kit
	wasp	M85	Found dead holding unused kit (Could not assemble it?)
Used	milk	M12	Used 2 doses correctly (0.3 mg adrenaline) without benefit
	nut	M19	Instructed by GP to take only 2 inhalations of adrenaline spray
	nut	F20	Collapsed in pharmacy waiting for prescription to be dispensed
	food	F35	Used 3 doses of 0.3 mg adrenaline without benefit

anaphylaxis [15]. Fatal allergic reactions in children are commonly asthmatic reactions in asthmatic children; these pose particular problems for recognition of the specific allergic cause of the fatal reaction. The predominance of asthmatic symptoms in fatal food allergy has been noted previously [13,16,17]

The first treatment for noniatrogenic reactions was in some cases given by paramedics. Because all food-related reactions caused difficulty breathing, the paramedics commonly had difficulty deciding whether to use the protocol for anaphylaxis or for asthma. This led to delayed or inappropriate treatment that may have contributed to the fatality. Paramedic protocols should allow for this difficulty [18].

There may be similarity between panic attacks and breathing difficulty due to food allergy. In one case, the General Practitioner attending the patient considered up until the time of arrest that the symptoms were mostly due to panic; because of this, adrenaline was not given.

The interval from contact with allergen to arrest depended on the cause. Iatrogenic reactions were the most rapid, with arrest in 5 min or less in over half the cases. There is therefore no time to look up what treatment to give. Most doctors who had just caused a patient to have a reaction had never seen anything similar. While adrenaline is the most important first drug in the treatment of anaphylactic reactions and is safe when administered correctly [19], there was confusion between the use of adrenaline for resuscitation and for anaphylactic reactions. In some cases, the rate of injection was inappropriately high: two patients, one suffering only minor symptoms, received their first adrenaline as a high-dose bolus – both died. In the first case, a bolus dose of 3.5 mg intravenously in a small 13-year-old girl with mild allergic symptoms led to fatal pulmonary oedema. Pulmonary oedema following adrenaline overdose has been reported previously [20,21]; abnormal adrenaline secretion due to phaeochromocytoma may cause pulmonary oedema [22] and adrenaline infusion is the basis of an animal model for pulmonary oedema in rodents and dogs [23]. In the other case, 2.5 mg adrenaline was given as an intravenous bolus to a 63-year-old woman for a reaction to intravenous coamoxyclav; pink froth was noted at the mouth suggesting pulmonary oedema. This reaction was in a patient with known penicillin allergy and might have been fatal with more moderate adrenaline dosage – however, further appropriate resuscitation proved unsuccessful.

An infant with mild allergic symptoms is thought, following independent expert review, to have died from fluid overload and adrenaline overdose from repeated injections; the pallor induced by the adrenaline may have been mistaken for shock. In another case, adrenaline 1 mg given as an intravenous bolus to a 38-year-old woman for mild symptoms due to nut allergy led to immediate vomiting; inhalation of vomit was a major factor in the subsequent arrest. Rapid intravenous injection of 1.0 mg adrenaline was recorded in three out of 175 patients seen in our clinics between 1992 and 1996 after receiving adrenaline for treatment of suspected reactions. The first was given for a panic attack mistaken as fish anaphylaxis in a 35-year-old woman. The effect was severe palpitations, headache with visual disturbance (flashing lights) that persisted several hours, and vomiting; she was left with a homonymous partial hemianopia. The second was a 42-year-old man who had local swelling from a sting on the back of his neck 4 h earlier. He suffered severe palpitations and headache followed by collapse. He regained consciousness after 4 h of supportive treatment and made a full recovery. The third was a 45-year-old woman who experienced symptoms following a sting that were unlikely to be due to anaphylaxis: she suffered severe palpitations and headache, and was reported to have had subsequent persistent left-sided weakness. As none of these has genuine anaphylaxis, the adverse response was most likely due to the rapid injection of adrenaline. These incorrect treatments should not be seen as detracting from the value of adrenaline in management of severe acute allergic reactions: they do, however, highlight the need for doctors who may have to treat anaphylactic reactions to be able to recognize the indications for adrenaline, and to know the correct dose and route.

Three deaths due to myocardial infarction followed treatment with adrenaline for relatively mild iatrogenic

reactions. Two were elderly patients with pre-existing coronary artery disease and one a 26-year-old male; the latter fatality was assessed by an expert witness to have been due to the effects of adrenaline (1 mg intramuscular injection) given in treatment of the reaction. However, five further deaths were due to myocardial infarction occurring during iatrogenic reactions when adrenaline had not been given before arrest, so it is uncertain whether adrenaline or hypotension during the reaction led to the former three infarcts. Although adrenaline remains the first choice for treatment of anaphylaxis, for some patients its therapeutic range is narrow and overdose should be avoided. When used to treat anaphylactic reactions, intravenous adrenaline must be diluted, given slowly and titrated against its therapeutic effect in an adequately monitored patient [19].

Only 20% of those given adrenaline received this before they arrested (Table 3). This was due to both rate of reaction and availability of treatment. In view of the rapidity of iatrogenic reactions, protocols should be in place, drugs ready at hand and doses calculated prior to procedures where there is a risk. A report on food allergic reactions in children and adolescents suggested that recovery from an anaphylactic reaction is most likely if adrenaline is given within 30 min [17]. In the cases reported here, arrest occurred at 30 min or earlier in 91% of venom reactions and 62% of food reactions. On the other hand, some food reactions progressed slowly taking up to 6 h to arrest. In the early stages, the symptoms were commonly deceptively mild, escalating rapidly 5–10 min before arrest. Adrenaline was given repeatedly during this mild phase to one patient with brazil nut allergy but did not halt the final rapid progression to fatal respiratory arrest 6 h after ingestion of the food containing nuts.

It is widely thought that adrenaline self-treatment kit should be carried by patients with anaphylaxis and many thousands of patients in the UK have this kit. The indication is commonly taken to be a previous life-threatening reaction. This study found that only 22% of food-allergic and 18% of venom-allergic fatalities had had a previous severe reaction, suggesting that most of those at risk from their allergy will not be given adrenaline self-treatment kit. Nine out of the 14 (64%) with previous severe reactions had been issued self-medication that proved unsuccessful (Table 4).

When selecting the most appropriate kit for self-treatment, the likely mode of reaction should be taken into consideration. Shock is an important component of anaphylaxis to venom. In venom anaphylaxis where there is respiratory compromise, upper airway compromise is an important component. In contrast, in anaphylaxis to foods, the main compromise is respiratory rather than cardiac and lower respiratory problems seem a main component. The implication is that while early intramuscular adrenaline may be crucial in managing reactions to stings, inhaled beta agonist may be more important in many of those with food allergy. In this study, some of the self-treatment failure was due to incorrect instruction or inadequate training [24] but in two cases, adrenaline self-injection was used apparently correctly without resolution of the food-induced asthma. In such cases, inhaled beta agonist may be more appropriate than adrenaline, and good control of background asthma with inhaled steroid is critical to ensure that the airways will be responsive to the beta agonist in the event of a reaction.

The risk of unexpected exposure to food allergens can be reduced but never completely eliminated. Milligram quantities of nut may be sufficient to cause a reaction [25] and considering the high prevalence of nut allergy in children and adolescents, one would expect mistakes to be common. Despite dietary counselling, accidental exposure may cause repeated reactions [26]. A recent audit of 407 patients with kit seen in my clinics since 1992 revealed that 67 subsequently had reactions that might have benefited from self-administered adrenaline. Only 37 had used their adrenaline — 11 claimed immediate benefit, 7 claimed no benefit. Thirty did not have their kit at the time, or preferred to get medical assistance. None died. One might conclude that management should be directed more towards effective allergen avoidance than reliance on rescue by adrenaline kit.

Some reactions are so severe that treatment will be unsuccessful, emphasizing the importance of avoiding the allergen wherever this is possible. Advice on avoidance is best given in a specialist allergy clinic where it is more likely to be well informed. Patients medical records must clearly indicate their allergies. Patients must be informed about foods or medicines that might cause a further reaction and particularly about cross-reactive allergens. Cross-reactivity between penicillins and cephalosporins was repeatedly noted in this study [15].

There is also cross-reactivity between different types of nut. A study of IgE antibodies to nuts suggests that strong allergy and cross-reactivity occur at all ages [27] though no nut-allergic deaths on the register occurred below the age of 13. At least three fatal reactions in this study were most probably due to a type of nut that not previously caused a reaction. A conclusion from these observations is that anyone allergic to one nut should be tested for allergy to all nuts to raise their awareness of the potential danger of those nuts that they are found to be sensitive to. Nonetheless, the dietary advice should generally be to avoid all nuts, as substitution of one nut for another is common in catering. Commercial catering caused 76% of food-related reactions; details of events leading up to the fatal exposure to nuts prove that asking for a meal without nuts is not a successful avoidance strategy. Neither the person serving nor in some instances the caterer realized that the food contained nuts.

Fifty-six percent of iatrogenic reactions occurred in operating theatres where the patient was monitored and

full emergency treatment at hand. Even so, reactions were fatal. Iatrogenic reactions occurring at home were all due to oral antibiotics. Only half the identified fatal iatrogenic reactions had been reported to the Medicines Control Agency and it is likely that many more have occurred. It seems possible that doctors regard anaphylaxis as a well-recognized side-effect of drugs and so do not report it. New knowledge about frequencies of reactions and patterns of cross-reactivity will depend on improved reporting.

There were no fatal reactions to latex or vaccines. These potential allergens may uncommonly cause severe reactions but fatality must be rare. Around 20% of anaphylactic reactions are apparently idiopathic [28,29] but all the reactions on the register had a specific suspected cause identified. Biphasic anaphylactic reactions are reported to occur commonly [30]; only one reaction in this study was 'biphasic' in that the patient collapsed and died after leaving Hospital following treatment for a reaction to a wasp sting. It is possible that this was due to inadequate treatment rather than a truly biphasic reaction.

Mastocytosis may predispose to anaphylactoid reactions — particularly to anaesthetics and insect stings — and there were two cases on the register. It has been recommended that these patients carry adrenaline for self-treatment [31] though this is rarely done in the UK.

Reports of reactions to contrast media have suggested a female preponderance [32,33] though a study of fatal drug-related anaphylactic reactions in Denmark found 5 out of eight who reacted to contrast media were male [34]. It is interesting that seven out of eight fatal contrast media reactions reported here were in males, confirming a male preponderance.

The circumstances of these reactions indicate that a prospective controlled trail of treatment for anaphylactic reactions would not be feasible. This retrospective study has revealed how avoidance, self-treatment and medical management failed to prevent anaphylactic death. This insight should lead to better management of severe allergies by more effective advice on allergen avoidance; more appropriate prescribing of self-treatment kit and improved training in its use; improved protocols for paramedics, and increased awareness of the correct dose of adrenaline used in treatment of anaphylactic reactions. Findings from the register were taken into consideration in preparation of guidelines for treatment of anaphylaxis [18–23].

Acknowledgements

I thank the Anaphylaxis Campaign for early notification of many fatalities, and all Her Majesty's Coroners, pathologists and others who have helped collect this data, and Dr Chrys Tsakona for preparing the audit data on the use of adrenaline kit by my clinic patients.

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