

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Acetylcysteine for Acetaminophen Toxicity
10/2004

Recommendations

- Acetadote®, IV acetylcysteine, is not recommended for formulary inclusion; acetylcysteine for inhalation, a sterile product may be given IV and has been given IV since 1979. A 0.22 micro inline filter will be used to prepare the inhalation solution for IV use. The active ingredients, inactive ingredients, and pH are identical in the products. A savings of \$200-\$700 will be realized per 20.25 hour treatment for patients weighing 40-150 kg (16.5 times less expensive).
- The FDA recommended dose of acetylcysteine intravenous for patients treated within 10 hours of ingestion is:
 - 150 mg/kg IV over 15-60 minutes in 200 ml of D5W, followed by
 - 50 mg/kg in 500 ml of D5W over 4 hours, followed by
 - 100 mg/kg in 1000 ml of D5W over 16 hours.
- The 20.25 hour IV protocol is not recommended for patients treated greater than 10 hours post ingestion, as efficacy is less than acetylcysteine administered IV for 48 hours (140 mg/kg loading dose followed by 70 mg/kg every 4 hours for 11 doses) or orally for 72 hours (140 mg/kg loading dose, followed by 70 mg/kg every 4 hours for 17 doses), see table at end of findings.
- Among patients with fulminant hepatic failure, acetylcysteine should be given until there is recovery or death, 100 mg/kg continuous infusion every 16 hours, as mortality is reduced by 40%. (Br Med J. 1979;2:1097-100) Note: These patients were admitted 33 hours post ingestion and started the IV protocol (150 mg/kg loading dose, 50 mg/kg over 4 hours, 100 mg/kg every 16 hours) 53 hours post ingestion and were already in fulminant hepatic failure.

Protocol: see Rumack-Matthew nomogram on the next page

- Activated charcoal should be administered within one hour of acetaminophen ingestion. Activated charcoal has no clinically significant effect on acetylcysteine concentrations and should be administered before a serum acetaminophen concentration at four hours is obtained. Acetylcysteine should then be administered if the acetaminophen concentration exceeds the treatment line on the Rumack-Matthew nomogram.
- Draw an acetaminophen level at 4 hours post ingestion or as soon as possible thereafter. Acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. If an extended release preparation was ingested, an acetaminophen level drawn less than 8 hours post ingestion may be misleading. Draw a second level 4-6 hours after the initial level. If either falls above the toxicity line, acetylcysteine treatment should be initiated.
- Treatment may be delayed until acetaminophen assay results are available as long as initiation of treatment is not delayed beyond 8 hours post ingestion. If more than 8 hours post-ingestion, start acetylcysteine treatment immediately.
- Follow liver function tests, renal function, blood sugar, electrolytes, prothrombin time or INR daily in patients with toxic acetaminophen levels.
- Administer vitamin K, if prothrombin ratio exceeds 1.5 or fresh frozen plasma if the PT ratio exceeds 3.

Indications for IV acetylcysteine

- Oral acetylcysteine is not tolerated
- Gastrointestinal decontamination needed for coingestant
- GI bleeding or obstruction
- Medical or surgical conditions precluding oral acetylcysteine administration
- Encephalopathy
- Neonatal acetaminophen toxicity from maternal overdose

Interpretation of Acetaminophen Assays

1. When results of the plasma acetaminophen assay are available, refer to the nomogram below to determine if plasma concentration is in the potentially toxic range. Values above the line connecting 200 mcg/mL at 4 hours with 50 mcg/mL at 12 hours (probable line) are associated with a probability of hepatic toxicity if an antidote is not administered.
2. If the predetoxification plasma level is above the line connecting 150 mcg/mL at 4 hours with 37.5 mcg/mL at 12 hours (possible line), continue with maintenance doses of acetylcysteine. It is better to err on the safe side and thus this line, defining possible toxicity, is plotted 25% below the line defining probable toxicity.
3. If the predetoxification plasma level is below the line connecting 150 mcg/mL at 4 hours with 37.5 mcg/mL at 12 hours (possible line), there is minimal risk of hepatic toxicity, and acetylcysteine treatment may be discontinued.

ESTIMATING POTENTIAL FOR HEPATOTOXICITY: The following depiction of the Rumack-Matthew nomogram (Figure 2) has been developed to estimate the probability that plasma levels in relation to intervals post ingestion will result in hepatotoxicity.

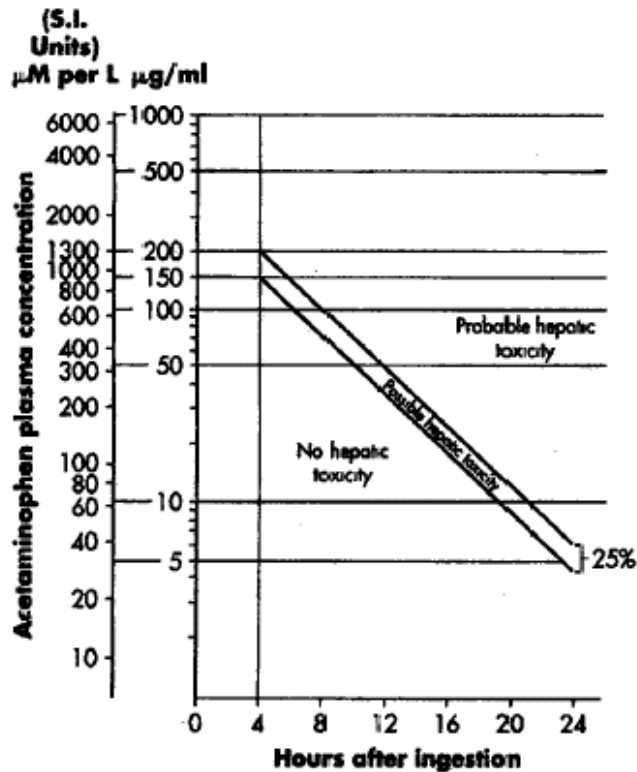


Figure 2 Rumack-Matthew Nomogram: Plasma or Serum Acetaminophen Concentration vs. Time Post Acetaminophen Ingestion

The above nomogram has only been validated in nonalcoholic patients with no preexisting liver dysfunction.

Findings:

- In the United States, acetaminophen is the most common medication involved in drug overdose, 111,175 cases in 1995, with 103 deaths. Acetylcysteine was used in 10,033 of these cases.
- When acetaminophen is given in therapeutic doses 96% is metabolized by the liver. Glucuronidation or sulfation accounts for 90% of hepatic clearance of acetaminophen. Four percent is excreted unchanged in the urine. The remainder is converted to a toxic intermediate metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), which is quickly converted to a nontoxic compound by glutathione conjugation. Toxic ingestion saturates glucuronidation and sulfation pathways. Increased production of NAPQI exceeds the capacity of glutathione stores. NAPQI may covalently bond to and arylate critical hepatic cell proteins, which may result in hepatic necrosis and death of the patient.
- Acute ingestion of acetaminophen in quantities of greater than 7.5 gm in adults and 150 mg/kg in children may result in hepatic toxicity. Acetaminophen is rapidly absorbed from the upper GI tract with peak levels occurring between 30-60 minutes after therapeutic doses and usually within 4 hours following an overdose.
- Following ingestion of a large overdose of acetaminophen (≥ 150 mg/kg) the glucuronide and sulfate conjugation pathways are saturated resulting in a large fraction of the drug being metabolized via the P-450 pathway. This increases the formation of reactive metabolite, which may deplete the hepatic stores of glutathione with subsequent binding of the metabolite to protein molecules within the hepatocyte and result in cellular necrosis.

- Acetylcysteine likely protects the liver by maintaining or restoring the glutathione levels, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite.
- The Rumack-Matthew nomogram was designed to be sensitive rather than specific. The nomogram predicts the likelihood that AST or ALT concentration will exceed 1000 IU/L. Bond found that only 0.4% of 662 patients with an acetaminophen concentration below the lower line developed hypotoxicity.
- Clinical features of acetaminophen toxicity are divided into four stages:
 - Stage 1, 1st 24 hours post ingestion: GI symptoms, nausea, vomiting, abdominal pain, malaise, and diaphoresis.
 - Stage 2, 24-72 hours post ingestion: right-upper-quadrant pain, increases in bilirubin, prothrombin time, and liver transaminase levels.
 - Stage 3, 72-96 hours post ingestion: symptoms range from asymptomatic to suffering from fulminant hepatic failure with encephalopathy and coma. Liver enzymes peak. Death if it occurs is usually 3-5 days post ingestion and results from multiple-organ-system failure and complications from hepatic failure.
 - Stage 4, recovery: clinical symptoms subside and liver transaminases return to normal.
- Acetaminophen crosses the human placenta and can cause fetal hepatotoxicity and death after maternal overdose. Acetaminophen overdose in pregnant patients should be managed the same way as in non pregnant patients.
- Activated charcoal should be administered within one hour of acetaminophen ingestion. Activated charcoal has no clinically significant effect on acetylcysteine concentrations and should be administered before a serum acetaminophen concentration at four hours is obtained. Acetylcysteine should then be administered if the acetaminophen concentration exceeds the treatment line on the Rumack-Matthew nomogram.
- When patients are treated within 10 hours of acetaminophen ingestion the risk of hepatotoxicity is low.
- Acetylcysteine is most effective when given early, with benefit seen mostly in patients treated within 8-10 hours of the overdose.
- IV acetylcysteine is indicated to prevent or lessen hepatic injury when administered within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen.
- In patients treated 10-24 hours after ingestion oral acetylcysteine given for either 48 hours IV (140 mg/kg loading dose, followed by 70 mg/kg every 4 hours for 11 doses) or 72 hours oral (140 mg/kg loading dose, followed by 70 mg/kg every 4 hours for 17 doses) is more effective than the 20.25 hour IV regimen.
- Among patients with fulminant hepatic failure, acetylcysteine should be given until there is recovery or death, 100 mg/kg continuous infusion every 16 hours, as mortality has been shown to be reduced by 40%.
- Contraindications
 - Patients with hypersensitivity or previous anaphylactoid reactions to acetylcysteine
- Warnings
 - Adverse reactions related to IV infusion occur in approximately 6% of patients and are usually related to the initial loading dose.
 - Serious anaphylactoid reactions such as rash, hypotension, wheezing, and/or shortness of breath (including death in a patient with asthma) have been reported in patients administered IV acetylcysteine.
 - Anaphylactoid reactions (hypersensitivity): rash, hypotension, wheezing, and/or shortness of breath have been reported and occur shortly after starting the IV infusion.
 - Stop infusion, administered antihistaminic drugs as well as epinephrine in severe cases.
 - Restart the infusion after treatment.
 - The loading dose may be administered over a longer duration, up to 1 hour, to minimize adverse effects.
 - Acute flushing and erythema of the skin may occur 30 to 60 minutes after initiating the infusion and often resolve spontaneously despite continued infusion.
 - The total volume administered should be adjusted for patients less than 40 kg and for those requiring fluid restriction. To avoid fluid overload, the volume of 5% dextrose should be reduced as needed. If the volume is not adjusted fluid overload can occur, potentially resulting in hyponatremia, seizure, and death.
- Drug Interactions
 - Drug stability and safety of IV acetylcysteine when mixed with other drugs have not been established.

Acetylcysteine Clinical Trials							
Study		High Risk Patient		Probable Risk		Possible Risk	
	Time Acetylcysteine Administered Post Ingestion	AST/ALT > 1000 IU/L	Death	AST/ALT > 1000 IU/L	Death	AST/ALT > 1000 IU/L	Death
Prescott N=100							
IV for 20 hours (300 mg/kg total)	Within 10 hours	3%	0				
	10-24 hours	63%					
	> 15 hours	82%					
Smilkstein*N=2540							
Standard Oral for 72 hours (1330 mg/kg total)	Within 10 hours	8.3%		6.1%			
	10-24 hours	34.4%		26.4%			
	16-24 hours	41%					
Smilkstein*N=179							
IV for 48 hour (980 mg/kg total)							
	Within 10 hours	4.2%		10%		4.3%	
	10-24 hours	32%		27.1%		4.8%	
	16-24 hours	57.7%					

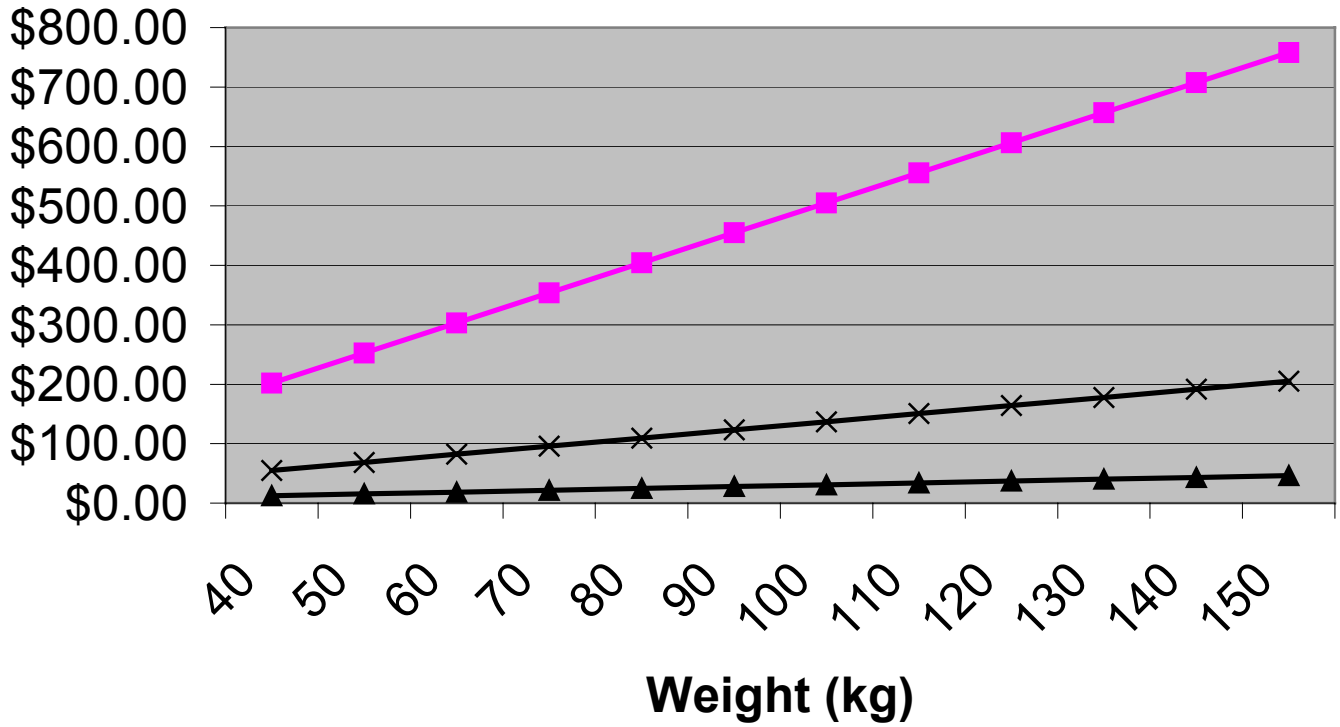
*High-risk: acetaminophen level ≥ 300 mg/l at 4 hours, or ≥ 75 mg/l at 12 hours or > 45 mg/l at 15 hours.

*Probable-risk: acetaminophen level ≥ 200 mg/l at 4 hours, or ≥ 50 mg/l at 12 hours

* Possible-risk: acetaminophen level ≥ 150 mg/l at 4 hours, or ≥ 37.5 mg/l at 12 hours

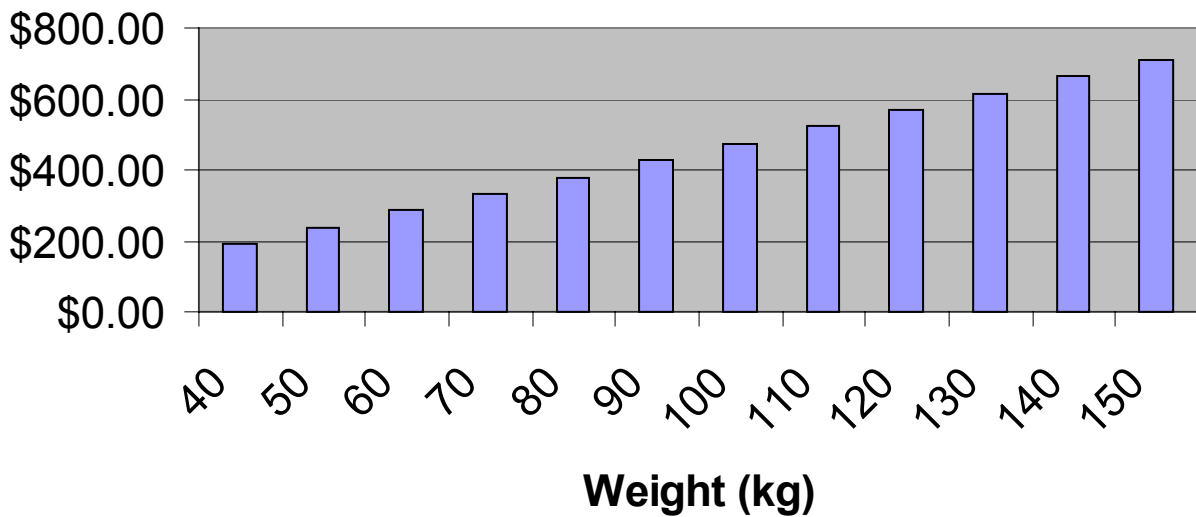
	Acetylcysteine Inhalation Solution	IV acetylcysteine
Indication	Adjunctive mucolytic therapy in patients with abnormal or viscid mucous secretions in acute and chronic bronchopulmonary diseases; pulmonary complications of surgery and cystic fibrosis; diagnostic bronchial studies; antidote for acute acetaminophen toxicity	Administered within 8-10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen to prevent or lessen hepatic injury
Ingredients	Sterile 20% Solution pH 6-7.5 EDTA	Sterile 20% pH 6-7.5 0.5 mg/ml EDTA
Mechanism of Action	Thought to be acting by providing substrate for conjugation with the toxic metabolite	Likely protects the liver by maintaining or restoring the glutathione levels, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite.
Half life (Hours)	5.5	Adult 5.6 Newborn 11
Half life (Hours) Liver Damage Child-Pugh 7-13 Primary/secondary biliary cirrhosis		10.26
Volume of Distribution L/Kg		0.47
Clearance (l/kg/hr)		0.11 (30% renally)
Dosage	140 mg/kg; followed by 17 doses of 70 mg/kg every 4 hours; repeat dose if emesis occurs within 1 hour of administration; therapy should continue until all doses are administered even though the acetaminophen plasma level has dropped below the toxic range	Loading Dose: 150 mg/kg in 200 mL of 5% dextrose, infuse intravenously over 15 minutes. Maintenance Dose: 50 mg/kg in 500 mL of 5% dextrose, infuse intravenously over 4 hours followed by 100 mg/kg in 1000 mL of 5% dextrose, infuse intravenously over 16 hours.
Adverse Reactions	Drowsiness, chills, fever, vomiting, nausea	Angioedema, vasodilation, hypotension, tachycardia, syncope, vomiting, nausea, flushing, and urticaria

Cost per Treatment



- Acetadote For 20.25 Hours
- ▲ Mucomyst IV For 20.25 Hours
- × Mucomyst Oral For 72 Hours

Cost Savings per Treatment (Mucomyst IV Versus Acetadote for 20.25 Hours)



Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial.

Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, Williams R.

Institute of Liver Studies, King's College School of Medicine and Dentistry, London.

OBJECTIVE--To see whether intravenous acetylcysteine would improve outcome in patients with fulminant hepatic failure after paracetamol overdose. **DESIGN**--A prospective randomised controlled study. **SETTING**--The Institute of Liver Studies, King's College Hospital, London. **PATIENTS**--50 consecutive patients (21 male) aged 16-60 with fulminant hepatic failure after paracetamol overdose who had not previously received acetylcysteine. **INTERVENTIONS**--Conventional intensive liver care plus either acetylcysteine (25 patients) in the same dose regimen as used early after a paracetamol overdose (150 mg/kg over 15 minutes, followed by 50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours), except that the infusion was continued until recovery from encephalopathy or death, or an equivalent volume of 5% dextrose (25 patients). **MAIN OUTCOME MEASURES**--Survival; incidence of cerebral oedema, renal failure, and hypotension requiring inotropic support; liver function as assessed by prolongation of the prothrombin time; and degree of encephalopathy. **RESULTS**--The rate of survival was significantly higher in the acetylcysteine treated group than in the controls (48% (12/25 patients) v 20% (5/25); $p = 0.037$, 95% confidence interval for difference in proportions surviving 3% to 53%). Acetylcysteine treated patients had a lower incidence of cerebral oedema (40% (10/25) v 68% (17/25); $p = 0.047$, 95% confidence interval for difference in incidence 2% to 54%), and fewer developed hypotension requiring inotropic support (48% (12/25) v 80% (20/25); $p = 0.018$, 95% confidence interval 7% to 57%). Rates of deterioration and recovery of liver function, however, were similar in the two groups. No adverse reactions to acetylcysteine were seen. **CONCLUSIONS**--Acetylcysteine is safe and effective in fulminant hepatic failure after paracetamol overdose.

Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol.

Smilkstein MJ, Bronstein AC, Linden C, Augenstein WL, Kulig KW, Rumack BH.

Section of Trauma and Emergency Medicine, University of Colorado Health Sciences Center, Denver.

STUDY OBJECTIVE: To determine the safety and efficacy of a 48-hour IV N-acetylcysteine (IV NAC) treatment protocol for acute acetaminophen overdose. **DESIGN:** Nonrandomized trial open to all eligible patients. **SETTING:** Multicenter; hospitals included moderate- and high-volume private, university, and municipal hospitals in urban and suburban settings. **TYPE OF PARTICIPANTS:** Two hundred twenty-three patients were entered. Of these, 179 met inclusion criteria: acute acetaminophen overdose, plasma acetaminophen concentration above the treatment nomogram line, treatment with IV NAC according to the protocol, and sufficient data to determine outcome. **INTERVENTIONS:** IV NAC treatment consisted of a loading dose of 140 mg/kg followed by 12 doses of 70 mg/kg every four hours. **MEASUREMENTS AND MAIN RESULTS:** Patients were grouped for analysis according to risk group based on the initial plasma acetaminophen concentration. Hepatotoxicity (aspartate aminotransferase or alanine aminotransferase of more than 1,000 IU/L) developed in 10% (five of 50) of patients at "probable risk" when IV NAC was started within ten hours of acetaminophen ingestion and in 27.1% (23 of 85) when therapy was begun after ten to 24 hours. Among "high-risk" patients first treated 16 to 24 hours after overdose, hepatotoxicity occurred in 57.9% (11 of 19). There were two deaths (two of 179, 1.1%). Adverse reactions resulting from NAC occurred in 32 of 223 cases (14.3%), consisting in 29 of 32 patients (91% of reactions) of transient, patchy, skin erythema or mild urticaria during the loading dose that did not require discontinuation of therapy. **CONCLUSION:** This 48-hour IV NAC protocol is safe and effective antidotal therapy for acetaminophen overdose. Based on available data, it is equal to 72-hour oral and 20-hour IV treatment protocols when started early and superior to the 20-hour IV regimen when treatment is delayed. Further study will be required to determine its relative efficacy in the high-risk patient treated very late.

Publication Types:

- Clinical Trial
- Multicenter Study



2: N Engl J Med. 1988 Dec 15;319(24):1557-62.

[Related Articles.](#)

[Links](#)

Comment in:

- [N Engl J Med. 1989 May 25;320\(21\):1417-8.](#)

Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985)

Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH.

Rocky Mountain Poison and Drug Center, Denver, CO 80204-4507.

During the investigational use of oral N-acetylcysteine as an antidote for poisoning with acetaminophen, 11,195 cases of suspected acetaminophen overdose were reported. We describe the outcomes of 2540 patients with acetaminophen ingestions treated with a loading dose of 140 mg of oral N-acetylcysteine per kilogram of body weight, followed four hours later by 70 mg per kilogram given every four hours for an additional 17 doses. Patients were categorized for analysis on the basis of initial plasma acetaminophen concentrations and the interval between ingestion and treatment. Hepatotoxicity developed in 6.1 percent of patients at probable risk when N-acetylcysteine was started within 10 hours of acetaminophen ingestion and in 26.4 percent of such patients when therapy was begun 10 to 24 hours after ingestion. Among patients at high risk who were treated 16 to 24 hours after an acetaminophen overdose, hepatotoxicity developed in 41 percent--a rate lower than that among historical controls. When given within eight hours of acetaminophen ingestion, N-acetylcysteine was protective regardless of the initial plasma acetaminophen concentration. There was no difference in outcome whether N-acetylcysteine was started zero to four or four to eight hours after ingestion, but efficacy decreased with further delay. There were 11 deaths among the 2540 patients (0.43 percent); in the nine fatal cases in which aminotransferase was measured before treatment, values were elevated before N-acetylcysteine was started. No deaths were clearly caused by acetaminophen among patients in whom N-acetylcysteine therapy was begun within 16 hours. We conclude that N-acetylcysteine treatment should be started within eight hours of an acetaminophen overdose, but that treatment is still indicated at least as late as 24 hours after ingestion. On the basis of available data, the 72-hour regimen of oral N-acetylcysteine is as effective as the 20-hour intravenous regimen described previously, and it may be superior when treatment is delayed.

Publication Types:

- Clinical Trial
- Multicenter Study

PMID: 3059186 [PubMed - indexed for MEDLINE]

1: J Pediatr. 1998 Jan;132(1):149-52.

Efficacy of oral versus intravenous N-acetylcysteine in acetaminophen overdose: results of an open-label, clinical trial.

Perry HE, Shannon MW.

Division of Emergency Medicine, Children's Hospital, Boston, Massachusetts, USA.

We compared the clinical course of pediatric patients (n = 25) with acetaminophen poisoning treated with an investigational intravenous preparation of N-acetylcysteine (IV-NAC) with that of historical control subjects (n = 29) treated with conventional

oral NAC (O-NAC) therapy. Patients received IV-NAC for 52 hours; historical control subjects received O-NAC (72 hours). There were no significant intergroup differences between treatment groups in age (15.5 vs 15.9 years), gender (88% vs 90% female) or distribution of risk categories (probable risk, 12 vs 15; high risk; 13 vs 14). The peak prothrombin time was significantly higher in the IV-NAC group (14.2 vs 13.6 seconds; $p = 0.048$). Mean treatment delay was significantly longer in the IV-NAC group (14.4 vs 10.4 hours; $p = 0.001$). Hepatotoxicity was noted in two (8.0%) patients in the IV-NAC treatment group and two (6.9%) patients in the O-NAC group. All patients recovered. Our results indicate that 52 hours of intravenous NAC is as effective as 72 hours of oral NAC.

Publication Types:

- Clinical Trial

PMID: 9470017 [PubMed - indexed for MEDLINE]

2: Crit Care Med. 1998 Jan;26(1):40-3.

Intravenous administration of oral N-acetylcysteine.

Yip L, Dart RC, Hurlbut KM.

Rocky Mountain Poison and Drug Center and Denver Health Medical Center, Department of Surgery, University of Colorado Health Science Center 80220, USA.

OBJECTIVE: To report the indications and adverse events associated with administration of the oral N-acetylcysteine preparation by the intravenous route. **DESIGN:** Retrospective consecutive case series analysis of 226,720 Toxic Exposure Surveillance System data sheets from a certified regional poison center during the period January 1, 1992 through December 31, 1993. **SETTING:** A regional poison center certified by the American Association of Poison Control Centers. **PATIENTS:** Seventy-six patients treated with the oral N-acetylcysteine solution by the intravenous route. **INTERVENTIONS:** None. **MEASUREMENTS AND MAIN RESULTS:** We report the indications and adverse events associated with the intravenous administration of the oral N-acetylcysteine preparation. Four (4/76, 5.3%) patients developed adverse events attributable to N-acetylcysteine. None of these events involved hemodynamic, cardiovascular, or pulmonary effects. All reactions occurred during infusion of the initial N-acetylcysteine dose. There were three (3/76, 3.9%) deaths overall; however, they were not attributable to the intravenous administration of the oral N-acetylcysteine preparation. **CONCLUSIONS:** Intravenous administration of the oral N-acetylcysteine preparation appears to have limited adverse effects and offers another mechanism of delivery of the potentially lifesaving N-acetylcysteine when oral administration is not possible.

PMID: 9428541 [PubMed - indexed for MEDLINE]

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

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

Buckley NA, Whyte IM, O'Connell DL, Dawson AH.

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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 artifactual 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.

Publication Types:

- Meta-Analysis

PMID: 10584588 [PubMed - indexed for MEDLINE]

4: Arch Intern Med. 1981 Feb 23;141(3 Spec No):386-9.

Treatment of severe acetaminophen poisoning with intravenous acetylcysteine.

Prescott LF.

Intravenous (IV) acetylcysteine, cysteamine, and methionine treatments were compared in patients with severe acetaminophen poisoning; a control group consisted of patients receiving supportive therapy only. Acetylcysteine proved the safest and most effective mode of treatment. Acetylcysteine was effective in preventing liver damage, hepatic failure, renal damage, and death when given eight to ten hours after poisoning. When treatment was delayed for ten to 24 hours, results were the same as in the supportive-therapy group. The alanine aminotransferase (ALT) activity remained normal in 76% of the patients treated within ten hours, as compared with 40% in both cysteamine- and methionine-treated groups and with 16% in the supportive-therapy group. The ingestion-treatment interval for complete protection with all three drugs was eight hours; beyond that time, the incidence of damage increased steadily. After 15 hours, all treatments were pointless. Based on my experience, IV administration is preferable, since nausea and vomiting may limit the effectiveness of oral therapy.

PMID: 7469630 [PubMed - indexed for MEDLINE]



1: Br Med J. 1979 Nov 3;2(6198):1097-100.

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Intravenous N-acetylcystine: the treatment of choice for paracetamol poisoning.

Prescott LF, Illingworth RN, Critchley JA, Stewart MJ, Adam RD, Proudfoot AT.

One hundred cases of severe paracetamol poisoning were treated with intravenous N-acetylcysteine (acetyl-cysteine). There was virtually complete protection against liver damage in 40 patients treated within eight hours after ingestion (mean maximum serum alanine transaminase activity 27 IU/l). Only one out of 62 patients treated within 10 hours developed severe liver damage compared with 33 out of 57 patients (58%) studied retrospectively who received supportive treatment alone. Early treatment and acetylcysteine also prevented renal impairment and death. The critical ingestion-treatment interval for complete protection against severe liver damage was eight hours. Efficacy diminished progressively thereafter, and treatment after 15 hours was completely ineffective. Intravenous acetylcysteine was more effective than cysteamine and methionine and noticeably free of adverse effects. It is the treatment of choice for paracetamol poisoning.

Drug Metab Dispos. 2003 Dec;31(12):1499-506
Acetaminophen-induced hepatotoxicity.

James LP, Mayeux PR, Hinson JA.

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The analgesic acetaminophen causes a potentially fatal, hepatic centrilobular necrosis when taken in overdose. The initial phases of toxicity were described in Dr. Gillette's laboratory in the 1970s. These findings indicated that acetaminophen was metabolically activated by cytochrome P450 enzymes to a reactive metabolite that depleted glutathione (GSH) and covalently bound to protein. It was shown that repletion of GSH prevented the toxicity. This finding led to the development of the currently used antidote N-acetylcysteine. The reactive metabolite was subsequently identified to be N-acetyl-p-benzoquinone imine (NAPQI). Although covalent binding has been shown to be an excellent correlate of toxicity, a number of other events have been shown to occur and are likely important in the initiation and repair of toxicity. Recent data have shown that nitrated tyrosine residues as well as acetaminophen adducts occur in the necrotic cells following toxic doses of acetaminophen. Nitrotyrosine was postulated to be mediated by peroxynitrite, a reactive nitrogen species formed by the very rapid reaction of superoxide and nitric oxide (NO). Peroxynitrite is normally detoxified by GSH, which is depleted in acetaminophen toxicity. NO synthesis (serum nitrate plus nitrite) was dramatically increased following acetaminophen. In inducible nitric oxide synthase (iNOS) knockout mice, acetaminophen did not increase NO synthesis or tyrosine nitration; however, histological evidence indicated no difference in toxicity. Acetaminophen did not cause hepatic lipid peroxidation in wild-type mice but did cause lipid peroxidation in iNOS knockout mice. These data suggest that NO may play a role in controlling lipid peroxidation and that reactive nitrogen/oxygen species may be important in toxicity. The source of the superoxide has not been identified, but our recent finding that NADPH oxidase knockout mice were equally sensitive to acetaminophen and had equal nitration of tyrosine suggests that the superoxide is not from the activation of Kupffer cells. It was postulated that NAPQI-mediated mitochondrial injury may be the source of the superoxide. In addition, the significance of cytokines and chemokines in the development of toxicity and repair processes has been demonstrated by several recent studies. IL-1beta is increased early in acetaminophen toxicity and may be important in iNOS induction. Other cytokines, such as IL-10, macrophage inhibitory protein-2 (MIP-2), and monocyte chemoattractant protein-1 (MCP-1), appear to be involved in hepatocyte repair and the regulation of proinflammatory cytokines.

Publication Types:

- Review
- Review, Tutorial

PMID: 14625346 [PubMed - indexed for MEDLINE]



2: Semin Liver Dis. 2003 Aug;23(3):217-26.

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Thieme connect

Acute liver failure in the United States.

Lee WM.

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In the last 5 years the use of a multicenter approach has helped to define acute liver failure (ALF) in the United States. Drug-related hepatotoxicity comprises more than 50% of cases of ALF, including acetaminophen toxicity (40%) and idiosyncratic drugs (approximately 12%). Nearly 20% of cases remain of unknown etiology. Outcome of ALF is determined by etiology; by the degree of hepatic encephalopathy present on admission; and by complications, principally infection. More than 43% survive without a transplant, 28% die, and 29% undergo liver transplantation. Liver support machines have had no impact on this condition to date. A trial of N-acetylcysteine for the treatment of ALF not related to acetaminophen toxicity is underway. Future research in ALF in the United States should focus on limiting the number of cases related to drugs, searching for causes of the indeterminate cases, and developing more effective temporary liver support.

Publication Types:

- Review
- Review, Multicase

PMID: 14523675 [PubMed - indexed for MEDLINE]

3: Pharmacotherapy. 2003 Aug;23(8):1052-9.

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

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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.

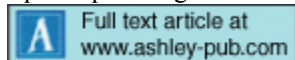
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PMID: 12921251 [PubMed - indexed for MEDLINE]

4: Expert Opin Drug Saf. 2002 Jul;1(2):159-72.

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The rational use of potentially hepatotoxic medications in patients with underlying liver disease.

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Given the fact that as many as 9% of all adverse drug reactions involve toxic effects on the liver and with upwards of 50% of all cases of fulminant hepatic failure being ascribed to acetaminophen and other agents, the safe use of medications takes on an even greater importance whenever the prescription of potentially hepatotoxic drugs to patients with underlying liver disease is considered. In general, it is thought that most drugs can be safely administered in the setting of liver disease without an increased risk of hepatotoxicity, although the evidence on which this statement is based often relies more on clinical judgement than on clinical studies. Several drugs appear to have an increased risk of hepatotoxicity in patients with underlying liver disease based on either clinical reports or extrapolated pharmacological data. These agents, including methotrexate, niacin and the antiretroviral and antituberculosis drugs, carry warnings about their use in patients with a variety of liver conditions. The data supporting the hepatotoxic risk of scores of additional drugs, such as the 3-Hydroxy-3-

methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins"), the newer thiazolidinediones (rosiglitazone, pioglitazone), and tamoxifen, among others, in patients with liver disease are generally lacking by evidence-based studies. However, clinical and biochemical monitoring is routinely recommended or required, often to make up for the lack of information on the true risk of clinically significant liver toxicity of these agents in individuals both with and without underlying liver disease. This article will review what is and what is not known about prescribing in the setting of acute and chronic liver disease and offers recommendations to help promote the safe and rational use of potentially hepatotoxic medications in these patients.

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5: Chest. 2003 Mar;123(3):897-922.

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Adult toxicology in critical care: Part II: specific poisonings.

Mokhlesi B, Leikin JB, Murray P, Corbridge TC.

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6: J Emerg Med. 2002 Oct;23(3):253-6.

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Chronic acetaminophen toxicity: a case report and review of the literature.

Lane JE, Belson MG, Brown DK, Scheetz A.

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Acetaminophen is one of the most frequently used medications in the United States. While usual dosing of acetaminophen is considered harmless, both acute and chronic overdoses can be fatal. The majority of reported cases of chronic acetaminophen toxicity in adults occur in chronic alcohol abusers, patients taking P450-inducing medications, or following massive dosing. We describe a case of toxic hepatitis free of the aforementioned risk factors associated with chronic ingestion of moderately excessive doses of acetaminophen. Our patient ingested approximately 5.0 to 6.5 g of acetaminophen daily for 6 to 8 weeks via multiple medications. The inclusion of acetaminophen in numerous medications combined with the frequency of use of acetaminophen necessitates an increased concern for not only acute but also chronic acetaminophen toxicity. Copyright 2002 Elsevier Science Inc.

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7: QJM. 2002 Sep;95(9):609-19.

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Paracetamol toxicity: epidemiology, prevention and costs to the health-care system.

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Paracetamol has been used as an analgesic and antipyretic for many years, with toxicity first noted in the 1960s. Since then the incidence of poisoning has increased, and paracetamol is now the most common drug in self-poisoning, with a high rate of morbidity and mortality. The use, abuse and ways of reducing paracetamol toxicity are reviewed, but in view of the potential for harm, serious consideration should be given to changing the legal status of paracetamol, possibly to a prescription-only medicine.

Publication Types:

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8: Am J Respir Crit Care Med. 2002 Jul 1;166(1):9-15.

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Update in clinical toxicology.

Chu J, Wang RY, Hill NS.

Division of Pulmonary, Critical Care, and Sleep Medicine, Tufts-New England Medical Center, Boston, Massachusetts 02111, USA.

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9: Br J Clin Pharmacol. 2001;52 Suppl 1:97S-102S.

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Therapeutic drug monitoring in drug overdose.

Dawson AH, Whyte IM.

Department of Clinical Toxicology and Pharmacology, Newcastle Mater Hospital, Hunter Regional Mail Centre, NSW 2310, Australia. mdahd@cc.newcastle.edu.au

The treatment of poisoned patients is still largely defined by history, clinical assessment and interpretation of ancillary investigations. Measurement of drug concentrations is clinically important for relatively few compounds. Most measurements form an adjunct to and should not be considered a substitute for clinical assessment. Drug concentrations are particularly important for those compounds where the concentration is predictive of serious toxicity in an otherwise asymptomatic patient.

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PMID: 11564057 [PubMed - indexed for MEDLINE]

□ **10:** Drug Saf. 2001;24(7):503-12.

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Management of paracetamol overdose: current controversies.

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Paracetamol (acetaminophen) is one of the most frequently used analgesics, and is the most commonly used substance in self-poisoning in the US and UK. Paracetamol toxicity is manifested primarily in the liver. Treatment with N-acetyl-cysteine (NAC), if started within 10 hours from ingestion, can prevent hepatic damage in most cases. Pharmacokinetic data relating plasma paracetamol concentration to time after ingestion have been used to generate a 'probable hepatotoxicity line' to predict which cases of paracetamol overdose will result in hepatotoxicity and should be treated with NAC. However, later studies use a 25% lower line as their 'possible hepatotoxicity line'. Although adopting the original line may save considerable resources, further studies are needed to determine whether such an approach is safe. On the basis of the metabolism of paracetamol, several risk factors for paracetamol toxicity have been proposed. These risk factors include long term alcohol (ethanol) ingestion, fasting and treatment with drugs that induce the cytochrome P450 2E1 enzyme system. Although some studies have suggested that these risk factors may be associated with worse prognosis, the data are inconclusive. However, until further evidence is available, we suggest that the lower line should be used when risk factors are present. In Canada and the UK, the intravenous regimen for NAC is used almost exclusively; in the US, an oral regimen is used. Both regimens have been shown to be effective. There is no large scale study with direct comparison between these 2 therapeutic protocols and controversy still exists as to which regimen is superior. During the last few years there has been an increase in the number of reports of liver failure associated with prolonged paracetamol administration for therapeutic reasons. The true incidence of this phenomenon is not known. We suggest testing liver enzyme levels if a child has received more than 75 mg/kg/day of paracetamol for more than 24 hours during febrile illness, and to treat with NAC when transaminase levels are elevated. Paracetamol overdose during pregnancy should be treated with either oral or intravenous NAC according to the regular protocols in order to prevent maternal, and potentially fetal, toxicity. Unless severe maternal toxicity develops, paracetamol overdose does not appear to increase the risk for adverse pregnancy outcome.

Publication Types:

- Review
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PMID: 11444723 [PubMed - indexed for MEDLINE]

□ **11:** Arch Dis Child Fetal Neonatal Ed. 2001 Jul;85(1):F70-2.

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Paracetamol overdose in a preterm neonate.**Isbister GK, Bucens IK, Whyte IM.**Royal Darwin Hospital, Northern Territory, Australia. gsbite@bigpond.com

The first oral overdose of paracetamol in a neonate is reported. A 55 day old neonate, born 29 weeks premature, was accidentally given 136 mg/kg paracetamol. Treatment was with activated charcoal, supportive care, and N-acetylcysteine. There was no biochemical evidence of hepatotoxicity, and no long term sequelae. After modelling of the data, the following pharmacokinetic variables were calculated: absorption half life (t_{abs}), 0.51 hours; volume of distribution ($V/F(oral)$), 0.80 litres/kg; clearance ($CL/F(oral)$), 0.22 litres/h; they were consistent with population pharmacokinetic studies. The increased plasma half life (T_{beta}) of 5.69 hours thus reflected normal slower metabolism in infants, rather than toxicity. The toxicity of paracetamol in neonates is unclear, but appears to be low because of slow oxidative metabolism and rapid glutathione synthesis. In an overdose, estimates of toxicity can be made from dose and T_{beta} in neonates, or from maternal toxicity in transplacental poisoning. Treatment includes N-acetylcysteine and supportive care, with activated charcoal for oral poisoning.

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PMID: 11420329 [PubMed - indexed for MEDLINE]

**12:** Crit Rev Toxicol. 2001 Jan;31(1):55-138.[Related Articles.](#) [Links](#)**Paracetamol (acetaminophen)-induced toxicity: molecular and biochemical mechanisms, analogues and protective approaches.****Bessem JG, Vermeulen NP.**

Leiden/Amsterdam Center for Drug Research, Department of Pharmacochimistry, Vrije Universiteit, Amsterdam, The Netherlands.

An overview is presented on the molecular aspects of toxicity due to paracetamol (acetaminophen) and structural analogues. The emphasis is on four main topics, that is, bioactivation, detoxication, chemoprevention, and chemoprotection. In addition, some pharmacological and clinical aspects are discussed briefly. A general introduction is presented on the biokinetics, biotransformation, and structural modification of paracetamol. Phase II biotransformation in relation to marked species differences and interorgan transport of metabolites are described in detail, as are bioactivation by cytochrome P450 and peroxidases, two important phase I enzyme families. Hepatotoxicity is described in depth, as it is the most frequent clinical observation after paracetamol-intoxication. In this context, covalent protein binding and oxidative stress are two important initial (Stage I) events highlighted. In addition, the more recently reported nuclear effects are discussed as well as secondary events (Stage II) that spread over the whole liver and may be relevant targets for clinical treatment. The second most frequent clinical observation, renal toxicity, is described with respect to the involvement of prostaglandin synthase, N-deacetylase, cytochrome P450 and glutathione S-transferase. Lastly, mechanism-based developments of chemoprotective agents and progress in the development of structural analogues with an improved therapeutic index are outlined.

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13: J Clin Pharm Ther. 2000 Oct;25(5):325-32.

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Update: the clinical importance of acetaminophen hepatotoxicity in non-alcoholic and alcoholic subjects.

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Acetaminophen (paracetamol) is one of the most commonly used over-the-counter medications. Taken in doses greater than 150 mg/kg/day (>10 g), it usually causes acute liver failure. The authors review mainly the management of acetaminophen toxicity in both users and nonusers of alcohol. Chronic alcoholics are a special subgroup, who risk serious toxicity when taking acetaminophen, even in therapeutic doses. The acetaminophen-alcohol interaction is complex, because acute and chronic ethanol have opposite effects. This review also considers physiological and clinical changes, as well as the diagnosis and treatment of acetaminophen poisoning.

Publication Types:

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- Review, Tutorial

PMID: 11123483 [PubMed - indexed for MEDLINE]

14: Geriatrics. 2000 Nov;55(11):44, 49-50, 53 passim.

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Prescribing analgesics. How to improve function and avoid toxicity when treating chronic pain.

Feinberg SD.

Department of Anesthesia, Stanford University Medical Center, USA.

Analgesic drugs are used more often than nondrug therapies for the treatment of pain in older patients. Despite the risk of adverse reactions, analgesics can be used safely for chronic pain in older patients when physicians prescribe with care. Nonopoid analgesics include acetaminophen, aspirin, NSAIDs, and COX-2 inhibitors. Opioid analgesics may be useful, but they should be continued only if side effects can be controlled and the patient demonstrates improved function. Adjuvant medications include antidepressants, anticonvulsants, neuroleptics, and oral membrane stabilizers. Benzodiazepines may be harmful in older patients, and muscle relaxants tend to be overused. Topical agents may be useful for certain neuropathic pain conditions.

Publication Types:

- Review
- Review, Tutorial

PMID: 11086472 [PubMed - indexed for MEDLINE]

15: Indian J Pediatr. 1998 May-Jun;65(3):393-400.

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Paracetamol poisoning in children.

Lall SB, Paul R.

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.

Paracetamol (acetaminophen) has become an antipyretic drug of choice. Due to its widespread use, toxicity secondary to overdose has increased in recent years. Children are especially vulnerable to accidental exposure due to non availability of child proof containers in India. The main clinical features of acute toxicity include anorexia, vomiting, abdominal pain, jaundice, hematuria and metabolic acidoses. Diagnosis is based on history and laboratory findings of acidosis and abnormal liver function tests. N-acetylcysteine is the specific antidote. This article reviews in detail the toxicokinetics, pathophysiology, clinical features and management of paracetamol poisoning in children.

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- Review
- Review, Tutorial

PMID: 10771990 [PubMed - indexed for MEDLINE]

16: Br J Clin Pharmacol. 1999 Sep;48(3):278-83.

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Therapeutic drug monitoring in drug overdose.

Dawson AH, Whyte IM.

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The treatment of poisoned patients is still largely defined by history, clinical assessment and interpretation of ancillary investigations. Measurement of drug concentrations is clinically important for relatively few compounds. Most measurements form an adjunct to and should not be considered a substitute for clinical assessment. Drug concentrations are particularly important for those compounds where the concentration is predictive of serious toxicity in an otherwise asymptomatic patient.

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PMID: 10510137 [PubMed - indexed for MEDLINE]

17: Medicine (Baltimore). 1997 May;76(3):185-91.

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Enhanced hepatotoxicity of acetaminophen in the alcoholic patient. Two case reports and a review of the literature.

Johnston SC, Pelletier LL Jr.

Department of Internal Medicine, University of Kansas School of Medicine-Wichita 67214-3199, USA.

We report 2 fatal cases of the acetaminophen-alcohol syndrome and review 51 reported cases in the medical literature. The MEDLINE database from January 1966 to December 1995 and bibliographies of selected articles were used to obtain the case reports. Inclusion criteria were a clear history of alcohol use, a history of acetaminophen use and/or an elevated serum acetaminophen level, peak aspartate aminotransferase (AST) greater than 800 U/L, and exclusion of other causes of hepatotoxicity by negative hepatitis serologies and/or a liver biopsy showing typical findings of acetaminophen toxicity. Demographic characteristics, clinical features, treatment, and outcome were extracted from reports meeting inclusion criteria and our own 2 cases. This syndrome affected relatively young, frequently healthy patients. Acetaminophen was invariably taken for nonsuicidal intent. The mortality rate was 32%. A typical laboratory picture was defined, characterized by an extraordinarily high AST level. Treatment with N-acetylcysteine was not effective due to delayed presentation and diagnosis. Patients who use alcohol and health care providers should be educated about this potentially fatal syndrome. Prevention is the key to reducing its occurrence.

Publication Types:

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PMID: 9193453 [PubMed - indexed for MEDLINE]

❑ **18:** Am Fam Physician. 1996 Jan;53(1):185-90.

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Management of acetaminophen toxicity.

Larsen LC, Fuller SH.

East Carolina University School of Medicine, Greenville, North Carolina, USA.

Acetaminophen poisoning is a significant medical problem in the United States and is frequently managed by family physicians. The primary clinical effect of acetaminophen poisoning is hepatotoxicity that occurs after ingestion of large single doses of acetaminophen or after ingestion of smaller doses in patients with hepatic metabolism that is altered by drugs or concurrent medical conditions. Hepatocellular damage is probably caused by accumulation of the toxic intermediate metabolite N-acetyl-p-benzoquinoneimine when hepatic glutathione stores are depleted. Treatment of acetaminophen poisoning consists of preventing gastrointestinal absorption of the drug, use of the antidote N-acetylcysteine and supportive care.

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❑ **19:** Pharmacol Ther. 1993 Oct;60(1):91-120.

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Paracetamol (acetaminophen) poisoning.

Thomas SH.

Wolfson Department of Clinical Pharmacology, University of Newcastle upon Tyne, U.K.

Paracetamol poisoning caused by intentional overdose remains a common cause of morbidity. In this article the mechanism of toxicity and the clinical effects and treatment of poisoning, including specific antidotal therapy, are reviewed. Areas for further research directed at reducing morbidity and mortality from paracetamol poisoning are considered.

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- Review
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