Acetaminophen: a practical pharmacologic overview

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Acetaminophen is an effective analgesic and antipyretic agent with few adverse effects when used in recommended dosages. The drug is metabolized mainly in the liver, and the several end products have no harmful effects. An intermediate compound in a minor metabolic pathway, however, is toxic; it is normally inactivated by glutathione. In the case of an acetaminophen overdose the hepatic stores of glutathione seem to become depleted, leaving the toxic intermediate free to damage liver tissue. Such damage is unlikely to occur unless the plasma concentration of acetaminophen peaks above 150 μg/mL — a level far in excess of the 5 to 20 μg/mL achieved with therapeutic doses of the drug. Long-term therapeutic use of acetaminophen does not appear to be associated with liver damage, although some case reports suggest the possibility. Acetaminophen poisoning follows an acute overdose and, if untreated, is manifested clinically by an initial phase of nonspecific signs and symptoms, a latent period in which the liver transaminase levels rise and then, 3 to 5 days after the ingestion, signs of more serious hepatic dysfunction. Most patients do not progress beyond the first or second phase. They and those who survive the third phase recover with no residual injury to the liver. Appropriate antidotal therapy markedly reduces the severity of the initial damage.

L'acétaminophène est un bon analgésique et antipyrétique. Aux doses recommandées il a peu d'effets indésirables. Il est métabolisé principalement par le foie, et les produits de la voie catabolique sont inoffensifs. L'un des composés intermédiaires d'une voie secondaire est cependant toxique; il est normalement inactivé par le glutathion hépatique. Si la dose d'acétaminophène est excessive la réserve en glutathion peut être épuisée, d'où possibilité de lésions hépatocellulaires par ce métabolite. Celles-ci ne s'observent pas en l'absence d'un pic de la concentration plasmatique du médicament au-dessus de 150 μg/mL, alors que le pic réalisé par les doses thérapeutiques est de l'ordre de 5 à 20 μg/mL. L'emploi prolongé de l'acétaminophène ne semble pas causer de lésions hépatiques, bien qu'à propos de certaines observations on en ait suggéré la possibilité. L'intoxication par l'acétaminophène résulte d'une surdose aiguë. Cliniquement on observe une première phase où les symptômes n'ont rien de spécifique. Après une seconde phase de latence durant laquelle le taux sérique des transaminases hépatiques augmente on voit apparaître, de 3 à 5 jours après l'ingestion du médicament, les symptômes d'une perturbation grave de la fonction hépatique. Dans la plupart des cas les choses ne vont pas plus loin que les deux premières phases; ces malades, ainsi que ceux qui survivent à la troisième phase, conservent une fonction hépatique normale. L'emploi correct des antidotes abaisse la gravité des lésions initiales.

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Acetaminophen (*N*-acetyl-*p*-aminophenol; also known as paracetamol) was first described as an analgesic and antipyretic by Von Mering in 1893.[1] In the 1940s Brodie and Axelrod[2,3] confirmed its analgesic and antipyretic activity. They concluded that it was the therapeutically active metabolite of both acetanilide and phenacetin but that it did not share the propensity of these parent congeners to produce methemoglobinemia. Interest in its clinical use followed. Acetaminophen was introduced onto the Canadian market in the 1950s both as an antipyretic and as an analgesic for relief of mild to moderate pain.

Clinical pharmacology

The rate at which acetaminophen is absorbed is influenced by the rate of gastric emptying, with peak plasma levels usually being achieved within 30 to 90 minutes.[4] The usual therapeutic doses produce plasma concentrations of 5 to 20 μg/mL.[5,6] Acetaminophen is distributed throughout most body tissues, with an apparent volume of distribution of approximately 1 L/kg of body weight. A clinically insignificant proportion of the drug binds to plasma proteins.[6]

A single therapeutic dose of acetaminophen has a plasma half-life of 2 to 3 hours. Acetaminophen is metabolized primarily in the liver, the major pathway involving glucuronyl transferase and the minor one the cytochrome P-450 mixed function oxidase system (Fig. 1). In adults the proportions of metabolites

typically appearing in the urine are acetaminophen glucuronide (55%), acetaminophen sulfate (30%), unchanged acetaminophen (4%) and the cysteine and mercapturic acid conjugates of acetaminophen (4% each).[6] The last two are produced by the minor pathway, the cytochrome P-450 system, which is also postulated to form an intermediate, arylating compound, *N*-acetyl-*p*-benzoquinoneimine.[8] This metabolite is normally inactivated by immediate reaction with liver glutathione; the subsequently formed cysteine and mercapturic acid conjugates are excreted by the kidneys.[6] Other metabolites have been described, each accounting for 1% or less of a therapeutic dose.[6]

The specific mechanism of acetaminophen's action is still unknown. Recent reviews relate its analgesic and antipyretic effects to the inhibition of prostaglandin synthetase (a mechanism shared by acetylsalicylic acid [ASA] and related drugs).[9-11] Unlike other drugs in this therapeutic class, however, it does not have an anti-inflammatory effect at clinically relevant doses in humans, perhaps because it has different dose–response relations with the prostaglandins involved in fever, pain and the process of inflammation.[11,12] Animal studies have indicated that acetaminophen strongly inhibits prostaglandin synthetase in the brain (which may account for its antipyretic and analgesic effects) but that it has little effect on peripheral tissue prostaglandins (which are involved in inflammatory reactions).[12] This dose–response relation is observed clinically with ASA in that a higher dose is required for anti-inflammatory effects than for analgesia or antipyresis.[13,14]

Therapeutic use

Analysis of studies on the antipyretic activity of acetaminophen[15-17] supports the use of doses of 10 to 15 mg/kg of body weight given at 4- to 6-hour intervals but not exceeding 65 mg/kg in 24 hours.[18]

Although calculations based on body weight, or even body surface area, would be more accurate for individual children, the most convenient recommendations are based on age. The schedule in Table I includes that described for children aged 2 to 12 years by the health protection branch of the Department of National Health and Welfare[19] and approximates the 10- to 15-mg/kg doses suggested. The package labelling for acetaminophen products in Canada advises that in children under 2 years of age they should be used with the supervision of a physician.

Randomized, controlled, double-blind studies have substantiated the efficacy of acetaminophen in treating the mild to moderately intense pain associated with episiotomy,[20,21] osteoarthritis[22] and dentistry.[23,24] It is also an effective alternative when more potent analgesics are not indicated in chronic conditions such as headache or the less severe degrees

Table I—Recommended doses of acetaminophen

Patient's age*	Single dose (mg)†
< 4 mo	40
4–11 mo	80
12–23 mo	120
2–3 yr	160
4–5 yr	240
6–8 yr	320
9–10 yr	400
11–12 yr	480
> 12 yr (adult)	650–1000

*In children less than 2 years old acetaminophen should be used with the supervision of a physician.
†Doses may be repeated every 4 to 6 hours but should not exceed five in children and a total dose of 4000 mg in adults in 24 hours.

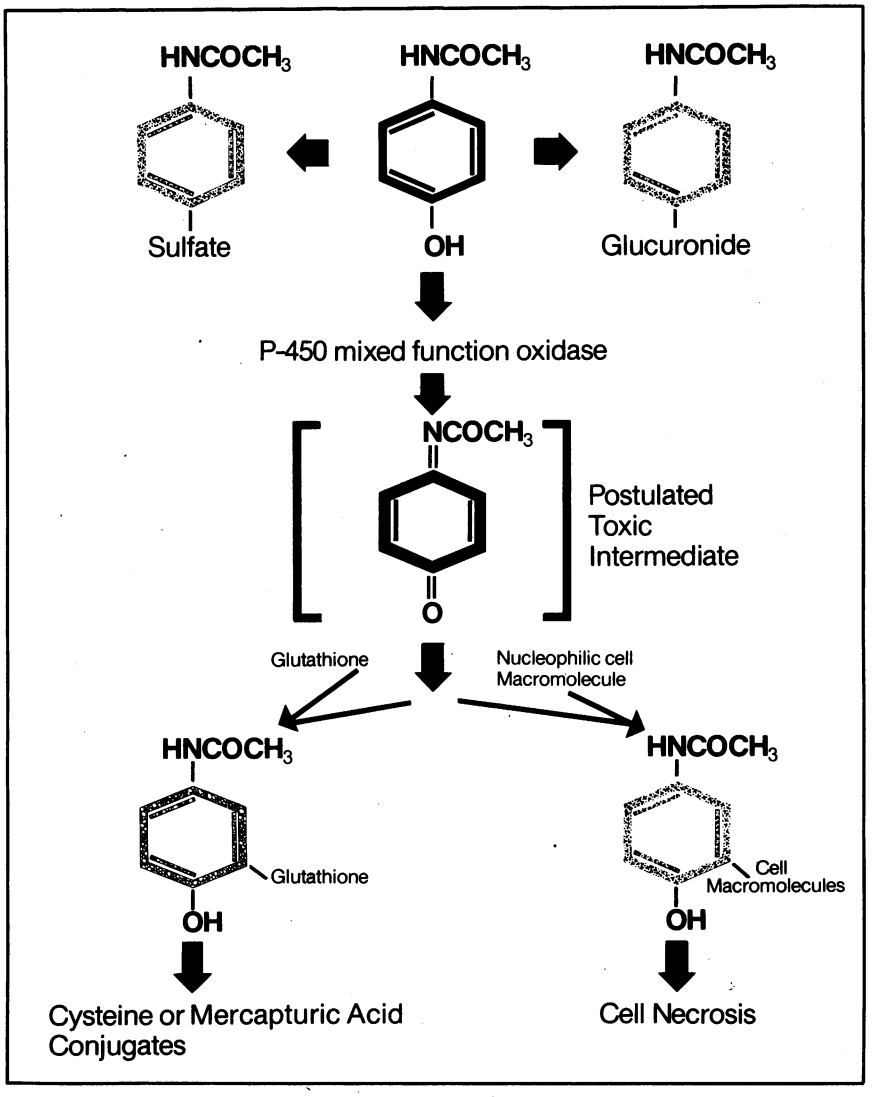

Fig. 1—Pathways of acetaminophen metabolism: glucuronidation and sulfation predominate. When hepatic stores of glutathione are depleted, toxic intermediate compound of minor pathway is free to combine with liver cell macromolecules, resulting in damage to liver. Adapted from reference 7 with permission.

of cancer pain.[25-28] On a milligram-for-milligram basis acetaminophen is considered equipotent in analgesic effect to ASA.[29] Most studies on acetaminophen in adults have involved a dose of 650 mg, but more recent experience indicates that a 1000-mg dose has greater therapeutic efficacy.[30-32]

The currently recommended dosage for adults is 650 to 1000 mg every 4 to 6 hours, not to exceed 4000 mg in 24 hours. The labelling of acetaminophen products intended for self-medication in Canada will soon caution the user to consult a physician if the underlying condition persists for more than 5 days. There is no contraindication to the more extended administration of acetaminophen at recommended doses, but supervision by a physician of the use of any analgesic for treatment of chronic conditions seems appropriate.

In a few recent studies the longer-term use of acetaminophen has been investigated. Patients with osteoarthritis[22] and a group with stable chronic liver disease[33] were given 4 g/d over several weeks with no major adverse effects and no alterations in the results of liver function tests. Specialists in the management of chronic pain have also described the lack of adverse effects in the long-term use of acetaminophen at dosages of 1.2 to 3.2 g/d, which often allowed them to reduce the dosage of more potent analgesics or to discontinue them altogether.[34]

Toxic effects

Serious adverse reactions to acetaminophen taken at recommended therapeutic doses are uncommon. Hypersensitivity rarely occurs, and in the few cases documented the reactions were controlled by withdrawing the drug and treating the symptoms.[35,36] A rare association with several reversible hematologic abnormalities has also been inferred from case reports.[37,38]

Hepatic

Much concern has been expressed about the possibility that liver damage may be associated with the use of acetaminophen. Fulminant hepatic failure induced by acetaminophen was reported first in the United Kingdom in 1966[39] and subsequently in North America.[40,41] However, liver damage clearly attributable to acetaminophen occurs only with a massive overdose of the drug.

Overdoses of acetaminophen have been associated with liver damage ranging from minor to severe and manifested by elevations of hepatic enzyme concentrations ranging from minimal to striking (serum glutamic oxaloacetic transaminase [SGOT] or pyruvic transaminase [SGPT] levels above 1000 U/L). Death resulting from complete liver failure has been estimated to occur in 2% to 4% of severely poisoned, untreated patients.[42-44] In the majority of patients, though, even during recovery from severe hepatic dysfunction, serial liver biopsies and liver function tests show prompt resolution of the damage, with no clinically significant residual functional or architectural alteration of the liver.[45] Hamlyn and coworkers[45] concluded that in the usual spectrum of acetaminophen poisoning requiring hospitalization there is no evidence of lasting liver damage.

A few anecdotal reports have suggested that long-term ingestion of acetaminophen for therapeutic purposes may cause either reversible toxic hepatitis or chronic active hepatitis.[46-49] In most of these cases either acetaminophen was used at doses higher than recommended or complications in the patient's history were not ruled out.[50,51] From the evidence available it is not possible to either implicate or exonerate acetaminophen as the sole causative factor. If there is an as yet unidentifiable patient group at risk for this type of reaction, the indications are that it must be very small.[52] In an attempt to detect an association between acetaminophen use and chronic active hepatitis Neuberger and colleagues[51] compared the clinical and biochemical patterns recorded for patients who had a history of acetaminophen use before the disease's onset with the patterns of patients who had had no previous exposure to acetaminophen. They found no causal association with acetaminophen. Furthermore, there were no differences in the results of liver function tests in the patients who continued to use acetaminophen periodically during the follow-up period.

The major pathological feature of liver damage due to acetaminophen is centrizonal necrosis. Much of the basic work on the mechanism involved has been provided by Mitchell and associates.[7] They demonstrated in animal models that liver cell injury resulted not from acetaminophen but from a toxic intermediate compound, the reactive arylating agent formed in the minor metabolic pathway of acetaminophen's oxidation. They further demonstrated the crucial role of glutathione. As increasing doses of radiolabelled acetaminophen were administered, the hepatic concentration of glutathione progressively decreased, and when it was depleted to 25% or 30% of normal there was increased binding of the toxic intermediate to the protein macromolecules of the liver.

From these observations the theory was developed that in a massive overdose, as the toxic intermediate is formed and the supply of liver glutathione becomes depleted, the toxic intermediate is freed to combine with liver cell protein macromolecules, resulting in cellular injury. The potential for acetaminophen to cause hepatic damage, therefore, depends theoretically on the following factors:

- The total quantity of acetaminophen ingested.
- The plasma levels of acetaminophen.
- The rate of elimination of acetaminophen.
- The relative activity of the metabolic pathways of glucuronidation, sulfation and the cytochrome P-450 system.
- The hepatic glutathione levels.

Unfortunately, if the quantity of acetaminophen ingested is not known, estimates are often inaccurate.[53-56] On the basis of results with animal models it has been calculated that a dose of 15 g is necessary to deplete the liver glutathione concentration in a 70-kg man by 70%.[56] In fact, the clinical experience reviewed by Prescott[44] indicates that there is no liver damage following the absorption of less than 125 mg/kg but that the incidence and severity of damage increase when more than 250 mg/kg is involved.

Plasma levels of the drug are the

preferred indicator of the potential hepatotoxic effects of acetaminophen. Peak levels above 300 μg/mL 4 hours after ingestion are consistently predictive of severe liver damage.[43,44] Rumack and collaborators[57] indicated that the risk of even mild toxic effects is minimal at peak levels below 150 μg/mL 4 hours after ingestion. These concentrations far exceed the peak therapeutic levels of 10 to 15 μg/mL seen after a single dose of 650 to 1000 mg.[5]

Studies of microsomal enzymes have shown that chemical stimulation can decrease and chemical inhibition increase the dose of acetaminophen required to induce hepatic damage in animals.[58] How relevant this is to human metabolism depends on the relative induction of the major and minor metabolic pathways.

There is no evidence that enzyme induction has a clinically significant effect on acetaminophen metabolism at recommended therapeutic doses,[59] but liver damage seen after an acute acetaminophen overdose may be more severe in patients with chronic alcoholism and in those who have previously taken drugs likely to cause liver enzyme induction.[60] Long-term alcohol ingestion has been reported to predispose patients to the hepatotoxic effects of acetaminophen taken for therapeutic purposes, but in most cases the acetaminophen had been taken for a long period, and the dosages had clearly been excessive.[61-63] A study of the effects of recognized enzyme inducers (e.g., anticonvulsants and rifampicin) on the drug's metabolism showed that after a 20-mg/kg dose of acetaminophen glucuronidation was clearly increased[59] but that the urinary excretion of the cysteine and mercapturic acid conjugates that are associated with the production of the toxic metabolite was not concurrently increased. Likewise, the observation that cimetidine inhibits drug oxidation via the cytochrome P-450 system without interfering with the glucuronidation and sulfation of acetaminophen has led to recent suggestions that this differential effect may be useful for preventing the production of the toxic metabolite in cases of acetaminophen overdose.[64,65] The clinical significance of these observations has yet to be determined, however, as Critchley and coworkers[66] reported that cimetidine had no effect on the metabolism of acetaminophen at a dose of 20 mg/kg in healthy volunteers.

Studies in animals have indicated that hepatic glutathione levels may be directly affected by nutritional status; thus, the risk of hepatic injury due to acetaminophen overdose may be increased in malnourished individuals.[44]

The risk of hepatic toxic effects has not been shown to be increased in patients with pre-existing liver disease during the short-term use of therapeutic doses of acetaminophen.[33,51,67,68] Forrest and associates[67] found that even if hepatic function was so reduced that the plasma half-life of acetaminophen was approximately doubled following a single dose of 1.5 g the conjugation of acetaminophen with glutathione did not appear to be compromised, as the proportions of the drug excreted as cysteine and mercapturic acid conjugates were normal. Andreasen and Hutters[68] gave 1 g three times daily for 3 to 5 days to patients with chronic liver disease and demonstrated that there was no accumulation of acetaminophen and no alteration of the drug's plasma half-life throughout the study. Benson[33] also assessed patients with stable chronic liver disease who were given 1 g of acetaminophen every 4 hours up to a total daily dose of 4 g for 2 weeks. Although the plasma half-life was increased by approximately 70%, there was no evidence of drug accumulation or decreased liver function.

Renal

Acute tubular necrosis occasionally occurs following a massive overdose of acetaminophen and is usually secondary to fulminant hepatic failure.[69] However, there are several reports of acute renal failure in the absence of hepatic toxic effects.[44,70,71] Mitchell and collaborators[72] have reported the dose-dependent occurrence of renal tubular damage in animal models as a result of the in-situ production of the toxic arylating compound in the oxidative metabolism of acetaminophen. While these observations cannot be applied directly to clinical situations, they provide a plausible explanation for the occasional development of acute renal failure after an overdose.

Chronic renal failure considered to be associated with the abuse of analgesic mixtures (analgesic nephropathy)[73] has not been shown to occur after long-term ingestion of acetaminophen alone.[74]

Overdose

In the overall consideration of overdose and potential toxic effects it is wise to bear in mind the words of Paracelsus (1493–1541): "All substances are poisons; there is none which is not. The right dose differentiates a poison and remedy."

Most of the acetaminophen poisonings documented have resulted from the deliberate ingestion of a large overdose.[42] A recent multicentre study by the Rocky Mountain Poison Center in Colorado, however, revealed that only one in seven patients presenting to emergency departments with an acetaminophen overdose actually had blood levels of the drug that were regarded as potentially toxic.[75] As with other substances, patients may be using acetaminophen in a pretence of attempted suicide and exaggerate the amount they claim to have ingested. The plasma level of acetaminophen should therefore be determined to assist with the management of the patient.

In theory, 15 g of acetaminophen must be absorbed by a 70-kg adult to reduce the liver glutathione stores by 70%. With allowances for differences in weight and for biologic variability, 7.5 g ingested and fully absorbed is generally considered the potentially toxic dose in adults.[75,76] Animal models and clinical experience suggest that children are less susceptible to hepatic damage than adults, but the minimum potentially toxic dose in children, as extrapolated from data for adults, is considered to be 150 mg/kg of body weight.[77,78] The lower toxic potential in children may be explained by observations that children are more likely to have severe and early vomiting after ingesting large quantities of acetaminophen and by the possibility that there are differences in the way acetaminophen is metabo-

lized by children.[42] An in-vitro experiment with fetal liver tissue has indicated that acetaminophen is oxidized to the reactive intermediate 10 times slower in the fetal liver tissue than in adult liver tissue.[77] Developmental differences in susceptibility to acetaminophen toxicity have been reported in rats and mice, but the mechanism was not defined, and the applicability of the results to humans is not known.[78]

Table II—Clinical course of an acetaminophen overdose

Phase and time	Symptoms and signs
I: initial 12–24 h	Gastrointestinal irritability, nausea, vomiting, anorexia, diaphoresis and pallor.
II: lasting up to 4 d	Patient feels well, but hepatic transaminase levels and bilirubin concentration in serum plus prothrombin time begin to rise. Right upper quadrant pain may develop.
III: beginning 3–5 d after ingestion	Anorexia, nausea, malaise and abdominal pain; progressive evidence of liver dysfunction, signs of liver failure, and possibly hepatic coma and renal failure. If death does not occur, normal liver function returns over a few weeks.

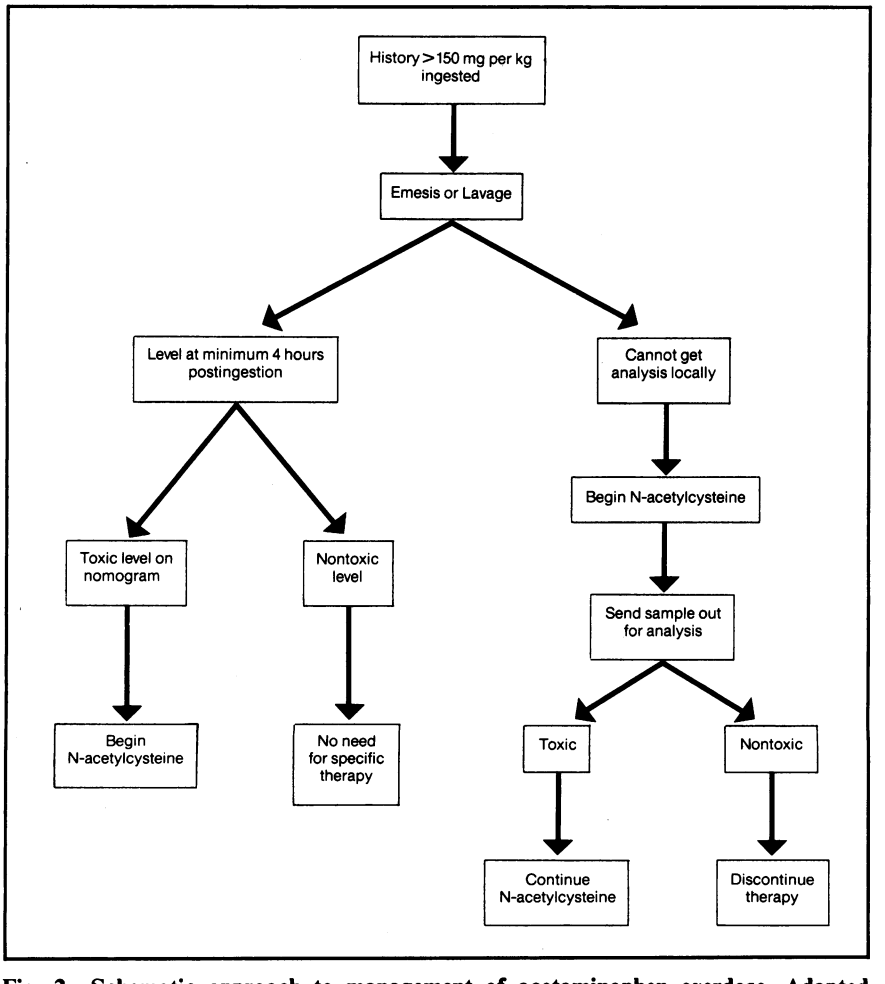

Fig. 2—Schematic approach to management of acetaminophen overdose. Adapted from reference 75 with permission of Aspen Systems Corporation.

Clinical course

The clinical course following an acute acetaminophen overdose can be conveniently divided into three phases (Table II).[76] The signs and symptoms show a consistent pattern, but those seen within the first few hours (phase I) are not diagnostic for poisoning with this drug. The more severe the overdose, though, the more likely it is that the symptoms will be present. In small children spontaneous vomiting is very frequent following a substantial overdose.

Most patients exhibit the initial symptoms and recover without additional problems. Others, particularly if no antidote is administered, may show evidence of liver damage after a latent period of 1 to 4 days. During this latent period (phase II) the initial symptoms abate, and the patient feels and looks better. However, measurement of the SGOT and SGPT concentrations may show a progressive rise, often to striking levels. Right upper quadrant tenderness may appear. Most patients who reach this phase do not progress further, and their liver function gradually returns to normal.

In the more serious cases evidence of greater hepatic dysfunction, characterized by rising serum bilirubin levels or prolongation of the prothrombin time, will follow (phase III). Death, when it occurs, results from hepatic failure. Generally, though, once the hepatic enzyme levels and prothrombin times have peaked, the patient recovers rapidly. Normal hepatic function returns within a few weeks. Follow-up of even severely poisoned patients who have survived has shown no residual liver damage, either clinically or histologically.[45,75]

Appropriate antidotal therapy changes the clinical course by preventing or reducing the severity of the initial liver injury.[44,75]

Antidotal therapy

The knowledge that the toxic oxidative metabolite of acetaminophen binds covalently to liver cell protein and an understanding of the normal mechanisms of detoxification have led to the development of effective antidotes that moderate or prevent

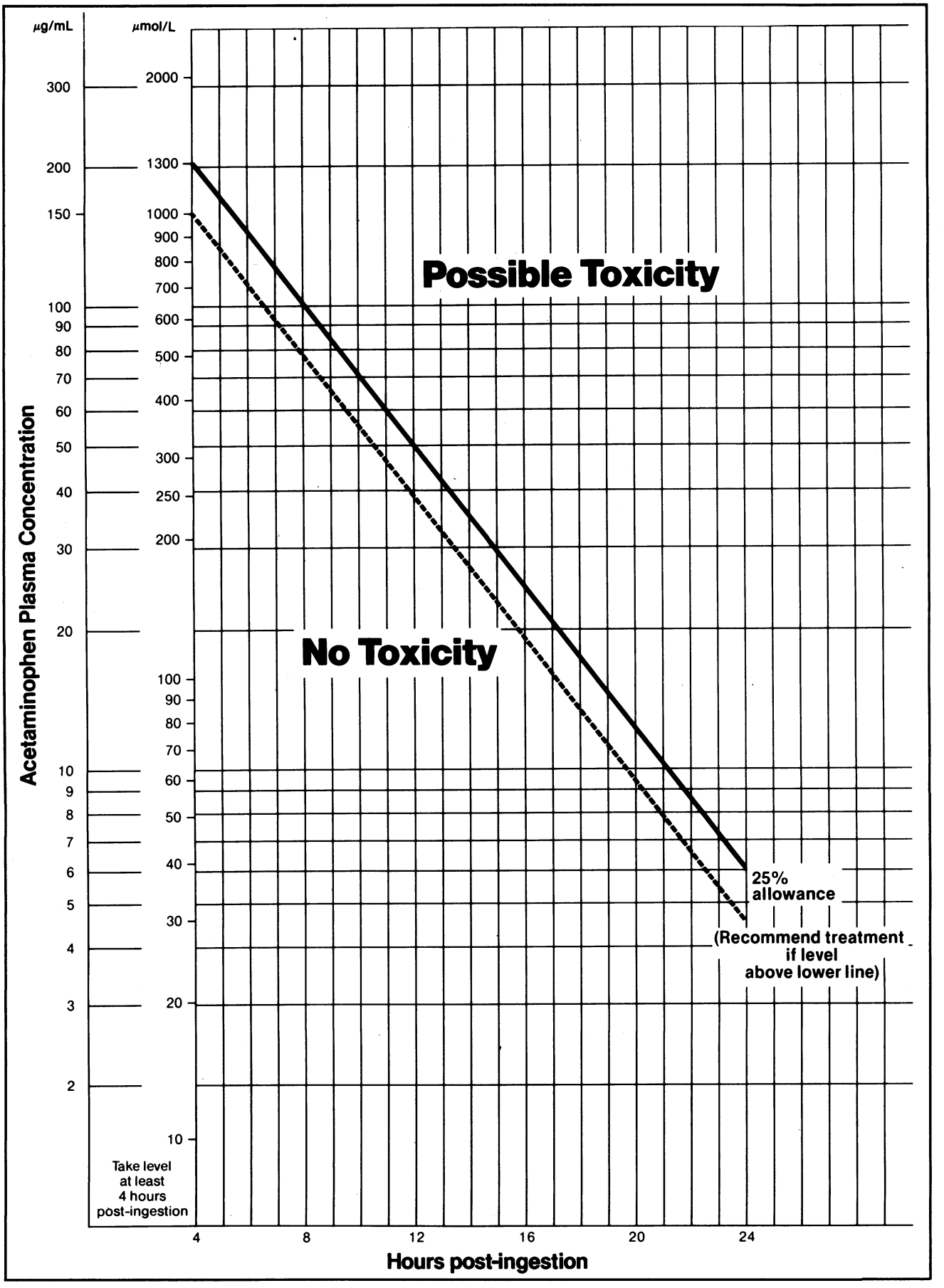

Fig. 3—Nomogram for assessing potential toxicity of acetaminophen overdose from drug's plasma levels and for judging whether treatment with *N*-acetylcysteine is indicated. Adapted from reference 57 with permission.

liver damage. Although their mechanisms of action are not entirely clear, they appear to take the place of glutathione in the process of converting the reactive metabolite to a nontoxic compound that is readily eliminated from the body.[7,76]

Two of these new compounds are of clinical interest: methionine and *N*-acetylcysteine. Only the latter has been cleared for use in Canada; it is commercially available for both oral and intravenous administration. To be effective as specific antidotal therapy, treatment with *N*-acetylcysteine must be initiated within 10 to 24 hours of the time of overdose.

Management

Several recent publications have thoroughly reviewed the management of acetaminophen overdose.[42,44,75,79,80] A schematic approach is outlined in Fig. 2.

The basic principles of emergency management of an overdose apply to acetaminophen. Following ingestion, attempts should be made to remove the drug from the stomach as rapidly as possible by inducing emesis or by using lavage. While acetaminophen is generally absorbed very rapidly, we do not know when emesis and lavage become ineffective, and efforts to empty the stomach should be undertaken any time within at least the first 8 to 12 hours after ingestion. Activated charcoal should be withheld if oral administration of the antidote is likely because the charcoal binds *N*-acetylcysteine in vitro and may interfere with its absorption. If other drugs for which activated charcoal is specifically indicated were also ingested or if the patient is vomiting severely, then *N*-acetylcysteine should be administered intravenously. Cathartics, particularly magnesium or sodium sulfate, also may be useful. These agents may also enhance the sulfation of acetaminophen, but their effectiveness in reducing the toxicity of an acetaminophen overdose by this means has not been demonstrated.[76]

To accurately estimate the extent of the drug's absorption, plasma levels of acetaminophen should be determined not less than 4 hours after ingestion. With these values the likelihood of toxic effects can be assessed on a standard nomogram (Fig. 3).[57] Plasma samples collected earlier than 4 hours after ingestion are not reliable prognostic indicators because the acetaminophen level may not yet have peaked.

The preferred method for assaying acetaminophen is high-performance liquid chromatography.[75] In the event that this method is not available, colorimetric or enzyme immunoassay methods are recommended.[81] Even when the plasma concentration cannot be determined antidotal treatment should not be delayed if a toxic amount of acetaminophen is thought to have been ingested. Administered orally, *N*-acetylcysteine is effective and fairly well tolerated. It is given in an initial loading dose of 140 mg/kg followed by 17 maintenance doses of 70 mg/kg every 4 hours.[41] When it is mixed into fruit juice or a soft drink with ice most patients can readily ingest the antidote, even though it has a rather foul smell and taste, but if necessary it can be given via gastric intubation. No significant side effects other than nausea and vomiting have been noted. *N*-acetylcysteine is also effective when administered intravenously, the recommended dosage regimen being 150 mg/kg over 15 minutes, followed by 50 mg/kg over 4 hours, then 100 mg/kg over the next 16 hours, for a total dose of 300 mg/kg in 20 hours.[43] Hypersensitivity reactions, although rare, have been reported following intravenous administration of *N*-acetylcysteine.[44,82-84]

By far the most important and effective treatment for patients with toxic plasma levels of acetaminophen or those whose ingestion history provides sufficient suspicion is the use of the specific antidote. With prompt *N*-acetylcysteine treatment most, if not all, hepatic damage can be prevented.[75]

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