

CHAPTER 7

PHARMACEUTICAL TOXICITY

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Abstract

Pharmaceutical agents represent the most common causes of poisoning, with both intentional overdoses and therapeutic misadventures contributing significantly to morbidity and mortality. Analgesic toxicity varies widely by class, with acetaminophen causing delayed hepatotoxicity through toxic metabolite formation, while salicylates produce complex acid-base disturbances, hyperthermia, and multi-organ dysfunction. Opioid overdose presents with the classic triad of respiratory depression, miosis, and decreased consciousness, requiring prompt naloxone administration. Cardiovascular medication poisonings include beta-blocker and calcium channel blocker overdoses characterized by bradycardia, hypotension, and cardiogenic shock, often requiring high-dose insulin-euglycemia therapy or lipid emulsion treatment. Digoxin toxicity manifests with gastrointestinal symptoms, visual disturbances, and cardiac dysrhythmias responsive to specific antibody fragments. Among psychiatric medications, tricyclic antidepressant overdoses can cause life-threatening sodium channel blockade with QRS widening and seizures, while SSRI toxicity ranges from mild serotonin excess to life-threatening serotonin syndrome. Lithium's narrow therapeutic index leads to neurological toxicity with tremor, altered mental status, and seizures. Antimicrobial toxicities include aminoglycoside ototoxicity and nephrotoxicity, fluoroquinolone tendinopathies, and sulfonamide hypersensitivity reactions. Management principles emphasize toxin-specific interventions alongside supportive care tailored to the pharmaceutical agent's unique toxicokinetics and toxicodynamics.

Keywords: *Acetaminophen, Opioids, Cardiovascular Medications, Antidepressants, Antipsychotics, Antimicrobial Toxicity*

Learning Objectives

After completion of the chapter, the learners should be able to:

- Identify the clinical manifestations of acetaminophen toxicity and implement appropriate N-acetylcysteine therapy based on ingestion time and serum levels.
- Recognize and manage salicylate poisoning with particular attention to acid-base disturbances, enhanced elimination, and indications for hemodialysis.
- Evaluate cardiovascular medication toxicity including beta-blockers, calcium channel blockers, and digoxin, and implement appropriate treatment including antidotes and advanced cardiovascular support.
- Differentiate between various psychiatric medication overdoses based on clinical presentation and ECG findings, with emphasis on managing life-threatening complications.
- Apply specific treatment approaches for tricyclic antidepressant toxicity including sodium bicarbonate therapy and benzodiazepines for seizures.
- Recognize antimicrobial toxicities including hypersensitivity reactions, organ-specific adverse effects, and drug interactions requiring monitoring or intervention.

ANALGESICS

Analgesic medications represent among the most common agents involved in pharmaceutical poisonings, with diverse mechanisms creating varied toxicological syndromes requiring specific management approaches.

Acetaminophen

Acetaminophen (paracetamol) toxicity represents one of the most common pharmaceutical poisonings worldwide, with its ubiquity, narrow therapeutic index, and potential for severe hepatotoxicity creating significant public health impact. Normal therapeutic metabolism occurs predominantly through glucuronidation (50-60%) and sulfation (25-35%), with a minor pathway (5-10%) involving cytochrome P450 2E1 oxidation to the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). This toxic metabolite normally undergoes rapid glutathione conjugation and elimination. In overdose, however, saturation of primary metabolic pathways shunts more acetaminophen through the CYP2E1 system, depleting glutathione

stores and allowing NAPQI to form covalent bonds with hepatocellular proteins, leading to cellular death and potential liver failure.

Table 7.1: Analgesic Toxicity - Clinical Presentation and Management

Analgesic Class	Laboratory Abnormalities	Treatment Approach	Antidote
Acetaminophen	↑AST/ALT, ↑PT/INR, ↑bilirubin	Based on Rumack-Matthew nomogram	N-acetylcysteine
Salicylates	Mixed acid-base disorder, ↑anion gap	Alkalinization, fluid resuscitation, HD in severe cases	None specific
NSAIDs	↑Cr, ↑BUN, prolonged bleeding time	Supportive care, H ₂ blockers or PPI	None
Opioids	Hypoxemia, hypercarbia	Airway management, ventilatory support	Naloxone
TCAs (used for pain)	ECG abnormalities	Sodium bicarbonate for cardiotoxicity	None specific

Clinical manifestations evolve through four characteristic stages. Stage 1 (0-24 hours) presents with nonspecific symptoms including nausea, vomiting, diaphoresis, and malaise, though many patients remain asymptomatic despite potentially toxic ingestions. Stage 2 (24-72 hours) demonstrates apparent improvement in gastrointestinal symptoms while hepatic injury develops subclinically, with rising transaminases and right upper quadrant pain sometimes emerging. Stage 3 (72-96 hours) marks peak hepatotoxicity, with potential progression to fulminant hepatic failure manifesting as jaundice, coagulopathy, hypoglycemia, encephalopathy, and multiorgan dysfunction. Stage 4 (4-14 days) involves either resolution with gradual

normalization of hepatic function or death from complications of hepatic failure.

Diagnostic evaluation centers on serum acetaminophen level measurement and correlation with time since ingestion using the Rumack-Matthew nomogram. Blood sampling should occur at least 4 hours post-ingestion to allow complete absorption, with earlier levels potentially misleading due to ongoing absorption. The nomogram plots acetaminophen concentration against time, with the standard treatment line beginning at 150 µg/mL at 4 hours and declining with a 4-hour half-life to 4.7 µg/mL at 24 hours. Levels above this line indicate potential hepatotoxicity warranting antidotal therapy. Modified nomograms with lower treatment thresholds apply to high-risk patients including those with induced CYP2E1 activity from alcohol use, those taking enzyme-inducing medications, and those with glutathione depletion from malnutrition or HIV. Extended-release formulations, massive ingestions (>30 g), and co-ingestants affecting gastrointestinal motility may require additional level measurements to capture peak concentration adequately.

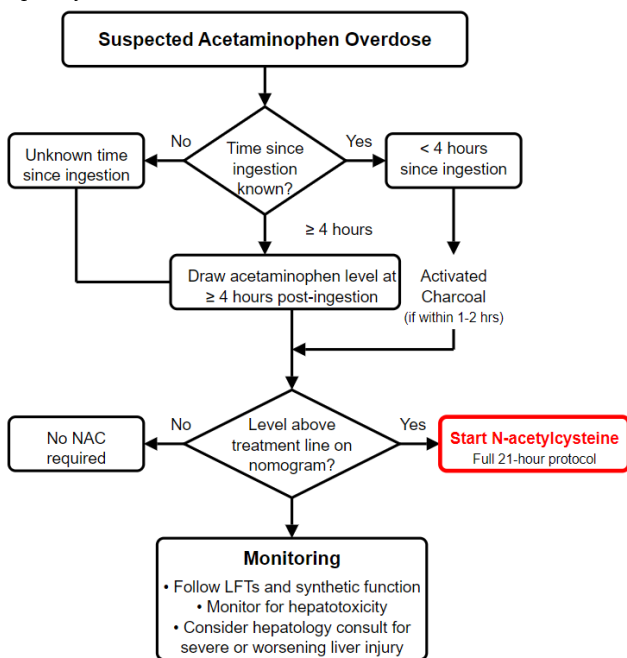


Figure 7.1: Acetaminophen Toxicity Management Algorithm

N-acetylcysteine (NAC) provides the definitive antidote for acetaminophen poisoning through multiple mechanisms: primarily replenishing glutathione stores, but also enhancing sulfation pathways, directly scavenging NAPQI, and providing anti-inflammatory and antioxidant effects that may reduce liver injury even after NAPQI formation. Oral administration follows a 72-hour protocol beginning with a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours for 17 additional doses. Intravenous administration employs a 21-hour protocol with 150 mg/kg over 60 minutes, followed by 50 mg/kg over 4 hours, and 100 mg/kg over 16 hours. Efficacy correlates strongly with early administration, approaching 100% hepatoprotection when initiated within 8 hours of ingestion but still providing benefit even in delayed presentations with established hepatotoxicity. Treatment indications include levels above the nomogram line, ingestions exceeding 150 mg/kg (or 7.5 g in adults) when levels cannot be obtained within 8 hours, evidence of hepatotoxicity, or concerning ingestions with unreliable history.



Remember

Acetaminophen toxicity causes predictable, dose-dependent hepatotoxicity through toxic metabolite formation, with N-acetylcysteine being highly effective when administered within 8-10 hours of ingestion but still beneficial even in delayed presentations

Management strategies beyond NAC administration include careful monitoring of hepatic synthetic function through serial prothrombin time/INR measurements, transaminases, bilirubin, albumin, and clinical assessments for encephalopathy development. Severe cases progressing to acute liver

failure require intensive care management addressing potential complications including cerebral edema, coagulopathy, renal failure, hypoglycemia, and infection. Specific prognostic criteria including the King's College Criteria help identify patients who may benefit from liver transplantation evaluation, though decisions require careful consideration of intentionality assessment and psychiatric comorbidity when overdose was suicidal in nature. Prevention strategies include public education about acetaminophen presence in multiple over-the-counter preparations, blister packaging limiting quantity available, and placing antidotes in healthcare facilities serving remote locations with limited access to advanced care.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) includes a diverse medication class united by their inhibition of cyclooxygenase enzymes and resulting reduction in prostaglandin synthesis, with toxicological manifestations reflecting this mechanism alongside agent-specific effects. Most acute NSAID overdoses produce limited toxicity due to favorable safety profiles and relatively high therapeutic indices for most agents within this class. Significant exceptions include mefenamic acid, which can cause seizures in overdose, and phenylbutazone, associated with aplastic anemia and agranulocytosis even at therapeutic doses. Massive ingestions of even safer NSAIDs may produce serious toxicity, with ibuprofen ingestions exceeding 400 mg/kg sometimes causing severe metabolic acidosis, altered mental status, renal failure, and rarely cardiovascular collapse.

Gastrointestinal manifestations predominate in most NSAID toxicity presentations, reflecting both direct irritant effects and prostaglandin reduction impairing mucosal protective mechanisms. Symptoms typically include nausea, vomiting, epigastric pain, and occasionally gastrointestinal hemorrhage, particularly in patients with pre-existing ulcerative disease or concurrent anticoagulant use. Central nervous system effects remain generally limited to mild headache and dizziness at lower doses, though significant toxicity may produce lethargy, confusion, and rarely seizures, particularly with mefenamic acid or with severe acidosis complicating massive ibuprofen ingestions. Renal effects include acute kidney injury through multiple mechanisms: hemodynamically-mediated through prostaglandin inhibition reducing renal perfusion, acute interstitial nephritis representing hypersensitivity reactions, and rarely direct tubular toxicity.

Specific NSAID agents present unique toxicological considerations. Salicylates (discussed separately) create complex acid-base disturbances and multi-system toxicity distinct from other NSAIDs. Mefenamic acid demonstrates greater seizure risk in overdose, with convulsions sometimes occurring with ingestions just 3-5 times therapeutic doses. Phenylbutazone causes severe hematological toxicity including aplastic anemia, though rarely seen in contemporary practice due to limited clinical use. Ketorolac demonstrates particularly potent gastrointestinal toxicity, with bleeding risk substantially increased compared to most other NSAIDs. COX-2 selective inhibitors like celecoxib were initially developed to reduce gastrointestinal toxicity while maintaining anti-inflammatory efficacy, though subsequent recognition of cardiovascular risks has limited their use.

Management of NSAID overdoses generally employs supportive care addressing specific organ system effects without available antidotes. Gastrointestinal decontamination with activated charcoal

may benefit patients presenting within 1-2 hours of significant ingestions, though generally unnecessary for minor overdoses. Intravenous fluid administration addresses potential dehydration from gastrointestinal losses while supporting renal perfusion. Acid-base monitoring identifies significant metabolic acidosis requiring intervention, most typically occurring with massive ibuprofen ingestions. Renal function requires monitoring with attention to fluid status, avoiding additional nephrotoxic agents, and occasionally temporary renal replacement therapy for significant acute kidney injury. Gastrointestinal bleeding management follows standard approaches including proton pump inhibitors, endoscopic intervention when indicated, and blood product support as needed.

Ibuprofen, the most commonly ingested NSAID, deserves specific consideration given its widespread availability and involvement in numerous overdoses. Acute toxicity severity correlates approximately with ingested amount: ingestions below 100 mg/kg typically produce minimal symptoms; doses between 100-400 mg/kg may cause significant gastrointestinal symptoms, mild central nervous system depression, and occasionally mild renal dysfunction; while ingestions exceeding 400 mg/kg risk severe toxicity with metabolic acidosis, seizures, coma, and cardiovascular depression. Anion gap metabolic acidosis represents a key marker of serious toxicity, with severe persistent acidosis despite appropriate bicarbonate therapy and fluid resuscitation indicating potential need for hemodialysis in extreme cases. Cardiovascular effects include myocardial depression and hypotension in severe overdoses, occasionally necessitating vasopressor support. Prognosis remains generally favorable even in significant overdoses when appropriate supportive care addresses complications.

Salicylates

Salicylate poisoning creates a distinctive toxidrome affecting multiple organ systems through mechanisms including direct cellular effects, uncoupling of oxidative phosphorylation, and complex acid-base disturbances. Sources include aspirin (acetylsalicylic acid) in various formulations, oil of wintergreen (methyl salicylate, with 1 teaspoon equivalent to approximately 7 g of aspirin), and various topical preparations. Toxicokinetics demonstrate notable complexities, including saturable protein binding causing disproportionate increases in free drug concentrations with rising levels, pH-dependent ionization affecting distribution (with decreased serum pH enhancing central nervous system penetration), and dose-dependent elimination kinetics leading to prolonged half-lives in severe toxicity.

Pathophysiology encompasses multiple mechanisms creating the characteristic clinical presentation. Direct stimulation of the medullary

respiratory center produces respiratory alkalosis, typically the earliest acid-base disturbance. Uncoupling of oxidative phosphorylation increases metabolic demands while impairing ATP production, resulting in hyperthermia, hypoglycemia, and lactic acidosis. Enhanced lipolysis produces ketoacids contributing to the metabolic acidosis component. Direct irritant effects cause gastrointestinal symptoms and potential pulmonary injury. These combined processes create the classic mixed acid-base disturbance, with respiratory alkalosis predominating initially, followed by concurrent metabolic acidosis in moderate to severe poisonings as compensatory mechanisms become overwhelmed.

Clinical manifestations evolve from initial predominance of respiratory alkalosis with tachypnea, tinnitus, nausea, and vomiting, to more severe presentations including hyperthermia, altered mental status, non-cardiogenic pulmonary edema, coagulopathy, renal failure, and seizures. Chronic toxicity presents differently from acute poisoning, often with more insidious onset of confusion, delirium, and metabolic findings without prominent early respiratory alkalosis or tinnitus, creating diagnostic challenges. Special population considerations include children's vulnerability to rapid deterioration from relatively smaller ingestions and the entity of Reye's syndrome, a rare but potentially fatal hepatic encephalopathy historically associated with aspirin administration during viral illnesses in children.

Diagnostic evaluation centers on serum salicylate level measurement interpreted in clinical context, as correlation between levels and symptoms varies considerably between individuals and exposures. The Done nomogram, which correlates salicylate levels with time since ingestion and toxicity severity, provides general guidance but requires cautious application due to limitations including enteric-coated or sustained-release formulations causing delayed peak levels, chronic toxicity having poorer correlation with measured concentrations, and significant individual variation in susceptibility. Comprehensive assessment includes arterial blood gas analysis demonstrating the characteristic acid-base disturbances, electrolytes revealing potential abnormalities (including hypokalemia from renal potassium wasting), glucose measurement addressing hypoglycemia risk, and renal and hepatic function evaluation. Additional studies based on clinical presentation may include coagulation studies, complete blood count, chest radiography for non-cardiogenic pulmonary edema, and neuroimaging when altered mental status etiology remains uncertain.

Management strategies address the complex pathophysiology through multiple interventions. Gastrointestinal decontamination with activated charcoal benefits patients presenting within 1-2 hours of ingestion, with multiple-dose regimens potentially valuable for enteric-coated preparations. Enhanced elimination through urinary

END OF PREVIEW

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