

# Therapeutic Review

## Treatment of acetaminophen poisoning

EDWARD M. SELLERS, MD, PH D, FRCP[C], FACP  
FRED FREEDMAN, MD

Acetaminophen is an analgesic that is frequently used in Canada, and the occurrence of overdoses with this drug seems to be increasing. The most serious complication of acetaminophen overdose is hepatic failure. Because pathophysiologic effects of acetaminophen poisoning and the mechanisms of its toxic effects are now better understood, a rational approach to treatment is possible. Several precursors of glutathione, acetylcysteine in particular, are effective in preventing liver damage if administered within 10 hours of acetaminophen ingestion. Plasma acetaminophen levels are a helpful guide to therapy.

L'acétaminophène est un analgésique d'usage fréquent au Canada, et le nombre de surdosages à ce médicament semble être en augmentation. L'insuffisance hépatique représente la complication la plus sérieuse du surdosage à l'acétaminophène. Comme les effets pathophysiologiques de l'empoisonnement à l'acétaminophène et les mécanismes responsables de ses effets toxiques sont maintenant mieux connus, une démarche de traitement rationnelle est possible. Plusieurs précurseurs du glutathion, l'acétylcystéine en particulier, sont efficaces pour prévenir les dommages hépatiques quand ils sont administrés moins de 10 heures après l'ingestion d'acétaminophène. Les taux plasmatiques d'acétaminophène orientent utilement le traitement.

The principles for the management of drug overdose are generally well recognized.<sup>1</sup> For most overdoses in adults medical management consists of good supportive care to restore or maintain adequate ventilation and circulation. With such care, deaths due to drug overdose should be rare as long as the patient reaches hospital before irreversible organ damage has occurred. In contrast to this, the management of some drug overdoses or poisonings involves administering specific drugs. In these cases the exact nature of the problem

must be recognized early and followed by the appropriate treatment to ensure an optimal outcome.<sup>1-5</sup>

Acetaminophen (Tylenol) is a commonly taken analgesic drug. In the United Kingdom overdoses of this drug alone or with other analgesics are relatively frequent.<sup>1,4,5</sup> The number of such overdoses seems to be increasing in Canada although precise figures are not available. A recent inquest highlighted the fact that little information on the management of this treatable overdose has been published in Canadian medical journals and that physicians therefore may not be sufficiently aware of the appropriate treatment problem (*Toronto Sun*, Dec. 21, 1978: 29).

There is a wide variation between individuals in susceptibility to the toxic effects of acetaminophen, but in an adult a seriously toxic state typically may result after the ingestion of about 20 to 30 tablets (325 mg each). The most serious complication of acute acetaminophen overdose is hepatic failure;<sup>1,6</sup> before effective treatment was available hepatic necrosis developed in approximately 20% of patients.<sup>1,6-8</sup>

The clinically deceptive aspect of acetaminophen poisoning is that patients present without neurologic effects from the drug and in apparent good health. However, 12 to 24 hours later the hepatic damage caused by the drug becomes apparent, and it may cause death within 3 to 5 days.<sup>1,3,7,8</sup>

The most important step in recognizing this problem is to obtain a detailed history or corroborating evidence, or both, of what and how much was taken. Contrary to common belief, patients actually have taken what they allege to have taken in at least 80% of cases.<sup>9</sup> No effort should be spared in obtaining information from friends, relatives, police, pharmacists and physicians to establish what drug has been taken.

### Pathophysiologic effects

Acetaminophen is rapidly absorbed from the stomach and upper gastrointestinal tract and then is metabolized in the liver by hydroxylation and conjugation.

From the clinical pharmacology program, the Clinical Institute, Addiction Research Foundation of Ontario, and the departments of pharmacology and medicine, University of Toronto

Reprint requests to: Dr. Edward M. Sellers, Addiction Research Foundation of Ontario, 33 Russell St., Toronto, Ont. M5S 2S1

Only 4% is excreted unchanged in the urine.<sup>1</sup> In normal therapeutic doses approximately 7% is excreted as the product of hydroxylation, a step involving the creation of a toxic metabolite. This metabolite is normally conjugated with glutathione. However, in the presence of increased levels of acetaminophen in the plasma the glutathione in the liver is depleted, allowing the level of the hydroxylation metabolite to increase.<sup>10</sup> This compound binds irreversibly to macromolecules in hepatic cells, causing centrilobular hepatic necrosis.<sup>11,12</sup> Patients who already have a liver disease and are taking enzyme-inducing drugs (such as ethanol or barbiturates) seem to be at increased risk of this necrosis.<sup>3</sup>

### Treatment

Various forms of therapy for acetaminophen overdose have been advocated, but until recently none had proved effective in preventing the hepatic necrosis.<sup>1</sup> After the biochemical mechanisms of the hepatotoxic effects of acetaminophen were established, the first specific, rational and successful treatment of severe acetaminophen poisoning was described by Prescott and associates<sup>14</sup> in 1974. Although it has not been possible to conduct controlled clinical trials of this treatment, other reports have confirmed its efficacy.<sup>13-15</sup>

The aim of the treatment is to decrease the amount of free toxic metabolite by increasing the level of hepatic glutathione. Glutathione itself does not penetrate hepatic cells and is ineffective therapeutically. However, its precursors, such as cysteamine, methionine and acetylcysteine have been shown to prevent or reduce acetaminophen-induced hepatic necrosis.<sup>12</sup> Although cysteamine hydrochloride and L-methionine

may cause unpleasant side effects, some clinicians, considering the dangers of acetaminophen overdose, view these effects as acceptable. Acetylcysteine (Mucomyst) seems to be the agent most readily available and is now the choice for preventing acetaminophen-induced hepatic necrosis. When it is taken orally in the recommended dosage no serious toxicity has been reported.<sup>3</sup> To be effective, therapy with acetylcysteine must be started within 10 hours of the ingestion of acetaminophen. After 10 to 12 hours it is of no proven value, and there is the theoretical possibility of hepatotoxic effects from the antidote itself if the patient has liver damage from the acetaminophen. When acetylcysteine is being administered the patient *should not be given charcoal or a cathartic orally*, as this will interfere with absorption of the antidote.

An important aspect of treating acetaminophen intoxication is knowing when to begin treatment. It is essential for clinicians to be aware of the potential dangers of this overdose and to make an early and accurate assessment of the situation. Except for mild nausea and vomiting and some mild abdominal discomfort, these patients are usually asymptomatic, and the appearance of clinical signs or symptoms of hepatotoxic effects may be delayed by up to 5 days, although biochemical changes can occur within 12 hours. The dosage associated with toxic effects is quite variable. In general, patients who have ingested 6 g or more should be considered at risk, although in typical cases serious hepatic damage is more likely in those who take 12 to 15 g. The patient's serum acetaminophen level is the best, albeit imperfect, guide to therapy. Although the half-life of acetaminophen in the plasma has been shown to be the best method of predicting hepatic failure,<sup>16</sup> the difficulties related to obtaining multiple blood samples and other practical considerations can make this method of limited value.

The first measure of the concentration of acetaminophen in the plasma can provide both a guide to treat-

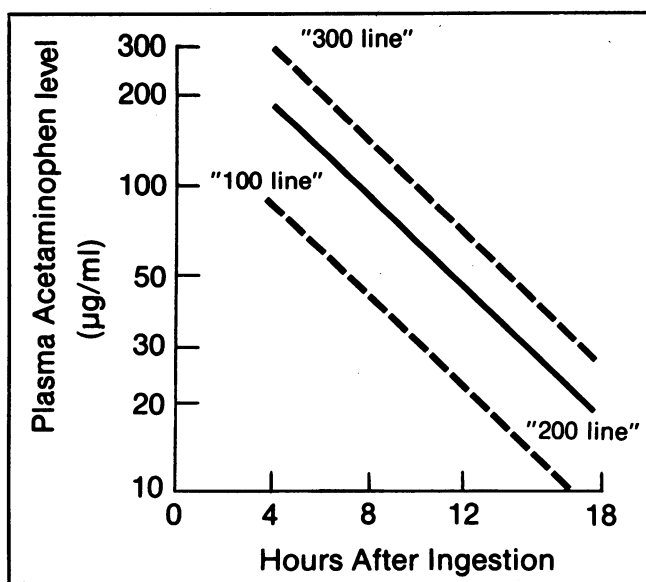


FIG. 1—Plasma acetaminophen levels related to time elapsed since ingestion of overdose, as a guide to treatment and an indication of prognosis.<sup>3</sup> A level of 300 µg/ml 4 hours after ingestion is represented by the "300 line", 200 µg/ml by the "200 line" and 100 µg/ml by the "100 line".

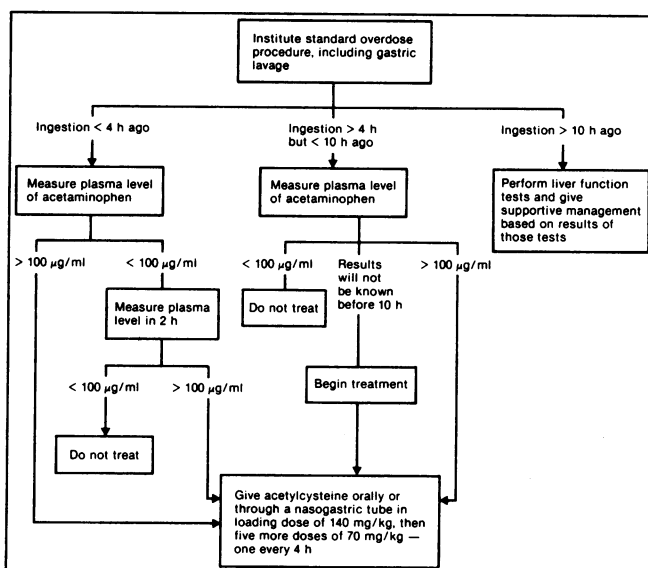


FIG. 2—Flow chart for management of an acetaminophen overdose.

ment and an indication of prognosis. Fig. 1 shows a semilogarithmic graph relating levels of acetaminophen in the plasma to time since ingestion. In patients with a plasma concentration below 100 µg/ml 4 hours after ingestion (below the "100 line") the risk of serious hepatic damage is negligible. For those with a plasma concentration above 200 µg/ml the risk is approximately 20%.<sup>1,3</sup> Virtually all patients with plasma concentrations greater than 300 µg/ml (above the "300 line") can be expected to suffer serious liver damage. All patients whose plasma levels of acetaminophen are above 100 µg/ml should be given acetylcysteine orally or through a nasogastric tube in an initial dose of 140 mg per kg of body weight, followed by five doses of 70 mg/kg at 4-hour intervals (Fig. 2). The drug should be diluted in juice or a flavoured beverage, such as ginger ale, if given orally. In rare cases acetylcysteine may have to be given intravenously. Although no intravenous formulation has been approved, in an emergency situation a sterile (not pyrogen-tested) 20% aqueous solution of acetylcysteine could be used. An initial dose of 150 mg/kg diluted in 200 ml of dextrose could be given intravenously over 15 minutes, followed by 50 mg/kg in 500 ml of 5% dextrose over the next 4 hours and a further 100 mg/kg in 1 litre of 5% dextrose over the next 16 hours (total dose 300 mg/kg in 20 hours).<sup>1,3</sup> Nasogastric, rather than intravenous, administration is preferred by far.

We thank Dr. Usanda Busto for her editorial assistance.

## References

- MATTHEW H, LAWSON AAH: *Treatment of Common Acute Poisonings*, 4th ed, Churchill, Edinburgh, 1979: 82-93
- BURKS JS, WALKER JE, RUMACK BH, OTT JE: Tricyclic antidepressant poisoning. Reversal of coma, choreoathetosis, and myoclonus by physostigmine. *JAMA* 1974; 230: 1405-1407
- PRESCOTT LF: Prevention of hepatic necrosis following paracetamol overdose. *Health Bull (Edinb)* 1978; 36: 204-212
- KOCH-WESER J: Acetaminophen. *N Engl J Med* 1976; 295: 1297-1300
- PROUDFOOT AT, PARK J: Changing patterns of drugs used for self-poisoning. *Br Med J* 1978; 1: 90-93
- MACLEAN D, PETERS TJ, BROWN RAG, MCCATHIE M, BAINES GF, ROBERTSON PGC: Treatment of acute paracetamol poisoning. *Lancet* 1968; 2: 849-852
- LESNA M, WATSON AJ, DOUGLAS AP, HAMLYN AN, JAMES O: Toxicity of paracetamol (C). *Lancet* 1976; 1: 191
- DIXON MF: Paracetamol hepatotoxicity (C). *Ibid*: 35
- GOULDING R, VOLANS GN, CROME P, WIDDOP B, WILLIAMS R: Paracetamol hepatotoxicity (C). *Ibid*: 358
- MITCHELL JR, JOLLOW DJ, POTTER WZ, GILLETTE JR, BRODIE BB: Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione. *J Pharmacol Exp Ther* 1973; 187: 211-217
- SELLERS EM, MARSHMAN JA, KAPLAN HL: Acute and chronic drug abuse emergencies in Metropolitan Toronto. *Int J Addict* (in press)
- MITCHELL JR, JOLLOW DJ, POTTER WZ, DAVIS DC, GILLETTE JR, BRODIE BB: Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. *J Pharmacol Exp Ther* 1973; 187: 185-194
- MITCHELL JR, THORGEIRSSON SS, POTTER WZ, JOLLOW DJ, KEISER H: Acetaminophen-induced hepatic injury: protective role of glutathione in man for rational therapy. *Clin Pharmacol Ther* 1974; 16: 676-690
- PRESCOTT LF, NEWTON RW, SWAINSON CP, WRIGHT N, FORREST ARW, MATTHEW H: Successful treatment of severe paracetamol overdose with cysteamine. *Lancet* 1974; 1: 588-592
- HUGHES RD, GAZZARD BG, HAMID MA, TREWBY PN, MURRAY-LYON IM, DAVIS M, WILLIAMS R, BENNETT JR: Controlled trial of cysteamine and dimercaprol after paracetamol overdose. *Br Med J* 1977; 2: 1395
- SMITH JM, ROBERTS WO, HALL SM, WHITE TA, GILBERTSON AA: Late treatment of paracetamol poisoning with mercaptamine. *Br Med J* 1978; 1: 331-333

# Lectopam<sup>®</sup> (bromazepam)

## Rx Summary

### Indications

Useful for short-term, symptomatic relief of manifestations of excessive anxiety in patients with anxiety neurosis.

### Contraindications

Patients with known hypersensitivity to benzodiazepines or with myasthenia gravis.

### Warnings

Not recommended for patients with depressive disorders or psychosis. Advise patients against concurrent use of alcohol and other CNS depressants.

**Pediatric Use:** Because of lack of sufficient clinical experience, not recommended for patients younger than 18 years.

**Driving & Hazardous Activities:** In view of CNS depressant effect, warn patients against driving, operating dangerous machinery, or engaging in other hazardous activities requiring mental alertness and physical coordination. Caution patients on possible potentiation of effects of alcohol on such activities.

**Use in Pregnancy:** Since safety in pregnancy has not been established, should not be used during pregnancy. Because of risk of congenital malformations associated with minor tranquilizer use during first trimester, if prescribed for women of child-bearing potential, warn patients to consult physician regarding discontinuation if they intend to become or suspect they are pregnant.

**Use by Nursing Mothers:** Since 'Lectopam' and its metabolites are probably secreted in milk, should not be given to nursing mothers.

### Precautions

**Use in Elderly:** The elderly, debilitated, or those with organic brain syndrome are prone to CNS depression with benzodiazepines. Initiate medication with very low doses (3 mg/day 'Lectopam' or less) and increment gradually to avoid over-sedation or neurological impairment.

**Dependence Liability:** Should not be administered to individuals prone to drug abuse; caution in patients with potential for psychological dependence. Since withdrawal symptoms, similar both to those occurring with other benzodiazepines and alcohol and to the symptoms for which the patient is being treated, have been observed after abrupt discontinuation of 'Lectopam', withdraw gradually if used in prolonged high doses or if the individual is suspected of being dependent.

**Mental and Emotional Disorders:** Any suicidal tendency in patients with emotional disorders should be recognized, and treated promptly and appropriately. 'Lectopam' should not be used in ambulatory psychotic patients because of possible paradoxical reactions.

Benzodiazepines should not be used for physiological anxiety or normal daily stresses, but only for pathological anxiety with disabling manifestations. They are not effective in characterological, personality or obsessive-compulsive disorders.

Not recommended for depressive or psychotic disorders.

**Patients with Impaired Hepatic or Renal Function:** Initiate therapy at very low dose and increase dosage appropriately to residual organ function. Monitor patient closely, with periodic laboratory assessments.

**Laboratory Tests:** If administered for repeated cycles of therapy, periodic blood counts and liver function tests are advisable.

**Drug Interactions:** May produce additive or synergistic effects in combination with other CNS drugs. Caution patients against concomitant use of other CNS depressants and alcohol.

### Adverse Reactions

Most frequent are drowsiness, ataxia and dizziness. Paradoxical effects, e.g. release of hostility, irritability and excitability can occur with benzodiazepines. Less frequent side effects include visual disturbances, headache, seizures, slurred speech, mental confusion, elevated or depressed mood, nervousness, sleep disorders, lethargy, stupor, dry mouth, nausea, vomiting, non-specific gastrointestinal disturbances, muscle spasm or weakness, hypotension, tachycardia, pruritis, rash, incontinence, change in libido, decreased hematocrit, increased or decreased leukocyte count, elevated alkaline phosphatase, bilirubin, SGOT or SGPT and increased or decreased blood sugar.

### Symptoms and Treatment of Overdosage

**Symptoms:** Manifestations of CNS depression. Hypotension and respiratory depression may follow large overdoses.

**Treatment:** General supportive measures with monitoring of vital signs. Gastric lavage as soon as possible. Induced vomiting helpful if patient is fully awake. Value of dialysis not determined. The probability of multiple drug ingestion should be considered.

### Dosage and Administration

Individualize and titrate dosage to avoid excessive CNS depression. For symptomatic relief of excessive anxiety, short treatment course should usually be the rule. Initial treatment course should be no longer than one week without reassessment of need for limited extension. If necessary, adjust drug dosage after one week. Initially, not more than one week's supply of drug should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short course of therapy.

**Usual Adult Dosage:** Initially, 6 to 18 mg daily in equally divided doses, depending on severity of symptoms and response. Treatment should be initiated at lower doses and adjusted as necessary. Optimal dosage range 6 to 30 mg daily in divided doses. Up to 60 mg daily may be used in exceptional cases.

**Elderly and Debilitated:** Initial dose should not exceed 3 mg daily in divided doses. Adjust dosage carefully, depending on tolerance and response.

### SUPPLY

Pink, cylindrical biplane scored tablet, edges bevelled:

**LECTOPAM**  
3 engraved on one side; other side scored, with ROCHE above and C below  
the score: each containing 3 mg bromazepam.

Green, cylindrical biplane scored tablet, edges bevelled:

**LECTOPAM**  
6 engraved on one side; other side scored, with ROCHE above and C below  
the score: each containing 6 mg bromazepam.

Bottles of 100.

Product monograph available on request.

\*Reg. Trade Mark

\*Lectopam is trademarked under other names in various countries



Hoffmann-La Roche Limited  
Vaudreuil, Québec J7V 6B3

