

BEST EVIDENCE TOPIC REPORTS

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

Edited by K Mackway-Jones

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. The BETs published below were first reported at the Critical Appraisal Journal Club at the Manchester Royal Infirmary.¹ 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 Six BETs are included in this issue of the journal.

- ▶ Oral or intravenous antidote for paracetamol overdose
- ▶ Vomiting in paracetamol overdose
- ▶ Intravenous or intramuscular/subcutaneous naloxone in opioid overdose
- ▶ Intravenous bolus or infusion of naloxone in opioid overdose
- ▶ Discharge of patients who have taken an overdose of opioids
- ▶ Gastric lavage in iron overdose

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- 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](http://www.bestbets.org): Odds on favourite for evidence in emergency medicine reaches the worldwide web. *J Accid Emerg Med* 2000;**17**:235–6.

Oral or intravenous antidote for paracetamol overdose

Report by Simon Clarke, Specialist Registrar

Checked by Katrina Herren, Research Fellow

Abstract

A short cut review was carried out to establish whether there was any evidence to decide between oral or intravenous antidote in paracetamol (acetaminophen) poisoning. Altogether 330 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

A 23 year old woman attends an emergency department having taken sixty 500 mg paracetamol tablets. Her four hour paracetamol levels are above the treatment line. She does not want to be treated with intravenous therapy. You wonder whether oral antidote is as effective.

Three part question

In [patients who need an antidote for paracetamol overdose] is [intravenous therapy better than oral therapy] at [preventing liver damage and death]?

Search strategy

Medline 1966 to 12/01 using the OVID interface. [exp acetylcysteine OR acetylcysteine.mp OR n-acetylcysteine.mp OR exp methionine/ OR methionine.mp OR exp antidote OR antidote.mp] AND [exp overdose/ OR overdos\$.mp OR exp poisons OR poison\$.mp OR acute intoxic\$.mp OR acute toxic\$.mp] AND [exp acetaminophen OR acetaminophen.mp OR exp paracetamol OR paracetamol.mp OR (co-codamol OR co-dydramol OR co-proxamol).mp] LIMIT to human AND English language.

Search outcome

Altogether 330 papers were identified, of which two were directly relevant to the question (table 1).

Comment(s)

Perry's study used historical controls although the demographic characteristics of the two groups were remarkably similar. It was not included in Buckley's meta-analysis because the patients were not recruited sequentially and it was unclear whether the patients were treated solely at the study centre (possible variations in other treatment modalities could act as confounding factors).

There have been no RCTs in this area. A meta-analysis of observational studies has failed to show a difference in efficacy between the oral and intravenous routes. However, these studies do not address other factors that may influence the choice of route, which include: activated charcoal adsorbs antidote and therefore precludes its use; the IV regimen is shorter than the oral (24 hours and 52 hours respectively); the IV route is safer with patients with altered levels of consciousness (for example due to coingestants) who may subsequently lose their airway protective reflexes.

▶ CLINICAL BOTTOM LINE

The IV route is the treatment of choice for paracetamol poisoning, but the oral route has a similar efficacy and is a suitable alternative if IV access is difficult (for example IV drug abusers) or refused by the patient.

Perry HE, Shannon MW. Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial. *J Pediatr* 1998;**132**:149–52.

Buckley NA, Whyte IM, O'Connell DL, *et al*. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999;**37**:759–67.

Table 1

Author, date and country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Perry HE, <i>et al</i> , 1998, USA	25 patients (<16 years) attending an emergency department less than 24 hours after a single, potentially toxic overdose of paracetamol, given IV N-acetylcysteine (NAC). 29 patients previously given oral NAC were used as historical controls.	Observational	Hepatotoxicity (transaminases >1000 u/l) Encephalopathy Coagulopathy requiring FFP	8% IV; 6.9% oral; 0% either group when treated <10 hours after ingestion 0% IV; 3.4% oral None noted	Small non-randomised study
Buckley NA, <i>et al</i> , 1999, Australia	5 observational studies	Meta-analysis	Hepatotoxicity	There was no significant difference in the hepatotoxicity rates between IV and oral NAC.	Meta-analysis IV data was pooled from 4 studies (total of 341 patients) but oral data was taken from only one (1462 patients) of the 3 eligible studies (248 patients excluded)

Vomiting in paracetamol overdose

Report by Katrina Herren, *Research Fellow*

Checked by Simon Clarke, *Specialist Registrar*

Abstract

A short cut review was carried out to establish whether vomiting was a significant consequence of paracetamol (acetaminophen) overdose. Altogether 48 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

A 27 year old woman presents to the emergency department having taken a paracetamol overdose; she is not vomiting. You have been told that people with a significant overdose of paracetamol will vomit. You wonder whether this is true.

Three part question

In [patients who have taken an overdose of paracetamol] what [is the incidence] of [vomiting]?

Search strategy

Medline 1966–12/01 using the OVID interface. [exp overdose OR overdos\$.mp OR exp poisons OR poison\$.mp OR acute intoxic\$.mp OR toxic\$.mp] AND [exp acetaminophen OR

acetaminophen.mp OR exp paracetamol OR paracetamol.mp OR (co-codamol OR co-dydramol OR co-proxamol).mp] AND [exp vomiting OR vomit\$.mp OR nause\$.mp OR emesis.mp] LIMIT to human AND English.

Search outcome

Altogether 48 papers of which two were relevant (table 2).

Comment(s)

Adams' paper quoted two further estimates of vomiting: the first (77%) referred to an anecdotal report in another paper³; the second (16%) was a value obtained from a prospective, observational study of 132 patients with four hourly levels above the 22 mg/l level all treated with methionine, only 5% vomited after the antidote.⁴ The paper quotes two further sources that describe frequent vomiting.

No mention was made about any delay in starting antidote therapy in this group. Neither study addresses other factors such as adsorption of oral antidote by activated charcoal, nor the fact that oral therapy lasts longer than IV (72 and 24 hours respectively).

► CLINICAL BOTTOM LINE

The incidence of vomiting after paracetamol is relatively low and is amenable to antiemetic therapy.

Adams RA, Dallas V, Daniels RG, *et al*. Vomiting in paracetamol poisoning. *BMJ* 1980;**280**:560–1.

Scharman EJ. Use of ondansetron and other antiemetics in the management of toxic acetaminophen ingestions. *J Toxicol Clin Toxicol* 1998;**36**:19–25.

Table 2

Author, date and country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Adams RA, <i>et al</i> , 1980, UK	392 patients with paracetamol overdose of whom 120 took paracetamol alone	Observational	Vomiting	11.7% vomited before the onset of antidote therapy	Does not report the incidence of vomiting in the paracetamol alone group Cannot exclude the confounding influence of co-ingestants (eg dextropropoxyphene in 112 patients)
Scharman EJ, 1998, USA	1009 adult patients with a paracetamol overdose, who were reported to a poisons centre.	Observational	Vomiting Antiemetic used and its effectiveness	12.5% vomited (61% were in the toxic range and 41% had taken co-ingestants) 33% failed first line antiemetic therapy and were given ondansetron: of these 16% failed (ie 4% required IV antidote)	No attempt to assess the proportion of patients in the non-vomiting group who had taken co-ingestants or who were in the toxic range

Table 3

Author, date and country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Sporer KA <i>et al</i> , 1996, USA	609 patients treated with prehospital naloxone for clinical evidence of opioid overdose. 487 were given IM; 69 IV; 53 both routes.	Observational	Response rate (increased GCS or RR) within 5 minutes of naloxone administration	94% IM; 90% IV; 98% both	Not randomised. The doses given were not standardised. Complication rates were recorded but no attempt was made to compare between routes of administration.
Wanger K <i>et al</i> , 1998, Canada	Patients treated with prehospital naloxone for clinical suspicion of opioid od. 74 patients given 0.4 mg IV; 122 given 0.8 mg SC	Observational	Time from arrival at scene to time patients RR >10/min Need for further doses of naloxone	No time difference Significantly less need for further doses with SC route (15% cf 35%).	Not randomised (treatment groups sequential). Poor follow up (missed delayed complications/ prolonged withdrawal symptoms).

Intravenous or intramuscular/subcutaneous naloxone in opioid overdose

Report by Simon Clarke, *Specialist Registrar*
Checked by Paul Dargan, *Specialist Registrar*

Abstract

A short cut review was carried out to establish whether intramuscular/subcutaneous naloxone is better than intravenous naloxone in opioid overdose. Altogether 185 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

A 30 year old man who is a known opioid addict is brought to the emergency department after an overdose of heroin. He had a Glasgow Coma Scale score of 3, a respiratory rate of 4 breaths per minute, and pinpoint pupils. You are aware that many addicts self discharge on reversal of opioid intoxication (possibly due to precipitation of acute withdrawal symptoms), and that because naloxone has a shorter duration of action than most opioid agonists, there is a risk of harm to the patient if he becomes renarcotised away from the hospital. You wonder if use of the intramuscular or subcutaneous route reduces this risk by prolonging the duration of action of naloxone.

Three part question

In [patients acutely intoxicated with opioids] does [intramuscular/subcutaneous or intravenous naloxone] reduce [the need for subsequent doses and risk of death from recurrent opioid toxicity]?

Search strategy

Medline 1966–09/2001 using the OVID interface. [{exp naloxone OR "naloxone".mp} AND {exp narcotics OR "opioid".mp OR "opiate".mp OR (morphine OR buprenorphine OR codeine OR dextromoramide OR diphenoxylate OR dipipanone OR dextropropoxyphene OR diamorphine OR dihydrocodeine OR alfentanil OR fentanyl OR remifentanyl OR meptazinol OR methadone OR nalbuphine OR oxycodone OR pentazocine OR pethidine OR phenazocine OR tramadol).mp} AND {exp overdose OR "overdos\$.mp OR exp poisons OR "poison\$.mp OR "acute intoxic\$.mp OR "acute toxic\$.mp}] LIMIT to human AND English.

Search outcome

Altogether 185 papers were found of which two addressed the question directly (table 3).

Comment(s)

Both studies were set in the prehospital environment and different criteria were used to define opioid intoxication, which means that it is difficult to assess applicability to other patient populations. In Sporer's study there were 16 patients who were found to be asystolic at the scene; these have been excluded from this discussion because no note was made of which treatment was given, and, in any case, none of this group survived.

► CLINICAL BOTTOM LINE

There is no evidence from these studies to suggest that the subcutaneous or intramuscular routes are inferior to IV administration of naloxone, but significant theoretical concerns have not been addressed, requiring further research. They may be useful alternative routes if intravenous access is difficult to obtain.

Sporer KA, Firestone J, Isaacs SM. Out-of-hospital treatment of opioid overdoses in an urban setting. *Acad Emerg Med* 1996;3:660–7.

Wanger K, Brough L, MacMillan I, *et al*. Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose. *Acad Emerg Med* 1998;5:293–9.

Intravenous bolus or infusion of naloxone in opioid overdose

Report by Simon Clarke, *Specialist Registrar*
Checked by Paul Dargan, *Specialist Registrar*

Abstract

A short cut review was carried out to establish whether intravenous boluses of naloxone are better than intravenous infusion in opioid overdose. Altogether 188 papers were found using the reported search, of which one 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 this best paper is tabulated. A clinical bottom line is stated.

Clinical scenario

A 30 year old man who is a known opioid addict is brought to the emergency department after an overdose of methadone. He had a Glasgow Coma Scale score of 3, a respiratory rate of 4 breaths per minute, and pinpoint pupils. You are aware that the action of naloxone is shorter than that of methadone and wonder if naloxone infusion is less likely to precipitate acute withdrawal symptoms than repeated bolus doses.

Table 4

Author, date and country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Goldfrank L <i>et al</i> , 1986, USA	7 patients attending an ED with symptoms of opioid overdose, given single boluses of naloxone	Observational	Phase one: Serial naloxone levels Phase two: Serial naloxone levels; Comparing the measured levels with target levels predicted by the nomogram	Construction of a dosing nomogram from the pharmacokinetic data obtained Levels measured in phase two were consistently higher than those predicted by the nomogram; the nomogram was adjusted and tested with a computer simulation	Small study with a high drop out rate (20% in phase two). The revised nomogram has not been tested on a repeated phase two study

Three part question

In [patients acutely intoxicated with opioids] is [intravenous infusion of naloxone better than repeated bolus doses] at reducing [the risk of precipitation of acute withdrawal symptoms]?

Search strategy

Medline 1966–09/01 using the OVID interface. [{exp naloxone OR naloxone.mp} AND {exp infusions, intravenous OR exp injections, intravenous} AND {exp narcotics OR opioid.mp OR opiate.mp OR morphine.mp OR buprenorphine.mp OR codeine.mp OR dextromoramide.mp OR diphenoxylate.mp OR dipipanone.mp OR dextropropoxyphene.mp OR diamorphine.mp OR dihydrocodeine.mp OR alfentanil.mp OR fentanyl.mp OR remifentanil.mp OR meptazinol.mp OR methadone.mp OR nalbuphine.mp OR oxycodone.mp OR pentazocine.mp OR pethidine.mp OR phenazocine.mp OR tramadol.mp}] LIMIT to human AND English.

Search outcome

Altogether 188 studies were found of which five addressed the question directly (table 4).

Comment(s)

It was found that there was large variation in factors determining plasma naloxone concentrations between people, and the nomogram was constructed to ensure that those who eliminate naloxone rapidly would not experience a reduction in levels and thus risk re-narcotisation. This leads to an overestimation of the infusion rate for those who eliminate naloxone more slowly with the theoretical risk of precipitation of acute withdrawal symptoms. A practical regimen for titrating naloxone by infusion for opioid overdose has been calculated: (1) titrate the initial bolus of naloxone against clinical effect; (2) start an infusion of naloxone, giving two thirds of the initial bolus per hour; (3) consider a second bolus (at half of the initial dose) after 15 minutes, if there are signs of reduced respiratory rate or conscious levels. Further research is needed to: validate the regimen against clinical criteria; assess whether it is possible in practice to titrate the patient's response to a "safe" level (for example, breathing with a safe airway and a GCS of 14/15 rather than a GCS of 15/15 but agitated and at risk of leaving the ED prematurely) and compare the regimen with other routes of administration.

► CLINICAL BOTTOM LINE

A practical regimen for titrating naloxone by infusion for opioid overdose has been calculated.

Goldfrank L, Weisman RS, Errick JK, *et al*. A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med* 1986;**15**:566–70.

Discharge of patients who have taken an overdose of opioids

Report by Simon Clarke, Specialist Registrar
Checked by Paul Dargan, Specialist Registrar

Abstract

A short cut review was carried out to establish whether patients with no recurrence of symptoms one hour after receiving naloxone for an opioid overdose can safely be discharged. Altogether 195 papers were found using the reported search, of which five 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

A 30 year old opioid addict is brought to the emergency department having overdosed on heroin. He is successfully treated with a titrated bolus of naloxone. You wonder when it will be safe to discharge the patient.

Three part question

In [patients given naloxone for the treatment of opioid overdose] is [a lack of recurrence of symptoms after one hour] a sensitive predictor for [safe discharge from the department]?

Search strategy

Medline 1966–09/01 using the OVID interface. [{exp narcotics OR opioid.mp OR opiate.mp OR morphine.mp OR buprenorphine.mp OR codeine.mp OR dextromoramide.mp OR diphenoxylate.mp OR dipipanone.mp OR dextropropoxyphene.mp OR diamorphine.mp OR heroin.mp OR alfentanil.mp OR fentanyl.mp OR remifentanil.mp OR meptazinol.mp OR methadone.mp OR nalbuphine.mp OR oxycodone.mp OR pentazocine.mp OR pethidine.mp OR phenazocine.mp OR tramadol.mp} AND {exp overdose OR overdos\$.mp OR exp poisons OR poison\$.mp OR "acute intoxic\$.mp OR "acute toxic\$.mp} AND {exp patient admission OR admission.mp OR exp patient discharge OR discharge.mp OR observ\$.mp OR monitor\$.mp OR predict\$.mp}] LIMIT to human AND English.

Table 5

Author, date and country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Smith DA <i>et al</i> , 1992, USA	124 patients presenting to an ED with a heroin overdose	Observational	Time to decision Further treatment after discharge	20 min None	Treatments given were neither standardised nor randomised so analysis of outcome could not be performed in relation to mode of treatment. Follow up was poor so it is possible that patients who sought further treatment or who died elsewhere would have been missed.
Osterwalder JJ, 1995, Switzerland	192 patients attending an ED with clinical suspicion of opioid od	Observational	Time to decision Reattendance if discharged	15 min 1 patient died	No attempt was made to compare the outcomes of different treatment modes The period of observation in the ED was not recorded.
Watson WA <i>et al</i> , 1998, USA	84 patients attending an ED who had been given naloxone for a presumed opioid od	Observational	Subsequent recurrence of opioid toxicity	Patients who have taken a longacting opioid are more likely to experience a recurrence of toxicity	No follow up of patients was attempted after admission to hospital/discharge from the ED to assess the incidence of late complications. The period of observation in the ED was not recorded.
Vilke GM <i>et al</i> , 1999, USA	317 patients with a clinical suspicion of opioid od who refused to be transported to the ED after being given naloxone by the paramedics	Observational	Death Reattendance of the ambulance within 12 hours	No patients treated with naloxone died Nil	Variable doses and routes of administration of naloxone were used. No follow up of patients was attempted to ascertain if they received subsequent treatment or died in another area or attended the ED by other means of transport.
Christenson J <i>et al</i> , 2000, Canada	573 patients attending an ED with clinical evidence of opioid intoxication who had been given naloxone either in the prehospital setting or ED	Observational	Clinical prediction rule to predict safe discharge	Patients can be safely discharged one hour after administration of naloxone if they have normal mobility, SpO ₂ >92%, respiratory rate 10–20/min, heart rate 50–100/min, temperature 35–37.5°C, GCS 15/15	The rule has not been validated yet. The pattern of drug misuse in Vancouver is different from other cities, so there are concerns about whether these results can be applied to different populations (for example, those that misuse a higher proportion of longer acting agents).

Search outcome

Altogether 194 papers found. Of these only five were relevant to the preoperative setting (table 5).

Comment(s)

The evidence consists of observational studies, three of which are retrospective reviews of medical records and thus there are concerns regarding the reliability of the data collected. In addition, only Christenson's study attempts to apply a "rule out" strategy by attempting to identify the clinical variables that predict a low risk of delayed complications from the opioid overdose. Further work is required to validate the rule in different populations by further prospective studies. Also, comparative trials need to be undertaken to assess the validity of the rule for different opioid overdoses.

► CLINICAL BOTTOM LINE

The evidence suggests that if a patient remains well one hour after administration of naloxone, then it is safe to discharge them.

Smith DA, Leake L, Loflin JR, *et al*. Is admission after intravenous heroin overdose necessary? *Ann Emerg Med* 1992;**21**:1326–30.

Osterwalder JJ. Patients intoxicated with heroin or heroin mixtures: how long should they be monitored? *Eur J Emerg Med* 1995;**2**:97–101.

Watson WA, Steele MT, Muellemann RL, *et al*. Opioid toxicity recurrence after an initial response to naloxone. *J Toxicol Clin Toxicol* 1998;**36**:11–17.

Vilke GM, Buchanan J, Dunford JV, *et al*. Are heroin overdose deaths related to patient release after prehospital treatment with naloxone? *Prehospital Emerg Care* 1999;**3**:183–6.

Christenson J, Etherington J, Grafstein E, *et al*. Early discharge of patients with presumed opioid overdose: development of a clinical prediction rule. *Acad Emerg Med* 2000;**7**:1110–18.

Gastric lavage in iron overdose

Report by **Stuart Teece**, *Research Fellow*

Search checked by **Ian Crawford**, *Research Fellow*

Abstract

A short cut review was carried out to establish whether gastric lavage is of use after an overdose of ionic compounds. Altogether 74 papers were found using the reported search but none answered the question posed.

Clinical scenario

A 29 year old woman presents to the emergency department 30 minutes after swallowing 40 lithium tablets. Given the recent onset and the apparent low efficacy of activated charcoal in ionic compounds you wonder whether she is a candidate for gastric lavage.

Three part question

In [overdose with ionic compounds] is [gastric lavage better than no treatment] at [reducing toxicity]?

Search strategy

Medline 1966–01/02 using the Ovid interface. [exp irrigation OR lavage.mp OR exp gastric lavage OR gastric lavage.mp OR exp gastric emptying OR gastric emptying.mp OR wash-out.mp] AND [(exp iron OR iron.ar OR exp iron compounds OR exp ferrous compounds OR ferrous.ar OR exp ferric compounds OR ferric.ar)] AND [exp poisoning OR poisons.ar OR

exp overdose OR overdose.mp OR exp suicide OR exp suicide, attempted OR exp self-injurious behaviour OR suicid\$.ar OR deliberate adj5self adj5harm.ar OR dsh.ar] limit to human and English.

Search outcome

Altogether 56 papers were found, none of which were relevant to the three part question.

Comment

More research is needed.

► **CLINICAL BOTTOM LINE**

There is no currently available evidence to support the use of gastric lavage in iron overdose. Local advice should be followed.



Discharge of patients who have taken an overdose of opioids

Simon Clarke and Paul Dargan

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