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Occasional Survey

Adrenaline Auto-injector (EpiPen®) Use in Hong Kong: Experience of Queen Mary Hospital

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Abstract There is a paucity of local data about anaphylaxis and the use of adrenaline (epinephrine) prescribed for out-patient use. We described in this brief report our experience of out-patient-prescription of epinephrine of a university affiliated teaching hospital. The dispensing rate has been far below that of reported Western data. Our patients were prescribed upon fulfilling the current consensus but some may have suboptimal dosing. Lack of availability and carrying out-dated epinephrine auto-injector seems an issue. Issues of logistics, availability and clinical indications and were discussed. A local guideline to better define its usage seems warranted.

Key words Anaphylaxis; EpiPen®; Management plan

Introduction

A consensus panel of the National Institute of Allergy and Infectious Diseases, USA defined anaphylaxis as "acute onset of illness (within minutes to several hours) with involvement of the skin, mucosal tissue or both", following exposure to an allergenic substance, combined with one or more of the following: respiratory compromise, reduced blood pressure or associated symptoms of end-organ dysfunction, involvement of skin or mucosal tissues such as hives, and persistent gastrointestinal symptoms". Anaphylaxis is a severe life threatening reaction that can affect all age groups.[1-3] Deaths due to food anaphylaxis were reported among children, in particular with peanut allergy.[1-3] Intramuscular adrenaline (epinephrine) is the first line treatment for anaphylaxis.[4,5] Early use of adrenaline in anaphylaxis is associated with improved outcomes.[6] Any patient with a systemic allergic reaction should be considered an adrenaline auto-injector, depending on risk of further reactions. Life-threatening anaphylactic reactions to foods are under-diagnosed and under-treated, both in the community and in the emergency room.[7] Anaphylaxis occurs at home, at school, at camp, or on a plane or a bus or wherever they may happen to be. There is a clear need to improve education of both patient and physician on the use of and indication for adrenaline auto-injectors (EpiPen®).[6] There is a paucity of local data about incidence of anaphylaxis and adrenaline prescribed for out-patient use. We described our experience of out-patient-prescription of adrenaline of a university affiliated teaching hospital. Issues of logistics, availability and clinical indications were discussed.

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Methods and Patients

Conduct of the Study

EpiPen® is not a registered pharmaceutical product of Hong Kong. It is currently prescribed under named-patient basis and import licenses have to be applied via registration with Pharmaceutical Service of Department of Health (http: //www.psdh.gov.hk/eps/index.). A patient list (Jan 2002-Jan 2005) was retrieved from the central pharmacy

of Queen Mary Hospital, a university affiliated tertiary hospital. Medical records of patients aged below 18 years were reviewed retrospectively. Patients' demographic data such as ethnicity, gender, age at diagnosis, and clinical characteristics such as presenting incidents that warranted out-patient adrenaline prescription, possible allergen, dosage of adrenaline and form of auto-injectors were recorded. Availability of specialist care referral, personalised management plan, and written instruction were assessed.

Allergen Evaluation

In vivo skin prick testing (SPT) was performed using a single-head lancet technique with commercial allergen extracts (ALK-Abello, Horsholm, Denmark). Histamine (10 mg/ml) as a positive control and normal saline as a negative control were used. SPTs were performed on the backs of the infants and on the forearm of older children. The skin weal diameter (mm) to histamine was measured between 10 min and to allergen at 15 min. Irregular shapes were recorded as the mean of two perpendicular diameters. *In vitro* Food specific-IgE antibodies were measured with the CAP – Fluorescent-enzyme immunoassay FEIA (Uppsala, Sweden). The assay had a lower limit of detection of 0.35 kU_A/L. Levels exceeding 100 kU_A/L were reported as 100 kU_A/L. Currently, there are established *in vivo* and *in vitro* diagnostic criteria for food allergy with accuracy equal or greater than 95% positive predictive value, in comparing with gold standard- double blind placebo controlled food challenge (DBPCFC).[8] However, the validity for such criteria for local context is yet to be established.

Food Challenge

The procedure involved giving a child increasing amounts of a food over a period of time and observing for any objective clinical allergic response. This gave parents or families a scientific structure and the safety of knowing that any reaction will occur within a hospital setting. As the gold standard DBPCFC is very labour intensive, most of the challenges were conducted in open manner. An example of peanut challenge: Peanut butter was used as the challenge food.[9] The protocol was: Day 1: a smear was applied to the buccal mucosa of the lower lip, then at 30 minute intervals 1/8, 1/4, 1/2 and 1 teaspoon. Day 2-7: increasing by 1 teaspoon a day until 5 teaspoon/day (8 g peanut protein/day) reached. The child was reviewed on Day 7 and Day 28. From Day 2 onwards the challenge was conducted at home. A positive challenge was recorded if an unequivocal reaction to peanut observed i.e.. urticaria, eczema flare; vomiting, diarrhoea; sneezing, rhinorrhoea, stridor, wheeze, cough; or anaphylaxis. A negative challenge was recorded if normal amounts of peanut were ingested. One teaspoon (5 ml) of smooth peanut butter contains approximately 1.6 g of peanut protein. By the day 7 and day 28 review, an inconclusive challenge was recorded if the above criteria were not met.

The Diagnosis of Food Allergy

The diagnosis of food allergy was made basing on 1) a convincing history of immediate reaction to an isolated food item; and/or 2) demonstration of presence of food specific IgE by *in vivo*/skin prick test or *in vitro*/CAP-FEIA; and/or 3) a positive food challenge.

Results

A total 60 doses of adrenaline were distributed out to 52 patients for out-patient use (aged 1-85 years) over a 3-year-period. Nine patients (17.3%) were of non-Chinese ethnicity. 17/52 (32.7%) were below age of 17 years (M: F=12:5). All except one infant were given in the form auto-injector of either EpiPen® or EpiPen®Jr. EpiPen® was self-purchased at cost of Hong Kong Dollars $490 per item with an average valid period of 9 months. The infant weighted 5 kg with cow milk anaphylaxis was given ampoule/syringe preparation of adrenaline 1:1000 at 0.01 ml/kg. Two children had 2 auto-injectors prescribed at one signed out prescription. This was dispensed at the time travelling abroad.

The clinical characteristics of patients aged below 17 years were summarised in the Table 1. Two children's medical records were incomplete. Fifteen patients out of a total 17 (88%) were followed at Paediatric Immunology/ Allergy Clinic regularly and with written Management Plan issued (Appendix I). In this series, food allergy was the predominant cause of severe allergic reaction for children. Food challenges were performed in 2 cases with positive results. Peanut and shellfish allergy were almost equally represented. One atopic patient was suspected having exercise induced anaphylaxis. He had consumed wheat noodles prior exercise. He had strong skin test reaction to dust mite, peanut and wheat allergen extract. He was pending for food and exercise challenge.

Individual training sessions on use of EpiPen® were

Table 1 Clinical characteristics of the paediatric patients prescribed with adrenaline/EpiPen®

#	Age of diagnosis	Sex	Ethnicity	Allergen	Presentation	EpiPen® Dose(mg)
1	12m	F	Chinese	Cow milk	Generalised urticaria, cyanosis, and hypotension	0.09†
3	2yr	M	Chinese	Peanut	Angioedema of face, lips, and tongue; floppiness, cough and hoarseness of voice	0.15
4	4yr9m	F	Chinese	Shellfish	Angioedema of face and lips, hoarseness of voice	0.15
5	7yr	M	Chinese	Peanut	Angioedema of face and lips, cough	0.15
6	8yr	M	Chinese	Walnut	Angioedema of face, lips, tongue, generalised urticaria and shortness of breath	0.30
7	9yr	M	Chinese	Shellfish	Angioedema of eyelids and itchy tongue and throat	0.15
8	10yr	M	Chinese	Peanut	Angioedema of face and lips, vomiting	0.15
9	13yr	M	Chinese	Shellfish	Generalised urticaria and wheeze	0.15
10	13yr	F	Chinese	Peanut/fish	Angioedema of face, lips and wheeze and vomiting	0.30
11	14yr	F	Chinese	Shellfish	Angioedema of face and lips, itchy skins with acute flare up of eczema	0.30
12	17yr	M	Chinese	Food/exercise*	Angioedema of face, lips and wheeze and cough	0.30
13	17yr	M	Chinese	Paracetamol**	Generalised erythematous rash, palpitation and hypotension	0.30
14	16m	F	Caucasian-Phillipino	Egg/fish	Angioedema of face and lips, generalised urticaria, and floppiness	0.15
15	18m	M	Caucasian	Peanut	Angioedema of face and lips, barking cough	0.15
16	6yr	F	Caucasian	Peanut	Angioedema of face and lips and generalised urticaria, cough	0.15
17	13yr	M	Malaysian	Exotic food***	Angioedema of face and lips, generalised urticaria, hoarseness of voice	0.30

*Food/exercise: patient consumed wheat noodle 30 minutes prior exercise with evidence of *in vitro* and *in vivo* wheat- IgE sensitisation awaiting a formal challenge. **The symptoms were reproduced upon drug provocation test. ***A bowel of Malaysian style noodle, in which unable to identify the most probable content. †The adrenaline was prescribed in the form of syringe/ampoule

provided by doctors and 8 out of 15 patients (53%) had had retraining sessions. 6/15 patients (40%) were reportedly carrying an out-dated EpiPen®. 12/17 patients (72%) were co-morbid with asthma. Four teenagers of body weight >20 kg were prescribed with EpiPen®Jr (0.15 mg), a suboptimal dose of adrenaline recommended by some existing guidelines.[10] With due consideration of the catchments area and census data, the crude estimated dispensing rate for age below 17 years is 0.02% of our geographically defined population.

At the time of analysis, with a median duration of follow up 24 months, none of the subjects had actual self-use of the adrenaline auto-injector device in the community. Despite of avoidance measures, 2 out 15 patients had reported inadvertent reaction to allergen food while dined out, both suspected of peanuts and one necessitated emergency room attendance.

Discussion

To Whom Should EpiPen® Be Prescribed?

There have been concerns about over-prescription of EpiPen® in Western nations.[11] A pragmatic approach has been suggested. Six risk factors, which can be considered in evaluating the risk of a life-threatening reaction, are as follows: 1) Age over 5 years; 2) A history of respiratory tract involvement with the initial or subsequent reactions; 3) A history of asthma requiring prophylactic medication; 4) Peanut or tree nut sensitivity; 5) Reactions induced by trace or small amounts of allergen; 6) A strongly positive skin prick test. It is suggested that the greater the number that are positive, the lower the threshold for provision of an EpiPen®.[12]

In this series, 12/17 (82.3%) patients had more than 4 risk factors and 2 had all 6 risk factors. The estimated

dispensing rate of 0.02% is far below that of western data.[11,13] We are unable to ascertain that our dispensing rate is optimum or too low as we lack a good population study about peanut allergy or overall anaphylaxis incidence. Shown in a recent Manitoba, Canada study, 0.95% of a geographically-defined population was found to have had epinephrine dispensed for out-patient use; dispensing rates within that population varied from 1.44% for individuals under age 17 years to 0.32% for those older than 65 years.[9] This is in keeping with the estimated peanut allergy incidence of 1-2 per 100 children, in Canada,[14] as well as in UK,[15] Australia,[16] and United States.[17]

When Should Adrenaline be Administered?

Placing the burden of decision making on individuals without medical training may not be appropriate. Judgement at anaphylactic emergency may be clouded by panic and denial. Therefore the instruction has to be consistent and simple. In the first-aid treatment of anaphylaxis in the community, there is no question that intramuscular adrenaline injection is the treatment of choice.[4-6] The median time to respiratory or cardiac arrest in individuals with anaphylaxis from food is 30 minutes.[18] There is a fine line between a mild allergic reaction and anaphylaxis and at times quite difficult to diagnose an event as not being anaphylaxis! When in doubt, administer adrenaline. After using it, patients must be transported to an emergency facility for further evaluation.[19] Other medications such as antihistamines, inhaled asthma medications, or steroids that may be given by physicians in treating anaphylaxis should not be regarded as first-line medications.

Under-utilisation of adrenaline is probably common. In a series of 250 Australian children with peanut allergy and equipped with EpiPen® followed up to 5 years, only 4 episodes of actual firing of EpiPen® in the community despite of an inadvertent reaction rate of 5 episodes per 100 patient-year [Unpublished data, personal communication].

Dosage

Only two fixed doses of adrenaline auto-injector (EpiPen ®Jr 0.15 mg and EpiPen® 0.30 mg) are available. The latter auto-injector is used for adults, and recommended for children weighing 15 kg or more. The dosage for children is 0.01 mg per kg, so for children weighing less than 15 kg, using EpiPen®Jr would be over-dosing. Likewise, in children weighing between 15 and 30 kg, EpiPen®Jr would be under-dosing and regular EpiPen® overdosing. Until the pharmaceutical industry comes up with auto-injectors containing other dosing, it is recommending using EpiPen® Jr to children weigh above 10 kg and below 20 kg.[7] Additional fixed-dose formulations of adrenaline are needed to facilitate optimal first-aid dosing in patients of all ages and sizes.

Outdated EpiPen®

The valid period for an EpiPen® is up to 2 years from manufacturing date. The EpiPen® procured by our pharmacy normally has long shelf-life before shipping in. It translates into a shorter valid period of average 9-12 months and hence a higher cost to patients. It is part and parcel related to our low usage. More importantly, we are at low priority in terms of marketing perspectives.

For pre-hospital treatment of anaphylaxis, it is recommended the use of EpiPen® and EpiPen®Jr auto-injectors that are not outdated. If, however, the only auto-injector available is an outdated one, it could be used as long as no discoloration or precipitates are apparent because the potential benefit of using it is greater than the potential risk of a suboptimal adrenaline dose or of no epinephrine treatment at all, according to the only one study.[20]

Training in Use of EpiPen®

Video demonstration on proper usage and disposal of EpiPen® could be downloaded from Internet for free (http://www.epipen.co.uk). Now a trainer pen is available, which entails all the details of actual administration, except no piercing needle. Such dummy devices can be practiced for unlimited times by caregivers, families and school staffs involved in the care of at-risk children. In authors' practice, we also supervise caregivers to use outdated-EpiPen® for mock-practice. It gives them a feeling of actual firing.

Importance of Individualised Management Plan with Written Instruction

Provision for adrenaline auto-injectors is only part of the management and should not be viewed in isolation. The management should also include education to relevant care-takers on allergen avoidance, food labeling and the appropriate adrenaline usage.[21-23] Control of asthma and other allergies are important. Regular review of action plan and retraining on use of injectors are essential.[22] A written plan may alleviate parental anxiety and confusion.[24] An individualised management plan can greatly reduce the frequency and severity of further reactions.[24] It has positive impacts on the avoidance of allergens and appropriate responses of the care providers.[24,25]

Affordability and Availability of EpiPen®

According to an investigator-designed, validated survey instrument that was self-administered by members of the World Allergy Organization House of Delegates for 2003 to 2005, widespread availability in Europe, United States, Canada, and Australia contrasted with limited availability in Asia, South America, and Africa. This study raises concerns about lack of availability and affordability of adrenaline auto-injectors worldwide for individuals of all ages.

Hong Kong, as one of the most developed metropolitan cities of South East Asia, seems having limited availability of EpiPen® in both public and private hospitals/pharmacies (Personal communication). Two of our patients had had to purchase their EpiPen® from overseas in the past. A few allergy specialists in private sector could provide it. Adrenaline auto-injector is not a drug item enlisted under 'safety net' for poor. Some of our patients encountered difficulties in insurance reimbursement for purchasing EpiPen®. At times, syringe and ampoule of adrenaline was provided instead of auto-injectors which may pose difficulties for untrained people to administer correctly in emergency situation.

Do We Need a Local Guideline?

The newly founded Hong Kong Society for Paediatric Immunology and Infectious Disease could be the ideal arena for debating the related issues. EpiPen® use in paediatric context seems fulfilled the selection criteria for guideline development by the Hong Kong College of Paediatricians which includes: (1) Common conditions especially in the ambulatory settings; (2) Performance gap between the evidence based/best practice and the current practice; (3) Availability of good quality/high level of evidence for an evidence-based guideline. Instead of going through labour intensive literature review by local experts, we can adopt guidelines which are developed based on critical review of the current best evidence, with due consideration of local health care systems and disease prevalence.[26] We suggest setting up a central registry to monitor the use of EpiPen® longitudinally. Such registry could be used to estimate the disease burden of severe allergic reaction.[13]

Summary

Despite a much lower dispensing rate comparing to western data, prescribing auto-injectable adrenaline in the form of EpiPen® is not an infrequent event in a tertiary hospital of Hong Kong. Food allergy induced anaphylaxis was most commonly implicated in children. A local clinical practice guideline is currently lacking and probably warranted in the future. Setting up a central registry of anaphylaxis and/or use of EpiPen® may help in assessing the local prevalence of severe systemic allergy reactions.

Conflict of Interest

None to declare

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Appendix 1 Samples of action plan in English and Chinese version.