Acetaminophen

Availability: Over the counter medication, commonly ingested as 325 or 500 mg tabs (many other formulations exist: PO elixir, IR suppository, IV suspension, etc.). An extended release formulation is available with 325 mg of immediate release drug surrounding an additional 325 mg of slowly dissolving acetaminophen. The major metabolite of phenacetin, another medication, is acetaminophen. In the United Kingdom and Europe, acetaminophen is often called paracetamol.

Pharmacokinetics

Absorption: Rapidly and almost completely absorbed from the G.I. tract. Peak plasma concentrations are reached in 10-60 minutes. In an overdose (especially with extended release formulations) up to four hours may be required for peak levels.

Distribution: Rapidly and uniformly distributed into most body tissue. Volume of distribution is 0.7-1.2 l/kg. 15-20% of circulating acetaminophen is bound to plasma protein.

Elimination: Metabolism is complex and the key to understanding mechanism of toxicity (see below). In therapeutic dosages, ~90% of acetaminophen is glucuronidated in the liver and then excreted renally (along with small amounts of acetaminophen sulfate or mercaptate and unchanged drug). The remaining 10% is oxidized by the cytochrome P450 system to create the toxic metabolite, N-acetyl-*p*-benzoquinoneimine (NAPQI). Under normal circumstances, NAPQI is completely detoxified by conjugation with glutathione, which is further metabolized and excreted.

The overall clearance of acetaminophen is 0.15-0.40 L/hr/kg, with a plasma half-life of 1.25-3 hours. Note that both may be dramatically increased in overdoses or in patients with decreased liver function.

Interpretation of Ranges

Therapeutic: 10-30 μg/ml

Toxic: see below description of the Rumack-Matthew nomogram, Laboratory Medicine Resident informed for any value > 50 μg/ml.

Mechanism of Toxicity

As detailed above, acetaminophen is metabolized by the cytochrome P450 system to create NAPQI. When acetaminophen is ingested in toxic amounts, sufficient quantities of NAPQI accumulate intracellularly causing hepatocellular damage. The toxic mechanism of NAPQI is mostly unclear. NAPQI is highly reactive and binds covalently to cell proteins, inducing a series of events leading to cell death.

Acetaminophen toxicity is heightened with induction of the cytochrome P450 system (by alcohol, anticonvulsants or isoniazid, most frequently) or with depletion of hepatic glutathione/sulfation stores, both of which can occur in alcoholism, malnourishment, chronic illness and in neonates.

Clinical Presentation of Toxicity:

The upper limit of a therapeutic daily dosage for acetaminophen is 4 grams in adults or 75 mg/kg in children. Any single dose or accumulated daily dosage of 7.5 grams in adults (or 150 mg/kg in children) is considered potentially toxic and further evaluation for emergency treatment is recommended. This screening cutoff is considered very conservative and, in most cases, adult doses exceeding 12 g/day are required for significant hepato-toxicity.

The initial symptoms of acetaminophen overdose are minimal. Only mild anorexia, nausea, pallor, vomiting, diaphoresis and malaise may be present in the first 24 hours, or the patient may be entirely asymptomatic. Hepatic damage begins to manifest after 24-72 hours. Right upper quadrant pain may be present and the appropriate blood chemistries become abnormal.

Hepatic necrosis and fulminant failure occur after 72 hours. Multi-organ failure is a consequence of fulminant hepatic failure (cerebral edema, renal failure, ARDS, etc.); hence, it is has been difficult to assess whether NAPQI contributes to non-hepatic organ failure.

Case reports exist of significant toxicity occurring with chronic consumption of acetaminophen, most frequently associated with malnourishment or alcohol (or other "P450-inducers") consumption.

Overview of Therapeutic Management

As a highly effective antidote for acetaminophen poisoning is available (N-acetylcysteine or NAC), initial management is focused on assessment of the risk for hepatotoxicity after an overdose. Once a suspicion of toxic ingestion has been established, laboratory testing for acetaminophen concentration and AST is recommended. Algorithms for risk assessment, such as those provided from Goldfrank's textbook (Tables 31-2 and 31-3), are available.

The Rumack-Matthew nomogram classifies the risk for hepatotoxicity (defined as a subsequent increase in AST) after an acute overdose. This nomogram allows 4 hours after ingestion for complete absorption and also assumes a 4 hour half-life for elimination. The recommended U.S. threshold for risk of hepatotoxicity begins at an acetaminophen concentration of 150 μg/ml at 4 hours post-ingestion, declines to 75 μg/ml at 8 hours, 37.5 μg/ml at 12 hours, etc. The cutoffs are highly sensitive such that any patient maintaining acetaminophen levels below the line is considered to have virtually no risk for subsequent liver damage.

A second acetaminophen level, drawn approximately 4 hours after the first level, is often obtained. This second level is advantageous for many reasons. Often the time of ingestion is uncertain or absorption delayed, due either to extended release tablets or delayed gastric emptying; the second level assures complete absorption and can exceed the threshold for therapy even when the first level appeared below the line. A second level also allows estimation of an elimination half-life (although it has been shown that three serial 4 hour levels are required for accurate determination of the half-life; this is not routinely practical as NAC therapy should be initiated within 8 hours after ingestion to be maximally effective). An elimination half-life of > 4 hours has been shown to be highly predictive of subsequent liver damage. An equivalent concept in terms of the nomogram is threshold "crossing" which would be predicted when the half-life is > 4 hours, even when initial values are below the line.

The use of orally administered activated charcoal is limited to early presentation of an overdosed patient when ongoing acetaminophen absorption is likely. It is recommended that NAC therapy should not be administered simultaneously with activated charcoal as binding of NAC to the charcoal may limit its absorption.

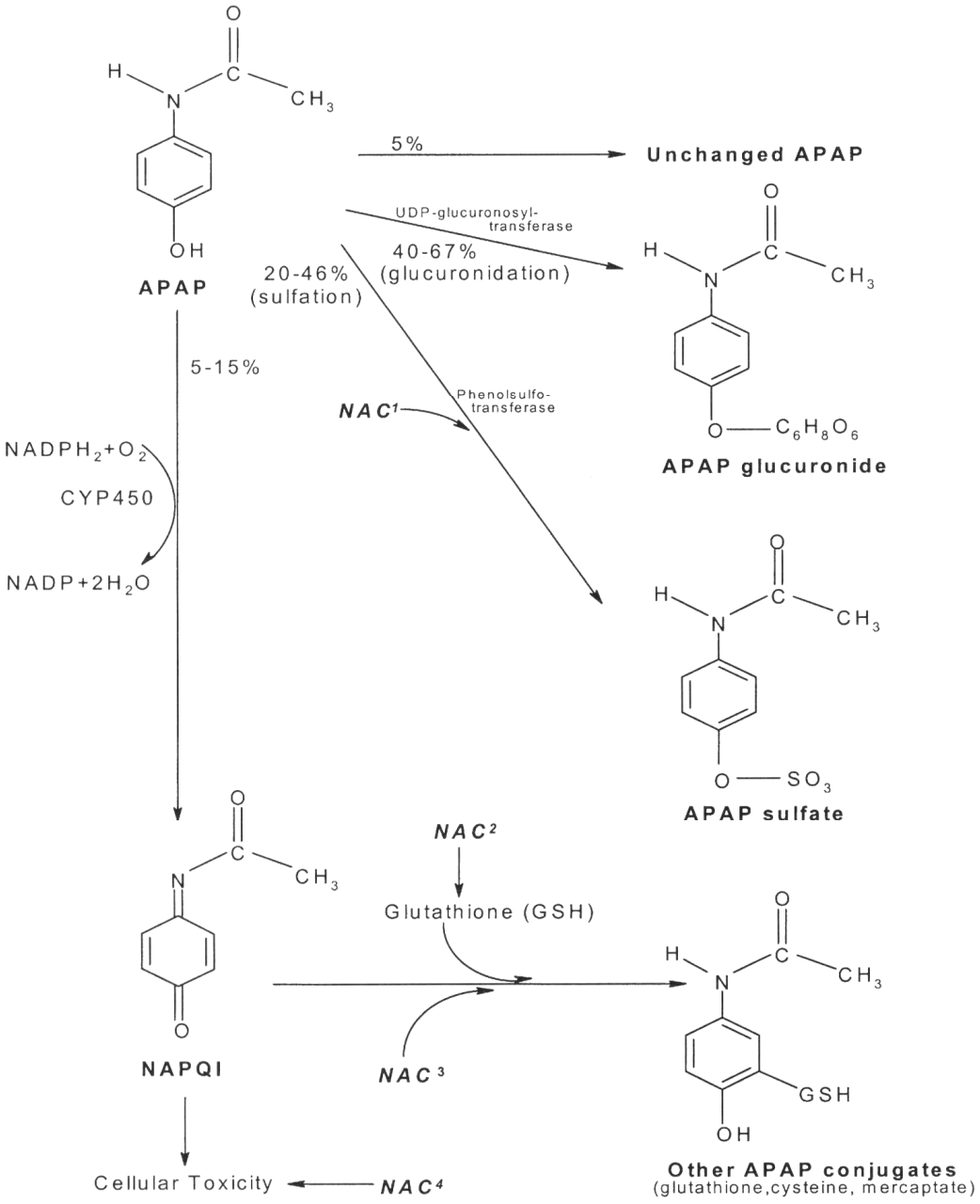
The standard NAC protocol calls for a single 140 mg/kg loading dose followed by 70 mg/kg maintenance doses every four hours for a total of 1+17 doses or 72 hours. In the absence of subsequent signs of liver damage, many practitioners limit the total length of NAC therapy but caution that formal studies have not established safety nor the efficacy of non-standard protocols.

NAC therapy initiated within 8 hours after an acute acetaminophen ingestion is nearly completely protective. Liver damage is only expected when there is delay in the administration of therapy. Even after signs of hepatotoxicity, NAC therapy appears effective at limiting the extent of liver damage and is recommended.

Laboratory Monitoring

Serum or plasma acetaminophen levels are provided 24 hours a day and performed by EMIT on the Roche Modular analyzers. Results are reportable from 1-300 μg/ml and are linear up to 200 μg/ml. There are no significant cross-reactivities nor negative interferences, except for severe hypertriglyceridemia, which is routinely removed by ultracentrifugation before analysis.

Metabolism of Acetaminophen



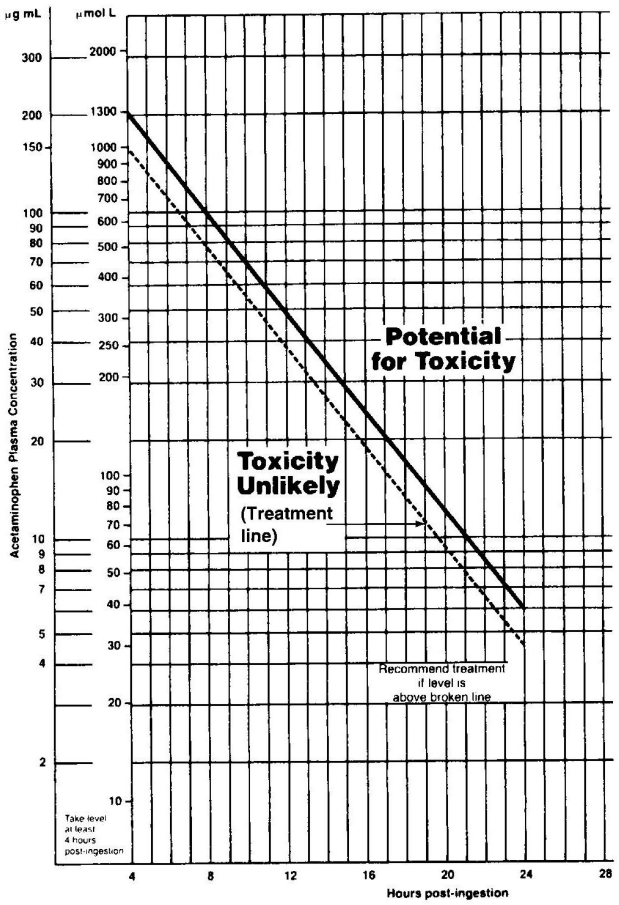


TABLE 32–2. A Risk Determination Strategy After Acute Acetaminophen Ingestion

A. Assess for risk of [APAP] toxicity:

1. If there is a history of acetaminophen overdose and the amount is >7.5 g in adults, >150 mg/kg in children, unknown, or the history is unreliable
2. If there is no history of acetaminophen ingestion, but another overdose is suspected, and there is an alteration in mental status, evidence of oral opioid exposure, or unreliable history
3. If there are signs or symptoms of hepatic injury

B. Initial laboratory assessment should consist of:

1. [APAP] 4 h after ingestion, or as soon as possible thereafter
2. AST[a] if [APAP] is above the treatment line, or signs or symptoms suggest hepatic injury
3. INR, electrolytes, glucose, BUN, and creatinine if very ill-appearing or marked elevation of AST.

C. On the basis of the initial laboratory assessment, consider the patient at risk:

1. If [APAP] is on or above the treatment line, *or*
2. If the AST is elevated, *or*
3. If the [APAP] is >10 µg/mL and the time of ingestion is completely unknown

[a]Early in the clinical course of toxicity, and particularly in certain subgroups, the AST may exceed ALT; therefore, AST is listed as the preferred measure. In most circumstances, however, ALT can be substituted for AST in patient assessment, particularly if nonhepatic sources of AST (eg, rhabdomyolysis) are suspected.

TABLE 32–3. A Risk Determination Strategy After Repeated Excessive Acetaminophen Dosing

A. Assess for risk of acetaminophen toxicity:

1. If there are signs or symptoms of hepatic injury, *or*
2. If the patient is a child with antecedent/concurrent febrile illness, and has received >75 mg/kg acetaminophen in any 24-h period, or
3. If there is evidence of chronic use of alcohol, anticonvulsants, or isoniazid; or malnourishment in a patient who has received >4 g acetaminophen in any 24-h period, or
4. If the patient is not in one of the above groups and has received >7.5–10 g acetaminophen (adults) or >150 mg/kg acetaminophen (children) in any 24-h period

B. Initial laboratory assessment should consist of:

1. [APAP] immediately if symptomatic or if time of last dose unknown; otherwise, 4 h after last acetaminophen dose or as soon as possible thereafter
2. AST[a]
3. INR, electrolytes, glucose, BUN, and creatinine if very ill-appearing or marked elevation of AST

C. On the basis of the initial laboratory assessment, consider the patient at risk (also see below for risk subgroups):

1. If the AST is elevated, *or*
2. If the [APAP] is >10 µg/mL

D. Determination of risk subgroups:

1. Consider the patient at *higher-risk* if any of the following occur:
   a. If [APAP] is above the treatment line when plotted on the acetaminophen nomogram
   b. If the patient is symptomatic and AST > normal
   c. If the AST > twice normal
   d. If the AST > normal and [APAP] >10 µg/mL
   e. If [APAP] > expected for the appropriate dose
2. Consider the patient at risk, but at *low-risk* if either of the following occur:
   a. If there are no symptoms, [APAP] <10 µg/mL, and AST < twice normal
   b. If AST is normal and [APAP] consistent with appropriate dose
3. Consider the patient at *minimal-risk* if the patient has [APAP] <10 µg/mL and AST is normal

[a]Early in the clinical course of toxicity, and particularly in certain subgroups, the AST may exceed ALT; therefore, AST is listed as the preferred measure. In most circumstances, however, ALT can be substituted for AST in patient assesssment, particularly if nonhepatic sources of AST (eg, rhabdomyolysis) are suspected.

TABLE 32–5. Administration of Oral *N*-Acetylcysteine (Mucomyst) in Acetaminophen Overdose

How supplied

As 10% (10 g/100 mL) solution

Dosing

Loading	140 mg/kg
Maintenance	70 mg/kg every 4 h for an additional 17 doses

Administration

Dilute each dose 1:4 (for 20% concentration with water, carbonated beverage, or fruit juice to make a 5% concentration (chilled is more palatable)).

Repeat dose if patient vomits within 1 h of administration.

Try antiemetic (eg, metoclopramide) if vomiting persists.

Use nasogastric tube if vomiting persists.

Salicylate

Availability: Acetylsalicylate (aspirin) is a very common over the counter medication used for its analgesic, antipyretic and anti-inflammatory effects. It is rapidly metabolized in vivo to salicylate, which produces most of the drugs therapeutic and toxic effects. Salicylate is also available as choline magnesium trisalicylate, the dimer salicylsalicylate (salasate) and methyl salicylate (oil of wintergreen), all of which are converted to salicylate. Aspirin is available as tablets, suppositories and IV suspension.

Pharmacokinetics

Absorption: Aspirin is about 68% absorbed after an oral dose with a peak serum level in 1-2 hours.

Distribution: Volume of distribution varies from 0.15-2.0 l/kg at usual therapeutic concentrations, but may be higher in neonates and increases with toxic doses. Circulating salicylate is 90% bound to plasma protein. The fraction of free salicylate increases at toxic levels as plasma binding sites become saturated.

Elimination: Salicylate is metabolized to gentisic acid or conjugated to glucuronide and uric acid. Unchanged and metabolized salicylates are eliminated by renal excretion. Clearance is concentration dependent, decreasing with increasing serum concentrations; at therapeutic levels in a 70 kg person, aspirin is cleared at 650 ± 80 ml/min, with a corresponding half-life of 2-4.5 hours.

Interpretation of Ranges:

Therapeutic: 5-20 mg/dl

Toxic: At > 30 mg/dl tinnitus will definitely occur (Laboratory Medicine Resident Notification)

At > 70 mg/dl severe toxicity definitely results

Mechanism of Toxicity

Salicylates inhibit enzymes involved in the Krebs cycle as well as uncouple oxidative phosphorylation. A wide variety of pathophysiologic effects result from this interference with energy metabolism. Separately, salicylates stimulate the respiratory center of the brain producing hyperventilation.

Clinical Presentation of Toxicity

General: The earliest signs and symptoms of salicylate toxicity include nausea, vomiting, diaphoresis and tinnitus. Other early CNS effects may include vertigo, hyperventilation, hyperactivity, agitation, delirium, hallucinations, convulsion, lethargy, stupor and, rarely, coma (suspect either massive ingestion of mixed overdose). Confusion of the symptoms of salicylate poisoning with other illnesses frequently occurs.

Acid-Base: Salicylate poisoning results in a mixed respiratory alkalosis and wide anion gap metabolic acidosis, although variations in presentations occur. In adults, the respiratory alkalosis predominates in the early stages of toxicity (first few hours). Later, the slower accumulation of lactic acid, ketones and other metabolic acids results in the widening of the anion gap and addition of a metabolic acidosis. In children, the anion gap metabolic acidosis may become significant much earlier, reducing the contribution of the respiratory alkalosis. A minority of salicylate overdoses will present with a respiratory *acidosis* resulting either from a mixed drug overdose (benzodiazapenes, barbiturates, alcohols and TCAs produce CNS depression and decreased respirations), salicylate-induced pulmonary edema or severe fatigue from prolonged hyperventilation coupled with decreased cellular energy production.

Glucose Metabolism: Interference with the Krebs cycle and oxidative phosphorylation increase reliance on glycolysis for energy resulting in increase glucose consumption. Eventually, when hepatic stores of glycogen are depleted and gluconeogenesis cannot match glucose consumption, hypoglycemia will result. Glucose in the CSF (and presumably the entire CNS) diminishes much sooner than plasma glucose resulting in some direct neurologic effects and mental status changes.

Hepatic Effects: Besides the increased metabolic demands on the liver for glucose and ketone production, salicylate-induced hepatitis occurs in children with high (~30 mg/dl) salicylate levels or chronic high dosages for treatment of rheumatic fever or rheumatic arthritis. Reye's syndrome is another well-known salicylate associated liver disease.

Pulmonary Effects: Salicylate overdose may result in a pulmonary edema resulting from a variety of etiologies. A syndrome of salicylate-induced non-cardiogenic pulmonary edema (NCPE) occurred in approximately 1/3 of patients over 30 years of age with peak salicylate levels > 30 mg/dl, with no cases in patients under 16 years of age. Risk factors for NCPE besides age included cigarette smoking, chronic salicylate consumption and the presence of neurologic symptoms on presentation. Other etiologies of pulmonary edema associated with salicylate ingestion include aspiration pneumonitis and postictal or neurogenic pulmonary edema.

Hematologic Effects: Platelet dysfunction due to inhibition of cyclooxygenase (COX-2), hyperprothrombinemia and anemia occurring with chronic salicylate abuse.

Gastrointestinal Effects: Nausea, vomiting, hemorrhagic gastritis, decreased gastric motility and pylorospasm occur with both acute overdoses and chronic salicylate use. These effects are more pronounced in the elderly.

Musculoskeletal Effects: Rhabdomyolysis can occur as a consequence of interference with oxidative energy metabolism.

Otolaryngologic Effects: Eventual hearing loss preceded by tinnitus occurs with serum salicylate concentrations over 20-40 mg/dl. This is considered one of the most consistent and specific early symptom of salicylate poisoning.

Overview of Therapeutic Management

Although serum or plasma salicylate concentrations are useful for identifying patients who may have overdosed on salicylates, the severity of toxicity correlates poorly with measured levels. The well-known Done nomogram for stratification of salicylate toxicity, based on a single serum level measured six hours more after ingestion, has severely limited applicability in a general population. Serum salicylate concentrations must be considered in conjunction with the effect of blood pH on the tissue distribution. A decrease in pH results in increased neutral salicylate with increased partitioning into tissue where toxicity may increase. Hence, observation of a decrease in the serum salicylate concentration concomitant with a decrease in blood pH may indicate a worsening situation as drug is shifted to tissue, increasing toxicity and subsequently further reducing blood pH.

Alkanization of both serum and urine by administration of parenteral sodium bicarbonate is critical for the treatment of a salicylate overdose. Alkanization of serum helps correct the dangerous acidemia of a poisoning as well as shifts the distribution of salicylate in the body away from the tissue compartment and into the blood. Alkanization of the urine is more dramatic than in serum as the pH of urine may vary from 4.5 to 8.0 resulting in 10-20 fold increase in the renal clearance of salicylate. Activated charcoal is effective for limiting gastrointestinal absorption of salicylates. For severe poisonings, extracorporeal removal of salicylates should be considered either by hemodialysis (preferred) or hemoperfusion.

Laboratory Monitoring

Serum or plasma salicylate concentrations are measured quantitatively on the Roche Modular Analyzer utilizing the enzyme salicylate hydroxylase which catalyzes the conversion of salicylate to catechol using NADH as an electron donor (oxygen is converted to water during the reaction). The resulting decrease in absorbance at 340 nm, due to conversion of NADH to NAD+, is directly proportional to the concentration of salicylate in the sample. The assay is available 24 hours a day. There are no significant cross reactivities nor interferents (except severe hypertriglyceridemia, which is removed by ultracentrifugation before analysis).

TABLE 33–1. Clinical and Laboratory Manifestations of Salicylate Toxicity

Acid-base and electrolyte disturbances
- Anion gap increased
- Metabolic acidosis
- Metabolic alkalosis (vomiting)
- Respiratory alkalosis (predominates early)
- Respiratory acidosis (late grave prognosis)
- Hyponatremia or hypernatremia
- Hypokalemia

CNS
- Tinnitus
- Diminished auditory acuity
- Vertigo
- Hallucinations
- Agitation
- Hyperactivity
- Delirium
- Stupor
- Coma
- Lethargy
- Convulsions
- Cerebral edema
- Syndrome of inappropriate secretion of antidiuretic hormone

Coagulation abnormalities
- Hypoprothrombinemia
- Inhibition of factors V, VII, X
- Platelet dysfunction

Gastrointestinal
- Nausea
- Vomiting
- Hemorrhagic gastritis
- Decreased motility
- Pylorospasm

Hepatic
- Abnormal liver enzymes
- Altered glucose metabolism

Metabolic
- Hyperthermia
- Hypoglycemia
- Hyperglycemia
- Hypoglycorrhachia
- Ketonemia
- Ketonuria

Pulmonary
- Hyperpnea
- Tachypnea
- Respiratory alkalosis
- Acute lung injury (non-cardiogenic pulmonary edema; salicylate-induced pulmonary edema

Renal
- Tubular damage
- Proteinuria
- NaCl and water retention
- Hypouricemia (hyperuricemia)

Volume status
- Nausea
- Vomiting
- Perspiration

TABLE 33–2. Differential Characteristics of Acute and Chronic Salicylate Poisoning

	Acute	Chronic
Age	Younger	Older
Etiology	Overdose rarely unintentional	Therapeutic misadventures; iatrogenic
Diagnosis	"Classic"	Frequently unrecognized
Other disease states	None	Underlying disorders (especially chronic pain conditions, etc)
Suicidal ideation	Typical	No
Clinical differences	Rapid progression of signs	Acute lung injury (ALI)* CNS abnormalities*
Serum concentrations	Marked elevation	Intermediate elevation
Mortality	Uncommon when recognized, unless ingestion massive	Approximately 25%

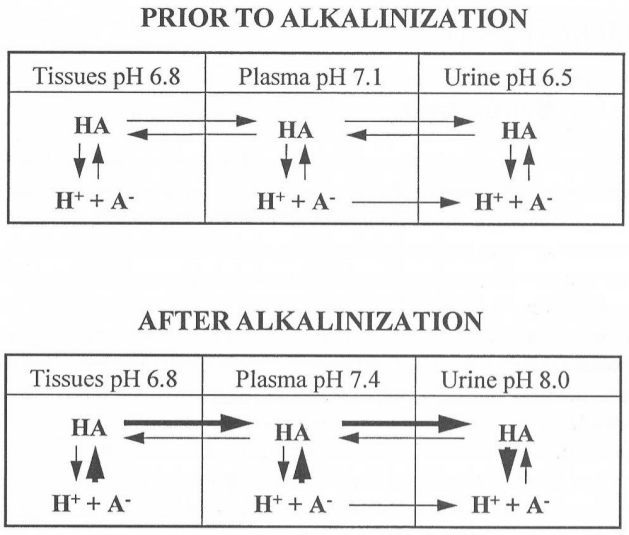


Figure 33–3. Rationale for alkalinization. Alkalinization of the plasma with respect to the tissues and alkalinization of the urine with respect to plasma shifts the equilibrium to the plasma and urine and away from the tissues (including the brain). This equilibrium shift has been called "ion trapping." *(Adapted, with permission, from Temple AR: Acute and chronic effects of aspirin toxicity and their treatment. Arch Intern Med 1981;141:367.)*

Tricyclic Antidepressants

Availability: Tricyclic antidepressants (TCAs) can be divided into multiple categories. The first generation initially included the "tertiary amines" imipramine, amitriptyline, clomipramine and doxepin. Subsequently, the corresponding "secondary amines" desipramine, nortriptyline and protriptyline were released. Although the secondary amines are less toxic than their predecessors, all the first generation antidepressants are highly toxic and have been one of the leading causes of mortality from a prescription drug overdose. The second generation of cyclic antidepressants contained the SSRIs (selective serotonin reuptake inhibitors) -fluoxetine, paroxetine, fluvoxamine and sertraline- along with other atypical antidepressants such as venlafaxine, trazodone, nefazadone and bupropion. In general, the second generation antidepressants are far less toxic than the first generation medications and the following discussion of TCA poisoning is meant to be specific for the latter.

Pharmacokinetics

(Note that the pharmacokinetics for individual TCAs can differ signficiantly. The following description is meant to be generic for the class. See additional handout for more details.)

Absorption: Generally are absorbed quickly in the gastrointestinal tract with peak levels reached in 0.5-6 hours depending on the TCA. However, in an overdose gastrointestinal motility can be dimished due to the anticholinergic effects of TCAs and can signficiantly delay absorption.

Distribution: TCAs are very lipophillic and, hence, widely distributed into body tissues with large volumes of distributions (10-50 l/kg). TCAs circulate bound to plasma protein, primarily α_1-glycoprotein. However, binding affinities differ widely amongst the TCAs, their metabolites and clinical situations resulting in an unpredictable fraction of free and bound drug. Acidemia increases the fraction of circulating, free TCA in all cases.

Elimination: TCA are metabolized on the "first pass" through the liver after absorption by the Phase I process of demethylation, essentially converting the tertiary amine group members into secondary amines. Both classes of compounds are slowly hydroxylated by the microsomal enzyme system into less active metabolites. Eventually, glucuronidation occurs in a Phase II complexation. Renal excretion of the parent TCA and all its metabolites are excreted renally with variable clearance. Elimination half-lives range from 2-4 hours to over 90 hours depending on the specific TCA and the many intra- and inter-patient variables, but are generally in the range of 10-30 hours (see the attached “Table 55-2”).

Interpretation of Ranges: Therapeutic ranges for most TCAs range from 50-300 ng/ml. The complexity of pH-dependent protein binding, large and variable volumes of distribution, and wide variability of the terminal elimination half-life limit the clinical utility of plasma TCA concentrations. Signs of toxicity may begin to manifest at concentrations above 300 ng/ml and become more pronounced over 500 ng/ml. However, note that as detailed below and in the aditional handout, the semi-quantitative immunoassay utilized for the overdose panel has a wide range of cross-reactivities with specific TCAs and their metabolites, making a specific therapeutic and toxic range hard to interpret. Of course, clinical parameters such as anticholinergic signs and EKG findings are of prime importance in establishing toxicity.

Mechanism of Effect

TCAs exert their therapeutic effects in the CNS through potentiation of biogenic amines (serotonin, norepinephrine and dopamine) by inhibiting their transport and reuptake at nerve terminals. Some degree of efficacy is mediated by inhibition of α-adrenergic and GABA receptors. Other neurochemical properties include blockade of peripheral and central muscarinic receptors, resulting in prominent anticholinergic effects, and inhibition of H1, H2 and D2 receptors. Blockade of voltage-gated Na^+ channels and K^+ channels in myocardial cells causes the dangerous wide complex dysrhythmias associated with TCA poisoning.

Clinical Presentation of Toxicity

Cardiovascular Effects: Inhibition of voltage-gated Na^+ channels in the myocardium, known as the quinidine-like effect, results in decreased conduction velocities and increased threshold for excitability. Further prolongation of the action potential is caused by a blockade of the potassium channel. Widening of the QRS complex, lengthening of the QTc and a rightward axis shift in the terminal 40 msec of the QRS are highly sensitive and specific signs for TCA poisoning on the EKG. These electrophysiological changes along with sinus tachycardia due to the anticholinergic effects of TCAs predispose patients to life-threatening tachydysrhythmias.

Hypotension is caused by a combination of blockade of peripheral α-adrenergic receptors and decreased cardiac output resulting from the depressive effects of TCAs on the myocardium. Significant hypotension decreases cardiac perfusion and worsens the electrophysiological depression of the myocardium.

Central Nervous System Effects: Toxicity on the CNS is primarily mediated by inhibtion of muscarinic receptors resulting in agitation, hallucinations, confusion, sedation, lethargy, respiratory depression, seizures and coma.

Peripheral Anticholinergic Effects: Urinary retention, mydriasis, dry and flushed skin, decreased gastrointestinal motility, hyperthermia, tachycardia and hypertension (although because of α-adrenergic blockade, hypotension usually predominates).

Overview of Therapeutic Management

A patient with a TCA overdose requires close management. A retrospective review of TCA fatalities found that half had initially presented to the hospital with trivial signs of toxicity and, subsequently, had a catastrophic deterioration within 1 hour. Admission to an ICU for monitoring and management is required. Criteria exist for discharge from the ICU to a telemetry or "step down" unit based on clinical parameters during the first 6 hours of admission.

Therapeutic management of a TCA overdose is tailored to the clinical manifestations. Hypotension, cardiac arrhythmias, seizures and other complications are treated with the appropriate "supportive" medical therapy (details beyond the scope of this discussion).

Alkanization of the serum with sodium bicarbonate is able to prevent and reverse the potentially fatal cardiotoxic effects of TCAs. The mechanism is complex but apparently involves both a direct protective effect on the Na^+ channel (such that it has been found beneficial in other medications with a "quinidine-like" effect) and a redistribution of the drug into an ionized form with a lower affinity for the myocardial membrane (along with its Na^+ and K^+ channels). Gastrointestinal decontamination with activated charcoal will limit absortpion of the unabsorbed drug.

Laboratory Monitoring

Our laboratory offers two TCA assays to clinicians. One is intended primarily to assist in the management of a suspected TCA overdose and the other is intended for therapeutic drug monitoring of a limited number of first-generation TCAs.

Immunoassay: As part of the overdose panel, a semi-quantitative TCA immunoassay is offered 24 hours a day on a STAT basis. We perform this assay in two steps. First, on the Roche Modular Analyzer an initial screen for the presence of TCAs is performed using EMIT. All positive results on the Modular Analyzer are followed by a second immunoassay on the AxSYM, detected by fluorescence polarization. The AxSYM semi-quantitates the TCA reactivity into reportable ranges:

Less than 25 ng/ml
0 – 300 ng/ml
300 – 500 ng/ml
500 – 1000 ng/ml
Greater than 1000 ng/ml.

The antibody used on the AxSYM was generated against desipramine and has high cross-reactivity against the other first-generation TCAs. However, enough variation exists to complicate interpretation of the results. **A major role of the Laboratory Medicine Resident in consultation with clinicians is to communicate the relative reactivities for the TCAs suspected in the overdose and assist in the interpretation of the result.**

• Desipramine has > 90% cross-reactivity and is relatively concentration independent.

• Amitriptyline and nortriptyline have a 100% cross-reactivity at low concentration. At 500 ng/ml cross-reactivity with amitriptyline increases to about 109% and cross-reactivity with nortriptyline reduces to about 86%. Since amitriptyline is metabolized to nortriptyline by the liver, patients taking amitriptyline may have significant concentrations of both in their serum.

• Doxepin, nordoxepin, clomipramine and norclomipramine have cross-reactivities of about 50% at low concentrations, falling to 20-30% at high concentrations.

• Maprotiline exhibits 10-20% cross-reactivity.

• Hydroxylated metabolites of all of the above have variable cross-reactivities. In an overdose, inactive metabolites may accumulate as metabolism proceeds (especially in patients with decreased renal function) and contribute significantly to the total reactivity. For this reason, the TCA immunoassay should not be used to "follow down" the TCA level.

• There is NO significant cross-reactivity with amoxopine, bupropion, loxapine, trazodone and fluoxetine.

• Unfortunately, the TDx antibody displays cross-reactivity with a number of other medications. These include carbamazepine (Tegretol), diphenhydramine (Benadryl), cyclobenzaprine (Flexeril), cyproheptadine (Periactin), chlorpromazine (Thorazine) and perphenazine (Trilafon). Generally, their cross-reactivity is minimal and *therapeutic* dosages of the interfering medications do NOT contribute significantly to the semi-quantitative reporting of the TCA level (i.e. the contribution of the interfering medication is unlikely to push the result into a higher category). However, *toxic* or *overdosed* levels of these medications may contribute significantly to the total reactivity. In the absence of any ingested "real" TCAs, overdoses of the above interfering medications generally result in a "0 – 300 ng/ml" reportable range for the TCA immunoassay.

• This assay uses polyclonal antibodies and cross-reactivities may vary from lot -to-lot of the reagents. Therefore, it is always a good idea to see the current package insert to verify cross-reactivites during consultation.

Once the resident has communicated the appropriate cross-reactivities and cautioned the clinician that the TCA immunoassay has a large degree of variability (20-40%!), the resident may choose to verbally report the TCA level to the nearest 100 ng/ml (e.g. 600-700 ng/ml).

The resident should explain to the clinician that serial TCA immunoassay levels are not warranted due to the semi-quantitative nature of the measurement, the high variability in the result and the cross reactivity with inactive metabolites and other medications. However, a second determination, a few hours after the first, is appropriate to determine whether continued absorption is ongoing. Further levels may also be obtained to confirm a concentration below 300 ng/ml in order to qualify the patient for discharge (if clinically warranted, of course), but only after sufficient time has elapsed to expect a concentration in this range.

HPLC: The antidepressants amitriptyline, nortriptyline, imipramine, desipramine, doxepin and nordoxepin can be quantitated using HPLC for separation and a diode array spectrophotometer for detection and quantification. This assay is NOT available STAT; it is run weekly (Thursdays). Very rarely, additional daily runs may be warranted for monitoring of a hospitalized overdosed patient. Routinely, the assay is utilized to confirm toxic TCA immunoassay results (on the first measurement

only) and for occasional confirmation of the therapeutic levels of a specific TCA. Routine therapeutic monitoring of TCAs is not necessary (nor recommended), but may be helpful in specific circumstances, for example in patients with decreased hepatic or renal function.

HPLC detection and quantification of a TCA level is not intended for the management of a suspected TCA overdose. However, after a toxic level has been identified by the TCA immunoassay, HPLC can confirm the identity of the specific TCA involved in the overdose as well as the precisely determine the initial concentration. Follow-up quantifications are not routinely necessary as patients are managed based upon clinical parameters (e.g. the EKG and anticholinergic signs and symptoms). As active and inactive TCA metabolites can be separated by HPLC, in patients with impaired hepatic or renal function, follow-up HPLC quantifications may be appropriate to monitor the rate of elimination of the active drug and confirm an appropriately low level to allow transfer out of the ICU or discharge (cases where the immunoassay may incorrectly overestimate the TCA level due to cross-reactivities), as clinically appropriate.

TABLE 57–2. Clinical Manifestations of Toxicity Caused by Cyclic Antidepressants

Cardiovascular Toxicity	
Conduction Delays	PR, QRS, QT interval prolongation
	T40-msec axis rightward rotation (120°–270°)
	Atrioventricular block
Dysrhythmias	Sinus tachycardia
	Supraventricular tachycardia
	Wide-complex tachycardia
	Sinus tachycardia with rate-dependent aberrancy
	Ventricular tachycardia
	Torsades de pointes
	Bradycardia
	Ventricular fibrillation
	Asystole
Hypotension	
Central Nervous System Toxicity	
Altered mental status	Delirium
	Psychosis
	Lethargy
	Coma
Myoclonus	
Seizures	
Anticholinergic Toxicity	
Altered mental status	
Hyperthermia	
Urinary retention	
Paralytic ileus	

Alcohols and Glycols

Availability: The commonly ingested alcohols and glycols include ethanol, methanol, isopropanol (and it metabolite acetone), ethylene glycol and propylene glycol. Availability of ethanol is obvious. Methanol is used extensively in windshield washing and deicing solutions (35 to 95%), carburetor cleaner (20%), duplicating fluids (95%), solid canned fuels (4%), shellac, paint removers and thinners, model airplane fuels, denatured alcohol, and embalming fluid. Isopropanol or isopropyl alcohol is common household rubbing alcohol (70%) and also in various toiletries, disinfectants, window cleaning solutions, antifreeze, paint removers, and industrial solvents. Ethylene glycol is used extensively as antifreeze (95%) and also in fire extinguishers, inks, pesticides, adhesives and air conditioning and solar energy systems. Propylene glycol has recently been utilized in antifreeze advertised as "pet safe" and has been used for some time as a diluent for injectable agents such as phenytoin, diazepam, digoxin and also some household items including food and cosmetics.

Pharmacokinetics

Absorption: Alcohols are colorless liquids (although often mixed with colored additives, e.g. the bright green fluorescein added to antifreeze) and are readily absorbed by ingestion, inhalation or transdermally. Peak serum levels after an oral ingestion are reached in 30 to 60 minutes.

Distribution: Alcohols are highly soluble in aqueous solutions and, therefore, highly distributed throughout body water with some lipid and protein binding. Volumes of distribution are between 0.5 – 0.7 l/kg.

Elimination: Alcohols are initially metabolized by hepatic alcohol dehydrogenase to the corresponding aldehyde or ketone. In a second metabolic step, the aldehyde is oxidized to the corresponding carboxylic acid by hepatic aldehyde dehydrogenase. Other metabolic steps are available to specific alcohols and their metabolites. Important metabolic steps include

• Ethanol is converted into acetaldehyde and then into acetic acid which is consumed by the Krebs cycle, in ketogenesis or fatty acid synthesis depending upon metabolic state.

• Methanol is converted into formaldehyde, which is rapidly metabolized to formic acid. Formic acid is slowly metabolized to carbon dioxide and water in a series of folate-dependent reactions.

• Isopropanol is metabolized to acetone.

• Ethylene glycol is metabolized to glycoaldehyde and then to glycolic acid by similar dehydrogenases as the alcohols. Glycolic acid is further metabolized by lactic dehydrogenase (glycolic acid oxidase) to glyoxylic acid, which can be metabolized in multiple directions. The most toxic final product of ethylene glycol metabolism is oxalic acid.

• Propylene glycol is metabolized to lactic acid.

Ethanol and methanol are eliminated by zero-order (constant rate) kinetics due to saturation of the hepatic enzymes. Ethanol is eliminated at 15-20 mg/dl/hr and methanol at 8.5 mg/dl/hr. A small amount is lost by pulmonary and renal excretion with first-order (characterized by a half-life) kinetics. At higher concentrations, the contribution from pulmonary and renal excretion increases and mixed zero-order and first-order elimination is observed.

Isoproponal, ethylene glycol and propylene glycol are eliminated primarily by first-order kinetics with half-lives of 2.5-3.5 hours, 2.5-4.5 hours and 2-5 hours, respectively.

Interpretation of Ranges

Ethanol is not uncommon in the serum of emergency department patients. Tolerance develops to the intoxicating effects of alcohol resulting in variability of the significance of serum ethanol concentrations.

For most people intoxication begins at 50-150 mg/dl and health is threatened at levels above 500 mg/dl. However, some patients tolerate ethanol levels of 500 mg/dl routinely.

Methanol is produced in very small amounts by normal metabolism and, as well, some naturally fermented alcoholic beverages may contain low levels of methanol. For these reasons, methanol levels of 1-5 mg/dl *may* not indicate a methanol overdose. In such cases of a low initial methanol value, a follow up value is recommended in order to check for continued absorption. Methanol levels above 10 mg/dl are likely to develop some degree of delayed toxicity and require treatment. Hemodialysis is recommended for methanol concentrations above 25 mg/dl.

Any level of ethylene glycol is abnormal and should be considered indicative of ingestion. Hemodialysis is recommended for levels above 25 mg/dl.

Isopropanol is much more intoxicating than ethanol but does not have the danger of delayed toxicity as is seen with methanol and ethylene glycol. Hemodialysis for isopropanol is not routine, but may become necessary for massive ingestions with serum concentrations greater than 400 mg/dl.

Propylene glycol is often found in the serum of hospitalized patients at levels of 1-25 mg/dl from the diluent of injectable medications. Like isopropanol, propylene glycol does not provide a risk for delayed toxicity and treatment is directed primarily at the initial intoxicating/depressive effects.

Mechanism of Toxicity

The intoxicating effects of alcohols are responsible for their initial toxicity. At high levels, these include ataxia, areflexia, slurred speech, visual disturbances, mental confusion, nausea and vomiting, unconsciousness, respiratory depression and coma. Longer chain alcohols are generally more intoxicating with isopropanol being the most potent and methanol the least. Ethylene glycol is more intoxicating than ethanol.

Methanol and ethylene glycol poisonings result in a more serious second phase of toxicity. Their metabolites cannot be integrated quickly into routine metabolic pathways like those of ethanol and propylene glycol. Accumulation of the toxic metabolites directly damages specific tissues and also contributes to the development of an anion gap metabolic acidosis. The terminal organic acid metabolites of alcohols (e.g. formic acid and oxalic acid) directly contribute to the acidosis. Indirectly, metabolism of alcohols results in a high ratio of NADH to NAD+ which facilitates conversion of pyruvate to lactic acid (in an effort to recycle NADH to NAD+ so that glycolysis can continue). As well, the toxic organic acids directly inhibit oxidative phosphorylation worsening the lactic acidosis. Hypoglycemia can quickly result as a consequence of this dependence on glycolysis for ATP production. In summary, these mechanisms imply that methanol and ethylene glycol generate the most severe metabolic acidosis, but also demonstrate how the other alcohols can indirectly produce a mild lactic acidosis with large ingestions.

Clinical Presentation of Toxicity

Methanol: Methanol is the least intoxicating alcohol on a per weight basis. Therefore, the initial intoxicating effects may be mild, although the delayed effects are severe. After a latent period of 10-24 hours, accumulation of formic acid produces an anion gap metabolic acidosis and the symptoms of toxicity. Formic acid contributes to the acidosis directly but also inhibits the cytochrome oxidase chain disrupting oxidative phosphorylation and resulting in a secondary lactic acidosis.

The most consistent findings in methanol poisoning are visual disturbances, eventually leading to blindness. Ophthalmologic examination usually reveals dilated pupils with absent or sluggish light reaction and poor accommodation. Hyperemia of the optic disc followed by retinal edema is routinely seen on fundoscopic examination. CNS symptoms commonly include inebriation, headache, dizziness, seizures and coma. Nausea, vomiting, meningismus, abdominal pain, obstipation and malaise are frequent complaints. Common laboratory findings are hypophosphatemia and an elevation of amylase and creatine kinase.

Ethylene Glycol: Ethylene glycol causes a more severe intoxication than methanol. Nausea and vomiting are pronounced with the gradual onset of inebriation, lethargy and coma during the first 4 to 8 hours. Visual disturbances as described for methanol are not characteristic of ethylene glycol ingestion. The anion gap metabolic acidosis which develops after 10-24 hours is the most severe for any of the alcohols. Cardiopulmonary compromise manifests during this phase, most likely as a consequence of the interference in energy metabolism. Specific signs and symptoms include unstable blood pressure, tachycardia, dysrhythmias, hyperventilation, pneumonitis and noncardiogenic pulmonary edema.

The final phase of ethylene glycol poisoning relates to the renal excretion of the toxic metabolites. The urine of patients who have ingested ethylene glycol reveals calcium oxalate or hippurate crystals in approximately 50% of cases. Red blood cells and increased protein are also found in the urine. Acute tubular necrosis secondary to the deposition of oxalate crystals or the direct toxic effect of metabolites on the tubules occurs in 12 to 48 hours after ingestion. Hypocalcemia may occur during this phase resulting in a prolonged QTc interval on the ECG, and tetany may develop. A leukocytosis and CSF pleocytosis may be seen. Late findings (after 24 to 48 hours) may include complete cardiopulmonary failure and renal failure.

Isopropanol: Unlike the other alcohols, metabolism of isopropanol produces relatively non-toxic acetone, which is eliminated by renal and pulmonary excretion. Being the most intoxicating alcohol, the initial CNS depressive effects of isopropanol ingestion represent its most serious toxicity. Whereas therapy of other alcohols may be characterized as preventing metabolism of the alcohol, for isopropanol the opposite is desired.

Propylene Glycol: Similar to isopropanol, toxicity of propylene glycol ingestion is associated with its intoxicating and CNS depressive effects. Its metabolite, lactic acid, is incorporated into routine cellular physiology with only a small increase in circulating lactic acid. However, with massive ingestions a clinically significant lactic acidosis may develop.

Overview of Therapeutic Management

Blocking conversion of methanol and ethylene glycol into their toxic metabolites is achieved by ethanol or fomepizole (4-methylpyrazole) administration. Ethanol is the preferred substrate for alcohol dehydrogenase and will act as a competitive inhibitor of the conversion of methanol and ethylene glycol into their toxic metabolites. Fomepizole is a pharmaceutical alternative, which achieves the same result. Fomepizole is expensive and has been criticized for its lack of cost-effectiveness relative to ethanol. An optimal blood ethanol level of 100 to 150 mg/dl is necessary for efficacy. Patients are placed on an I.V. ethanol drip and frequent monitoring is required to assure that ethanol levels are within the therapeutic range, yet below toxicity. This level of monitoring typically requires admission to an ICU. On the other hand, fomepizole is administered orally on a regular schedule without the need for laboratory monitoring. Most patients require admission to the ICU for supportive care of toxicity. However, for the subset of patients, which could otherwise avoid an ICU admission, fomepizole becomes cost effective if it allows admission to a routine ward. The half-lives of methanol or ethylene glycol increase to over 40 hours with blockade of alcohol dehydrogenase as the parent alcohols are then eliminated primarily by the first-order processes of renal and pulmonary excretion.

Hemodialysis effectively eliminates all the alcohols and their circulating metabolites. Hemodialysis is recommended for methanol or ethylene glycol levels above 25 mg/dl. Hemodialysis occurs concurrent with ethanol or fomepizole therapy. Alcohol half-lives reduce to 3-4 hours with the combination of hemodialysis and blockade of alcohol dehydrogenase.

Besides supportive care of the CNS depressive effects and cardiopulmonary compromise of a toxic alcohol poisoning, other specific therapies include administration of bicarbonate to reverse acidosis and increase renal elmination of the organic acid metabolites by “ion trapping” in the renal tubules. Orally administered activated charcoal will limit absorption if the patient presents early after ingestion. For

methanol poisoning, administration of folic acid facilitates metabolism of formic acid into carbon dioxide and water. Similarly, for ethylene glycol poisoning, administration of IV thiamine and pyridoxine IV facilitates metabolism of glyoxylic acid into less toxic (than oxalic acid) metabolites.

Laboratory Monitoring

Gas chromatography (GC) will separate the volatilized alcohols from serum or plasma, which are subsequently detected by flame ionization. Because of a significant difference in the volatility of the alcohols and the glycols, separate columns with different vaporization and running temperatures are required. Ethanol, methanol, isopropanol and acetone and detected and quantified using the GC alcohol panel and both ethylene glycol and propylene glycol and detected and quantified using the GC glycol panel. An alcohol panel (without detection of the glycols) is a routine part of the serum/plasma overdose panel.

Detection of ethylene and propylene glycol must be ordered separately from the overdose panel. Unfortunately, our glycol assay is labor-intensive as it utilizes a different GC instrument and column than the alcohol panel, which requires *ad hoc* setup and calibration when needed. As well, glycol poisoning is relatively uncommon and does not currently warrant inclusion in our routine panel. **On the other hand, we do not want to discourage testing for ethylene glycol whenever any reasonable clinical suspicion exists. Failure to recognize such a poisoning will have disastrous consequences for the patient.** For this reason, glycol testing no longer requires approval of the laboratory medicine resident, although the resident is often informed when a test is requested in order to provide consultation (and is ALWAYS informed of any positive results). We frequently perform glycol testing on samples sent from other Connecticut hospitals. We are willing to provide this service 24 hours/day and the laboratory medicine resident is often involved for proper communication of the result to the referring clinicians.

An important role of the laboratory medicine resident involved with a suspected (or confirmed) alcohol/glycol overdose is assistance with the measurement, calculation and interpretation of the osmolal gap. A misconception exists that an osmolal gap is expected after a toxic alcohol or glycol ingestion. As detailed below, a *normal* osmolal gap is frequently observed with methanol and ethylene glycol poisoning and should NOT be considered a prerequisite for testing. Calculation of the initial osmolal gap requires measurement of the serum osmolality, sodium, BUN and glucose from a SINGLE serum or plasma sample. A common error is to utilize measurements from separate samples in calculating the osmolal gap. Small variabilities between samples (primarily related to glucose levels) can create significant errors as the final calculated osmolal gap represents a relatively small difference between two large numbers. Consider the consequences of utilizing two samples drawn before and after administration of an ampule of 50% dextrose in calculation of the osmolal gap. Note that some laboratories provide a *calculated* osmolality in their reports, which can frequently be confused with the *measured* osmolality.

Many formulas exist for the calculation of serum osmolality. *Tietz's Textbook of Clinical Chemistry* recommends:

$$\text{mOsm/kg} = 1.86\ Na^{+}\ (\text{mmol/L}) + 0.056\ \text{glucose (mg/dL)} + 0.36\ \text{BUN (mg/dL)} + 9$$

More commonly,

$$\text{mOsm/kg} = 2.0\ \text{Na (mmol/L)} + \text{BUN (mg/dL)} \div 2.8 + \text{Glucose (mg/dL)} \div 18$$

Serum osmolality should be measured by "freezing point depression". The difference between the measured and the calculated represents the osmolal gap. The "normal range" of the osmolal gap is often presented as < 10 mOsm/kg and represents the remaining osmolytes in blood not included in the calculation. An increased osmolal gap can be caused by (1) the presence of small neutral molecules in blood (essentially only an alcohol, glycol, neutral sugar such as mannitol or a ketone such as acetone), (2) a drastically elevated cation besides sodium (e.g. hypermagnasemia) or (3) an artifactual hyponatremia secondary to severe hyperproteinemia or hyperlipidemia.

The contribution of a measured alcohol level to the osmolality can easily be calculated using only the molecular weight of the alcohol (Methanol MW=32, Ethanol MW=46, Isopropanol MW=60, Ethylene glycol MW=62 and Propylene glycol=76). For example, the contribution of 100 mg/dl of methanol can be calculated

100 mg/dl Methanol ÷ 32 mg/mmole * 10 dl/L = 31.25 mmole/L or ~31 mOsm/kg.

Note also that 25 mg/dl of ethylene glycol, a level requiring hemodialysis for treatment, is predicted to contribute to the measured osmolality as

25 mg/dl Ethylene Glycol ÷ 62 mg/mmole * 10 dl/L = 4.0 mmole/L or ~ 4 mOsm/kg.

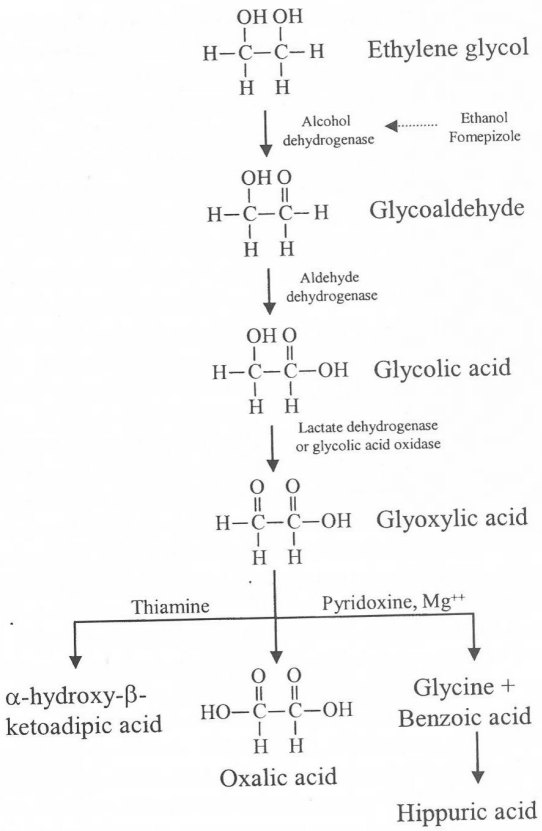
Assuming the patient began with an osmolal gap between 0-5 mOsm/kg, after ingestion of ethylene glycol to a level of 25 mg/dl, determination of the osmolal gap would likely still be < 10 mOsm/kg even though the patient had ingested a potentially severely toxic amount of ethylene glycol and would require immediate hemodialysis and blockade of alcohol dehydrogenase.

Alternatively, empirically determined conversion factors also exist (listed below) and may be used in an analogous manner to above.

	[alcohol (mg/dl)] for each mOsm/kg H_2O
Methanol	2.6
Ethanol	4.3
Ethylene Glycol	5.0
Acetone	5.5
Isopropanol	5.9
Propylene Glycol	7.1 (estimated)

Because isopropanol, methanol and ethylene glycol are often mixed in antifreeze, window cleaning, deicing and many industrial solutions, once an alcohol is detected by GC it can be useful to calculate whether unexplained excess osmoles are still present in the serum which may indicate a mixed overdose with an unmeasured glycol. Note that low levels of ethylene glycol may still be undetected using this method and, again, should not be used to *rule-out* glycol poisoning.

Lastly, many physicians employ a bedside test for the detection of antifreeze in urine. The procedure identifies fluorescein, an additive of antifreeze, which aids in the detection of radiator leaks. A sample of the patient's urine is observed under an ultraviolet lamp. If fluorescein is present, then the urine will fluoresce or "glow" under the light.



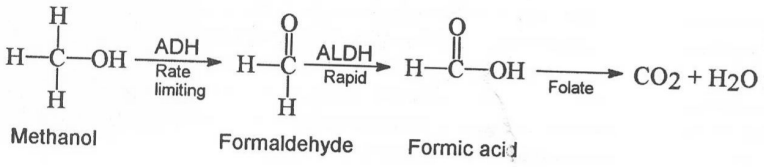


Figure 66–2. Methanol metabolism. Therapy is aimed at interfering with this conversion. Ethanol is a preferential substrate for alcohol dehydrogenase (ADH). 4-Methylpyrazole is a competitive inhibitor of the enzyme ADH. (ALDH = aldehyde dehydrogenase.)

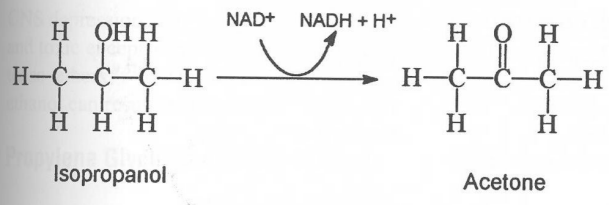


Figure 66–3. Isopropanol metabolism.

sult in the toxicity associated with ethylene glycol metabolism

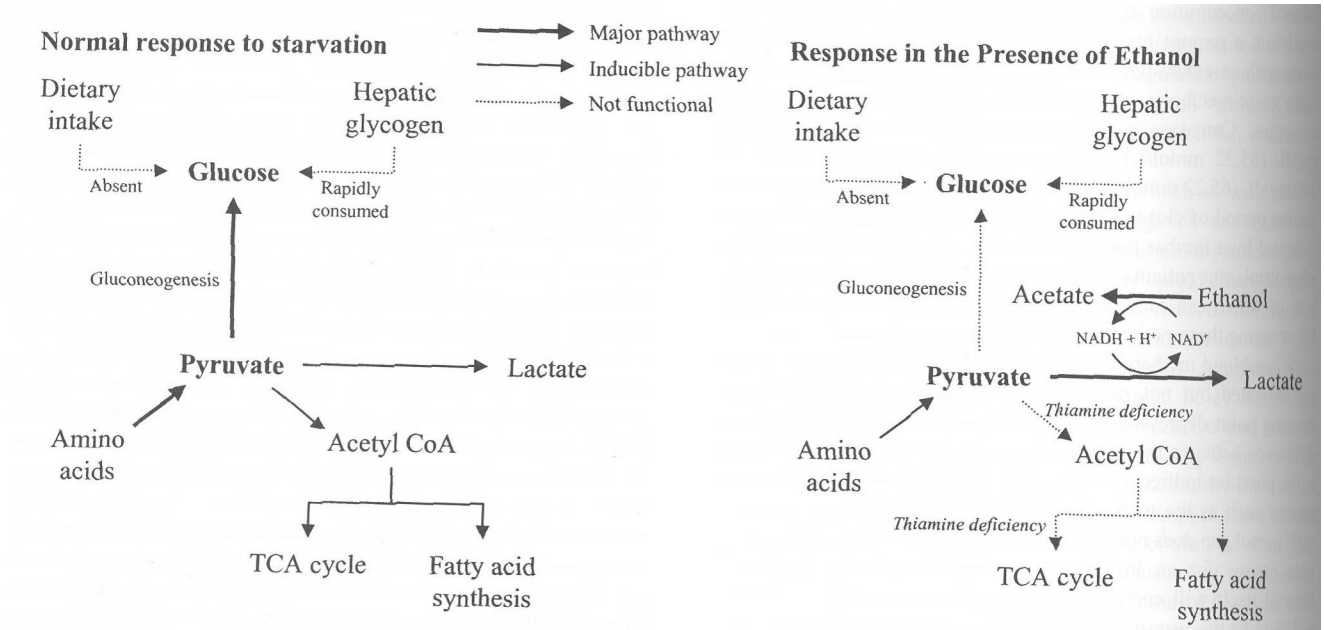


Figure 64–2. Central role of pyruvate in ethanol-induced hypoglycemia. TCA cycle = Tricarboxylic acid cycle. *(Modified, with permission, from Hoffman RS, Goldfrank LR: Ethanol-associated metabolic disorders in Endocrine metabolic disorders. Emerg Med Clin North Am 1989; 7:945.)*

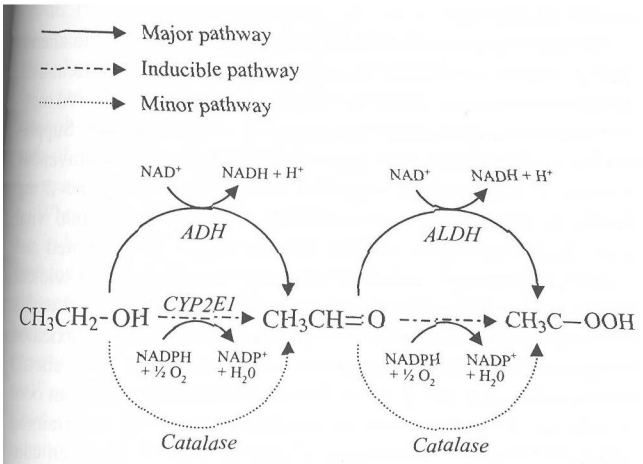


Figure 64–1. Ethanol oxidation. The major, minor and inducible pathways utilized for ethanol metabolism.

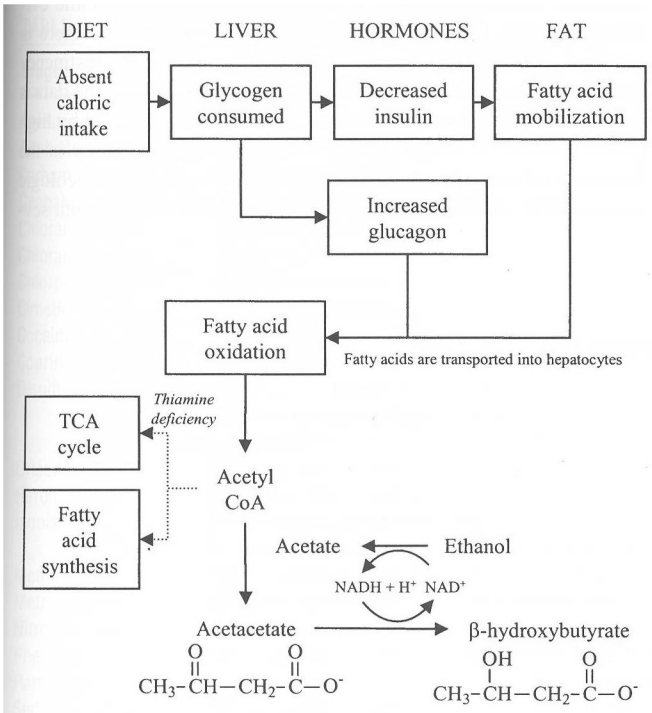


Figure 64–3. Mechanism of alcoholic ketoacidosis. *(Modified, with permission, from Hoffman RS, Goldfrank LR: Ethanol-associated metabolic disorders in endocrine metabolic disorders. Emerg Med Clin North Am 1989;7:952.)*

TABLE 66–3. Toxic Alcohols: Characteristics, Signs, and Symptoms of Toxicity

Substance	Formula	Half-life	Metabolites	High Anion Gap Acidosis	Ketosis	CNS Depression	Characteristic Findings	Commercial Sources
Benzyl alcohol	C_6H_6OH	?	Benzoic acid, hippuric acid	+	–	+	Neonatal "gasping syndrome"	Bacteriostatic preservatives
Ethanol[a]	CH_3CH_2OH	Zero-order kinetics 15–20 mg/dL/h	Acetaldehyde, acetic acid	+	+	+	Intoxication	Solvents, beverages, colognes
Ethylene glycol	CH_2OHCH_2OH	3–8.6h	Oxalic acid, glycolic acid	++	–	+	Renal failure, hypocalcemia, calcium oxalate crystals in urine	Antifreeze (95%), solvents, deicers, air-conditioning units
Glycol ether	$HOCH_2CH_2OR$	~3.1 h	Ethylene glycol and metabolites	+	–	+	Similar to ethylene glycol	Solvents, industrial coatings
Isopropanol	$CH_3CHOHCH_3$	2.5–3.5 h	Acetone	–	+	++	Ketosis without acidosis, hemorrhagic tracheobronchitis	Rubbing alcohol, solvents, lacquer
Methanol	CH_3OH	Zero-order kinetics 8.5mg/dL/h	Formaldehyde, formic acid	++	–	+	Blindness, pale edematous optic disc	Antifreeze, solvents, gasohol denaturant
Propylene glycol	$CH_2OHCHOHCH_3$	2–5 h	Lactic acid, pyruvic acid	+	–	+	Lactic acidosis	Solvents, deicers

+ = Presence and degree of symptoms; – = absence of symptoms.
[a]Only in the case of alcoholic ketoacidosis is there a high anion gap metabolic acidosis with ketonemia.

TABLE 66–2. Signs and Symptoms of Toxic Alcohol Exposures

Organ System	Ethylene Glycol	Isopropanol	Methanol
Cardiovascular	Tachycardia Hypertension/hypotension Dysrhythmias Myocarditis	Tachycardia Hypotension Myocardial depression	Tachycardia Hypotension
Central nervous	Ataxia Meningoencephalitis Convulsions CNS depression Inebriation Myoclonus	Areflexia Ataxia CNS depression Dizziness Headache Inebriation Muscle weakness Hypothermia	CNS depression Convulsions Dizziness Headache Hypothermia Inebriation
Gastrointestinal	Nausea, vomiting	Abdominal pain, cramping Gastritis Hematemesis Nausea, vomiting	Abdominal pain Anorexia Gastritis Nausea, vomiting Pancreatitis
Ophthalmic	Ophthalmoplegia Nystagmus		"Snow fields" Blurred vision Hyperemic optic discs Mydriasis Papilledema, blindness
Pulmonary	Hyperventilation, Tachypnea Pneumonitis Respiratory depression	Odor of acetone Respiratory depression Hemorrhagic tracheobronchitis	Respiratory depression
Renal	Crystalluria Renal insufficiency	Renal tubular acidosis	
Other		Rhabdomyolysis Hemolytic anemia	

Barbiturates

Availability: First prescribed in 1903, barbiturates were, until the introduction of the benzodiazapenes, the most commonly prescribed sedative-hypnotic medication. In the 1950s and 1960s, barbiturates were the most frequent abused prescription medication and responsible for the majority of drug-related suicides. Barbiturates are no longer commonly detected in the overdosed patient. Phenobarbital is still commonly prescribed as an anticonvulsant. A major goal of a barbiturate screen included within the overdose panel is to detect phenobarbital and to distinguish its presence from other barbiturates (given the difference in pharmacokinetics and reference ranges).

Pharmacokinetics

Absorption: Rapidly absorbed orally. Some are injected parenterally in order to rapidly achieve anesthesia.

Distribution: Distribution of the barbiturate is very important in determining the duration of action, plasma half-life, biological half-life and mechanism of elimination.

The shorter-acting barbiturates are taken up very rapidly by the brain and sleep is induced within a few circulation times. After that there is a slower redistribution phase when the drug is taken up by body fat and partitioned out of the CNS. This redistribution is responsible for their short duration of action. Although the plasma half-life of these short-acting barbiturates is very short, their biological half-life (time in the body) is much longer as they are slowly removed from fatty tissue and metabolized by the liver. Renal excretion of short-acting barbiturates is minimal because plasma concentrations are kept very low. As well, because plasma concentrations are low relative to tissue concentrations, reference ranges for short-acting barbiturates are very low. They are also highly protein-bound in the circulation.

Long-acting barbiturates behave very differently than their short-acting cousins. They are also absorbed rapidly after an oral dose. However, they reach peak levels in the blood only after 8 to 12 hours and in the brain after 10 to 15 hours. They do not have a dominant second redistribution phase like the short-acting barbiturates. Instead, they are slowly metabolized by the liver with 25-30% excreted unchanged in the urine. The plasma half-lives of the long-acting barbiturates are equivalent to their biological half-lives and are very long, e.g. phenobarbital has a 80-120 hour half-life. Long-acting barbiturates are not as highly protein bound in the circulation (20-45%) as the short-acting barbiturates.

Elimination: As already mentioned, short-acting barbitures are eliminated almost exclusively through hepatic metabolism with very little renal excretion due to their very low plasma levels and being highly protein bound in the circulation. Longer-acting barbiturates are eliminated by a combination of hepatic metabolism and renal excretion. Half-lives vary widely amongst the drugs and are provided in Table 61-1 of Goldfrank's Emergency Toxicology textbook.

Interpretation of Ranges

Barbiturate Class	Therapeutic Range	Toxic Level
Short-acting	1-3 μg/ml	7 μg/ml
Intermediate-acting	1-5 μg/ml	15 μg/ml
Long-acting	15-30 μg/ml	45 μg/ml

Mechanism of Effect

GABA is the major inhibitory neurotransmitter in the CNS. Barbiturates bind to GABA receptors and potentiate their effects. This is the probable mechanism of their therapeutic and toxic effects.

Clinical Presentation of Toxicity

Toxicity of barbiturates is manifested by CNS depression. Following an overdose, a patient will display slurred speech, ataxia, lethargy, nystagmus, headache and confusion. As toxicity becomes more severe, the degree of depression increases, patients may become unconscious or comatose. Severely poisoned patients may become anesthetized with total loss of neurologic function. Shock may occur due to medullary depression, peripheral vasodilation or impairment of myocardial contractility. Hypothermia and cutaneous bullae are also sometimes noted.

Overview of Therapeutic Management

The most important aspect of treatment of a barbiturate overdose is cardiopulmonary support.

For phenobarbital (and other long-acting barbiturates) administration of bicarbonate is a useful adjunct to supportive care. As the pKa of phenobarbital (7.24) is near blood pH, small changes in blood pH will have large effects on the ratio of charged to uncharged drug. Alkanization of the serum will increase the amount of charged drug, which has a lower affinity for functional sites within the brain. This will displace the drug from tissue into the serum. Alkanization of the urine will increase the rate of renal excretion of phenobarbital by "ion-trapping".

Note that for short-acting barbiturates administration of bicarbonate is contraindicated. The short-acting nature of these drugs is due to redistribution from active sites in the brain to fatty tissue. Alkanization would draw the drug out of hiding in the fat into the serum where it could be taken up again by the brain and increase its effect. This is clearly not desirable. This major difference in treatment between short-acting and long-acting barbiturates is one of the primary reasons for barbiturate detection and identification inclusion in the overdose panel (the other reason being the dramatic difference in reference range).

Laboratory Monitoring

We offer three separate tests for detection of barbiturates and all of them are utilized in the barbiturate component of the overdose panel. The 2nd and 3rd tests described below may also be separately ordered by clinicians for therapeutic drug monitoring of barbiturates.

Test 1, "Barbiturate Overdose Screen": A non-specific immunoassay on the Roche Modular Analyzer detects all barbiturates present at potentially ***toxic*** concentrations. Note that a barbiturate may be present at a therapeutic concentration but reported as negative on this screening assay. This will result in a report of "not present at toxic concentrations" for the barbiturate component of the overdose panel. On the other hand, if the barbiturate screening immunoassay is positive, further testing is employed to quantitate the barbiturate (Tests 2 and 3, below). Note that the non-specific, screening immunoassay cannot be employed for quantitation because of variable reactivity with different barbiturates. The lower limits of detection for this assay (and effectively for the overdose panel) are

Amobarbital – 15 μg/ml
Phenobarbital – 30 μg/ml
Butabarbital – 2.5 μg/ml
Secobarbital – 1.1 μg/ml
Pentobarbital – 0.5 μg/ml
Butalbital – 2.5 μg/ml
Barbital – 80 μg/ml
Sodium Thiopental – 6.0 μg/ml

Test 2, "Phenobarbital Quantitation": Phenobarbital is a common long-acting barbiturate. For the purposes of therapeutic drug monitoring, an immunoassay is available which is highly specific for phenobarbital on the Roche Modular Analyzer. If present, this assay can also quantitate the concentration

of phenobarbital in serum or plasma. The lower limit of detection for this assay is 1 μg/ml of Phenobarbital.

Test 3, "Total Barbiturate Quantitation": After extraction from serum/plasma, the "total" quantitation of all barbiturates can be achieved using UV/Vis spectrophotometry. Barbiturates share a similar absorbance band and a similar extinction coefficient for absorbance at 260 nm. Total barbiturates are extracted from serum in two steps. Serum (maintained at ph 7.4) is first extracted into chloroform and then back-extracted into a basic aqueous solution. The concentration of total barbiturates can then be determined from absorbance at 260 nm (with correction of baseline absorbance at 240 nm). The lower limit of detection for this assay is 2 μg/ml of total barbiturate (when ordered independently of the overdose panel, of course).

The barbiturate component of the overdose panel potentially involves all three of the above tests, in the case when the screening immunoassay detects barbiturates present at potentially toxic concentrations. Clinicians may order the 2nd and 3rd tests independently of the overdose panel for specific quantitation below the lower limits of detection of the screening immunoassay employed in the overdose panel.

Some clinicians may be confused about the report of barbiturates "not present at toxic concentrations" in the overdose panel. They may ask whether a barbiturate could be present at lower concentrations. It is important to communicate that barbiturates could absolutely be present at lower (or even therapeutic) concentrations. In this case, you should communicate the minimal detection limits for the relevant barbiturates in the screening immunoassay and also recommend use of the 2nd and 3rd tests for quantitation of Phenobarbital and total barbiturates, respectively.

TABLE 63–2. Sedative-Hypnotic Agents

	Plasma Half-Life (hours)	Protein Binding (%)	Vd (L/kg)	Active Metabolites
Benzodiazepines				
Alprazolam	10–14	80	0.8	None
Chlordiazepoxide	5–15	96	0.3	Desmethylchlordiazepoxide, desmethyldiazepam, oxazepam
Clorazepate		97	0.9	Desmethyldiazepam, oxazepam
Clonazepam	18–50	85.4	3.2	None
Diazepam	20–70	98.7	1.0–1.5	Desmethyldiazepam, hydroxydiazepam, oxazepam
Estazolam	8–31	93		None
Flunitrazepam	16–35	80		7-Amino-flunitrazepam
Flurazepam	2.3	97.2	3.4	*N*-Hydroxymethyl-flurazepam, desalkylflurazepam
Lorazepam	9–19	90	0.8–1.3	None
Midazolam	3–8	95	1.0–1.5	1-Hydroxymethylmidazolam
Oxazepam	5–15		0.6	None
Temazepam	10–16	97	0.75–1.37	None
Triazolam	1.5–5.5	90	0.7–1.5	None
Barbiturates				
Ultrashort acting				
Methohexital	3–6	73	2.2	Unclear
Thiopental	8–10	72–86	1.5–3.5	None
Short acting				
Pentobarbital	15–48	60–70	0.5–1.0	None
Secobarbital	15–40	46–70		None
Intermediate acting				
Amobarbital	8–42			None
Aprobarbital	14–34	20		None
Butabarbital	35–50	26		None
Long acting				
Barbital	6–12	25		
Mephobarbital	10–70	40–60		Phenobarbital
Phenobarbital	48–144	20–45	0.5–0.6	None
Primidone	3.3–22.4	19	0.6–0.8	Phenobarbital, phenylethylmalonamide
Others				
Alcohols				
Chloral hydrate	4.0–9.5	35–40	0.6–1.6	Trichloroethanol
Ethchlorvynol	10–25	30–40	4	
Phenols				
Propofol	0.5–1 (initial)	98	2–10	
Imidazolecarboxylate				
Etomidate	1.25	76	2.5–4.5	
Piperidinediones				
Glutethimide	5–22	47–59	2.7	4-Hydroxy-glutethimide
Methyprylon	3–6	60	0.97	5–Methylpyrithyldione
Propanediols				
Meprobamate	6–16	20	0.75	None
Carisoprodol	8			Meprobamate
Quinazolines				
Methaqualone	19	80–90	5.8–6.0	4-Hydroxymethaqualone
Imidazopyridine				
Zolpidem	1.4–4.5	92	0.54	None
Pyrazolopyrimidine				
Zaleplon	1.0	60	1.4	None