

EDITORIAL

Clinical and Experimental Allergy

Evidence of effectiveness of anaphylaxis management plans: are we waiting for godot?

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Anaphylaxis is defined as a life-threatening allergic reaction [1]. The annual incidence of anaphylaxis is 8.4/100 000 [2]. Single-centre studies show that anaphylaxis can represent up to 1% of emergency department attendances [3]. Hospital admissions for anaphylaxis have increased by 700% in the United Kingdom since 1990, probably reflecting both an increased awareness as well as a real increase in incidence [4].

There are understandable concerns regarding the evidence base for the practice of providing subjects at risk of anaphylaxis with rescue kits of adrenaline injections, although these concerns have largely been expressed by non-allergists [5, 6]. It is necessary to examine why most allergists are keen to provide such kits [7] and why some doctors are uncertain of their benefit [6].

Adrenaline is the treatment of choice for anaphylaxis [8, 9] and it is used regularly and safely for this indication as well as other life-threatening emergencies. The intramuscular route is preferred to the subcutaneous route and children tolerate intramuscular adrenaline well, even if they do not have an allergic reaction [10]. Animal studies show that if use of adrenaline is delayed until anaphylaxis is fully established, full recovery is less likely than if adrenaline is given earlier [11]. Case series report that delay of adrenaline use appears to be associated with a worse outcome in allergic reactions [12] but even its correct use does not guarantee survival [13, 14].

Opponents of widespread availability point to the rarity of anaphylaxis and the absence of certain effectiveness of adrenaline [15]. It is also difficult to administer in an emergency if not using preloaded autoinjectors [16]. Misuse has been reported: dropping an autoinjector or not firing it correctly [17], digital self-injection by inexperienced users

[18] and adverse cardiac events from intravenous overdose [15, 19]. Incorrect use in fatal cases has also been reported [13], emphasizing the need for prescription and training to be equal parts of the medical transaction [20].

Anecdotal reports of adrenaline provision causing anxiety appear to have more to do with lack of allergy awareness on the part of the prescribing doctors of how and when to use it than adrenaline kits themselves being directly responsible for the heightened anxiety [21]. The medium of the message has been blamed for the increased awareness of allergy risks that comes *pari passu* with the need to carry adrenaline.

The rarity of anaphylaxis on a population base, the possibility (albeit remote) of death from anaphylaxis, coupled with the inability of allergists to categorically identify those at highest risk all raise practical and ethical problems in the design of trials of rescue kit provision as part of a self-management plan. Physicians must currently base decisions about the long-term care of anaphylaxis patients on observation and clinical experience. In this context, it is perhaps worth noting that the great majority of fatal cases of anaphylaxis in the United Kingdom occur in subjects who have not been under the care of a recognized allergy service (H. Gowland, Allergy Action, UK, personal communication) and less than half had received any allergy specific advice from any health professional, let alone an allergist [14]. Furthermore, case series studies have suggested that detailed anaphylaxis plans can reduce the number and severity of reactions in patients with peanut and nut allergy [22]. However, in an increasingly evidence-based world, is such observational evidence sufficient to inform decisions about the usefulness of anaphylaxis management plans? Choo and Sheikh's [23] rigorously performed Cochrane-style systematic review suggests that it is not. Having found no studies that met their stringent inclusion criteria – a so-called 'empty' review – they conclude that 'randomized controlled trials of anaphylaxis action plans are urgently needed'.

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'Evidence-based practice is the integration of best research evidence with clinical expertise and patient values' [24]. This fundamental description emphasizes the integration of evidence with clinical expertise and doctor-patient dialogue. To dismiss the data regarding anaphylaxis that have been summarized here and that are available elsewhere, because they are not Level 1 evidence, proposes domination of one part of this definition of evidence-based practice over the other. It is no one's fault that the highest quality of evidence, as expounded in Cochrane reviews, does not exist for anaphylaxis management plans; it appears that it has been and may (or may not) remain impossible to collect it.

It is generally accepted that two prerequisites must be met in order to justify conducting a trial: firstly, there must be a state of genuine uncertainty in the expert medical community regarding the merits of the intervention(s) being tested; secondly, the trial must be designed in such a way to make it reasonable to expect that, if it is successfully conducted, equipoise will be disrupted and uncertainty will be reduced [25]. In their discussion, Choo and Sheikh address the first prerequisite and argue that sufficient equipoise exists to justify conducting such a trial. However, the second prerequisite is not addressed by the authors who provide no specific guidance as to how such a trial could or should be designed. The failure of systematic reviews to provide specific research recommendations and to tell us 'exactly what is required' has recently been described as 'a disappointing anticlimax for those wishing to use them to direct future research' [26]. This disappointment is particularly acute in an area such as long-term anaphylaxis management where trial design is likely to be fraught with complexity and where the ethical propriety of a trial can reasonably be challenged. The inclusion of an outline of a proposed trial would have rendered Choo and Sheikh's review a notable milestone on the anaphylaxis management road we must all travel with our patients. A detailed 'trial design prescription' could potentially have shifted the focus of future discussions away from the all too familiar lament about the 'absence of evidence' towards a more constructive debate about the practical and ethical issues involved in the design and conduct of studies to evaluate the effects of interventions for long-term anaphylaxis management.

Such a debate should undoubtedly commence by considering whether a trial of anaphylaxis management plans can in fact be justified. The answer to this question is far from clear cut. Authors of case-series studies of action plans have argued that the inclusion of a control group would be unethical [22]. Other commentators have highlighted the seemingly insurmountable practical issues that accompany the requirement to recruit enormous sample sizes for trials with rare end-points [27]. Indeed, it may transpire that by applying the standards of Level 1 evidence in this area, Choo and Sheikh have performed

an exercise in 'hyper-rationality' or 'irrational rationality' in an area where health service providers and funders simply have to live with the uncertainty that pertains to rare and occasionally fatal events [28]. We may have to learn to concede that the aspirational 'gold standard' evidence in this field may never be produced, leaving us with observation, patient values and clinical expertise to inform our decisions about the long-term management of people at risk of suffering anaphylaxis.

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