

EBM Applications in Acetaminophen Overdose: A Case Study

指導老師：林增記醫師

Intern 楊士賢

2007.06.25

貼心服務 真情照顧

教學 研究 服務



Case Presentation 1/6

- 32 year-old female, visited our ER at 09:48 AM for bilateral headache
- Swallowing 50# panadol last night at 12:30 AM
- Chronic headache, dizziness, insomnia

Case Presentation 2/6

- Past history
 - Diabetes Mellitus: denied
 - Hypertension: denied
 - Hepatitis B,C: denied
 - Other systemic disease: denied
 - Operation history: nil
 - Drug allergy: denied
 - Alcohol: (+)social / Betel nut: (-) / Cigarette: (-)

Case Presentation 3/6

- Physical Examination (at ER)
 - Vital Sign:
BT: 35.5°C PR: 74/min RR: 10~24/min
BP: 119/74mmHg
 - Height: 158cm Weight: **50kg** →BMI: 20.03
 - Consciousness: clear/lethargy
 - HEENT:
conjunctiva: not pale; sclera: not icteric
Neck: supple; JVD(-) LAP(-)
 - Chest: symmetric expansion
BS: bilateral clear
Heart: regular heart beat, no murmur
 - Abdomen: soft and flat,
bowel sound: normoactive
tenderness(-), rebounding pain(-),
 - Extremities: freely movable, L/L pitting edema(-)



Case Presentation 4/6

- Lab data
 - CBC:
 - Hgb = 13.8g/dl
 - WBC = 5990 x1000/ μ l
 - PLT = 220 x1000/ μ l
 - GOT/GPT: 24/11 IU/L
 - Benzodiazephen(Urine): <0.3ng/ml
 - Acetaminophen(Blood): **151.33** μ g/ml
(10 hr postingestion)

Case Presentation 5/6

- Treatment

- at ER:

- NAC 7500mg IVD for 15mins
 - NAC 2500mg + N/S 250cc IVD for 4hrs
 - NAC 2500mg + N/S 250cc IVD for 8hrs x2次

- Admitted to 肝膽內科

- 3rd day: Acetaminophen(Blood):0.1 μ g/ml
DC NAC and close follow up
 - 6th day: vital sign stable, discharge and
OPD follow up



Case Presentation 6/6

- Follow up Lab data at OPD (2 weeks later)
 - GOT/GPT: 15/16 IU/L
 - ALP: 60 IU/L
 - GGT 27 U/L
 - Creatinine: 0.7 mg/dl

Background Knowledge

貼心服務 真情照顧



教學



研究

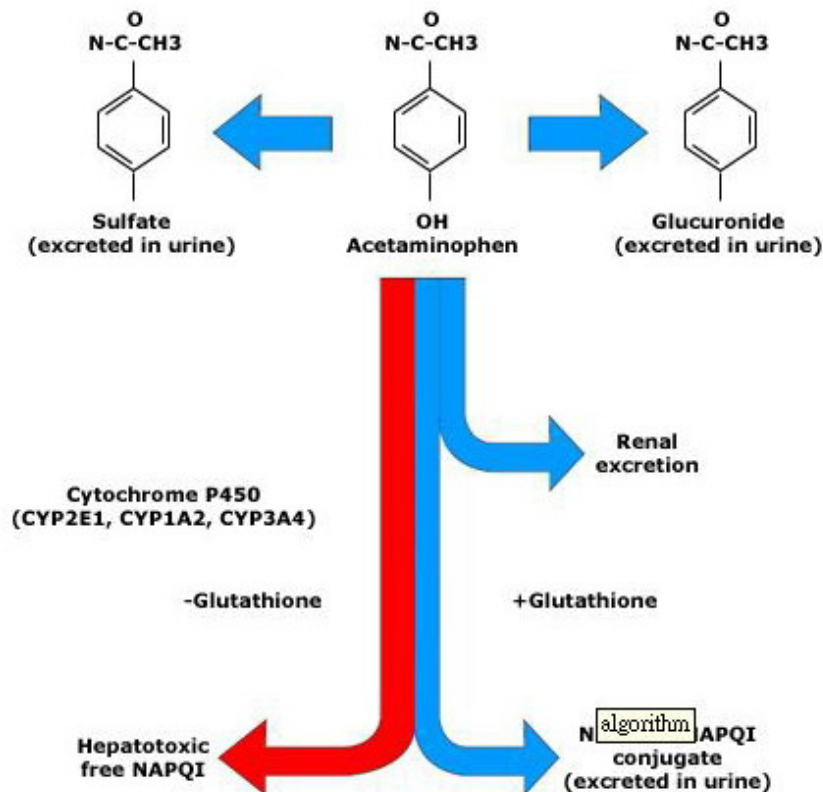


服務



Acetaminophen Metabolism

Acetaminophen metabolism



At therapeutic doses, 90 percent of acetaminophen is metabolized in the liver to sulfate and glucuronide conjugates that are then excreted in the urine. One-half of the remaining acetaminophen is excreted unchanged in the urine and one-half is metabolized via the hepatic cytochrome P450 (CYP2E1, CYP1A2, CYP3A4 subfamilies) mixed function oxidase pathway to N-acetyl-p-benzoquinoneimine (NAPQI), which is hepatotoxic. With normal doses (blue arrows), NAPQI is rapidly conjugated to hepatic glutathione, forming nontoxic cysteine and mercaptate compounds that are excreted in the urine. With toxic doses (red arrow), the sulfate and glucuronide pathways become saturated, resulting in an increased fraction of acetaminophen being metabolized by cytochrome P450 enzymes. Once glutathione stores are depleted, NAPQI begins to accumulate and hepatic injury ensues.

Acetaminophen Overdose

- Key Features
 - Toxic dose: > 140 mg/kg or 7.5 g (acute) or > 4–6 g/day (chronic)
 - Nausea, vomiting early after acute ingestion
 - Hepatic necrosis evident after 24–36 h
 - Fulminant hepatic failure can occur
- Clinical Findings
 - Early: nausea and vomiting
 - After 24–36 h: elevated transaminases, evidence of hepatic dysfunction and fulminant hepatic failure
 - Massive overdose (eg, levels > 600 mg/L) can cause coma, hypotension, metabolic acidosis soon after ingestion

Epidemiology

Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States.

Ann Intern Med. 2002 Dec
17;137(12):947-54.

PMID: 12484709



- DESIGN: Prospective cohort study.
SETTING: 17 tertiary care centers participating in the U.S. Acute Liver Failure Study Group.

- RESULTS:
Acetaminophen overdose was the most common apparent cause of acute liver failure, accounting for 39% of cases. Idiosyncratic drug reactions were the presumptive cause in 13% of cases, viral hepatitis A and B combined were implicated in 12% of cases, and 17% of cases were of indeterminate cause. Overall patient survival at 3 weeks was 67%. Twenty-nine percent of patients had liver transplantation, and 43% survived without transplantation. Short-term transplant-free survival varied greatly, from 68% for patients with acetaminophen-related liver failure to 25% and 17% for those with other drug reactions and liver failure of indeterminate cause, respectively. Coma grade at admission appeared to be associated with outcome, but age and symptom duration did not.

- CONCLUSIONS:
Acetaminophen overdose and idiosyncratic drug reactions have replaced viral hepatitis as the most frequent apparent causes of acute liver failure. Apparent cause and coma grade at admission were associated with outcome. Although transplantation may improve patient survival, it was unavailable or unnecessary for most patients.



Treatment of acetaminophen overdose

貼心服務 真情照顧

教學

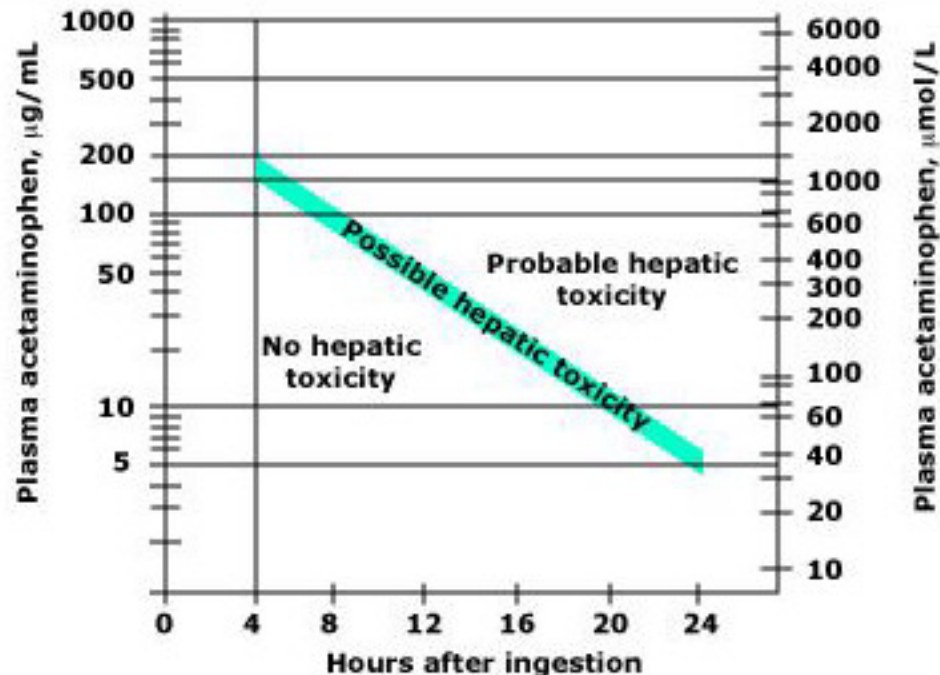
研究

服務



Acetaminophen nomogram

Severity of acetaminophen intoxication



Relationship between plasma acetaminophen concentration (in µg/mL or µmol/L), the time after drug ingestion, and the risk of hepatic toxicity. The thick diagonal line of possible hepatic toxicity represents a 25 percent likelihood of disease. A relatively low level (such as 10 µg/mL) is safe soon after ingestion, but associated with appreciable risk at 24 hours since it reflects a high initial load which has now distributed into the tissues. Adapted from Rumack, BH, Matthews, H, *Pediatrics* 1975; 55:873.

Nomogram

- 200 at 4hrs
50 at 12hrs
- When this relationship is known, n-acetylcysteine (NAC) therapy is indicated for acetaminophen levels above the lower nomogram line.
- NAC should also be given if there is >10 µg/mL acetaminophen and an unknown time of ingestion (but <24 hours), and if there is a history of overdose and a serum acetaminophen level is not immediately available.
- Serum levels obtained prior to 4 hours postingestion are uninterpretable because of ongoing absorption and distribution of the drug.



- Treatment with *N*-acetylcysteine is most effective if started within 8–10 hours after ingestion.
- If the precise time of ingestion is unknown or if the patient is at higher risk of hepatotoxicity (eg, alcoholic, liver disease, chronic use of P450-inducing drugs), then use a lower threshold for initiation of *N*-acetylcysteine (in some case reports, a level of 100 mg/L at 4 hours was suggested in very high-risk patients).

Washington Manual 32nd

- **PO: Traditional US oral regimen 72hr**
Loading: 140 mg/kg,
Maintains: 70 mg/kg q4h for 17 doses
(repeat the dose, if vomiting occurs < 1hr after administration)
- **IV: 24hr IV**
who cannot take oral NCA, who have bowel obstruction, GI bleeding, or fulminant hepatic failure, pregnancy
Loading: 150 mg/kg in 200ml D₅W over 1hr
Maintains: 50mg/kg in 500ml over 4hrs, followed by 100mg/kg in 500ml over 16hrs
=====
- **Other protocol:**
 - **PO: 24hr oral**
Loading: 140 mg/kg,
Maintains: 70 mg/kg q4h for 5 doses, if GOT/GPT WNL
 - **IV: 48hr IV**
Loading: 140 mg/kg
Maintains: 70 mg/kg q4h for 12 doses



Adverse reactions from intravenous NAC

- varied considerably, ranging from 0.2 to 21 percent
- include nausea, flushing, urticaria, bronchospasm, angioedema, fever, chills, hypotension, hemolysis, and, rarely, cardiovascular collapse.
- Anaphylactoid reactions are dose-dependent and usually occur within an hour of initiating NAC infusion.

- Lowering the infusion rate does not appear to decrease the efficacy of NAC therapy or lower the incidence of adverse events.

Evidence-Based Medicine

貼心服務 真情照顧

教學

研究

服務



實證醫學五大步驟

- Step.1: 整理出可回答的臨床問題
(Formulating an answerable clinical question)
- Step.2: 搜尋最佳證據
(Tracking down the best evidence)
- Step.3: 嚴格評析證據
(Appraising the evidence critically)
- Step.4: 應用證據於病患身上
(Applying evidence to patients)
- Step.5: 對過程進行稽核及評估
(Auditing performance and evaluation)



Formulating an answerable clinical question

- As for acetaminophen overdose in this case, is there a better treatment strategy?

==>

- As for intravenous and oral form N-acetylcysteine, which one is better?

Clarifying the problem using PICO model

| | |
|----------------------|--|
| P atient | acetaminophen overdose |
| I ntervention | intravenous N-acetylcysteine |
| C omparison | oral N-acetylcysteine |
| O utcome | patient outcome mortality/morbidity (e.g.liver failure) cost and safety length of Hospital Stay |

The Evidence Pyramid



Grades of Recommendation and Levels of Evidence

| Grades of Recommendation | Levels of Evidence | Description of Study Design |
|--------------------------|--------------------|--|
| A | 1a | Systematic review (with homogeneity) of randomized clinical trials |
| | 1b | Individual randomized clinical trials (with narrow confidence interval) |
| | 1c | All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.) |
| B | 2a | Systematic review (with homogeneity) of cohort studies |
| | 2b | Individual cohort study (including low quality randomized clinical trial) |
| | 2c | "Outcomes" research |
| | 3a | Systemic review (with homogeneity) of case-control studies |
| | 3b | Individual case-control study |
| C | 4 | Case series, single case reports (and poor quality cohort and case control studies) |
| D | 5 | Expert opinion without explicit critical appraisal or based on physiology or bench research |
| Z | 6 | Abstracts |

Grade I: Randomized controlled trials

Grade II-1: Controlled trials without randomization

Grade II-2: Cohort or case-control analytic studies

Grade II-3: Multiple time series, dramatic uncontrolled experiments

Grade III: Opinions of respected authorities, descriptive epidemiology

- Key word:
 - Acetaminophen overdose
 - Paracetamol poisoning
 - N-acetylcysteine, Acetaminophen
- Data base:
 - Guideline
 - National Guideline Clearinghouse (2)
 - 經過整理的文獻
 - ACP J. club (1)
 - UptoDate (1)
 - 未經過整理的文獻
 - PubMed (9)



Polson J, Lee WM. AASLD position paper: the management of acute liver failure.

Hepatology 2005 May; 41(5): 1179-97.
[179 references]

PMID: 15841455

Guideline

AASLD: American Association for the Study of Liver Diseases

貼心服務 真情照顧

教學

研究

服務



• Acetaminophen Hepatotoxicity

- For patients with known or suspected acetaminophen overdose within 4 hours of presentation, give activated charcoal just prior to starting N-acetylcysteine (NAC) (**Grade I**).
- Begin NAC promptly in all patients where the quantity of acetaminophen ingested, serum drug level, or rising aminotransferases indicate impending or evolving liver injury (**Grade II-1**).
- NAC may be used in cases of acute liver failure in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate (**Grade III**).



Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management.

Clin Toxicol (Phila)
2006; 44(1): 1-18. PubMed
PMID: 16496488

Guideline

貼心服務 真情照顧

教學

研究

服務



• MAJOR RECOMMENDATIONS

- The initial history obtained by the specialist in poison information should include the patient's age and intent (**Grade B**), the specific formulation and dose of acetaminophen, the ingestion pattern (single or multiple), duration of ingestion (**Grade B**), and concomitant medications that might have been ingested (**Grade D**).
- Any patient with stated or suspected self-harm or who is the recipient of a potentially malicious administration of acetaminophen should be referred to an emergency department immediately regardless of the amount ingested. This referral should be guided by local poison center procedures (**Grade D**).
- Activated charcoal can be considered if local poison center policies support its prehospital use, a toxic dose of acetaminophen has been taken, and fewer than 2 hours have elapsed since the ingestion (**Grade A**). Gastrointestinal decontamination could be particularly important if acetylcysteine cannot be administered within 8 hours of ingestion.



• Acute, Single, Unintentional Ingestion of Acetaminophen

- Any patient with signs consistent with acetaminophen poisoning (e.g., repeated vomiting, abdominal tenderness in the right upper quadrant, or mental status changes) should be referred to an emergency department for evaluation **(Grade D)**.
- Patients less than 6 years of age should be referred to an emergency department if the estimated acute ingestion amount is unknown or is 200 mg/kg or more. Patients can be observed at home if the dose ingested is less than 200 mg/kg **(Grade B)**.
- Patients 6 years of age or older should be referred to an emergency department if they have ingested at least 10 g or 200 mg/kg (whichever is lower) or when the amount ingested is unknown **(Grade D)**.
- Patients referred to an emergency department should arrive in time to have a stat serum acetaminophen concentration determined at 4 hours after ingestion or as soon as possible thereafter. If the time of ingestion is unknown, the patient should be referred to an emergency department immediately **(Grade D)**.
- If the initial contact with the poison center occurs more than 36 hours after the ingestion and the patient is well, the patient does not require further evaluation for acetaminophen toxicity **(Grade D)**.





Algorithm for Out-of-Hospital Management of Acute Acetaminophen Ingestions

Is self-harm, suicidal, or malicious intent suspected?

YES → Refer to emergency department.

NO ↓

Does patient have signs of liver failure (e.g., repeated vomiting, jaundice, right upper abdomen tenderness, mental changes)?

YES → Refer to emergency department.

NO ↓

Have more than 36 hours passed since the ingestion?

YES → Toxicity unlikely to occur. No referral or treatment is needed.

NO ↓

Has the patient ingested a potentially toxic dose of acetaminophen (i.e., ≥ 200 mg/kg for patients < 6 yr of age; ≥ 10 g or ≥ 200 mg/kg, whichever is less, for patients ≥ 6 yr of age)?*

YES → Refer to emergency department to have stat serum acetaminophen concentration determined at 4 hr after ingestion.

NO ↓

No referral or treatment is needed.

* Activated charcoal should be considered if local poison center policies support its prehospital use, if a toxic dose of acetaminophen has been taken and fewer than 2 hours have elapsed since the ingestion, or if acetylcysteine cannot be initiated within 8 hours after the ingestion.

Interventions for paracetamol (acetaminophen) overdose.

Cochrane Database Syst Rev.
2006 Apr 19; (2):CD003328.

PMID: 16625578

Grade: B



- Systemic review and Meta-analyses: randomised clinical trials and observational studies were included
- The primary outcome measure was all-cause mortality plus liver transplantation. Secondary outcome measures were clinical symptoms, (eg, hepatic encephalopathy, fulminant hepatic failure), hepatotoxicity, adverse events, and plasma paracetamol concentration

- **Activated charcoal**, gastric lavage, and ipecacuanha are able to reduce the absorption of paracetamol
- N-acetylcysteine seems preferable to placebo/supportive treatment, dimercaprol, and cysteamine, but N-acetylcysteine's superiority to methionine is unproven.
- It is not clear which N-acetylcysteine treatment protocol offers the best efficacy.



Treatment of acetaminophen overdose

Am J Health Syst Pharm.
1999 Jun 1;56(11):1081-91
PMID: 10385455

Grade: B

貼心服務 真情照顧

教學

研究

服務



- systemic review

- A single dose of activated **charcoal** should be administered within one hour of acetaminophen overdose.
- Acetylcysteine should be given if the acetaminophen concentration exceeds the treatment line in the **Rumack-Matthew nomogram**.
- If a patient is treated within **10 hours** of acetaminophen ingestion, the risk of hepatotoxicity is low.
- In patients 10-24 hours after ingestion, a 72-hour oral or 48-hour i.v. acetylcysteine regimen should be used.

Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning.

Am J Health Syst Pharm.
2006 Oct 1;63(19):1821-7.

PMID: 16990628

Grade: B



- Publication Types: Review

- PURPOSE:

The efficacy, safety, and cost issues that should be considered when deciding on the appropriate route of acetylcysteine for the treatment of patients with acetaminophen poisoning are reviewed.

- SUMMARY:

Oral and i.v. acetylcysteine appear to be equally effective when given within 8-10 hours of acetaminophen overdose. Anaphylactoid reactions to i.v. acetylcysteine have generally been reported in 3-6% of acetaminophen-poisoned patients. Dosing errors and hyponatremia have occurred in pediatric patients receiving i.v. acetylcysteine. Several investigators found an increased rate of anaphylactoid reactions in patients treated with i.v. acetylcysteine whose pretreatment serum acetaminophen levels were nontoxic. Compounding i.v. acetylcysteine from the oral preparation is less expensive than using premade i.v. solution. State pharmacy laws dictate whether extemporaneous compounding of acetylcysteine from the oral formulation is allowed. Oral acetylcysteine administration has resulted in minimal anaphylactoid reactions and is safer than i.v. acetylcysteine. Oral therapy should preferentially be considered in patients with asthma or atopic histories. **The most important factors to consider when selecting the route of acetylcysteine administration include individual susceptibility, the severity of acetaminophen toxicity, and the time interval between acetaminophen ingestion and initiation of acetylcysteine therapy.**

- CONCLUSION:

Oral acetylcysteine administered within 8-10 hours of acetaminophen overdose prevents liver toxicity in the majority of patients who tolerate it and have no contraindications to therapy. I.V. acetylcysteine should be administered when patients are treated more than 10 hours postingestion of acetaminophen overdose or have underlying conditions preventing oral treatment. Anaphylactoid reactions are rare and occur more frequently in patients treated with the i.v. preparation.

**What is the rate of
adverse events after oral
N-acetylcysteine
administered by the
intravenous route to
patients with suspected
acetaminophen poisoning?**

Ann Emerg Med. 2003
Dec; 42(6):741-50.

PMID: 14634597

Grade: B



- **STUDY OBJECTIVE:**

We conduct a study to determine the rate of adverse events (anaphylactoid and cardiorespiratory) associated with the use of oral N-acetylcysteine by the intravenous route for the treatment of suspected acetaminophen poisoning and to examine specific variables that may be associated with adverse events.

- **METHODS:**

We conducted a retrospective medical record review with explicit criteria. All patients who received oral N-acetylcysteine by the intravenous route from September 1995 to September 2001 were included. Patients were identified by cross-matching 3 databases. Adverse events were divided into categories of cutaneous, systemic, or life threatening. Five reviewers abstracted charts by using a standardized data collection form. Interrater reliability was calculated by using 24 medical records abstracted by all 5 reviewers.

- **RESULTS:**

There were 7 adverse events identified in 187 patients (3.7%; 95% confidence interval 1.0% to 6.5%). Six adverse events were cutaneous and responded rapidly to antihistamines. One adverse event was life threatening but not clearly related to N-acetylcysteine. A high rate of antihistamine exposure (53%) was identified before the administration of N-acetylcysteine. Interrater agreement was higher than 95%.

- **CONCLUSION:**

Intravenous administration of an oral solution of N-acetylcysteine is associated with a low rate of adverse events and should be considered for selected patients with suspected acetaminophen poisoning.

Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning?

J Toxicol Clin Toxicol.
1999;37(6):759-67.

PMID: 10584588

Grade: C



- **BACKGROUND:**

The optimal route and duration of administration for N-acetyl-cysteine in the management of acetaminophen (paracetamol) poisoning are controversial. It has been stated on the basis of a selected post-hoc analysis that oral N-acetylcysteine is superior to intravenous N-acetylcysteine in presentations later than 15 hours.

- **AIM OF STUDY:**

To investigate the efficacy of intravenous or oral N-acetylcysteine.

- **PATIENTS AND METHODS:**

We analyzed a series of acetaminophen poisonings treated with a protocol including activated charcoal and intravenous N-acetylcysteine. The outcomes assessed included use of N-acetylcysteine, adverse effects of intravenous N-acetylcysteine, and the occurrence of hepatotoxicity (transaminase > 1000 U/L). We incorporated these results in a meta-analysis of previously reported series of acetaminophen poisonings to compare the outcomes from intravenous and oral N-acetylcysteine use.

- **RESULTS:**

Of 981 patients admitted over 10 years, 4% (40) presented later than 24 hours and 10% (100) had concentrations of acetaminophen that indicated a probable or high risk of hepatotoxicity. The 30 patients who developed hepatotoxicity presented later, took larger amounts, had higher concentrations, and received N-acetylcysteine later than those who did not. No patients received a liver transplant but 2 patients died (one after referral to a transplant unit and one just before). Adverse reactions to intravenous N-acetylcysteine occurred in 6% (12/205) of patients but none prevented completion of the treatment. In the meta-analysis, those with probable or high risk concentrations had **similar outcomes** with intravenous (pooled n = 341) and oral N-acetylcysteine (pooled n = 1462) administration. Rates of hepatotoxicity for those treated within 10 hours (3 and 6%), late (10-24 hours: 30 and 26%), and overall (0-24 hours: 16 and 19%) were all similar. The proportion of patients classified as presenting later than 10 hours is much greater in the oral N-acetylcysteine studies (64%) than in many of the intravenous N-acetylcysteine studies (38%, 44%, and 63%).

- **CONCLUSIONS:**

The differences claimed between oral and intravenous N-acetylcysteine regimes are probably artificial and relate to inappropriate subgroup analysis. A shorter hospital stay, patient and doctor convenience, and the concerns over the reduction in bioavailability of oral N-acetylcysteine by charcoal and vomiting make intravenous N-acetylcysteine preferable for most patients with acetaminophen poisoning.



The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine.

Ann Emerg Med. 2005
Apr; 45(4): 402-8.
PMID: 15795719

Grade: A

貼心服務 真情照顧

教學

研究

服務



- **STUDY OBJECTIVE:**

We determine whether the incidence of adverse events caused by intravenous N -acetylcysteine is significantly less when the initial dose is infused over a 60-minute period compared with the standard infusion period of 15 minutes. A secondary objective is to assess the efficacy of the 2 treatment arms.

- **METHODS:**

This was a multicenter, randomized, prospective trial of patients who presented with acetaminophen poisoning and who were treated with N -acetylcysteine and had no history of hypersensitivity to N-acetylcysteine. Patients were randomly assigned to receive the initial dose of N-acetylcysteine over a 15-minute or 60-minute period. Baseline signs and symptoms and adverse events were serially evaluated before and during administration of N -acetylcysteine. Tests of liver injury and coagulation were collected at baseline and then at 12-hour intervals.

- **RESULTS:**

The study was designed with an 80% power to detect a halving of the incidence of adverse events. Of 180 evaluable patients, 109 patients were randomized to the 15-minute group and 71 patients were randomized to the 60-minute group. The incidence of drug-related adverse events was 45% in the 15-minute group and 38% in the 60-minute group (95% confidence interval -8% to 22%). The study did not demonstrate a reduction of drug-related adverse outcomes with the 60-minute infusion. Incidence of maximum alanine aminotransferase levels indicating hepatotoxicity (serum level >1,000 IU/L) was 6.8% (5.6% for 15-minute, 8.7% for 60-minute). The difference did not attain statistical significance.

- **CONCLUSION:**

This study did not demonstrate a reduction of drug-related adverse outcomes with the 60-minute infusion. The study also confirmed that early treatment with N -acetylcysteine (within 8 hours of ingestion) is more effective than later treatment.

Intravenous administration of N- acetylcysteine: oral and parenteral formulations are both acceptable.

Ann Emerg Med. 2005
Feb; 45(2): 223-4.

PMID: 15671984

Publication Types: Letter

Grade: D



- Oral administration of N-acetylcysteine is the standard treatment for acetaminophen poisoning in the United States.
- On January 23, 2004, the US Food and Drug Administration (FDA) approved an intravenous formulation of N-acetylcysteine (Acetadote[®], Cumberland Pharmaceuticals).
- The pharmacy cost for the first 20 hours of therapy for a 70-kg patient is US\$416 using Acetadote, US\$57 using Mucomyst, and US\$32 using the least-expensive generic.
- All forms of intravenous N-acetylcysteine can cause anaphylactoid reactions, including rash, angioedema, bronchospasm, and death.
- The cost of Acetadote may be justified if it is significantly safer than intravenous administration of N-acetylcysteine oral solution. However, at this time the available data do not support this assumption.



- On the basis of the cost and safety data available, we believe that both Acetadote and careful intravenous administration of N-acetylcysteine oral solution are appropriate treatment options in cases of severe acetaminophen poisoning when enteral therapy cannot be tolerated.



Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose.

Ann Emerg Med. 2000

Apr; 35(4): 363-8.

PMID: 10736123

Grade: C



- **STUDY OBJECTIVE:**

We sought to evaluate the safety and efficacy of a shorter N-acetylcysteine (NAC) regimen in the treatment of acute acetaminophen overdose.

- **METHODS:**

We performed a retrospective case series in a large urban county hospital. Of 305 patients identified through the emergency department, 75 patients met the criteria inclusion: an acute overdose ingestion, serum acetaminophen concentration in toxic range according to the Rumack-Matthew nomogram, and oral NAC treatment initiated within 24 hours of the ingestion. The regional poison control center recommended oral treatment with NAC 140 mg/kg, followed by maintenance doses of 70 mg/kg every 4 hours until the serum acetaminophen level was no longer detectable, rather than the standard 72-hour treatment regimen.

- **RESULTS:**

The primary outcome measure was the development of hepatotoxicity. Twenty-five (33.3%) patients were treated for a period of less than 24 hours, 25 (33.3%) were treated for 24 to 36 hours, and 25 (33.3%) were treated for 37 to 64 hours; the mean and median duration of treatment was 31 hours. None of the patients treated for less than 24 hours had evidence of hepatotoxicity (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] level >1,000 IU/L); hepatotoxicity developed in 2 (8%) patients treated for 24 to 36 hours and 4 (16%) patients treated for 37 to 64 hours. There were no deaths or patients who received liver transplantation. The overall incidence of hepatotoxicity in our patients was similar to that found in other protocols with administration of oral NAC for 72 hours or intravenous NAC for 20 or 48 hours.

- **CONCLUSION:**

This observational study suggests that a shorter course of oral NAC therapy in patients who do not show evidence of hepatotoxicity within 36 hours of an acute acetaminophen overdose is safe and effective.

Acetaminophen intoxication and length of treatment: how long is long enough?

Pharmacotherapy. 2003

Aug; 23(8):1052-9.

PMID: 12921251

Case Review

Grade: C

- The currently recommended dosing scheme for treating acetaminophen overdose in the United States consists of a loading dose of oral N-acetylcysteine 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 doses, for a total of 72 hours of oral N-acetylcysteine therapy. This protocol has been both effective and safe. We critically evaluated the evidence that supports reducing the course of N-acetylcysteine therapy from 72 hours to 24 or 36 hours. This shorter regimen offers important benefits for both the patient and the patient's family, such as increased drug tolerability and reduced hospital stay. Patients who intentionally ingested acetaminophen with harmful intent could receive appropriate psychosocial treatment more quickly. In addition, shorter courses of N-acetylcysteine therapy have positive financial ramifications by reducing the hospital stay by 1 or 2 days. Clearly, a shorter treatment regimen would not be appropriate for all patients, particularly those who seek treatment late (> 24 hrs after ingestion) and those with evidence of organ toxicity. In order to provide the necessary evidence to support a change in accepted clinical practice, further investigation on the safety and efficacy of a shorter N-acetylcysteine regimen should be conducted by clinical researchers in a controlled manner.



Summary

貼心服務，真情照顧



教學



研究



服務



- It is not clear which N-acetylcysteine treatment protocol offers the best efficacy. **(B) IV=PO**
- In patients 10-24 hours after ingestion, a 72-hour oral or 48-hour i.v. acetylcysteine regimen should be used. **(B) IV=PO**
- I.V. acetylcysteine should be administered when patients are treated more than 10 hours postingestion of acetaminophen overdose or have underlying conditions preventing oral treatment. **(B) IV>PO**
- Intravenous administration of an oral solution of N-acetylcysteine is associated with a low rate of adverse events and should be considered for selected patients with suspected acetaminophen poisoning. **(B) IV>PO**
- A shorter hospital stay, patient and doctor convenience, and the concerns over the reduction in bioavailability of oral N-acetylcysteine by charcoal and vomiting make intravenous N-acetylcysteine preferable for most patients with acetaminophen poisoning. **(C) IV>PO**
- This study did not demonstrate a reduction of drug-related adverse outcomes with the 60-minute infusion. **(A) IV**
- On the basis of the cost and safety data available, we believe that both Acetadote and careful intravenous administration of N-acetylcysteine oral solution are appropriate treatment options in cases of severe acetaminophen poisoning when enteral therapy cannot be tolerated. **(D) IV**
- We critically evaluated the evidence that supports reducing the course of N-acetylcysteine therapy from 72 hours to 24 or 36 hours. **(C) PO**
- This observational study suggests that a shorter course of oral NAC therapy in patients who do not show evidence of hepatotoxicity within 36 hours of an acute acetaminophen overdose is safe and effective. **(C) PO**



UpToDate

Treatment

Secure airway, breathing, and circulation

Give **activated charcoal (AC)** 50 g to all adult patients presenting within 4 hours of ingestion; AC may be useful for coingestants beyond 4 hours

Treat with **N-acetylcysteine (NAC)** if:

Serum APAP concentration drawn at 4 hours or more after a single acute ingestion is above the "possible hepatic toxicity" line of the Rumack-Matthew nomogram

Serum APAP concentration is unavailable or will not return within 8 hours of time of ingestion and APAP ingestion suspected

Time of ingestion is unknown and serum APAP level is greater than 10 micrograms/ml

There is evidence of ANY hepatotoxicity with a history of APAP ingestion

Patient reports or clinician suspects repeated excessive APAP ingestions, patient has risk factors for APAP-induced hepatotoxicity, and the serum APAP level is greater than 10 micrograms/mL

Oral dosing of NAC:

Oral dosing is acceptable for non-pregnant patients with a functional GI tract and no evidence of hepatotoxicity

Dose 140 mg/kg loading dose, followed by 17 doses of 70 mg/kg every 4 hours

If vomiting occurs within 1 hour of NAC dosing, a full NAC dose should be repeated as rapidly as possible

Therapy may be terminated by 36 hours after ingestion if the acetaminophen level is below 10 micrograms/ml, and patient does not develop evidence of hepatotoxicity, and patient remains clinically well

Intravenous (IV) dosing of NAC:

In patients with no biochemical evidence of hepatic failure (ie, those with INR <2.0), use 20 hour protocol: 150 mg/kg loading dose over 15 minutes, followed by 50 mg/kg infusion over 4 hours, with the final 100 mg/kg infused over the remaining 16 hours

In patients with biochemical evidence of hepatic failure (ie, those with INR >2.0), administer 150 mg/kg IV every 4 hours until INR <2.0

IV dosing is acceptable in all cases of acetaminophen toxicity, but should be used **INSTEAD** of oral dosing in patients unable to tolerate oral NAC (eg, intractable vomiting), patients with a medical condition precluding administration of oral NAC (eg, corrosive ingestion, GI bleed), patients with significant hepatotoxicity (INR >2.0), and pregnant patients

Antiemetic therapy:

May give 5-HT₃ receptor antagonist (eg, ondansetron) or metoclopramide

IV NAC indications and dosage

Indications and procedure for intravenous administration of oral N-acetylcysteine (NAC)

Recommended indications

Oral NAC cannot be tolerated

Coingestant with potential for morbidity and mortality necessitating ongoing gastrointestinal decontamination

Gastrointestinal bleeding or obstruction

Medical or surgical conditions precluding oral NAC administration

Acetaminophen toxicity presenting as encephalopathy

Neonatal acetaminophen toxicity from maternal overdose

Recommended procedure

Obtain informed consent

Dilute 20 percent NAC solution to 3 percent solution with 5 percent dextrose in water

Administer loading dose of NAC: 140 mg/kg infused through a peripheral intravenous catheter over 1 hour using an in-line 0.2 micron millipore filter

Administer maintenance doses of NAC (first maintenance dose 4 hours after the initiation of the loading dose): 70 mg/kg per dose every four hours, each infused over 1 hour through an in-line 0.2 micron millipore filter

Adapted from Yip, L, Dart, RC, Hurlbut, KM, Crit Care Med 1998; 26:40.

Thanks for your attention!!

貼心服務，真情照顧



教學



研究



服務

