



BET 1. EPINEPHRINE SELF-INJECTION FOR ANAPHYLAXIS IN CHILDREN

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Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary

Edited by Bernard A Foëx

BET 1

EPINEPHRINE SELF-INJECTION FOR ANAPHYLAXIS IN CHILDREN

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A short cut review was carried out to establish whether there is any evidence in favour of epinephrine self-injection for anaphylactic reactions in children. Only three papers provided evidence related to the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these papers are presented in table 1. The clinical bottom line is that although there are no clinical trials to answer the question there is other evidence to suggest that it can be effective.

THREE-PART QUESTION

In [children with anaphylaxis] does [self-injection of epinephrine] lead to [reduced mortality and morbidity]?

CLINICAL SCENARIO

A 5-year-old boy is admitted with anaphylactic shock having inadvertently ingested peanuts at a birthday party. He had a previous reaction 2 years ago and was given an epinephrine auto-injector for use at home. His mother had used this when the reaction first started, but to no avail. You administer intramuscular epinephrine while wondering whether there is any evidence for the effectiveness of epinephrine self-injection.

SEARCH STRATEGY

Ovid Medline 1950–2007 August week 5; Ovid Embase 1980–2007 week 35; The Cochrane Library 2007, Issue 3.

Medline, Embase: [exp Anaphylaxis/OR anaphyla\$.mp. OR exp Hypersensitivity/OR allerg\$.mp.] AND [epipen.mp. OR epi-pen.mp. OR “epi-EZ pen”.mp. OR “epi ez pen”.mp. OR anakit.mp. OR exp epinephrine/OR adrenalin.mp.] AND [(exp Home Care Services/

Best Evidence Topic reports (BETs) summarise the evidence pertaining to particular clinical questions. They are not systematic reviews, but rather contain the best (highest level) evidence that can be practically obtained by busy practising clinicians. The search strategies used to find the best evidence are reported in detail in order to allow clinicians to update searches whenever necessary. Each BET is based on a clinical scenario and ends with a clinical bottom line which indicates, in the light of the evidence found, what the reporting clinician would do if faced with the same scenario again. The BETs published below were first reported at the Critical Appraisal Journal Club at the Manchester Royal Infirmary¹ or placed on the BestBETs website. Each BET has been constructed in the four stages that have been described elsewhere.² The BETs shown here together with those published previously and those currently under construction can be seen at <http://www.bestbets.org>.³

1. **Carley SD**, Mackway-Jones K, Jones A, *et al*. Moving towards evidence based emergency medicine: use of a structured critical appraisal journal club. *J Accid Emerg Med* 1998;**15**:220–222.
2. **Mackway-Jones K**, Carley SD, Morton RJ, *et al*. The best evidence topic report: a modified CAT for summarising the available evidence in emergency medicine. *J Accid Emerg Med* 1998;**15**:222–226.
3. **Mackway-Jones K**, Carley SD. [bestbets.org](http://www.bestbets.org): Odds on favourite for evidence in emergency medicine reaches the worldwide web. *J Accid Emerg Med* 2000;**17**:235–6.

OR exp Outpatients/OR community.mp. OR out-patient\$.mp. OR self-administr\$.mp. OR home.mp. OR exp First Aid/OR first aid.mp.) OR (exp Infant Mortality/OR exp Child Mortality/OR mortality.mp. OR exp Hospital Mortality/OR exp Mortality/OR exp Death/OR exp “Cause of Death”/OR exp Death, Sudden/OR death.mp.)] AND limit to human and English language and All Child 0–18 years (Ovid filter).

Cochrane: ([MeSH heading Anaphylaxis] OR anaphyla*) AND ([MeSH heading Epinephrine]. OR adrenaline OR epinephrine OR epipen).

SEARCH OUTCOME

Altogether 94 papers were identified using Medline, 585 using Embase and 26 using Cochrane. Three papers provided evidence that was relevant to the three part question (table 1).

COMMENTS

Epinephrine is the drug of choice for initial treatment of severe anaphylaxis as it blocks mediator release and reverses systemic effects. Many children are now prescribed epinephrine auto-injectors for emergency use in the community.

The survey identified suggests that epinephrine self-injection may reduce subsequent hospital admission and need for epinephrine in hospital. However, it is notable that 76% of parents were not familiar with the correct procedure for using the devices, despite prior instruction (Gold *et al*, 2000).

There is evidence that prompt use of epinephrine improves prognosis in severe anaphylactic reactions. Sampson *et al* (1992) studied six children and adolescents who died of anaphylactic reactions to foods and seven others who nearly died and required intubation. The six who died had symptoms within 3–30 min of allergen ingestion and only two received epinephrine within the first hour. All patients who survived had symptoms within 5 min of allergen ingestion and all but one received epinephrine within 30 min. Bock *et al* (2001) found that only four of 32 fatal anaphylactic reactions identified from a registry had received timely epinephrine.

As 53% of children with reported allergic reactions in the UK and Ireland between 1998 and 2000 (MacDougall *et al*, 2002) have had a previous allergic reaction (9% requiring hospitalisation), there is certainly potential to identify children who may be eligible for epinephrine self-treatment in the future. However, the

Best Evidence Topic reports

Table 1 Epinephrine self-injection for anaphylaxis in children

Author, date, country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Pumphrey <i>et al</i> , 1999, UK	164 cases of fatality with anaphylaxis recorded as the cause of death between 1992 and 1998 (148 had records available for further analysis)	Analysis of registry data	Median time to respiratory or cardiac arrest. Details of patients who had been given epinephrine self-treatment kits	30 min for foods (range 6–360), 15 min for venom (range 4–120) and 5 min for iatrogenic reactions (range 1–80) 5 did not use the kit (not with patient in 2 cases, out of date in 1 case, may have collapsed too quickly in 1 case, found dead holding unused kit in 1 case (could not assemble it?))	Registry data, not specifically designed to answer this question. Only fatal cases included. Cases where epinephrine self-treatment prevented death therefore not included. Adults and children included
Gold <i>et al</i> , 2000, Australia	68 children with a history of anaphylaxis who were prescribed EpiPens by the paediatric allergy service. Data collected by telephone interview with parents	Retrospective telephone survey	Parental recall of method of administration with EpiPen EpiPen use in anaphylaxis Hospital admission	Only 16 (24%) of parents were able to recall all 4 steps required for the correct use of EpiPens; 5% could not recall any steps. EpiPen given in 13 (29%) of 45 anaphylactic reactions. Of those not given EpiPen, 15 (45%) were later given epinephrine in hospital. Of those given EpiPen, 2 of 13 (15%) later received epinephrine in hospital ($p<0.05$) EpiPen not given: 15 of 32 (47%) admitted; EpiPen given: 2 of 13 (15%) admitted ($p<0.05$)	Suboptimal study design to answer this question. A prospective observational cohort would be more informative (randomised controlled trial would be ideal but probably unethical). Possible selection bias—the parents of only 80% of the patients identified were interviewed. 19% could not be contacted—their outcome is unknown. No standard criteria for initial prescription of EpiPen. Time since index reaction not standardised. In-hospital epinephrine use apparently assessed by parental interview. Severity of episodes not objectively measured
Colver <i>et al</i> , 2005, UK	229 cases of children (aged under 16 years) admitted to hospital with food allergic reactions between 1998 and 2000	Prospective survey	Death Near fatal anaphylaxis Potential reduction in severity by use of epinephrine auto-injectors Potential benefits if epinephrine auto-injectors had been more widely available	3 children died. One received epinephrine via auto-injector at home Occurred in 6 children. In 3 children excess epinephrine administration (in hospital) was implicated in clinical deterioration. 6 severe cases and 7 non-severe cases received epinephrine via auto-injector before arriving at hospital. Auto-injectors could therefore have reduced the severity of a maximum of 13/229 reactions Of the 58 severe cases, a maximum of 6 could have benefited had auto-injectors been available to them (the remainder either did not have epinephrine at any point, already had an auto-injector but did not use it, had epinephrine administered by primary care or ambulance staff within 10 min, had not had a previous allergic reaction to food or were over 12 years old and their only previous reaction had been to allergens as babies)	Patients only included after reported hospital admission. Emergency department attendances without admission not included

number of patients who may benefit from widespread availability of epinephrine auto-injectors is likely to be small. A significant proportion of children will not have their auto-injector available at the time of the reaction. Others may be unfamiliar with the technique for self-injection, a small number may die despite treatment, and many patients have had no previous reaction (therefore being ineligible for prior epinephrine prescription).

It is known that epinephrine may lead to cardiac arrhythmia. Colver *et al* (2005) reported three cases where excess epinephrine administration in hospital was implicated in clinical deterioration. MacDougall *et al* (2002) reported one case

in which death was attributed to excess intravenous epinephrine administration. However, the reported search strategy did not reveal any evidence of death or cardiac arrhythmia following self-injection of intramuscular epinephrine.

Although there is no evidence of high quality available to answer the three-part question, there is a sound physiological basis for the early use of epinephrine in severe anaphylaxis. At present it would be unethical to perform a randomised controlled trial. As early epinephrine may be life-saving and in the absence of evidence of harm following self-injection, measures to increase its availability should be encouraged even in the absence of high level evidence.

Clinical bottom line

Where available, epinephrine auto-injectors should be utilised in the community at an early stage for severe anaphylactic reactions, although high quality evidence is lacking. To maximise any potential benefit it is important to provide education for patients, parents and carers regarding injection technique and ensuring auto-injector availability at all times.

LEVEL OF EVIDENCE

Level 3—small numbers of small studies or great heterogeneity or very different population.

- **Sampson HA**, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents *N Engl J Med* 1992;**327**:380–4.
- **Bock SA**, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods *J Allergy Clin Immunol* 2001;**107**:191–3.
- **MacDougall CF**, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child* 2002;**86**:236–9.
- **Pumphrey RSH**. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;**30**:1144–50.
- **Gold MS**, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000;**106**(1 1):171–6.
- **Colver AF**, Nevantaus H, MacDougall CF, et al. Severe food-allergic reactions in children across the UK

and Ireland, 1998–2000 *Acta Paediatr* 2005;**94**:689–95.

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BET 2

COMBINATION THERAPY WITH H₂ AND H₁ ANTIHISTAMINES IN ACUTE, NON-COMPROMISING ALLERGIC REACTIONS

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A short cut review was carried out to establish whether there was any benefit to using an H₂ antihistamine in the management of an acute allergic reaction. Four clinical trials were found to answer the question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these papers are presented in table 2. The clinical bottom line is that the combination of H₁ and H₂ antihistamines may accelerate the resolution of urticaria and angioedema.

Table 2 Combination therapy with H₂ and H₁ antihistamines in acute, non-compromising allergic reactions

Author, date, country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Moscato and Moore, 1990, USA	93 ED patients with urticaria <72 h duration, randomised to receive either 50 mg diphenhydramine (DPH) IM or 300 mg cimetidine (CMT) IM. Exclusions: respiratory signs or symptoms, hypotension, pregnancy, allergy to study drugs, current use of steroids or antihistamines, history of chronic respiratory, cardiovascular, renal or hepatic disease	Prospective double blind RCT	Relief of itch (scale 0–3) Relief of wheal intensity (scale 0–3) Relief of wheal extent (scale 1–3) Sedation (scale 0–2) Overall improvement (pt asked if felt same, worse, or better)	Scale fell by 1.174 CMT (p<0.0001) and 1.489 DPH (p<0.0001) (difference NS) Scale fell by 0.935 (p<0.0001) CMT and 0.915 DPH (p<0.0001) (difference NS) Scale fell by 1.304 CMT and 1.426 DPH (difference NS) DPH 1.085 (p<0.0001) vs CMT 0.37 (p<0.0006). DPH more sedating than CMT (p<0.0001) After 30 min CMT 87% vs DPH 76% (NS). No patients felt worse	Small numbers. Non-validated clinical measure. IM route no longer widely used. Overall score in favour of CMT likely due to less sedative effect rather than effect on rash
Runge et al, 1992, USA	39 ED patients aged 18–50, with signs of allergic reaction (urticaria, pruritus, etc) <12 h old, randomised to receive either cimetidine (CMT) 300 mg IV and placebo, or diphenhydramine (DPH) 50 mg IV and placebo, or CMT plus DPH. Patients rated their symptoms on a visual analogue scale (VAS) before and 30 min after treatment.	Double blind placebo controlled RCT	Relief of urticaria Relief of pruritus	33 patients with urticaria. Relief for 5/11 receiving DPH vs 8/10 receiving CMT (NS); relief for 5/11 receiving DPH vs 11/12 receiving DPH + CMT (p = 0.027) 35 patients with pruritus. Relief for 12/12 receiving DPH vs 6/10 receiving CMT (p = 0.029); Relief for 12/12 receiving DPH vs 12/13 receiving DPH + CMT (NS)	Small numbers Poor explanation of randomisation
Lin et al, 2000, USA	100 ED patients aged >18, with signs of allergic reaction (urticaria, pruritus, acute angioedema, acute unexplained stridor) <12 h old, randomised to receive either diphenhydramine (DPH) 50 mg and saline IV or DPH 50 mg and ranitidine (RAT) 50 mg IV. Effects rated by physician at 1 and 2 h after injection	Double blind placebo controlled RCT	Absence of urticaria at 2 h Absence of both angioedema and urticaria at 2 h Absence of angioedema irrespective of urticaria at 2 h	53 patients with urticaria initially. Urticaria resolved in 91.7% RAT group vs 73.8% saline group, p = 0.02. MVM OR 4.7 (95% CI 1.2 to 22.2) in favour of RAT 72 patients with angioedema and urticaria initially. These symptoms resolved in 70.5% RAT group vs 46.5% saline group, p = 0.02. MVM OR 2.8 (95% CI 1.03 to 8.08) in favour of RAT Angioedema resolved in 77.1% in RAT group vs 67.4% saline group, NS	Convenience sample, when study physician was available. Only 91 patients received the study medication. Non-validated clinical measure
Watson et al, 2000, USA	25 ED patients with urticaria <72 h duration, randomised to either famotidine (FAM) 20 mg IM or diphenhydramine (DPH) 50 mg IM. Patients rated their symptoms on a VAS before and 30 min after treatment. Exclusions: Allergies to FAM or DPH, pregnant or lactating, bronchospasm or pharyngeal oedema, haemodynamically unstable, angioedema, unable to understand to complete the questionnaire or informed consent	Prospective double blind RCT	Intensity of urticaria (100 mm VAS by doctor) Sedation (100 mm VAS) % body surface affected by urticaria (rule of 9s by doctor) Relief of itch (100 mm VAS)	FAM improved 34 mm, DPH 34 mm (p<0.0001 for each) FAM no sedation (NS), DPH 20 mm increase in sedation score (NS). Difference between drugs NS FAM improved by 20% (p<0.01), DPH 8% (NS). Difference between drugs NS FAM improved 36 mm, DPH 54 mm (<0.0001 for each). Difference between drugs NS	Very small numbers Method of randomisation not clarified IM route no longer widely used

CI, confidence interval; CMT, cimetidine; DPH, diphenhydramine; FAM, famotidine; IM, intramuscular; IV, intravenous; MVM, multivariate model; NS, not significant; OR, odds ratio; RAT, ranitidine; RCT, randomised controlled trial; VAS, visual analogue scale.