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

Edited by Bernard A Foëx

BET 1

SUBLINGUAL ADRENALINE TABLETS: HOW FEASIBLE IS THIS NOVEL APPROACH TO THE TREATMENT OF ACUTE ALLERGIC REACTIONS?

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A short-cut review was carried out to establish whether sublingual adrenaline tablets might be useful in the management of acute allergic reactions. Three animal studies and one case report were directly relevant to the question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these papers are shown in table 1. The clinical bottom line is that sublingual adrenaline tablets may have a future in clinical practice but first we need clinical trials of their safety and efficacy.

THREE-PART QUESTION

In a [patient with an acute allergic reaction] does [a sublingual adrenaline tablet as compared to an intramuscular injection] work [better at reversing symptoms and preventing adverse effects of adrenaline?]

CLINICAL SCENARIO

A 34-year-old man attended the emergency department after having his back tattooed. He had gross urticaria and swelling to his lips and face. His tongue was large and inflamed. You looked at the tongue and wondered if you could put a tablet of adrenaline under it and whether it would work as well as an intramuscular injection. You remember from your student days that sublingual and rectal absorption of tablets is much faster than intramuscular injection.

SEARCH STRATEGY

Medline 1950 to February week 4 2009 “((epinephrin\$.MP.) OR (adrenalin\$.MP.)) AND ((tablet\$.MP.) OR (sublingual\$.MP.))”.

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.

SEARCH OUTCOME

A total of 160 papers was found. Two reviews discussed sublingual adrenaline as a potential alternative to intramuscular injection. Three studies were directly relevant (all by the same group of researchers). One case report seemed interesting.

COMMENTS

Although intramuscular adrenaline is an effective treatment for anaphylaxis, out-of-hospital administration by auto-injector is not without problems (not always carried, not always used properly and sometimes not used at all or too late). A non-injectable form of adrenaline, such as a tablet, would be much easier to use. Unfortunately, adrenaline is rapidly conjugated and oxidised in the wall of the gastrointestinal tract making oral administration unrealistic. An alternative would be the sublingual route. Many drugs, in liquid form, can already be delivered by the sublingual route (for example, nitrates, nifedipine, captopril, benzodiazepines and opioids). The studies assessed used a rabbit model as rabbits are adrenaline-tolerant, so that human doses can be used without adverse effects. It seems that adrenaline can be administered sublingually in the rabbit. A 40 mg tablet may give fairly similar maximum plasma concentrations, time of maximum con-

Clinical bottom line

Epinephrine tablets are a novel fast disintegrating formulation. They may be a feasible alternative to intramuscular adrenaline in the future. Until clinical trials have shown this to be a safe and effective route of administration of adrenaline the intramuscular route should continue to be used.

centration and AUC as an intramuscular injection of 0.3 mg. However, the excipient used does make a difference. Different manufacturing characteristics have been studied to determine optimal dimensions (Rawas-Qalaji *et al*, 2007) and the effect of different adrenaline doses on tablet characteristics (Rawas-Qalaji *et al*, 2006 (3)).

- Rawas-Qalaji MM, Simons FER, Simons KJ. Sublingual epinephrine tablets versus intramuscular injection of epinephrine: dose equivalence for potential treatment of anaphylaxis *J Allergy Clin Immunol* 2006;**117**:398–403.
- Rawas-Qalaji MM, Simons FER, Simons KJ. Epinephrine for the treatment of anaphylaxis: do all 40 mg sublingual epinephrine tablet formulations with similar in vitro characteristics have the same bioavailability? *Biopharmaceut Drug Dispos* 2006;**27**:427–35.
- Rawas-Qalaji MM, Simons FER, Simons KJ. Fast-disintegrating sublingual tablets: effect of epinephrine load on tablet characteristics. *AAPS PharmSciTech* 2006;**7**:Article 41, ppE1–7.

Table 1 Relevant papers

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Rawas-Qalaji <i>et al</i> (1), 2006, Canada	5 New Zealand white rabbits (mean weight 4.8 kg). Each rabbit was administered a 10 mg, 20 mg, 40 mg and 0 mg (placebo) adrenaline tablet sublingually and an IM injection of 0.3 mg adrenaline to the thigh on five different study days at least 4 weeks apart. Blood samples were taken from an ear artery at regular intervals until 180 minutes after drug administration.	Prospective controlled five-way crossover study	Maximum plasma adrenaline concentration (C_{max}) (mean (SEM)) Time of C_{max} (mean (SEM)) Area under the plasma adrenaline concentration versus time curve (AUC) (mean (SEM))	40 mg sublingual adrenaline (31.0 ng/ml (13.1)), 0.3 mg IM (50.3 ng/ml (17.1)) NS. 10 mg and 20 mg tablets gave significantly lower C_{max} than 0.3 mg IM. 10 mg (3711 minutes (11)), 20 mg (31 minutes (9)), 40 mg (9 minutes (2)), 0.3 mg IM (21 minutes (5)) NS. 40 mg sublingual adrenaline (1861 ng/ml per minute (537)), 0.3 mg IM (2431 ng/ml per minute (386)) NS. 10 mg and 20 mg tablets gave significantly lower AUC than 0.3 mg IM.	Small numbers result in large SEM, so that although there are differences in means they do not reach statistical significance.
Rawas-Qalaji <i>et al</i> (2), 2006, Canada	5 New Zealand white rabbits (mean weight 4.7 kg). Each rabbit was administered four different tablet formulations of 40 mg adrenaline sublingually (using different excipients labelled A, B, C and D) and an IM injection of 0.3 mg adrenaline to the thigh on five different study days at least 4 weeks apart. Blood samples were taken from an ear artery at regular intervals until 180 minutes after drug administration.	Prospective controlled five-way crossover study	Area under the plasma adrenaline concentration versus time curve (AUC) (mean (SEM)) Maximum plasma adrenaline concentration (C_{max}) (mean (SEM)) Time of C_{max} (mean (SEM))	Formulation A 40 mg sublingual adrenaline (1861 ng/ml per minute (537)), 0.3 mg IM (2431 ng/ml per minute (386)) NS. Formulations B, C and D gave significantly lower AUC than 0.3 mg IM. Formulation A 40 mg sublingual adrenaline (31.0 ng/ml (13.1)), 0.3 mg IM (50.3 ng/ml (17.1)) NS. Formulations B, C and D gave significantly lower C_{max} than 0.3 mg IM. Formulation A (9 minutes (4)), formulation B (28 minutes (10)), formulation C (27 minutes (9)), formulation D (14 minutes (4)), 0.3 mg IM (21 minutes (11)) NS.	Small numbers result in large SEM, so that although there are differences in means they do not reach statistical significance.
Rothrock <i>et al</i> , 1993, USA	7-Month-old girl in cardiorespiratory arrest. Pre-hospital intubation and IV cannulation unsuccessful. Resuscitation drugs administered 13 minutes after cardiorespiratory arrest by sublingual injection.	Case report	Return of spontaneous circulation Survival	After sublingual injection of adrenaline (1.5 mg) and atropine (0.15 mg) Patient died in the ED 58 minutes after initial cardiorespiratory arrest.	No evidence that the sublingual injection of adrenaline and atropine was responsible for the return of spontaneous circulation.
Gu <i>et al</i> , 2002, Canada	6 New Zealand white rabbits (mean weight 4.2 kg). Each rabbit received a 2.5 mg and a 10 mg adrenaline tablet sublingually, an IM injection of 0.03 mg adrenaline and an IM injection of 0.9% saline (0.3 ml) to the thigh on four different study days at least 4 weeks apart. Blood samples were taken from an ear artery at regular intervals until 180 minutes after drug administration.	Prospective randomised controlled crossover study	Maximum plasma adrenaline concentration (C_{max}) (mean (SEM)) Time of C_{max} (mean (SEM))	2.5 mg adrenaline (2369 pg/ml (392)), 10 mg adrenaline (10 836 pg/ml (2234)), IM adrenaline (6445 pg/ml (4233)), saline (endogenous adrenaline) (518 pg/ml (142)). C_{max} for 10 mg sublingual adrenaline did not differ significantly from C_{max} for IM adrenaline. 2.5 mg adrenaline (20.8 minutes (5.7)), 10 mg adrenaline (21.7 minutes (5.4)), IM adrenaline (15.8 minutes (4.7)). T_{max} for sublingual adrenaline did not differ significantly from T_{max} for IM adrenaline.	Small numbers result in large SEM, so that although there are differences in means they do not reach statistical significance.

AUC, area under the curve; C_{max} , maximum plasma concentration; ED, emergency department; IM, intramuscular; IV, intravenous; NS, not statistically significant; SEM, standard error of the mean; T_{max} , time of maximum concentration.

- ▶ Rawas-Qalaji MM, Simons FER, Simons KJ. Fast-disintegrating sublingual epinephrine tablets: effect of tablet dimensions on tablet characteristics. *Drug Dev Indust Pharm* 2007;**33**: 523–30.
- ▶ Rothrock SG, Green SM, Schafermeyer RW, *et al*. Successful resuscitation from cardiac arrest using sublingual injection of medication delivery. *Ann Emerg Med* 1993;**22**:751–3.
- ▶ Gu X, Simons KJ, Simons ER. Is epinephrine administration by sublingual tablet feasible for the first-aid treatment of anaphylaxis? A proof-of-concept study. *Biopharmaceut Drug Dispos* 2002;**23**:213–16.

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BET 2

NEBULISED SALBUTAMOL OR NEBULISED ADRENALINE FOR WHEEZE IN ANAPHYLAXIS

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A short-cut review was carried out to establish whether nebulised salbutamol or

adrenaline should be used to manage wheeze in anaphylaxis. No studies were found that addressed this clinical question. The clinical bottom line is that patients with anaphylaxis and breathing difficulties should be managed according to the latest Resuscitation Council guidelines and should be given intramuscular adrenaline in the first instance.

THREE-PART QUESTION

In [patients with anaphylaxis] is [nebulised salbutamol better than nebulised adrenaline] at [reducing wheeze]?