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 safer with patients with altered levels of consciousness (for example due to coingestants) who may subsequently lose their airway protective reflexes.

Oral or intravenous antidote for paracetamol overdose

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. Each BET has been constructed in the four stages that have been described elsewhere. The BETs shown here together with those published previously and those currently under construction can be seen at http://www.bestbets.org. 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

K Mackway-Jones Department of Emergency Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK; kevin.mackway-jones@man.ac.uk

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.

Comment(s)
Adams’ paper quoted two further estimates of vomiting: the first (77%) referred to an anecdotal report in another paper 3; 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.


Table 1

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perry HE, et al, 1998, USA</td>
<td>25 patients (&lt;16 years) attending an emergency department less than 24 hours after a single, potentially toxic overdose of paracetamol, given IV N-acetylcysteine (NAC)</td>
<td>Observational</td>
<td>Hepatotoxicity (transaminases &gt;1000 u/l)</td>
<td>8% IV, 6.9% oral; 0% either group when treated &lt;10 hours after ingestion</td>
<td>Small non-randomised study</td>
</tr>
<tr>
<td>Buckley NA, et al, 1999, Australia</td>
<td>29 patients previously given oral NAC were used as historical controls. 5 observational studies</td>
<td>Meta-analysis</td>
<td>Encephalopathy Coagulopathy requiring FFP Hepatotoxicity</td>
<td>There was no significant difference in the hepatotoxicity rates between IV and oral NAC.</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams RA, et al, 1980, UK</td>
<td>392 patients with paracetamol overdose of whom 120 took paracetamol alone</td>
<td>Observational</td>
<td>Vomiting</td>
<td>11.7% vomited before the onset of antidote therapy</td>
<td>Does not report the incidence of vomiting in the paracetamol alone group</td>
</tr>
<tr>
<td>Scharman EJ, 1998, USA</td>
<td>1009 adult patients with a paracetamol overdose, who were reported to a poisons centre.</td>
<td>Observational</td>
<td>Vomiting</td>
<td>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)</td>
<td>Cannot exclude the confounding influence of co-ingestants (eg dextropropoxyphene in 112 patients) 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</td>
</tr>
</tbody>
</table>
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 5, 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 naloxone infusion is less likely to precipitate acute withdrawal symptoms than repeated bolus doses.

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 dicydromine OR alfentanil OR fentanyl OR remifentanil OR meptazinol OR methadone OR nalbuphine OR oxydодone OR pentazocine OR pethidine OR phentazocine OR tramadol).mp) AND (exp overdose OR “overdose”.mp OR exp poison OR “poison”.mp OR “acute intoxication”.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).

Table 3
<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporer KA et al, 1996, USA</td>
<td>609 patients treated with prehospital naloxone for clinical evidence of opioid overdose. 487 were given IM; 69 IV, 53 both routes.</td>
<td>Observational</td>
<td>Response rate (increased GCS or RR) within 5 minutes</td>
<td>94% IM, 90% IV, 98% both</td>
<td>Not randomised. The doses given were not standardised. Complication rates were recorded but no attempt was made to compare between routes of administration.</td>
</tr>
<tr>
<td>Wanger K et al, 1998, Canada</td>
<td>Patients treated with prehospital naloxone for clinical suspicion of opioid overdose. 74 patients given 0.4 mg IV, 122 given 0.8 mg SC.</td>
<td>Observational</td>
<td>Time from arrival at scene to time patients RR &gt; 10/min</td>
<td>No time difference</td>
<td>Not randomised (treatment groups sequential). Poor follow up. (missed delayed complications/ prolonged withdrawal symptoms).</td>
</tr>
</tbody>
</table>

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.


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 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 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.

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.

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 allantani.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 renarcotisation. 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 one third 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 and as such 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.

Table 4

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldfrank L et al, 1986, USA</td>
<td>7 patients attending an ED with symptoms of opioid overdose, given single boluses of naloxone</td>
<td>Observational Phase one: Serial naloxone levels</td>
<td>Construction of a dosing nomogram from the pharmacokinetic data obtained Levels measured in phase two were generally higher than those predicted by the nomogram; the nomogram was adjusted and tested with a computer simulation</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

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 dihydrocodeine.mp OR allantani.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.

► CLINICAL BOTTOM LINE
A practical regimen for titrating naloxone by infusion for opioid overdose has been calculated.

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 washout.mp] AND [exp iron OR iron compounds OR ferrous compounds OR fe OR ferrous compounds OR Fe OR iron compounds OR exp ferrous compounds OR ferrous.ar OR exp ferric compounds OR ferric.ar] AND [exp poisoning OR POISONS.or OR

Table 5

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Study type</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith DA et al, 1992, USA</td>
<td>124 patients presenting to an ED with a heroin overdose</td>
<td>Observational</td>
<td>Time to decision</td>
<td>20 min</td>
<td>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. No attempt was made to compare the outcomes of different treatment modes. The period of observation in the ED was not recorded.</td>
</tr>
<tr>
<td>Osterwalder JJ, 1995, Switzerland</td>
<td>192 patients attending an ED with clinical suspicion of opioid od</td>
<td>Observational</td>
<td>Time to decision</td>
<td>15 min</td>
<td>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.</td>
</tr>
<tr>
<td>Watson WA et al, 1998, USA</td>
<td>84 patients attending an ED who had been given naloxone for a presumed opioid od</td>
<td>Observational</td>
<td>Subsequent recurrence of opioid toxicity</td>
<td>Patients who have taken a long-acting opioid are more likely to experience a recurrence of toxicity</td>
<td>No attempt was made to compare the outcomes of different treatment modes. The period of observation in the ED was not recorded.</td>
</tr>
<tr>
<td>Vilk GM et al, 1999, USA</td>
<td>317 patients with a clinical suspicion of opioid od who refused to be transported to the ED after being given naloxone by the paramedics</td>
<td>Observational</td>
<td>Death</td>
<td>No patients treated with naloxone died</td>
<td>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.</td>
</tr>
<tr>
<td>Christenson J et al, 2000, Canada</td>
<td>573 patients attending an ED with clinical evidence of opioid intoxication who had been given naloxone either in the prehospital setting or ED</td>
<td>Observational</td>
<td>Clinical prediction rule to predict safe discharge</td>
<td>Patients can be safely discharged one hour after administration of naloxone if they have normal mobility, SpO 2 &gt;92%, respiratory rate 10–20/min, heart rate 50–100/min, temperature 35–37.5°C, GCS 15/15</td>
<td>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.</td>
</tr>
</tbody>
</table>

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
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.