BEST EVIDENCE TOPIC REPORTS

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

Edited by S D Carley

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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 Infirmary[1] 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] Four BETs are included in this issue of the journal.

- Buccal midazolam as an alternative to rectal diazepam for prolonged seizures in childhood and adolescence
- Aspirin in the treatment of acute pulmonary embolism
- Bone Injection Gun placement of intraosseous needles
- Nebulised levalbuterol or albuterol for lowering serum potassium

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**:220–2.
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**:222–6.
3 **Mackway-Jones K,** Carley SD. bestbets.org: Odds on favourite for evidence in emergency medicine reaches the worldwide web. *J Accid Emerg Med* 2000;**17**:235–6.

Buccal midazolam as an alternative to rectal diazepam for prolonged seizures in childhood and adolescence

Report by Richard Body, ***Senior House Officer***
Checked by Mawra Ijaz, ***Staff Grade***

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Abstract
A short cut review was carried out to establish whether buccal midazolam is better than rectal diazepam for treating prolonged seizures in childhood and adolescence. Eight papers were found using the reported search, of which two presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results, and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

Clinical scenario
An 11 year old girl, known to be epileptic, is brought to the Emergency Department with a prolonged seizure. You have no intravenous access at this point. A colleague recently mentioned that buccal midazolam is an available alternative to rectal diazepam. You are aware that this would be easier and more socially acceptable in the situation, but wonder if it would be as efficacious.

Three part question
In [children with prolonged seizures] does [buccal midazolam or rectal diazepam] lead to [quicker resolution of seizures]?

Search strategy
Medline 1966-01/2005 using the OVID interface and the *Cochrane Library*, Issue 4, 2004. Medline: [exp status epilepticus OR status epilepticus.mp OR exp seizures/ OR exp seizures, febrile/ or seizure.mp OR fit$.mp] AND [exp midazolam/ OR midazolam.mp OR exp Benzodiazepines] AND [exp Mouth Mucosa/ OR buccal.mp OR exp administration, buccal/] AND [exp diazepam OR diazepam.mp] AND [rectal.mp OR exp Rectum/ OR per rectum.mp OR exp Administration, Rectal] LIMIT to human AND English language. Cochrane: status epilepticus OR buccal.

Search outcome
Medline: Eight papers were identified, two of which were relevant to the three part question (table 1). Cochrane: Nine hits, none of which was relevant.

Comment(s)
Buccal midazolam is gaining in popularity as a treatment for prolonged seizures in children. It overcomes many of the disadvantages associated with rectal diazepam, including difficulty of administration in wheelchair users and in tonic seizures, potentially unpredictable absorption with constipation and bowel movements and social unacceptability, particularly in older children. Nasal midazolam has also been used,[3] although the greater surface area of the buccal mucosa could potentially confer advantages with regard to absorption.

One small trial suggests that buccal midazolam is at least as effective as rectal diazepam and one suboptimally designed telephone survey suggested a degree of parental satisfaction with the drug. However, the patient group in the randomised controlled trial is very different from that presenting to emergency departments. There remains a paucity of evidence regarding this topic.

► CLINICAL BOTTOM LINE
Buccal midazolam may be equal or superior to rectal diazepam for treatment of prolonged seizures in children but more evidence is needed for emergency patients.

Scott RC, Besag FMC, Neville BGR. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999;**353**:623–6.

Table 1

Author, date, and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Scott RC *et al*, 1999, UK	79 seizure episodes in 24 young people aged 5–22 years with severe epilepsy living at a residential centre	PRCT	Termination of seizure within 10 minutes of drug administration	Response to midazolam in 30 (75%) of 40 episodes; response to rectal diazepam in 23 (59%) of 39 episodes (p=0.016)	Small sample size (no power calculation)
	Randomised to receive either 2 ml (10 mg) buccal midazolam or 10 mg rectal diazepam upon having a seizure lasting longer than three minutes		Mean time to termination of seizure	Six minutes for midazolam and eight minutes for diazepam (p=0.31)	Nearly half the seizure episodes occurred in the same two patients
Wilson MT *et al*, 2004, UK	53 young people aged 3–21 years Identified from hospital prescriptions for nasal/buccal midazolam over a 16 month period	Telephone survey	Parental preference	24 of 40 families had used both rectal diazepam and buccal/nasal midazolam: 20/24 (83%) preferred midazolam	Aims of the study were to evaluate effectiveness and convenience of nasal/buccal midazolam in terminating prolonged seizures in the community. The study was not appropriately designed to investigate either outcome.
			Termination of seizures	33/40 who used midazolam (83%)	Patient group selected having already had midazolam prescribed. This may be because they had already stated a preference for midazolam, introducing selection bias. Further, not all prescriptions may have been identified. No sample size calculation and no statistical analysis Not all results were reported (for example parents were asked to grade ease of use from 1 to 5, no results were given)

Wilson MT, Macleod T, O'Regan ME. Nasal/buccal midazolam use in the community. *Arch Dis Child* 2004;**89**:50–51. http://www.bestbets.org/cgi-bin/bets.pl?record=00161

Aspirin in the treatment of acute pulmonary embolism

Report by Caroline Lee, *Senior Clinical Fellow*
Checked by Craig Ferguson, *Clinical Research Fellow*

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Abstract

A short cut review was carried out to establish whether aspirin is a useful adjunct in the treatment of acute pulmonary embolism. No papers were found using the reported search to answer the clinical question. A clinical bottom line is stated.

Clinical scenario

A 50 year old woman presents to the emergency department with shortness of breath and pleurtic chest pain, following a flight from Australia. Examination is unremarkable except for tachypnoea and mild hypoxia. Chest *x* ray is also normal, so you aim to treat for suspected pulmonary embolus (PE). You know that aspirin is used in the treatment of other acute thromboembolic conditions such as stroke or myocardial infarction, and in the prophylaxis of deep vein thrombsis/PE. You wonder if aspirin would also be beneficial in the treatment of acute PE?

Three part question

In [a patient with suspected acute pulmonary embolus] is [aspirin] effective in [reducing morbidity and mortality]?

Search strategy

Medline 1966-12/04 using the OVID interface and the *Cochrane Library*, Issue 3, 2004.

Medline: [exp ASPIRIN OR aspirin.mp OR exp Antifibrinolytic Agents OR Acetylsalicylic acid.mp] AND [exp Pulmonary Embolism OR pulmonary embol$.mp OR PE.mp] LIMIT to human AND English language. Cochrane: Aspirin or Pulmonary Embolism.

Search outcome

Altogether 267 papers were found. The majority discussed the use of aspirin in prophylaxis. None of these papers addressed the question of use in acute PE.

Comment(s)

Poullis suggests in a letter that aspirin administration after diagnosis of PE in combination with heparin could have beneficial effects but needs further study. Although this question has been raised many times in our clinical practice there appears to be little discussion in the literature. One possibility may be, as some haematologists suggest, that aspirin is more likely to be useful when the final occluding event is a platelet clump. This is more common in the presence of arterial atheromatous plaques which rupture and attract platelets to the site. This occurs in coronary artery disease and in the carotid vessels where aspirin is advocated. In venous disease, where the vessel walls are relatively smooth and stasis is more important, clots are more likely to occur as a result of the activation of the clotting system. Another consideration is that patients with proved PE are generally anticoagulated initially with heparin, and then with warfarin. The additional benefit of aspirin is therefore likely to be small. Such a small benefit must be weighed against the additional bleeding complications from concomitant aspirin use.

► CLINICAL BOTTOM LINE

There is no published evidence to support the use of aspirin in the treatment of acute pulmonary embolism.

Poullis M. Aspirin for the treatment of pulmonary embolism: vasoconstriction versus physical obstruction. *Am Heart J* 2000;**140**:E22.

Bone Injection Gun placement of intraosseous needles

Report by Andrew Curran, *Specialist Registrar Emergency Medicine*
Checked by Ayan Sen, *Clinical Fellow*

doi: 10.1136/emj.2005.024406

Abstract
A short cut review was carried out to establish whether the Bone Injection Gun is better than a standard intraosseous (IO) needle at obtaining IO access. A total of 129 papers were found using the reported search, of which three represent the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

Clinical scenario
A 23 year old shocked patient is brought to into the Emergency Department resuscitation room. The trauma team are trying to gain vascular access. After five minutes of being unable to gain intravenous access you remember a recent training session on a Bone Injection Gun (BIG) and you wonder if this would be better to use than the standard IO needles that you have previously used?

Three part question
In [patients requiring IO access] is [the Bone Injection Gun better than standard IO needles] at [safely and rapidly acquiring IO access]?

Search strategy
Medline 1966-01/05 using the OVID interface. [exp Infusions, Intraosseous OR intraosseous infusion$.mp OR intraosseous.mp OR IO.mp] AND [BIG.mp OR auto-injector.mp OR auto$.mp OR bone injection gun.mp] LIMIT to English

Search outcome
Altogether 129 papers were found, of which three were relevant to the three part question.

Comment(s)
There are no published studies looking at the use of the BIG in live adults or children. Though this would be ideal it is unlikely to be achievable as IO placement is a rare event and there would be ethical and consent issues. We must therefore extrapolate data from other models. The paper by Calkins *et al* shows that the technique itself is easy to learn by non-medical trained responders, this may have implications for its use in prehospital care. This paper also used the screw tipped IO needle as the standard needle but in practice people may be more used to the standard straight needle. Waismann and Waismann suggest that they can be used succesfully in practice. Olsen found a higher failure rate in anaesthetised dogs but explained this was due to poor landmark identification rather than device failure. The differences in time to placement are unlikely to be clinically significant. From a clinical perspective there appears to be little to choose between them and issues such as cost and training may influence local decisions.

► CLINICAL BOTTOM LINE
The Bone Injection Gun appears to be equivalent in terms of success and possibly (but not clinically significantly) faster to use than standard IO needles at achieving IO access.

Calkins MD, Fitzgerald G, Bentley TB, Burris D. Intraosseous infusion devices: a comparison for potential use in special operations *J Trauma* 2000;**48**:1068–74.
Waisman M, Waisman D. Bone marrow infusion in adults *J Trauma* 1997;**42**:288–93.
Olsen D, Packer BE, Perrett J, *et al*. Evaluation of the bone injection gun as a method for intraosseous placement for fluid therpay in adult dogs. *Veterinary Surg* 2002;**31**:533–40.

Nebulised levalbuterol or albuterol for lowering serum potassium

Report by Herald Ostovar, *Senior EM Resident*
Checked by Dr Jeffrey Jones, *Research Director of the Emergency Medicine Residency Program* and Dr Michael Brown, *Director of the Emergency Medicine Residency Program*

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Abstract
A short cut review was carried out to establish whether nebulised levalbuterol is better than or equivalent to albuterol

Table 2

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Calkins MD *et al*, 2000, USA	31 special operations corpsmen testing 4 IO devices on cadavers; BIG, screw tip IO needles (2 other devices not relevant to the three part question so results not given)	Randomised experimental trial	Success rate	BIG 94%, screw tip 97% (not significant)	Using non-medical responders. By using cadavers there is no ''clinical pressure'' to achieve vascular access
			Time to placement	BIG 70 s (SD 33), screw tip 88s (33) (not significant)	
			Rank of preference (1–4)	BIG average rank 2.3, screw tip average rank 2.5 (not significant)	
Waisman M and Waisman D, 1997, USA	19 patients for resuscitation in whom IV access could not be achieved within 10 minutes and 31 adults with fractures receiving regional anaesthesia	Prospective case series	Success rate	100% successful placement	Observational study with no comparisons. Small numbers. Lack of follow up in resuscitation group
			Time to placement	Time taken ''1–2 minutes''	
			Complications	None in 24 hours or 4 months for respective groups	
Olsen D, 2002, USA	Adult dogs randomised to either IO gun or a Jamshidi IO needle; 24 dogs in each group	PRCT (animal)	Successful placement	20/24 (83%) for BIG *v* 23/24 (96%) for the Jamshidi; p=0.3475	Animal study. Anaesthetised subjects. Direct relevance to humans questionable. Single operator did all procedures. They explain increased failure rate for BIG to be due to poor landmark identification rather than device failure
			Average time for placement	22.4 s for BIG *v* 42 s for Jamshidi	

Table 3

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Lipworth BJ *et al*, 1997, UK	12 volunteers were randomised into 4 study groups: nebulised R-albuterol (200–3200 μg), S-albuterol (200–3200 μg), RS-albuterol (400–6400 μg) or placebo	PCRT crossover	Pharmacodynamics at extrapulmonary β2 receptors (tremor, plasma potassium, heart rate) measured at 0-100 minutes at 20 minute intervals	No significant differences were found in baseline plasma potassium values (no p values provided)	Small doses of study drugs used in healthy volunteers Small sample size Mean age (20.6) may not be representative of majority of population presenting with hyperkalaemia
Gumbhir-Shah K *et al*, 1999, USA	13 asthmatic subjects randomised to receive four cumulative doses of either nebulised 1.25 mg levalbuterol or 2.5 mg albuterol at 30 minute intervals	RCT crossover	FEV_1, plasma potassium, plasma glucose, heart rate, QTc interval, and urine plasma drug concentration at 1, 2, 4, 6, 8 hours after final dose	No significant difference between R and RS albuterol in reduction of plasma potassium levels (AUC p=0.17)	Four consecutive small doses given at 30 minutes intervals may not be applicable to those patients presenting with pathological hyperkalaemia Small sample size
			Side effects	None severe. Included dizziness, tachycardia, nervousness (greater in R group), wheezing (greater in RS group). All events resolved spontaneously	
Lotvall J *et al*, 2001, Sweden	20 adult asthmatic patients were randomised into 4 study groups: nebulised R-albuterol (6.25–1600 μg), S-albuterol (6.25–1600 μg), RS-albuterol (12.5–3200 μg), or placebo	PCRT 4-way crossover	FEV_1, heart rate, and plasma potassium levels before dosing FEV_1, heart rate and plasma potassium levels 20 minutes after each dose	Differences/p values not documented Rapid increase in plasma potassium level (0.3–0.4 mmol/l) after placebo administration (no p value given)	Single K^+ level was measured 20 minutes after study drug Small sample size The dose of albuterol required to reverse hyperkalaemia is higher than standard bronchodilator doses used in this study
			Side effects	No serious adverse events and majority of adverse events were reported after treatment with R or RS albuterol. These included tremor, palpitations, and tachyarrhythmias	
Pancu D *et al*, 2003, USA	27 healthy adult volunteers; 9 nebulised normal saline, 9 albuterol (10 mg), 9 levalbuterol (2.5 mg)	Randomised, double blind, placebo controlled trial	Serum potassium values at baseline	No difference between any group: albuterol 3.9 (0.3) mEq/l, levalbuterol 4.1 (0.3) mEq/l, placebo 4.1 (0.3) mEq/l	This study measured potassium changes in a small sample of healthy volunteers. The clinical significance of these small changes in potassium is uncertain and these changes may not be applicable to those patients presenting with pathological hyperkalaemia. Objective vital signs were only recorded in those patients reporting side effects
			Serum potassium at 30 minutes	Albuterol reduced by 0.3 mEq /l; levalbuterol reduced by 0.3 mEq/l; placebo increased by 0.1 mEq/l; no significant difference between β agonists. Both β agonists better than placebo (p=0.005)	
			Serum potassium at 60 minutes	Albuterol reduced by 0.3 mEq /l; levalbuterol reduced by 0.5 mEq/l; placebo showed no change. No significant difference between β agonists. Both β agonists better than placebo (p=0.001)	
			Side effects	Levalbuterol caused fewer reported side effects than albuterol. Levalbuterol *v* albuterol: total percent reporting symptoms, 22% *v* 78%; tremor, 22% *v* 78%; nervousness, 0% *v* 56%; palpitations, 0% *v* 56%; tachycardia, 0% *v* 44% No p values provided	

for lowering serum potassium. Seven papers were found using the reported search, of which three presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. A clinical bottom line is stated.

Three part question

In [patients with hyperkalaemia] is [levalbuterol better than albuterol] at reducing [serum potassium]?

Clinical scenario

A 67 year old man presents to the emergency department with chest pain and syncope. The electrocardiogram shows a wide QRS and peaked T-waves. Stat electrolytes show a potassium level of 7.3. While starting calcium gluconate, glucose/insulin, nebulised albuterol and kayexelate you wonder if substitution of levalbuterol for albuterol would have the same lowering effect on serum potassium and have fewer side effects.

Search strategy

Medline 1966–October 2004 using the OVID interface. [levalbuterol.mp or exp Albuterol/OR (albuterol or salbutamol).mp OR exp bronchodilator agents/OR exp adrenergic beta-agonists/OR beta-agonists.mp] AND [exp stereoisomerism/OR enantiomers.mp OR racemic.mp] AND [hyperkalemia.mp. or exp hyperkalemia/OR hyperkalaemia.mp OR exp potassium] LIMIT to human AND English language

Search outcome

Seven papers were found of which three were irrelevant to the study question. The remaining four papers are shown in table 3.

Comment

Equipotent nebulised levalbuterol appears to be as effective as albuterol in lowering serum potassium in healthy and asthmatic adults. Studies comparing these two medications in hyperkalaemic patients with comorbidities and on various medications would be helpful in establishing their comparative efficacy in treating common presenters to the emergency department.

► CLINICAL BOTTOM LINE

Nebulised levalbuterol appears to be as effective as albuterol in lowering serum potassium in adults.

Pancu D, LaFlamme M, Evans E, *et al*. Levalbuterol is as effective as racemic albuterol in lowering serum potassium. *J Emerg Med* 2003;**25**:13–16.
Lotvall J, Palmqvist M, Arvidsson P, *et al*. The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients. *J Allergy Clin Immunol* 2001;**108**:726–31.
Lipworth BJ, Clark DJ, Koch P, *et al*. Pharmacokinetics and exrapulmonary B2-adrenoceptor activity of nebulized racemic salbutamol and its R and S isomers in healthy volunteers. *Thorax* 1997;**53**:849–52.
Gumbhir-Shah K, Kellerman DJ, DeGraw S, *et al*. Pharmacokinetics and parmacodynamics of cumulative single doses of inhaled salbutamol enantiomers in asthmatic subjects. *Pulm Pharmacol Ther* 1999;**12**:353–62.