

DIAGNOSIS AND TREATMENT

Acetaminophen

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Acetaminophen is an effective mild analgesic and antipyretic agent. In double-blind, controlled experimental pain studies of short duration, acetaminophen is superior to placebo and produces analgesia comparable to that produced by aspirin. The frequency of adverse reactions to therapeutic doses of acetaminophen is low, as is that of aspirin. Overdosage with acetaminophen, however, may result in irreversible hepatotoxicity. Since clinical manifestations of intoxication can be of slow onset, physicians may tend to delay initiation of definitive therapy. Intravenous cysteamine, and possibly oral methionine, appear to be effective in preventing hepatotoxicity if they are administered with 10 h of drug ingestion. Physicians should be aware of the potential danger of acetaminophen overdosage and alerted to its clinical manifestations.

ACETAMINOPHEN (paracetamol, *N*-acetyl-*para*-aminophenol) is commonly used as a mild analgesic and antipyretic. Alone or in combination with other drugs, it is found in more than 200 formulations promoted for symptomatic relief of pain, cough, and colds (Table 1) (1). Its popular use is partly due to the low incidence of adverse effects relative to aspirin (2). At therapeutic doses, adverse effects rarely occur with acetaminophen. However, overdoses of the drug have been associated with fatal hepatotoxicity. Because acetaminophen is widely available and forcefully promoted as a "safe" aspirin substitute, there is a need to reevaluate its status as an analgesic-antipyretic agent in clinical medicine.

History

Acetaminophen was synthesized at Johns Hopkins University in 1877 and was first used in clinical medicine in 1893 by von Mehring (3). Its use did not become extensive until 1949, when Brodie and Axelrod recognized it as the principal active metabolite of acetanilid and phenacetin. In 1950 acetaminophen was marketed in the United States as a substitute for phenacetin in an analgesic mixture. After a few case reports of blood dyscrasias, the manufacturer recalled the drug in 1951; the following year it was again made available but only by prescription.

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Since 1955 acetaminophen has been marketed without prescription in the United States (3).

Pharmacologic Properties

Analgesia and antipyresis are the major therapeutic actions of acetaminophen. The drug is devoid of anti-inflammatory and antirheumatic properties (4). Acetaminophen's mechanism of action appears to be related to its inhibition of prostaglandin biosynthesis.

ANIMAL PHARMACOLOGY

In 1953 Frommel observed that acetaminophen elevated the pain threshold of rabbits given electric shock (5). Boréus and Sandberg (6) gave oral doses to rats and produced analgesia comparable to that of phenacetin. Significant analgesia was produced within 1 h and diminished over the following 2 h (7).

In dogs, fever produced by intravenous pyrogens was decreased significantly by simultaneous administration of acetaminophen. In guinea pigs with fever induced by a vaccine, acetaminophen's antipyresis was similar to that produced by phenacetin (5).

EARLY HUMAN STUDIES

In an experimental pain study, Flinn and Brodie (8) found that the threshold for pain due to cutaneous heat radiation was elevated within 30 minutes of acetaminophen ingestion. The maximum rise in threshold, achieved at 2.5 h postingestion, was 30% above control. Within 4 h of drug administration, the threshold returned to normal. These effects were comparable to those of acetanilid.

Pain relief in 27 cancer patients was similar with acetaminophen (600 mg) or aspirin (600 mg) in a double-blind, placebo-controlled study (9). Patients with musculoskeletal pain reported better analgesia from acetaminophen than from aspirin (10). In two double-blind studies, pain relief in patients with chronic rheumatic disease was comparable from acetaminophen and a codeine analgesic mixture (11), while patients with arthritis reported a codeine compound to be superior to acetaminophen (12).

MECHANISM OF ACTION

Aspirin and aspirinlike drugs block the biosynthesis of prostaglandins from arachidonic or structurally related fatty acid precursors (13). Such precursors and the enzyme responsible for prostaglandin synthesis are distributed widely throughout the body (14). Aspirin and aspi-

Table 1. Brand Names of Acetaminophen-Containing Products Available in the United States*

Aceta	Demerol-APAP	Midran	Scotgesic
Acetagesic	Dengesic	Midrin	Scotuss
Actamin	Desa-Hist AT	Minotal	Sedacane
Akes-N-Pain	Dialog	Mydocalm	Sedalgesic
Al-Ay Modified	Dimindol	Myolate	Sedapap
Algecol	Dolanex	Naldegescic	Sedragesic
Allylgesic	Dolene AP-65	Naldetuss	Sialco
Allylvon	Dolmar	N-C-P	Sinacet
Alumadrine	Dolopar	N-D Gesic	Sinacon
Amaphen	Dolor	Nebs	Sinaphen
Amino-Bar	Drinacet	Neopap	Sinarest
Aminodyne	Drinophen	Neo-Pyranistan	Singlet
Amphenol	D-Sinus	Neo-Synephrine Compound	Sinoze
Anapap	Duadcin	Neo-Vadrin	Sinubid
Anaphen	Dularin	Nilain	Sinudan
Anelix	Duc-Gesic	Nilprin	Sinu-Lets
Anodynos	Duoprin	Nokane	Sinulin
Anuphen	Duo-3X	Novahistine	Sinumal
Apadon	Duradyne	Nylorac PB	Sinus Tab
Apamide	Duramid	Nyquil	Sinustat
Apap	Dynosal	Opacedrin	Sinutab
Apapalone	Elixodyne	Ornex	Sinuwes
Arthralgen	Empracet	Ossionate-Plus	SK-Apap
Arthrol	Endecon	Panitrol	Soltice Decongestant Tablets
Bancaps	Enpayne	Panodynes	Spantuss
Bancaps-S	Enz-Cold	Panritis	Spendrisin
Bancesin-Forte	Esemgesic	Parafon Forte	St. Joseph
Bayer Non-Aspirin	Esgic	Parten	Stopain
Bexahist	Euphene	Partuss-A	Sub-Due
Biophens-S	Excedrine	Partuss T.D.	Sunril
Bowman	Febridol	Pavadon	Supac
B-Pap	Febrinol	Pedituss	Super-Anahist
Bromo Quinine	Febrogesic	Pedic	Supercitin Sugar Free
Bromo Seltzer	Febrolin	Percocet-5	Suppress
Burgesic	Fendol	Percogesic	Symptomax
Butigetic	Fendon	Pertussin Plus	Tabalgin†
Calm Aids	Flavahist	Phenahist	Taper
Capex	Gaysol	Phenaphen	T-Caps
Capital	G-1; G-2; G-3	Phendex	Tega-Code
Capron	Guaiaamine	Phrenilin	Tegapap
Cen-Apap	Hasacode	Pirin	Temetan
Cerose Compound	Her-Caps	Presalin	Temptra
Chexit	Histalets	Prodolor	Tenlap
Chlor-A-Tyl	Histogesic	Proval	Tenol
Christodyne-DHC	Histosal	Pyradyne	Teragen
Coastaldyne	Hi-Temp	Pyrapap	T-Gesic
Coastalgesic	Hycamine Compound	Pyrilhist	Trendar
Codalan	Indogesic	Quiet-Nite	Triaminicin
Codap	Isomel	Quiet World	Triaprin
Codimal	Janupap	Renpap	Trigesic
Codrene	Kiddies Sialco	Rentuss	Trind
Coldene	Kleer	Repan	Trind-DM
Colrex	Koly-Tabs	Rhinex	Tussagesic
Comeback	Koryza	Rhinidrin	Tussapap
Conacetol	Lestemp	Rhinogesic	Two-Dyne
Conar-A	Liquiprin	Rhinspec	Tylaprin
Conex	Liquix-C	Romex	Tylenol
Cory-ban D	Lyteca	Romilar	Valadol
Corzans	Maranax	S.A.C. Sinus	Valihist
Co-Tylenol	Maxigesic	Salatin	Valorin
Covangesic	Medache	Saleto	Vannor
Dapa	Med-Apap	Saleto-D	Vanquish
Dapase	Medigesic	Salimeph	Windolor
Darvocet-N	Menalgisia	Salphenyl	Wygesic
Datril	Mense	Sanspen	X-otag Plus
Day Care	Metrogesic	Santussin	Zenex

* Adapted in part from ANONYMOUS: Brand names of acetaminophen-containing products. *Pediatrics* 52:885, 1973, with permission of the publisher.

† British product.

Table 2. Pharmacokinetic Variables for Acetaminophen After Intravenous Injection in Humans*

	Subject		
	1	2	3
Elimination half-life, <i>h</i>	3.05	2.10	1.72
Volume of distribution, <i>litre/kg</i>	1.36	1.00	0.83
Total clearance, <i>ml/min·kg</i>	5.15	5.50	5.57
Extent of first-pass metabolism †, % of oral dose	24.5	26.2	26.5

* Adapted from Reference 39 (CLEMENTS JA, PRESCOTT LF: Data point weighting in pharmacokinetic analysis: intravenous paracetamol in man. *J Pharm Pharmacol* 28:707-709, 1976).

† Assuming hepatic blood flow of 21 ml/min · kg.

rinlike drugs interfere with one or more of these enzymes; this probably accounts for their mechanism of action (15).

Collier and Schneider (16) showed that intraperitoneal injection of prostaglandins in mice produced pain manifested by a writhing response. Equivalent doses of morphine were required to inhibit the writhing response to three different prostaglandins, whereas variable doses of aspirin were required. Collier and Schneider conclude that morphine's primary site of action is in the central nervous system (CNS), whereas aspirin acts at the site where pain is generated.

In one clinical study (17), E-type prostaglandins were infused subdermally to mimic the continuous release of endogenous prostaglandins. In addition to overt pain produced during the infusion, there was a persistent hyperalgesia, that is, increased sensitivity to pressure or injected bradykin and histamine. Thus, prostaglandins appear to increase the sensitivity of pain receptors to mechanical and chemical stimuli (17). Aspirin injected before prostaglandin administration did not prevent the hyperalgesia, suggesting that aspirin inhibits the synthesis of prostaglandins but does not alter their end-organ effects.

Pyrogens may increase production and release of prostaglandins anywhere in the CNS; fever, however, occurs only when an E-type prostaglandin acts on the anterior hypothalamus (18). Feldberg and associates (19) injected pyrogens intravenously and intraventricularly to cats. The ensuing fever and elevated prostaglandin-E₁ activity in cerebrospinal fluid were decreased by intraperitoneal injection of acetaminophen, aspirin, or indomethacin.

Nonsteroidal anti-inflammatory drugs also appear to act through inhibition of prostaglandin synthesis (20). Although acetaminophen is a prostaglandin synthetase inhibitor, the drug does not have anti-inflammatory action. This paradoxical observation may be explained by a differential sensitivity of prostaglandin synthetase from different tissues. Flower and Vane (21) found that rabbit and dog brain synthetase was sensitive to inhibition by acetaminophen while dog spleen enzyme was not. Thus, analgesic-antipyretics devoid of anti-inflammatory properties may more strongly inhibit the synthetase system in the CNS than the synthetase in peripheral tissue (15, 21).

Pharmacokinetics

Acetaminophen is a weak acid with a pK_a of 9.5. The

drug is rapidly absorbed from the gastrointestinal tract, reaching peak plasma levels within 40 to 60 minutes of ingestion (22). Binding to plasma proteins is variable but considerably less extensive than that of aspirin (23). A case report provides evidence of placental transfer of acetaminophen in humans (24).

Rate of absorption of acetaminophen is faster from an alcoholic solution than from tablet or suspension formulations (25). Delayed gastric emptying may decrease the rate of absorption (26).

Acetaminophen is metabolized in the liver, and the metabolic products are excreted by the kidney. The elimination half-life ranges from 2 to 4 h in healthy persons (27-32). In cases of acetaminophen overdosage or in patients with liver disease, the apparent elimination half-life is prolonged (32, 33). In renal dysfunction, however, the half-life is unchanged (31).

After ingestion of a radiolabelled dose of acetaminophen, 84% of the radioactivity was recovered in the urine within 12 h and 90% after 24 h (34). Using high-resolution anion-exchange chromatography, Mrochek and associates (35) observed that 100% of a 1950-mg oral dose was recovered in the urine within 24 h in two healthy male adults. The mean percentage of drug and metabolites recovered in the urine was 63% for glucuronide conjugates, 34% sulfate conjugates, 3% cysteine conjugate, and 1% free drug. The relative amounts of metabolites reported by Mrochek and associates parallel the findings of others (36, 37). Thus, renal clearance of unchanged acetaminophen contributes very little to its total metabolic clearance. Since hepatic stores of sulphate and glucuronide are limited, acetaminophen overdose results in a larger percentage of the dose being oxidized to cysteine and mercapturic acid conjugates (38).

Clements and Prescott (39) infused acetaminophen (12 mg/kg) intravenously in four healthy subjects. Reliable pharmacokinetic analysis of acetaminophen was possible for three of these subjects (Table 2). As reported by others (27-32), the apparent elimination half-life ranged from 1.7 to 3.1 h. The volume of distribution ranged from 0.83 to 1.36 litres/kg and the total metabolic clearance from 5.15 to 5.57 ml/min·kg. In all cases the hepatic extraction ratio was estimated to fall between 0.245 and 0.265, indicating that about 25% to 26% of an oral dose of acetaminophen will fail to reach the systemic circulation due to first-pass metabolism.

Miller, Roberts, and Fischer (29) studied acetaminophen metabolism and elimination kinetics in neonates, children, and adults. Although there were no age-related differences in the total clearance, the route of conjugation differed among the groups. The major metabolite found in the urine of adults and 12-year-olds was the glucuronide conjugate. In contrast, neonates and children (aged 3 to 9 years) excreted primarily the sulfate conjugate (29, 40), suggesting that infants and children have a limited capacity to conjugate phenolic drugs with glucuronic acid. Sulfate conjugation represents an alternate, compensatory metabolic pathway. If this alternate route is not available, excessive drug accumulation could result (29).

Clinical Effects

ANALGESIA

The analgesia produced by acetaminophen has been studied mainly in postpartum women with episiotomy pain. This model is useful because the patient population is a relatively homogeneous group of females between the ages of 16 and 39. Furthermore, the pain is of similar origin and uncomplicated by inflammation. Thus, the model is specific for pain and is not influenced by anti-inflammatory effects of the drug. Finally, patients generally are not seriously ill and their pain is not associated with much anxiety or emotional disturbance that might exacerbate their perception of pain. A disadvantage of the model is that the pain is of short duration and not conducive to crossover studies.

In all of the five double-blind, placebo-controlled trials in episiotomy patients, analgesia produced by acetaminophen was significantly superior to placebo (41-45). Analgesia was measured by patients' reports of pain relief and reduction of pain intensity, by the investigator's global evaluation, and by the need for supplemental analgesics after the one-dose trial. When acetaminophen was tested at single doses of 650 mg and 1000 mg, no "ceiling effect" was observed (42).

Acetaminophen has been compared to other mild analgesics, including aspirin, propoxyphene, codeine, and combinations of these drugs. The clinical trials reviewed below used a placebo control, a double-blind study design (except where noted), and more than one means of assessing pain.

Comparable single doses of aspirin and acetaminophen produced statistically indistinguishable degrees of analgesia. Study populations consisted of patients with mild to moderate pain due to orthopedic surgery (acetaminophen, 1000 mg, versus aspirin, 600 mg) (46) or unresectable cancer (acetaminophen versus aspirin, 650 mg of each) (47). Similar results were found in a postpartum pain study that was not double-blind (acetaminophen versus aspirin, 1200 mg of each) (43).

In two trials with postpartum patients, 1000 mg of acetaminophen was more effective than 65 mg of propoxyphene hydrochloride or a combination of propoxyphene, aspirin, and caffeine. The difference was significant with respect to patient reports of pain intensity and relief and the investigator's overall evaluation (41, 45).

Combinations of acetaminophen (600 mg) with codeine (30 mg) or of acetaminophen (1000 mg) with propoxyphene (65 mg) were superior to acetaminophen alone in postpartum patients (44) and patients with rheumatoid arthritis (48).

Since most studies involved single doses, results cannot be extrapolated to chronic use or to other kinds of pain. Analgesic efficacy may depend on the cause of pain. Cooper and Beaver (49) reported that the peripherally acting analgesics, acetaminophen (600 mg) and aspirin (650 mg), were more effective than codeine (60 mg) in relieving moderate to severe pain in ambulatory patients after oral surgery. With the episiotomy pain model, on the other hand, a dose of only 30 mg of codeine was

statistically superior to 600 mg of acetaminophen (44).

ANTIPYRESIS

In a placebo-controlled trial comparing the antipyretic action of aspirin and acetaminophen in infants and children, effects of both drugs were significantly superior to those of placebo (50). In three studies using aspirin as an antipyretic standard, there was no significant difference between equivalent doses of the two drugs over a 6-h period (51-53). One of these studies (51) was particularly well designed and showed no significant difference between the time of onset, time of peak (3 h postingestion), and duration of antipyretic action (6 h postingestion) for the two drugs. The other two studies had deficiencies in their study design. In one trial (52) about one third of the children continued to receive antibiotics, which may have influenced the course of the fever. In the other (53), the 52 patients were not matched for age, nor were they randomly assigned to treatment groups; the acetaminophen-treated group also had a lower initial temperature.

Unwanted Effects

NEPHROPATHY

Since acetaminophen is a metabolite of phenacetin, acetaminophen has long been viewed as a possible cause of renal damage. To date, chronic abuse of analgesic mixtures containing acetaminophen as the major component has been associated with only three cases of renal papillary necrosis (54-56). As in the case of phenacetin, it is difficult to implicate one drug when a mixture of analgesics are consumed.

Chronic use of acetaminophen has been studied in rheumatic outpatients. Among patients whose major analgesic consumption was acetaminophen (at least 1 g daily for a year or more), none had clinically significant renal impairment (57). Although the potential for causing nephrotoxicity with chronic use is unclear, there is no evidence that acetaminophen causes renal damage with short-term use of therapeutic doses.

HEMOSTASIS

The effects of acetaminophen on hemostasis have been compared to those of aspirin. In normal volunteers receiving a single dose of acetaminophen (975 mg or 1950 mg) and multiple doses of acetaminophen (1.9 g daily for 6 weeks), no change in bleeding time or platelet aggregation was observed. In contrast, a single dose of 975 mg of aspirin prolonged the bleeding time (58). Similar results with single doses of aspirin or acetaminophen were found by Sutor, Boure, and Owen (59) and by Mielke and Britten (60). Hemophilic patients receiving aspirin (60) or multiple doses (58) of acetaminophen showed no significant changes in bleeding time.

In the studies cited, acetaminophen did not produce immediate or delayed effects on small vessel hemostasis, as measured by bleeding time. Thus, acetaminophen appears to be the mild analgesic of choice for conditions in which aspirin's antiplatelet effect would be undesirable. Such conditions probably include hemophilia, thrombocytopenia, and after surgical procedures. Short-term ac-

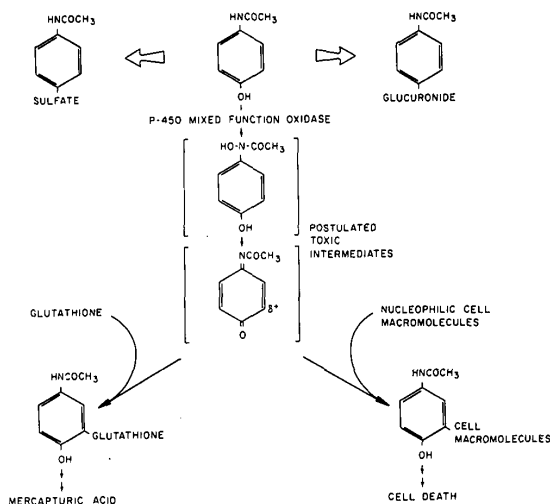


Figure 1. Proposed pathways of acetaminophen disposition. Adapted from Reference 75 (POTTER WZ, THORGEIRSSON SS, JOLLOV DJ: Acetaminophen-induced hepatic necrosis. V. Correlation of hepatic necrosis, covalent binding and glutathione depletion in hamsters. *Pharmacology* 12:129-143, 1974, p. 140), with permission of the authors and editor.

etaminophen therapy causes no interaction with oral anticoagulants (61). A slight potentiation of oral anticoagulant action has been observed after 1 to 2 weeks of repeated daily treatment with acetaminophen (650 mg four times daily) (62). The clinical significance of this interaction is not established, but it suggests that prothrombin times should be closely monitored in anticoagulant-treated patients for whom long-term acetaminophen administration is necessary.

Two cases of thrombocytopenia associated with acetaminophen appear in the literature (63, 64). One of these cases appeared to be an immune thrombocytopenia (64).

Repeated aspirin ingestion causes some gastrointestinal bleeding. Regular long-term ingestion (4 or more days a week) is associated with major upper gastrointestinal bleeding and benign gastric ulcers (65). Short-term use of acetaminophen does not appear to cause gastrointestinal bleeding. In one study 45 inpatients received 4 g of acetaminophen for 5 consecutive days. There was no significant difference in fecal blood loss during the drug trial as compared to the control period. In contrast, 10 patients receiving a 5-day trial of aspirin (2.6 g/day) had a significant increase in fecal blood loss (66). No studies on the long-term effects of acetaminophen on gastrointestinal bleeding have been done to date.

Poisoning

CLINICAL MANIFESTATIONS

In adults with normal liver function, 15 g of acetaminophen may produce serious intoxication (32, 67). Chronic ingestion of alcohol and drugs that induce drug-metabolizing enzymes lowers the toxic dose to about 10 g (32, 34, 67, 68). These figures, however, are only esti-

mates based on clinical observations and extrapolation from animal data.

Before effective treatment was found, acetaminophen poisoning often resulted in hepatotoxicity. Of 60 overdose cases seen in a treatment unit specializing in liver disease, 49 progressed to liver damage (67). A 20% mortality rate was observed and attributed to fulminant hepatic failure (67). The 2% of cases that proved fatal in another series of patients were attributed to acute hepatic failure with severe coagulation disturbances (69).

Onset of symptoms is gradual after an overdose of acetaminophen. Within the first 12 to 24 h, pallor, nausea, and vomiting appear. Microscopic liver damage is thought to occur rapidly, but clinical evidence of hepatotoxicity may not become evident until 4 to 6 days after ingestion. There is an initial sharp rise in serum aspartate aminotransferase (AST or SGOT, serum glutamic oxalacetic transaminase) and alanine aminotransferase (ALT or SGPT, serum glutamic pyruvic transaminase), which return to normal levels within 1 to 2 weeks. Mild acidosis, jaundice, and prolongation of the prothrombin time may also occur. In acute hepatic necrosis, coagulation disorders may be severe and may include disseminated intravascular coagulation (70).

Liver tissue in acetaminophen-induced hepatic necrosis shows centrilobular reticulum collapse and congestion. Cirrhosis rarely occurs (67). Since drug-metabolizing functions may be impaired, other drugs required during the 2- to 3-week period after a severe intoxication probably should be administered in reduced dosages (71).

MECHANISM OF HEPATOTOXICITY

A metabolite of acetaminophen is probably responsible for centrilobular liver necrosis after overdoses. Pretreatment of rats and mice with phenobarbital, a stimulant of metabolic enzymes, enhances production of the toxic metabolite and potentiates hepatic necrosis (72). Conversely, pretreatment with a metabolic enzyme inhibitor, such as piperonyl butoxide or cobaltous chloride, protects against hepatic necrosis in animals (72).

Once formed, the toxic metabolite of acetaminophen binds covalently to liver macromolecules, producing liver necrosis (73). Covalent binding is dose-dependent, and the extent of binding influences the severity of the liver necrosis. Within 1 to 2 h of the peak level of binding, necrosis appears (73).

The cytochrome P-450-dependent, mixed-function oxidase in liver microsomes mediates the binding. Cytochrome P-450 also mediates the conversion of 2-acetylaminofluorene to its toxic *N*-hydroxy metabolite. The toxic metabolite of acetaminophen may also be an *N*-hydroxy derivative (74, 75).

Normally, in-vivo glutathione protects tissues against electrophilic attack by drug metabolites and other alkylating agents. Acetaminophen depletes hepatic glutathione (76). Only after endogenous supplies of glutathione are exhausted does covalent binding to the liver occur.

Figure 1 illustrates the proposed disposition of acetaminophen in the body, including the production of the tox-

ic metabolite and protection by glutathione (75). As the dose of acetaminophen is increased to hepatotoxic levels, hepatic glutathione is depleted and a smaller fraction of the dose is excreted as a mercapturic acid conjugate. In the absence of glutathione, the electrophilic metabolite of acetaminophen arylates liver macromolecules, resulting in cell death (77).

TREATMENT

Standard modes of treatment of poisoning have been used with varying degrees of success. Hemodialysis (78) and peritoneal dialysis (79) have little effect on the clinical course. Activated charcoal significantly reduces the drug's absorption when administered 30 minutes after acetaminophen (25) but not when administered 60 minutes after ingestion (22). As with other toxic ingestions, gastric aspiration and lavage are effective within the first few hours of overdose. Supportive therapy has included parenteral fluids, antiemetics, and phytonadione, fresh frozen plasma, or clotting factors. None of these measures, however, markedly alters the clinical course.

Protection from hepatotoxicity has been attempted with amino acid precursors of glutathione, since glutathione itself does not penetrate cells easily (33). In animals, both methionine and cystine decreased hepatotoxicity (80, 81). Cysteine induced repletion of liver glutathione in mice, but the mechanism of this protective effect is not clear (82). In humans, methionine and cysteamine (β -mercaptoethylamine) have been used, the latter with much success.

Unlike glutathione, cysteamine does not appear to combine with the toxic metabolite of acetaminophen to form an inactive complex. Cysteamine may act by increasing glutathione stores or, more likely, preventing formation of the toxic metabolite (83, 84). As expected, the interval between acetaminophen ingestion and administration of cysteamine is critical (34, 85).

Protection against acetaminophen-induced hepatotoxicity by cysteamine has been demonstrated by Prescott, Park, and Proudfoot (86). The "control" group consisted of poisoning cases treated before cysteamine was available. None of the 19 patients treated with cysteamine within 10 h of ingestion had significant liver or kidney damage. In contrast, 71% of the "retrospective" control subjects developed liver damage, as indicated by both aspartate and alanine aminotransferase levels. An earlier study from the same poison center reported similar findings (33).

The results of one randomized control trial challenge the need for prompt administration of cysteamine (87). However, the study does not define the critical interval between ingestion and cysteamine therapy; therefore the author's conclusion that cysteamine treatment was no better than supportive therapy alone may not be justified by the data.

A recent study by Prescott and associates (85) confirms the efficacy of cysteamine and suggests that further studies using control groups receiving only supportive therapy may no longer be ethically justified. The investigators compared the efficacy of intravenous cysteamine, L-me-

thionine, D-penicillamine, and supportive therapy alone (85). The risk of liver damage, as indicated by the plasma acetaminophen concentration 4 h after ingestion, was comparable among patients in all four treatment regimens. In the group receiving only supportive therapy, all 16 patients with plasma levels exceeding 300 $\mu\text{g/ml}$ developed severe liver damage. Three of these patients died because of liver failure, and four others developed acute renal failure. In contrast, of the 23 patients receiving the additional treatment of cysteamine within 10 h, none developed severe liver damage or renal dysfunction ($P < 0.001$).

A 20-g dose of L-methionine was superior to supportive therapy alone but less effective than cysteamine (85). Side effects of L-methionine, however, were less severe than with cysteamine. A higher dose of L-methionine might have provided more protection but also might have been more toxic. The potential risks and benefits of this agent in relation to dosage require further study.

D-Penicillamine was abandoned after possible drug-induced renal toxicity in two of the five cases in which it was administered (85).

In a preliminary uncontrolled investigation, oral methionine was of value in preventing liver damage (88). However, based on extensive experience and consistent results, cysteamine is preferred over L-methionine for acetaminophen intoxication. In the study by Prescott and associates (85), a loading dose of 2 g of cysteamine base administered within 10 h of the ingestion followed by an infusion of 1.6 g over 20 h provided protection for severe liver damage.

Side effects during intravenous cysteamine administration include flushing, drowsiness, a rapid onset of anorexia, and repeated vomiting. These effects persist up to 36 h after the infusion is discontinued (33, 87). Several episodes of acetaminophen overdosage were accompanied by cardiotoxicity and renal toxicity (87, 89), but it has not been established whether those effects were attributable to liver failure, cysteamine, acetaminophen overdosage, or other drugs taken with acetaminophen.

Since only a few acetaminophen overdosage cases will be at risk of developing severe hepatic damage, and since cysteamine is far from innocuous, criteria for cysteamine therapy are needed. Both the elimination half-life and serum concentrations of acetaminophen have been used to predict hepatocellular damage (32, 33, 90). Single serum levels are of value only if the time since ingestion is known. Levels over 300 $\mu\text{g/ml}$ 4 h after ingestion are associated with severe hepatic lesions, while levels under 120 $\mu\text{g/ml}$ usually are not.

In addition to serum levels, liver function tests assist in the prediction of hepatic damage. Based on the upper limits of normal for several liver function tests, a "liver damage score" was employed by Prescott and associates (85). Values of serum aspartate aminotransferase or alanine aminotransferase over 1000 international units per litre also are prognostic for severe liver damage.

Conclusion

Acetaminophen is an effective mild analgesic and anti-

pyretic agent. The frequency of adverse reactions to therapeutic doses of acetaminophen is somewhat less than that associated with aspirin. Acetaminophen overdosage, however, is presently less manageable than aspirin overdosage and carries considerable hazard, particularly when the poisoning syndrome is not promptly recognized and aggressively treated. Clinical and experimental evidence strongly suggest that early cysteamine therapy, together with effective supportive measures, considerably reduces the morbidity of acetaminophen overdosage.

Acetaminophen poisoning cases are infrequently reported from sources within the United States (91, 92), and the incidence of acetaminophen overdosage in the United States appears to be substantially lower than that in the United Kingdom. The proposed change of acetaminophen's status to a "prescription-only" drug would reduce its extent of use and probably reduce the incidence of poisoning (93). However, the importance of such regulation is secondary to the need for increasing physicians' awareness of the potential hazards of excessive doses of acetaminophen.

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