Drugs and pharmaceuticals: management of intoxication and antidotes

Silas W. Smith

New York City Poison Control Center, New York University School of Medicine, New York, USA

Abstract. The treatment of patients poisoned with drugs and pharmaceuticals can be quite challenging. Diverse exposure circumstances, varied clinical presentations, unique patient-specific factors, and inconsistent diagnostic and therapeutic infrastructure support, coupled with relatively few definitive antidotes, may complicate evaluation and management. The historical approach to poisoned patients (patient arousal, toxin elimination, and toxin identification) has given way to rigorous attention to the fundamental aspects of basic life support – airway management, oxygenation and ventilation, circulatory competence, thermoregulation, and substrate availability. Selected patients may benefit from methods to alter toxin pharmacokinetics to minimize systemic, target organ, or tissue compartment exposure (either by decreasing absorption or increasing elimination). These may include syrup of ipecac, orogastric lavage, activated single- or multi-dose charcoal, whole bowel irrigation, endoscopy and surgery, urinary alkalinization, saline diuresis, or extracorporeal methods (hemodialysis, charcoal hemoperfusion, continuous venovenous hemofiltration, and exchange transfusion). Pharmaceutical adjuncts and antidotes may be useful in toxicant-induced hyperthermias. In the context of analgesic, anti-inflammatory, anticholinergic, anticonvulsant, antihyperglycemic, antimicrobial, antineoplastic, cardiovascular, opioid, or sedative-hypnotic agents overdose, *N*-acetylcysteine, physostigmine, L-carnitine, dextrose, octreotide, pyridoxine, dexrazoxane, leucovorin, glucarpidase, atropine, calcium, digoxin-specific antibody fragments, glucagon, high-dose insulin euglycemia therapy, lipid emulsion, magnesium, sodium bicarbonate, naloxone, and flumazenil are specifically reviewed. In summary, patients generally benefit from aggressive support of vital functions, careful history and physical examination, specific laboratory analyses, a thoughtful consideration of the risks and benefits of decontamination and enhanced elimination, and the use of specific antidotes where warranted. Data supporting antidotes effectiveness vary considerably. Clinicians are encouraged to utilize consultation with regional poison centers or those with toxicology training to assist with diagnosis, management, and administration of antidotes, particularly in unfamiliar cases.

Introduction

The challenges to effective evaluation and management of a patient poisoned by drugs and pharmaceuticals are diverse. The circumstances surrounding exposure are often incompletely accessible. Poisoning signs or symptoms may be subtle or delayed. Patient-specific factors – pharmacogenetics and unique susceptibilities, drug-drug interactions, cultural or geographic practices, and underlying comorbidities – may complicate presentation, response to treatment, and outcome. Polypharmacy or mixed exposures may confuse the clinical presentation. Compared to the near-inexhaustible list of products and possible combinations, few specific antidotes exist. The toxicological profiles of newly intro-

duced pharmaceuticals may be incompletely characterized or unfamiliar to the treating practitioner. Finally, medical infrastructure may offer inconsistent support for diagnosis (*via* monitoring, radiological, or laboratory equipment) or treatment (through clinical service capacities or specific antidotes' availability). This chapter seeks to provide a rational approach to treatment of the poisoned patient and the use of specific antidotes where warranted.

General approach to the poisoned patient

The historical approach to poisoned patients placed undue emphasis on three areas – patient arousal, toxin elimination, and toxin identification. Beginning in the early 1900s in the setting of increased barbiturate poisonings and the limitations of airway management of the time, a sense of compulsion to "awaken" patients resulted in administration of various analeptics (from the Greek *analeptikos* – restorative, strengthening). These arousal agents included proconvulsants (picrotoxin, strychnine, pentylenetetrazol, and camphor), as well as sympathomimetics (amphetamines and methylphenidate), xanthines (caffeine, ethamivan), and nonspecific stimulants such as nikethamide, bemegride, prethcamide, and amiphenazole [1–6]. More recent "coma cocktails" have variously included dextrose or glucagon, thiamine, naloxone, flumazenil, and physostigmine [7–9]. This concept of the utility of nonselective "coma cocktails" persists despite efforts to educate on the risks of this paradigm [10].

Aggressive efforts to antagonize central nervous system (CNS) and respiratory depression were joined with similarly forceful measures aimed at detoxification, with the conviction that as much of any toxin should be removed as possible. Prehospital or in-hospital administration of apomorphine or emetics of ipecac, saltwater, mustard water, copper sulfate, zinc sulfate, antimony or potassium tartrate were once routinely recommended [11–13]. Binding agents such as Fullers earth and later, activated charcoal, kayexalate, and cholestyramine were introduced into clinical practice, and orogastric lavage and evacuants such as mercurials, saline, magnesium salts, sorbitol and whole bowel irrigation were enthusiastically endorsed [14].

Lastly, excessive emphasis was placed on determining the type, nature, and quantity of the drug ingested. Indeed, according to the "principles of therapy" of the time, toxin identification, removal, and dilution (in order of importance) *preceded* support of vital functions [15].

A more rational approach to poisoning (specifically by barbiturates) began in Denmark and Sweden in the late 1940s [16]. This "Scandinavian method" emphasized "close and constant attention to the support of vital functions" – i.e., cardiovascular and pulmonary support – as opposed to aggressive gastrointestinal decontamination and stimulant administration. Mortality consequently decreased precipitously from upwards of 20% to 1–2%. Initially derided as "pharmacotherapeutic nihilism", it was ultimately accepted that "intensive supportive therapy alone" sufficed for the vast majority of patients [17].

Thus, most poisoned patients can be treated in a straightforward manner that focuses on the patient, as opposed to the poison. Rigorous attention to the fundamental aspects of basic life support – airway management, oxygenation and ventilation, circulatory competence, thermoregulation, and substrate (glucose) availability – ensures good outcome in the vast majority of poisoned patients. An algorithmic strategy is summarized in Figure 1, realizing that many actions may occur simultaneously.
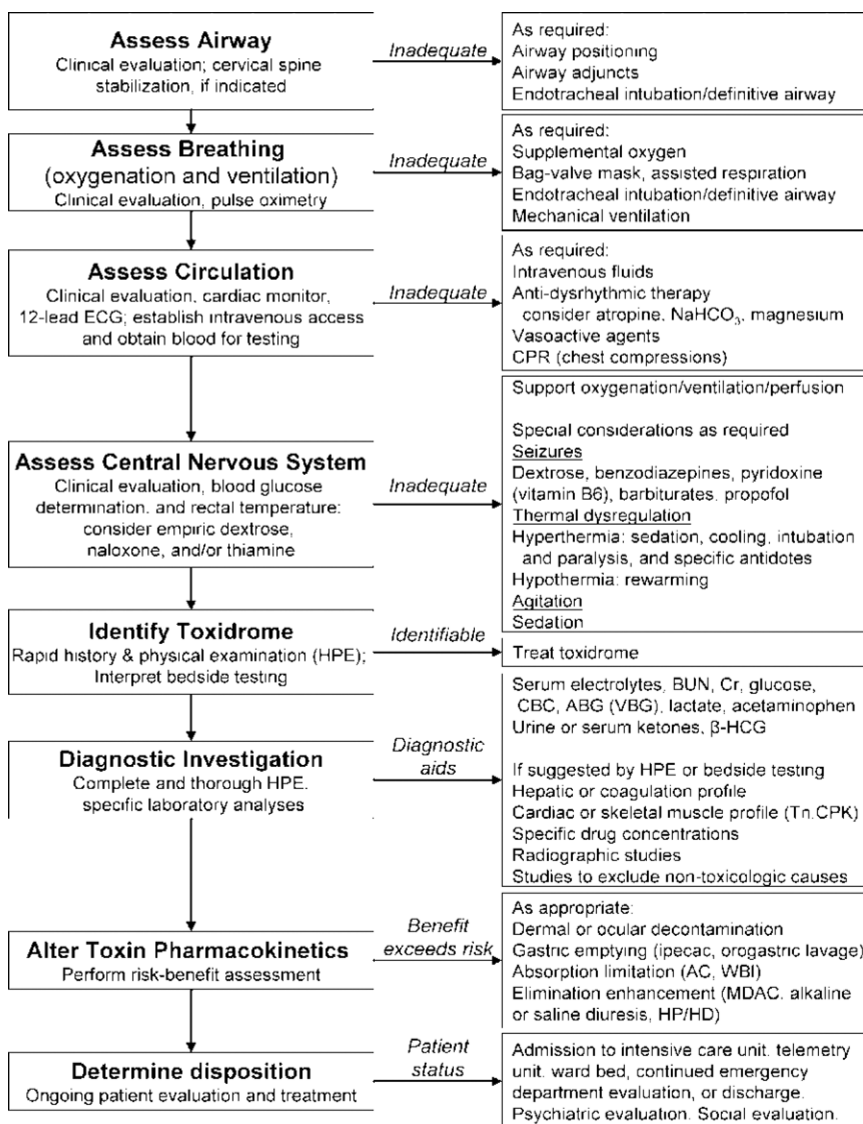

Figure 1. An algorithmic approach to the poisoned patient.

The specific details of the following maneuvers are explained in detail in emergency medicine, critical care, and anesthesiology textbooks and reviews. The patient is first assessed for airway patency and adequacy, with cervical spine stabilization if required. An inadequate airway mandates attention with airway positioning *via* head-tilt chin-lift or jaw thrust, airway adjuncts (nasopharyngeal or oropharyngeal airways), or endotracheal intubation (or surgical airway), depending upon circumstances. Inadequate breathing from either an oxygenation or ventilation standpoint is rectified with supplemental oxygen, assisted mask ventilation, or endotracheal intubation and mandatory mechanical ventilation.

Circulation is then assessed by clinical evaluation and adjuncts such as continuous cardiac monitoring and a 12-lead ECG, and intravenous (i.v.) access is obtained with simultaneous retrieval of blood for testing. Hypotension may necessitate resuscitation with i.v. fluids, colloids, or blood products, inotropic or chronotropic agents, anti-dysrhythmic therapy, or active chest compressions (CPR, cardio-pulmonary resuscitation). Conversely, life-threatening hypertension (from sympathomimetics, monoamine oxidase inhibitors, clonidine withdrawal, etc.) may require vasodilatory agents. In general, easily titratable, short-acting, direct agonists or antagonists that do not require metabolic conversion for activation are preferred – e.g., norepinephrine, phenylephrine, or epinephrine for hypotension, and nitroprusside, nitroglycerine, or phentolamine for hypertension. In the setting of a poisoned patient with a wide-complex dysrhythmia, empiric administration of sodium bicarbonate should be considered given the number of agents with cardiac sodium channel antagonism (cyclic antidepressants, Vaughan-Williams class IA and IC agents, cocaine, diphenhydramine, bupropion, propoxyphene, venlafaxine, carbamazepine, amantidine, lamotrigine, etc.). Similarly, as numerous medications are capable of inducing QT prolongation (citalopram, methadone, antipsychotics, etc.), in the setting of polymorphic ventricular tachycardia, torsade de pointes, or significantly abnormal QT interval, administration of magnesium might be advisable.

CNS manifestations of pharmaceutical intoxication are broad and may include depression or coma (e.g., benzodiazepines, barbiturates, opioids, and lithium), agitation with or without delirium (e.g., sympathomimetics, anticholinergics, and salicylates), apparent cerebrovascular accident (e.g., hypoglycemia secondary to sulfonylureas, propranolol, quinine, or salicylates), or frank seizures (e.g., bupropion, isoniazid, methylxanthines, sedative-hypnotic withdrawal, and sympathomimetics). The primary consideration is maintenance of an appropriate homeostatic milieu with adequate oxygenation, ventilation, and perfusion. During the assessment of a patient's mental status, a core (rectal) temperature should be obtained as well as bedside determination of blood glucose. Hyperthermia may be secondary to the drug itself, agitation, seizure activity, failure of feedback mechanisms, or reflect an environmental contribution. It must be immediately addressed by rapid cooling to below 38.9 °C. Failure to do so may result in irreversible cerebral injury, seizure, rhabdomyolysis, myoglobin-associated renal failure, coagulopathy, or other

organ injury. Specific management of toxicant-induced hyperthermias follows later. Hypothermia may require active or passive rewarming techniques. Clinical hypoglycemia, which implies neuroglycopenia, must be rapidly reversed with administration of 0.5–1.0 g/kg of age-appropriate dextrose-containing solutions (D50 in adults, D25 in children, and D10 in neonates). Benzodiazepines (e.g., diazepam, midazolam, and lorazepam) are generally well tolerated and are first line agents for drug- and withdrawal-induced seizures and agitation. Persistent or refractory seizures should prompt consideration of empiric administration of pyridoxine and barbiturates (phenobarbital, pentobarbital), propofol, or ultimately, general anesthesia. Coincident endotracheal intubation may be required. Phenytoin and non-barbiturate anticonvulsants are typically ineffective or harmful in toxin-induced seizures [18, 19]. Altered mental status should also prompt parenteral administration of 100 mg thiamine hydrochloride. Alcohol-dependent patients without clinically apparent Wernicke's encephalopathy may require at least 200 mg of parenteral thiamine to improve neurological symptoms; overt Wernicke's encephalopathy necessitates a minimum of 500 mg thiamine hydrochloride three times daily for 2–3 days [20]. Naloxone use is considered in a separate section.

Toxidromes (toxic syndromes) are characteristic signs and symptoms that correlate with exposure to certain xenobiotics. Identifying toxidromes suggests the etiology of the patient's condition and helps guide management. "Classic" class-effect toxidromes include anticholinergic, cholinergic, sedative-hypnotic, sedative-hypnotic withdrawal, opioid, and opioid withdrawal. These should be actively sought and managed if identified.

While the patient is being stabilized, diagnostic investigations including a complete and thorough history and physical examination, laboratory analyses, and radiological studies may be undertaken to further characterize the exposure and effect. For significantly compromised patients, a typical "chemistry panel" (providing electrolytes, blood urea nitrogen, creatinine, and indirectly the anion gap), a complete blood count, arterial (or venous) blood gas, and lactate are reasonable studies. Urine or serum ketones may be required to determine the etiology of acidemia. Female patients benefit from an assessment of pregnancy status. It is useful to determine a serum acetaminophen concentration in suicidal patients or those with altered consciousness, as patients with significant acetaminophen poisoning may present without a toxidrome. Serum acetaminophen is detectable in 2–3% of patients without a reported history of ingestion; treatable concentrations are found slightly less frequently [21, 22]. Toxin-specific studies and other serum determinations are often not rapidly returned and should be obtained only if suggested by the history, physical examination, or bedside testing. Urine drug screening (UDS) is of minimal use in the acute management of intoxication. Results are not typically returned for hours; a reported "positive" substance may not be the proximate cause of the presenting condition (as the measured metabolites may persist in urine for days to weeks); and the UDS lacks sensitivity and specificity (particularly for opioids, benzodiazepines and other sedative-hypnotics, and amphetamines).

Selected patients may benefit from methods to alter toxin pharmacokinetics – limiting exposure. A discussion of these modalities and their risks and benefits occurs in the following section. Ultimately, patients will require disposition depending of severity of presentation and anticipated sequelae, which may range from admission to intensive care units, cardiac monitoring (telemetry) units, ward beds, continued emergency department evaluation, to discharge. A psychiatric assessment and social assessment, when appropriate, should precede release from medical care. Appropriate and early consultation with medical toxicologists or regional poison centers may also assist with diagnosis and management. In the U.S., this has been simplified by a uniform telephone number (1.800.222.1222) for regional poison center consultation. The International Programme on Chemical Safety (IPCS) maintains a world directory of poison centers (http://www.who.int/ipcs/poisons/centre/directory/en/).

Adjuncts to alter toxicant pharmacokinetics

Adjuncts to alter toxicant pharmacokinetics aim to minimize systemic exposure (either by decreasing absorption or increasing elimination) or to minimize exposure of a target organ or tissue compartment. In practice, this is achieved by expulsion or removal from the upper gastrointestinal tract (induced emesis, gastric lavage, or endoscopy); intraluminal binding to adsorptive materials (activated charcoal); or increasing intestinal transit time (cathartics and whole bowel irrigation). Endogenous elimination may be improved by more effective urinary clearance (urinary alkalinization and forced diuresis), improved hepatobiliary clearance, or "gut dialysis" with multiple-dose activated charcoal. Rarely, hepatic metabolism is altered to preclude ultimate toxicant formation (e.g., cimetidine to mitigate production of dapsone's methemoglobinemia inducing metabolite). Exogenous clearance utilizes hemodialysis, charcoal hemoperfusion, continuous renal replacement therapies, and exchange transfusion. All the adjuncts attempt to shift where a patient lies upon a particular dose-response curve (Fig. 2).

Drug recovery following gastrointestinal emptying techniques has been inconsistent; human studies attempting to demonstrate a survival benefit of any decontamination modality are inconclusive. Randomized trials in which a control group might not receive any decontamination could be considered unethical; volunteer studies using sublethal doses of xenobiotic cannot show mortality benefit. As might be anticipated from the fact that supportive care suffices for the majority of poisoned patients, a typical study of routine administration of charcoal following oral overdose of primarily benzodiazepines, acetaminophen, and selective serotonin reuptake inhibitors could not demonstrate benefit [16, 17, 23]. Past studies have suffered from significant exclusions. Recommendations are based both on theoretical grounds (animal and *in vitro* studies demonstrating lower peak serum concentration or faster serum
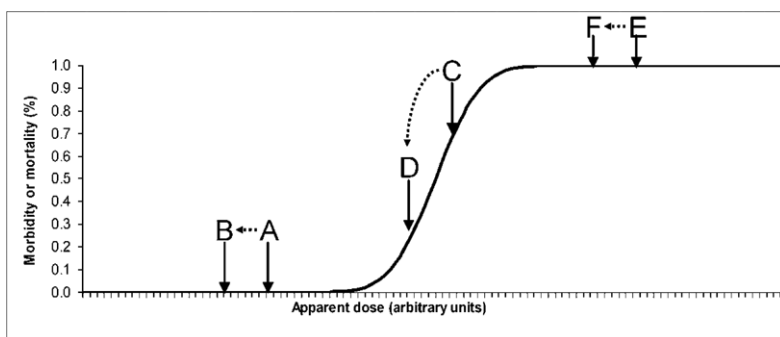
Figure 2. Adjuncts to alter toxicant pharmacokinetics attempt to shift where a patient lies upon a particular (idealized) dose-response curve. Risk will likely outweigh benefit if the patient begins at point A (negligible morbidity and mortality) and systemic exposure is reduced to B. This is the case for many drug poisonings which are managed effectively by supportive care alone. Decontamination might provide significant benefit if the patient lies upon the steep aspect of the curve [reduction from C to D – the same fixed amount as from A to B (although a percentage reduction could also be envisaged)]. With overwhelming overdose (point E), despite decontamination, benefit would be unlikely (point F).

clearance) and human studies with surrogate endpoints such as marker studies or area under the curve of plasma concentration *versus* time (AUC) improvement. Aggressive detoxification may be required for certain lethal toxins for which few antidotal options exist.

Most gastric emptying techniques are thought to be relatively ineffective beyond 1 hour. These constraints diminish possible benefit. For example, the median time from ingestion to arrival at a health care facility is on the order of 2 hours, and only about 10% of patients can be lavaged within the idealized 1-hour time frame [24]. Although in ideal situations (patients presenting early to experienced health care providers with readily available ipecac syrup) pill retrieval averages 45–55%, ipecac's benefits can be completely negated when administration is delayed as briefly as 30 min [25–28]. When orogastric lavage is performed by experienced providers within 5 min of ingestion, clinical manifestations of ingested xenobiotics have been prevented [29]. Practically, efficacy of tablet retrieval rates reduces to 45% in some cases and improvements in AUC vary from zero to 60% (averaging ~35%) [27, 30–32]. Similarly, restricting activated charcoal (AC) administration to patients presenting to health care within the first hour post ingestion would exclude up to 90% of poisoned patients from the potential benefits of AC when administered beyond an hour [24, 33]. Earlier administration of AC is more efficacious [34]. However, home and prehospital use of AC decreases the time to treatment, but has not improved clinical outcomes [35]. Drugs with opioid or anticholinergic properties that decrease peristalsis or particularly large ingestions, which independently decrease intestinal motility, may modify decision making in delayed presentations [36, 37].

Independent of side effects, the efficacy of one modality over another or combination therapy is debated. Some studies rate ipecac syrup more efficacious than orogastric lavage, but most studies have found little or no difference, and neither has been shown to be more effective than spontaneous emesis [26, 27, 31, 38]. AC has demonstrated ~50% better reductions in AUC than ipecac, which may improve or worsen its efficacy [31, 39, 40]. Gastric lavage adds no benefit to AC, except for the most critically ill patients [34, 41, 42]. Compared directly, AC has better impact than lavage on AUC and clinical effect [29, 31, 43]. Data are equivocal regarding whole bowel irrigation's ability to function similar to multiple-dose AC (MDAC) as a medium for "gut dialysis" [44, 45].

Syrup of ipecac

Syrup of ipecac is obtained from a root extract of the Amazonian flowering plant *Psychotria ipecacuanha* [46]. Its active alkaloid components, cephaeline and emetine, induce emesis *via* local irritation and central stimulation of 5-hydroxytryptamine (serotonin) 5-HT$_3$ receptors [47]. Following appropriate dose (10 mL for infants, 15–20 mL for children under 12, and 30 mL otherwise), roughly 90% of patients have a first episode of emesis within 20 min [48, 49]. Patients average three episodes in 30 min [50]. However, since ipecac's removal from most homes, the median time to administration in the acute care setting is delayed on the order of an hour, with only one-third of patients successfully vomiting within the first hour post ingestion [51].

Indications for ipecac are limited. A routinely cited example is a patient known to have taken multiple lithium tablets, which do not bind AC and may not fit through a lavage tube, who presents early to health care [50]. The American Academy of Pediatrics no longer recommends ipecac syrup for home use; ipecac use does not impact outcomes or decrease utilization of emergency services [52, 53]. Ipecac may or may not have a role in other rare ingestions that mandate gastrointestinal decontamination, but are not amenable to orogastric lavage, AC, whole bowel irrigation, or an antidote; the patient must present alert and early (<60 min post ingestion) to medical care [50].

Unsurprisingly, ipecac's most common side effect is persistent emesis. As many as eight emetic episodes occurring more than 60 min after ipecac administration have been reported [54]. This impairs administration of oral therapeutic agents, as induced emesis can last up to several hours [55]. Prolonged vomiting associated with induced sedation or absent airway reflexes increases the risk of aspiration bronchospasm, pneumonitis, and pneumonia [28, 50]. Other life-threatening side effects have been reported, including bradycardia, CNS depression, Mallory-Weiss esophageal tears, pneumomediastinum, pneumoretroperitoneum, and intracranial hemorrhage [50]. Emesis of caustics re-exposes damaged esophageal mucosa to the caustic agent. Analogous pulmonary aspiration concerns accompany induced emesis of hydrocarbons.

Orogastric lavage

Orogastric lavage is performed *via* a large bore orogastric tube (adults, 36–40 French; children, 24–28 French) with fenestrae large enough to accommodate whole tablets [32]. Serial 500-mL aliquots (100–250 mL in pediatric patients) of normal saline or lactated Ringer's solution are administered and suctioned until retrieved liquid is clear. Orogastric lavage can be expected to have its best risk-to-benefit ratio when patients present early enough to have a significant gastric burden, and when severe toxicological effects are manifest or expected to become manifest [32, 42]. Because advancement of stomach contents does occur despite proper left lateral decubitus positioning [26], AC (see below) is sometimes provided prior to crystalline lavage [32, 43].

Introduction of a large, relatively rigid tube requires a cooperative patient with a protected airway (typically an endotracheal tube if the patient is ill enough to warrant gastric lavage). Orogastric lavage risks hypoxia, dysrhythmia, laryngospasm, hypothermia, gastrointestinal or pharyngeal traumatic laceration or perforation, fluid and electrolyte abnormalities, and vomiting with subsequent aspiration pneumonia [32, 56, 57].

Activated charcoal and multiple-dose activated charcoal

AC is a convoluted macromolecule created *via* pyrolysis of carbonaceous material and subsequently "activated" with steam to further increase surface area [58]. The multiple pores of various size on the surface of each macromolecule of AC account for its high adsorptive affinity for a multitude of xenobiotics – particularly chemical species that are nonionized, aromatic, and/or branched [34, 53, 59]. Maximal xenobiotic binding occurs in 10–25 min [60].

AC decreases AUC by as much as 60%, seems to improve clinical outcomes for critically ill patients, and may benefit in certain poisonings such as acetaminophen [31, 40, 61, 62]. It also increases the rate of endogenous clearance of drugs with long half-lives and some degree of entero-enteric or enterohepatic circulation [59, 63, 64]. Those findings suggested the use of MDAC as a "gut dialysis" for toxins with slow pharmacokinetics [65, 66]. A meta-analysis of volunteer studies demonstrated increased clearance of xenobiotics with longer half-lives, but not necessarily improved clinical outcome [67, 68]. MDAC has enhanced amitriptyline, carbamazepine, dapsone, dextromethorphan, phenobarbital, phenytoin, quinine, and theophylline elimination, although without definitive clinical benefit in controlled trials [63, 64, 69]. Two studies provided conflicting results for survival benefit of MDAC for yellow oleander poisoning [70, 71].

The fraction of unbound xenobiotic decreases as the charcoal-to-toxin ratio increases from 2.5:1 up to 50:1, although the yield curve levels off near 10:1 [59, 72]. In theory, the dose of AC administered to a poisoned patient would be ten times the mass of ingested xenobiotic, but those values are unknown in

most clinical situations [73]. AC is practically dosed based on the patient's weight (1 g/kg), which can be divided into multiple smaller doses to be administered every 2–4 hours [59]. Although optimum dosing is unclear, MDAC is administered hourly, every 2 hours, or every 4 hours at a dose equivalent to 12.5 g/hour [66]. Pediatric charcoal doses are lower due to generally smaller ingestions and gut capacity. The total dose administered is the major determinant of efficacy particularly for larger overdoses, and can be administered continuously [74].

Emesis occurs in up to 12% of patients receiving AC; patients receiving AC *via* nasogastric tube or who vomited previously are at greater risk for emesis [75, 76]. Rarer complications include aspiration and intestinal obstruction or perforation [55, 59, 77, 78]. Aspirated AC may produce bronchiolitis obliterans, acute respiratory distress syndrome (ARDS), and death [79]. AC adheres to mucosa and obscures endoscopy; mineral acids and bases will not adhere to charcoal. AC poorly adsorbs short chain alcohols and metals such as iron, lead, and lithium [80]. AC administration requires an intact mental status or protected airway. Flavoring agents increase the palatability of AC for volunteers, but poisoned patients do not show increased compliance/tolerance with flavored AC [81].

Cathartics

Cathartics induce watery evacuation of bowel within a few hours. Hyperosmotic cathartic agents such as sorbitol are non-absorbed, osmotically active substances that draw water into the lumen, where increased intestinal volume and pressure promote peristalsis. So-called "saline" cathartic agents such as magnesium salts also directly stimulate smooth muscle to induce peristalsis [82]. Cathartics alone are not recommended for ingested poisons [83]. Cathartics have many adverse effects, including volume depletion, hypernatremia, hypermagnesemia, hyperphosphatemia, hypocalcemia, metabolic alkalosis, pain, nausea, emesis, and flatus [84, 85]. Sorbitol or laxatives are sometimes used in conjunction with the first dose of AC. While theoretically beneficial – minimizing the possible constipation of AC or promptly delivering AC to the duodenum, they do not increase the efficacy of AC [74, 86, 87]. Sorbitol is implicated in the fluid/electrolyte changes that occur with MDAC: hypermagnesemia, hypernatremia, and volume depletion [55, 84, 88]. Repetitive cathartic doses have been associated with rectal prolapse and death [89, 90].

Whole bowel irrigation

Whole bowel irrigation (WBI) employs polyethylene glycol (PEG), a large, non-absorbable organic polymer and an electrolyte lavage solution (ELS) is-

osmotic to serum. Large PEG-ELS volumes are introduced into the alimentary canal with less risk for fluid and electrolyte shifts caused by traditional cathartics. PEG-ELS provides non-viscous bulk for rapid transit of material in a normally functioning gastrointestinal tract. WBI should induce evacuation within 60 min, but requires 6 hours on average for complete effect. Reported improvements in AUC are modest given the more rapid absorption time for most pharmaceuticals [91]. However, reduction in AUC can be as high as 30% with poorly absorbed products or modified release preparations [92]. WBI might be considered for slowly absorbed significant ingestions such as iron, lead, and lithium, as well as modified-release preparations of β-adrenergic antagonists, bupropion, calcium-channel antagonists, carbamazepine, and theophylline [93–96]. WBI is also employed to rid patients of enterally transported illicit substances which produce toxicity upon packet rupture or leakage (e.g., cocaine, heroin, and methamphetamine) [97].

Standard dosing protocols are 1.5–2 L/h (25 mL/kg per h) enterally until rectal effluent is clear [92]. At this point, intestinal contents are assumed to have been displaced, although this is not always true [91, 98]. Nasogastric tube placement is generally required to sustain compliance with the large volume requirements, and pretreatment with an antiemetic is prudent [98]. WBI may produce nausea, vomiting, cramping, and flatus. PEG-ELS for colonoscopy has precipitated colonic perforation [99]. Unintentional bronchial administration of PEG-ELS can produce acute lung injury [100]. Ileus, obstruction, perforation or threatened perforation should preclude WBI; a protected airway is required. Desorption of toxins from AC by PEG has been demonstrated *in vitro* and *in vivo* [93, 101].

Endoscopy and surgery

Support for endoscopic therapy consists of limited case reports of retrieval in ingestions of cocaine packets, lead pellets, and medication such as sustained release calcium channel antagonists, clomipramine, iron, and meprobamate [102–106]. The procedure might be warranted for certain ingestions or cases of pharmacobezoar formation of toxic substances. Complications include perforation, aspiration, hemorrhage, and anesthetic-associated hemodynamic changes. When endoscopy fails, surgery may be required for definitive removal [107, 108]. Surgery may be required in patients with enterally transported illicit substances either due to failure of passage (with or without WBI), obstruction, or severe toxicity upon packet rupture or leakage [109, 110].

Urinary alkalinization

Weak acids in an alkaline environment exist predominantly in ionized form. Biological membranes are relatively impermeable to these charged molecules.

Alkaline serum thus inhibits the diffusion of acidic toxins (low pK_a) across cellular membranes. Similarly, an alkaline urinary pH promotes renal sequestration (or "ion-trapping") of acidic species from the systemic circulation. The relative intolerance of biological systems to acidosis limits the effectiveness of converse urinary acidification (*via* ascorbic acid or diluted HCl solutions) for renal sequestration of weak bases.

Critically ill patients may have reduced drug clearances due to decreased hepatic and renal perfusion, and thus interventions that increase clearance/elimination have the potential to significantly reduce toxicity [111]. Alkalinization improves renal elimination of chlorpropamide, 2,4-dichlorophenoxyacetic acid, diflunisal, fluoride, mecoprop, methotrexate, phenobarbital, and salicylate [112]. Urine alkalinization is considered first line therapy in patients with moderate salicylism who do not meet hemodialysis indications.

Dosing of 1–2 mEq/kg of 7.5–8.4% bicarbonate provided over 1–2 min is followed by "normal" bicarbonate infused at double the standard rate of i.v. fluid maintenance. The "normal" bicarbonate solution is prepared by adding three ampules of sodium bicarbonate (totaling 132–150 mEq) in 1 L 5% dextrose in water (D5W). The rate is titrated to maintain an alkaline urinary pH, without exceeding a serum pH of 7.55 [112].

Alkalemia decreases ionized calcium. Volume overload may occur, particularly in patients with congestive heart failure, acute renal failure, or end-stage liver disease. Bicarbonate treatment induces hypokalemia. As the proximal renal tubular cells conserve serum potassium by exchanging protons for urinary potassium, this defeats urinary alkalinization. Therefore, maintaining a normal serum potassium, with frequent monitoring and supplemental administration and/or inclusion in the bicarbonate solution, are important components of urine alkalinization.

Saline diuresis

Saline diuresis is utilized to improve excretion and minimize toxicity of overdose of ions such as magnesium, calcium, and lithium in patients who do not meet hemodialysis indications [113–115]. Hypermagnesemia may occur with excessive antacid use, gargling or ingesting magnesium sulfate compounds, and iatrogenic error [113, 116]. Hypercalcemia can result from excess calcium (in antacid tablets) or vitamin D ingestion or parenteral administration [117, 118]. Renal lithium toxicity presumably results from cytotoxic accumulation of lithium entering *via* the apical epithelial sodium channel [119]. Ensuing nephrogenic diabetes insipidus, characterized by increased water and sodium diuresis, can result in dehydration, hyperchloremic metabolic acidosis, and renal tubular acidosis. In volume depletion, activation of the renin-angiotensin-aldosterone axis leads to active resorption of sodium, and thus lithium, from the distal convoluted tubules. Therefore, adequate volume repletion with saline is prerequisite for effective renal elimination of lithium.

Boluses of 0.9% sodium chloride are administered until the patient is clinically euvolemic. Saline infusion is then provided at 1.5–2 times a standard maintenance rate. Throughout treatment renal function, urine output, and electrolytes are monitored. Congestive heart failure, renal failure, or end-stage liver disease moderate volume administration and make saline diuresis less attractive than hemodialysis in significant ingestions. Loop diuretics such as furosemide inhibit sodium resorption in the proximal convoluted tubules, and would theoretically promote elimination of lithium as natriuretics. However, these effects are countered by the action of the renin-angiotensin-aldosterone axis on the distal convoluted tubules, and diuretics do not seem to improve outcomes in lithium overdose or radiographic contrast exposure [120, 121].

Hemodialysis, charcoal hemoperfusion, and continuous renal replacement therapies

In hemodialysis (HD) the patient's blood is pumped through a circuit that includes a cartridge consisting of thousands of semi-permeable, membrane-lined capillary tubes. The blood traverses the cartridge counter-current to a circulating buffered salt solution (a.k.a. dialysate) before returning to the patient's venous circulation. Diffusible molecules flow down their electrochemical gradient from the serum to the dialysate. Hemoperfusion (HP) employs a similar circuit, but the cartridge is enveloped with AC (rather than a circulating dialysate) to adsorb xenobiotics regardless of plasma protein binding, and leave serum electrolytes largely unchanged. Continuous arteriovenous or venovenous hemofiltration (CAVH or CVVH) employ lower pressures and flow rates than HD over longer sessions for patients unable to tolerate HD or to remove xenobiotics with slow tissue redistribution [122, 123]. Peritoneal dialysis (PD) is ineffective in poisoning management, given its inherently slow kinetics and the availability of HD [124].

Extracorporeal therapies may be warranted when criteria are met for both the xenobiotic and the patient [125]. Favorable dialyzable toxin properties include low volume of distribution (V_d), relatively low molecular weight, and poor serum protein binding (or binding that worsens in overdose, as is the case for salicylate and valproate) [126]. Patient characteristics suggesting extracorporeal therapy include signs or symptoms of significant end organ toxicity; impaired elimination secondary to baseline comorbidities or critical illness-induced hypoperfusion; inability to tolerate or refractory to antidotal strategies (such as bicarbonate or saline); inadequate response to supportive care measures; concurrent electrolyte derangements (e.g., metformin-associated lactic acidosis); or serum drug concentrations historically associated with severe outcome [127]. Traditionally, charcoal HP was used for xenobiotics significantly bound to plasma proteins, but its use is declining while (high-flux membrane) HD increases.

Methanol, ethylene glycol, salicylates, lithium, halides, theophylline, and metformin-associated lactic acidosis are commonly treated with dialysis [125].

HD is used for valproate and carbamazepine poisoning; however, in the absence of high-flux dialysis membranes, the characteristics of charcoal HP may more appropriately address the larger V_d and protein binding [128].

Common side effects of extracorporeal elimination include hypotension, bleeding, and infection. Enhanced clearance of therapeutic medications and antidotes (e.g., antibiotics, fomepizole, *N*-acetylcysteine, water-soluble vitamins) may occur. The need for dialysis must be anticipated early; several hours of preparation time may be required to secure vascular access, equipment, and personnel.

Exchange transfusion

Exchange transfusion is a total blood volume exchange administered in small aliquots. Serial frequent phlebotomy of a small amount of circulating blood occurs with simultaneous transfusion of equivalent donor blood. This process is repeated until two to four vascular volumes have been exchanged. While the procedure is very rarely used for toxin removal, exchange transfusion is more familiar to clinicians treating severe hemolytic diseases of the newborn, hyperbilirubinemia without hemolysis, and sickle cell crisis.

Exchange transfusion removes xenobiotics that are large or bound to plasma proteins, such as thyroxine, iron, or theophylline [129, 130]. For life-threatening ingestions, exchange transfusion is a viable option for neonates and infants whose immature vasculature cannot tolerate extracorporeal elimination modalities or in institutions lacking pediatric dialysis capacity. Exchange transfusion has been successfully employed in pediatric iron, isoniazid, phenobarbital, salicylate, theophylline, and vincristine overdose [129–134]. It has also been suggested for refractory drug-induced methemoglobinemia [135]. Whole blood exchange was utilized in an adult with a 50-fold cyclosporine dosing error [136]. Anticipated complications arise from vascular access, bleeding, hypoglycemia, hypotension, and blood product administration (immune-mediated reactions, blood incompatibility, and infections).

Toxicant-induced hyperthermia

Several hyperthermic syndromes are caused by xenobiotics. These are generally spectrum disorders, whose features may overlap with other conditions such as CNS infection, agitated delirium, and sepsis. Malignant hyperthermia (MH) occurs in patients with an autosomal-dominant defect in genes encoding the skeletal muscle ryanodine receptor (RyR-1) or the voltage-gated calcium channel (Cav1.1) who are exposed to volatile anesthetics or depolarizing muscle relaxants (succinylcholine) [137]. Hypomagnesemia may increase the probability and possibly severity of an MH event [138]. The subsequent rapid

increase in myoplasmic calcium concentration increases muscle metabolism and heat production and produces muscle contractures and hyperthermia. Neuroleptic malignant syndrome (NMS) is characterized by high fever, autonomic instability, altered mental status, and muscle rigidity. Potent antipsychotics (neuroleptics) such as haloperidol and other medications (metoclopramide, droperidol, and promethazine) with significant dopamine antagonism, as well as abrupt cessation of dopaminergic agents such as those used in Parkinsonism, can precipitate this life-threatening syndrome [139]. NMS typically develops over several days and is characterized by ''lead-pipe'' rigidity [139]. Drugs that impair serotonin breakdown or re-uptake, those that act as serotonin precursors or enhance its release, or those that are serotonin agonists may lead to serotonin syndrome. Like NMS, serotonin syndrome is a spectrum disorder for which various signs and symptoms have been proposed to establish diagnosis (e.g., Sternbach and Hunter criteria) [140, 141]. In its most severe form it consists of high fever, autonomic instability, altered mental status, and may have associated diaphoresis, shivering, tremor, diarrhea, or spontaneous clonus. In serotonin syndrome, onset of symptoms is usually rapid, with 60% of patients with the serotonin syndrome presenting within 6 hours of drug exposure, and tremor and hyperreflexia predominant in the lower extremities may be a prominent feature [142]. Sympathomimetic-associated hyperthermia, seen with acute intoxication with cocaine, amphetamines, substituted amphetamines, and phencyclidine, may be clinically indistinguishable from serotonin syndrome [143]. Additionally, the agitated delirium engendered by these agents may be difficult to distinguish from that induced by hyperthermia itself. Patients with anticholinergic-associated hyperthermia will generally present with a compatible "toxidrome" – agitation; mydriasis; dry, hot, and erythematous skin; hypoactive bowel sounds; and urinary retention. While rare, thyrotoxicosis factitia, the ingestion of excess thyroid hormones due to inadvertent intake (pharmaceutical or food contamination), misuse (dieting), or significant intentional ingestion may produce hyperthermia [144, 145]. Hyperthermia may accompany toxicity with agents that uncouple oxidative phosphorylation (e.g., salicylates, dinitrophenol, pentachlorophenol) [146].

Multiple medications can also complicate or contribute to environmental hyperthermia. Several reviews and epidemiological data from major heat waves have demonstrated that anticholinergics, antiepileptics, antihistamines, antihypertensives in general and diuretics in particular, antipsychotics, and others contribute to excess morbidity and mortality [147, 148]. Conversely, exogenous heat stress can increase mortality from specific xenobiotics. In an urban setting at ambient temperatures above 31.1 °C, the mean daily number of fatal cocaine overdoses increased markedly [149].

Regardless of the cause for the hyperthermic syndrome, cessation of any possible offending or contributing agents and rapid cooling is critical. The degree of hyperthermia produced correlates with death and neurotoxicity in animal models, and temperature normalizing intervention is critically impor-

tant in attenuating CNS injury and mortality [150]. Studies from the Chicago and France heat waves show that this is rarely done in a timely manner (if at all) in cases of environmental hyperthermia, with devastating results [147, 148]. The benefits of rapid cooling by ice water immersion were demonstrated over 80 years ago [151]. A large review concluded that cooling methods based on evaporative heat loss are less efficient than immersion in ice water in dissipating heat [152]. Additional studies demonstrate that cooling rates of up to 0.15–0.20 °C/min can be achieved with immersion, two to three times that of evaporation [153, 154]. Regardless of the method used, effectiveness should be repeatedly assessed.

Sedation with benzodiazepines and rigorous supportive care are necessary adjuncts in significant cases. This is primarily accomplished with titrated doses of benzodiazepines to inhibit muscle rigidity and control agitation. Animal models have demonstrated the benefit of benzodiazepines in prolonging survival, preventing seizure, and attenuating agitation in the toxicological hyperthermias [155, 156]. Phenytoin is ineffective in animal models [157]. Phenothiazines and butyrophenones, while reported, may have delayed onset and compromise mental status, lower seizure threshold, impair heat dissipation, and worsen hypotension [143].

Neuromuscular paralysis may be required to limit further heat generation in cases of NMS, serotonin syndrome, and sympathomimetic-associated hyperthermia. As the pathophysiology of MH is beyond the neuromuscular junction, paralytics are unlikely to provide benefit. Rapid i.v. administration of dantrolene, a direct-acting skeletal muscle relaxant, is the only drug proven effective for prevention and treatment of MH. Dantrolene disrupts the pathogenic excitation-contraction coupling by acting at RyR-1 to suppress depolarization-induced sarcoplasmic reticulum calcium release and normalize the voltage dependence of contractile activation [158]. Reversal of increased myotube sensitivity may also play a role [159]. Intravenous 2–3 mg/kg dantrolene is repeated until symptoms are controlled or 10 mg/kg (or more) has been administered. Following initial treatment, 1–2 mg/kg i.v. or per os is given every 6 hours for 24–72 hours to prevent recurrence. Dantrolene is packaged in vials containing 20 mg dantrolene sodium; thus, multiple vials are needed for treatment of adult patients. A large review of NMS cases did not suggest a beneficial role for dantrolene, although one case-controlled analysis found benefit [160, 161]. Bromocriptine, a dopamine agonist, has been used (off-label) to treat NMS at doses ranging from 5 to 20 mg every 6 hours [143]. Common side effects include hypotension, dyskinesia, erythromelalgia, and hallucinations. Cyproheptadine, developed as an antihistamine, additionally antagonizes 5-HT$_2$ receptors. Cyproheptadine for serotonin syndrome (off-label) is initially used in a dose range of 4–12 mg, followed by 2 mg every 2 hours for persistent symptoms; upon symptom control, 8 mg maintenance dosing is provided every 6 hours [142]. The tablet form necessitates administration orally or crushed *via* nasogastric tube.

Analgesic and anti-inflammatory antidotes

N-Acetylcysteine

N-Acetylcysteine (NAC) provides an effective means of prevention and treatment of acetaminophen (*N*-acetyl-*p*-aminophenol, APAP; paracetamol)-induced hepatotoxicity. NAC is also employed to preclude radiographic contrast-induced nephropathy [162]. The ultimate toxicant of APAP, *N*-acetyl-*p*-benzoquinone imine (NAPQI) generated primarily by CYP2E1 and CYP3A4, depletes glutathione (GSH), binds intracellular components, and, through an incompletely understood process, produces hepatic injury, centrilobular necrosis, or hepatic failure [163, 164]. NAC works by multiple mechanisms. It augments APAP sulfation to a nontoxic metabolite, it acts as a glutathione precursor or glutathione substitute to detoxify NAPQI, and possibly reverses NAPQI oxidation [165, 166]. NAC provides substantial benefit even in cases of delayed presentation following overdose [167]. Extra-hepatic benefits of NAC include improving cardiac index and systemic mean oxygen delivery despite decreasing systemic vascular resistance [168]. In a range of hepatic disorders, NAC improved baseline oxygen delivery, oxygen consumption, and dye clearance in a majority of patients [169]. Liver blood flow and cardiac index improved in septic shock patients provided NAC [170]. Only L-NAC is beneficial. Animal experiments demonstrate that the L-isomer, derived from physiological L-cysteine, prevents hepatotoxicity and provides prolonged elevations of hepatic glutathione [171]. Nonphysiological D-NAC cannot increase glutathione stores or prevent hepatotoxicity, despite increasing acetaminophen sulfation [172].

According to Rumack [163], the oral NAC dosing strategy was reached by estimating the absorption and turnover rate of glutathione at 6 mg/kg per h and an FDA safety factor of 3, to yield 70 mg/kg every 4 hours [6 (mg/kg per h) × 4 (h) × 3 (safety factor) = 72 ≈ 70 mg/kg every 4 h]. There were several assumptions as to "normal" hepatic glutathione levels and APAP to NAPQI conversion. A 140 mg/kg loading dose was added to provide an early high hepatic dose. The 72-hour duration of oral therapy was based on previous observations of multiple patients with prolonged APAP half-lives and a desire to implement a protocol that would accommodate those with half-lives longer than 12 hours (anticipating disappearance after five half-lives). While many have suggested that the 72-hour oral course is excessive, particularly after APAP has disappeared from the serum, the optimal duration of therapy is unclear. Studies assessing a shortened or "patient-tailored" approach have been small or methodologically limited [173, 174].

The Rumack-Matthew nomogram guides initiation of NAC therapy in single acute ingestions. The "treatment line" is anchored at an APAP serum concentration of either 200 μg/mL ("200 line") or 150 μg/mL ("150 line") at 4 hours post ingestion and decreased by 50% every 4 hours. The slope of the treatment line does not reflect APAP kinetics. The "150 line" is utilized in all

patients in the U.S. and Australia; in the U.K. and elsewhere the "200 line" is employed, with a "100 line" modification for an array of individuals deemed at "high-risk": ethanol tolerant, those at risk for glutathione depletion (malnutrition, HIV, eating disorders, cystic fibrosis), pregnancy, and those prescribed enzyme-inducing drugs (carbamazepine, phenytoin, phenobarbitone rifampacin, isoniazid, etc.) [165, 175]. The U.S. multicenter study substantiated the safety and efficacy of its approach [176]. Proponents of the "150 line" point to the fact that 3.45–12.9% of patients above the "150 line" but below the "200 line" developed biochemical hepatotoxicity (aspartate aminotransferase, AST >1000 IU/L at any time during their course) in the U.S. multicenter trial and that patient deaths have occurred in untreated patients "between the lines" [177, 178]. In patients presenting near 8 hours after ingestion, or if a level is not available before 8 hours post ingestion, NAC is begun while awaiting APAP results and then continued or stopped once the results are available and have been plotted on the nomogram. If the time of ingestion is unknown or more than 24 hours has passed, NAC is administered. When APAP concentration and transaminase results are obtained, if transaminases are elevated or if measurable APAP exists, a full course of treatment is provided. With normal aminotransferases and without detectable APAP, treatment is not required. Concentrations obtained less than 4 hours post ingestion are not useful except to completely exclude ingestion (i.e., it is useful only if the APAP concentration is undetectable). Ongoing absorption may place individuals above the line at 4 hours, or metabolism or charcoal administration may result in a patient falling below the nomogram at 4 hours. In cases of chronic ingestion (>7.5 g/day in adult), laboratory evaluation and treatment are provided as for an unknown time of ingestion. With elevated transaminases or measurable APAP, NAC is provided.

Oral NAC is cheap and familiar to clinicians. It has minimal side effects (other than vomiting and odor) and is preferred in patients with bronchospastic disease. Its use can become problematic in cases where oral delivery is compromised, e.g., in patients with depressed mental status, significant vomiting, or impaired gastric motility. Use of an anti-emetic is encouraged.

Intravenous NAC appears to be similarly efficacious to oral NAC and eliminates many delivery issues. It has a much shorter therapy course (21 hours), expediting medical and psychiatric disposition. It avoids first pass metabolism in cases where the liver is not the only target or interest, such as those with cerebral edema or pregnancy. While i.v. NAC is slightly more expensive, total hospital charges may be less due to decreased treatment time. Histamine-mediated anaphylactoid reactions are more commonly seen with rapid i.v. loading and in patients with lower APAP levels [179]. Mild reactions have been treated by slowing the infusion rate and providing i.v. diphenhydramine, although this might alter NAC and APAP kinetics. Dosing complexity – 150 mg/kg in 200 mL of 5% dextrose over 1 hour, followed by 50 mg/kg in 500 mL of 5% dextrose over 4 hours (12.5 mg/kg per h), and then 100 mg/kg in 1000 mL of 5% dextrose over 16 hours (6.25 mg/kg per h) – yields frequent administration

errors [180]. The supplied 20% solution was too concentrated for children, and dilution according to adult guidelines resulted in excess free water, and cases of hyponatremia and seizures [181]. The current U.S. package prescribing information (http://www.acetadote.net/PI_Acetadote_Revised_Apr09.pdf) and dosage calculator website (http://www.acetadote.net/dosecalc.shtml) provide dosing and administration guidelines in patients of less than 40 kg.

In a study limited by different comparison groups, data acquisition methodology, treatment location and several other factors, 20-hour only i.v. NAC was favored in patients with early presentation (<12 hours), whereas late presentation favored oral 72-hour NAC [182]. However, continuous i.v. infusion in delayed presentations with APAP-induced fulminant hepatic failure showed clear benefit in a prospective study [167]. Whatever the route, prior to cessation of NAC therapy, negative APAP concentrations and normal transaminases must be ensured, particularly in cases of massive ingestion; hepatotoxicity may follow premature cessation of therapy [183, 184]. The 16-hour maintenance dose is continued in patients receiving i.v. NAC until APAP is undetectable and transaminases are normal (or at baseline). Experimental evidence and human case reports demonstrate both delayed absorption, delayed increase following initial decline, and "crossing the nomogram" with extended-relief, opioid- or anticholinergic-containing APAP products, or co-ingestants [185, 186]. In cases of hepatic failure, i.v. NAC is continued until resolution, transplant, or death.

Anticholinergic antidotes

Physostigmine

Historically, physostigmine (eserine), a reversible carbamate inhibitor derived from the seed (Calabar bean) of the vine *Physostigma venenosum* Balfour, was used in the ancient trial by ordeal [187]. Medicinal use of physostigmine was first reported in 1864 to reverse severe atropine poisoning [188]. Naturally available (–)-physostigmine is over 100 times more effective in inhibiting acetylcholinesterase and butylcholinesterase in tissue, erythrocytes, and serum in humans and animal models than its stereoisomer [189, 190]. This activity depends upon interactions within the hydrophobic pocket of the acetylcholinesterase active center, which is distinct from the catalytic site [191]. Additionally, physostigmine binds nicotinic receptors close to, but distinct from, the acetylcholine binding site on the α-subunit [192]. At low doses, physostigmine functions as an ineffective nicotinic receptor agonist, while at higher doses it produces marked channel blockade.

Physostigmine's nonspecific analeptic properties [8] are no longer considered useful in overdose, given the clear benefits of supportive care. Indiscriminate use of physostigmine and an incomplete understanding of the pathophysiology of tricyclic antidepressant (TCA) poisoning was associated

with bradydysrhythmias including asystole, seizure, and several deaths [193, 194]. In animal models, physostigmine is ineffective in attenuating TCA-induced seizures [195]. It failed to abolish dysrhythmias, decreased blood pressure, and at high doses enhanced TCA toxicity [196]. Physostigmine is currently recommended as a diagnostic and therapeutic agent for antimuscarinic poisoning [197]. Patients should have clear peripheral or central manifestations of the anticholinergic toxidrome. As a tertiary amine, physostigmine can cross the blood-brain barrier to reverse the central effects. An ECG should exclude sodium or potassium channel blockade (QRS or QT prolongation). Excessive physostigmine will produce a cholinergic syndrome, with muscarinic and nicotinic effects. As the adverse effects of bradycardia and bronchorrhea can produce significant morbidity, continuous cardiac monitoring and immediate access to atropine are recommended during physostigmine administration. Physostigmine, 1–2 mg in adults and 0.02 mg/kg (maximum 1.0 mg) in children is infused slowly over at least 5 min [198]. Repeat doses every 10–15 min can be provided if an adequate response does not occur and adverse effects are absent. Re-bolusing may be required in the setting of antimuscarinics with a prolonged duration of action.

Anticonvulsant antidotes

L-Carnitine

The anticonvulsants include carbamazepine, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproic acid (VPA), vigabatrin, and zonisamide. These drugs enjoy widespread approved and off-label use for additional conditions, e.g., fibromyalgia (pregabalin); neuropathy and neuropathic pain (carbamazepine, gabapentin, lamotrigine, levetiracetam, and pregabalin); panic disorder (tiagabine); migraine prophylaxis and treatment of obesity, ethanol dependence, and depression (topiramate); and bipolar disorder (carbamazepine, lamotrigine, and VPA). Treatment of anticonvulsant overdose is largely supportive, with particular attention to the CNS-depressant and cardiovascular effects of some of these agents. L-(R)-Carnitine exists as the sole specific antidote in this class for significant VPA (di-n-dipropylacetic acid, 2-propylpentanoic acid) poisoning. Patients with drug-associated mitochondrial toxicity (particularly from nucleoside analogs) and anthracycline cardiotoxicity might also benefit from its administration [199, 200].

The anticonvulsant properties of VPA derive from its ability to increase γ-aminobutyric acid (GABA) availability *via* inhibition of GABA transaminase and succinic semialdehyde dehydrogenase, to attenuate *N*-methyl-D-aspartate (NMDA)-type glutamate receptor excitatory effects, and to slow the rate of recovery from sodium channel inactivation [201–203]. Additionally, VPA appears to affect inositol levels similar to lithium. Therapeutic concen-

trations are 50–100 mg/L. Potentially toxic concentrations are greater than 120 mg/L. Oral absorption of VPA is excellent [204]. Peak plasma concentrations are generally seen in 1–4 hours, although this may be markedly delayed by overdose, enteric coating, or meals [205]. Manifestations of significant VPA toxicity include CNS effects (lethargy, seizure, coma, cerebral edema), respiratory depression, metabolic derangement (hypernatremia, hyperammonemia, hypocalcemia, metabolic acidosis, carnitine deficiency), gastrointestinal effects (nausea, vomiting, and abdominal pain), pancytopenia, pancreatitis, and hepatotoxicity [206, 207]. Valproate toxicity is seen both in intentional acute overdose and in those on chronic therapy, either without adequate carnitine supplementation or on complex regimes.

Cells attempt to metabolize the VPA that is not directly excreted or glucuronidated in a manner similar to other fatty acids (Fig. 3). Thus, VPA is conjugated with coenzyme A (CoA). Carnitine enters *via* an ATP-dependent transporter. VPA is then transferred to carnitine, the normal mechanism for fatty acids entry into the mitochondrion. However, VPA-carnitine both inhibits the carnitine transporter and also diffuses out of the cell to be lost *via* renal excretion [208]. Renal resorption of carnitine is also impaired [209]. These factors contribute to intracellular carnitine depletion. Once VPA-carnitine is shuttled into the mitochondrion, it is reattached to CoA. It then undergoes β-oxidation, in an attempt to generate 2-carbon molecules for entry into the Krebs cycle. The 2-en-VPA-CoA product is neurotoxic with a prolonged half-life. The terminal 3-keto-VPA product traps CoA, leading to its mitochondrial depletion. Decreased mitochondrial CoA yields decreased ATP production, diminishing usable cellular energy currency and further limiting carnitine entry into the cell (*via* an ATP-dependent carnitine transporter). Once carnitine is depleted, normal fatty acid metabolism cannot occur [206]. Fatty acid build up is thought to underlie the Reye's-like steatohepatitis, which can be seen in toxicity [210]. CoA is also needed to make *N*-acetylglutamate, an activator of carbamoylphosphate synthetase I (CPS I), a critical enzyme in the urea cycle. When its effectiveness is limited due to inadequate activator, ammonia cannot be incorporated, and consequently, its concentrations increase. Furthermore, as CoA is depleted, β-oxidation shifts to omega (ω), or terminal carbon oxidation. This creates (among others) the hepatotoxic 4-en-VPA product. 4-en-VPA additionally inhibits CPS I, further preventing nitrogen elimination and contributing to hyperammonemia.

L-Carnitine (levocarnitine) supplementation has been recommended to reverse the adverse metabolic effects of VPA in cases of VPA-induced hepatotoxicity, VPA overdose, and primary carnitine-transporter defects [211, 212]. Hyperammonemia and serum and muscle carnitine deficiency are well described in patients chronically taking VPA [213–215]. Several studies and case reports demonstrate that carnitine supplementation reverses clinical symptoms, hypocarnitinemia, hyperammonemia, and VPA half-life prolongation in patients with toxicity due to chronic administration [216–218]. In patients with acute VPA overdose, limited clinical and laboratory data derived
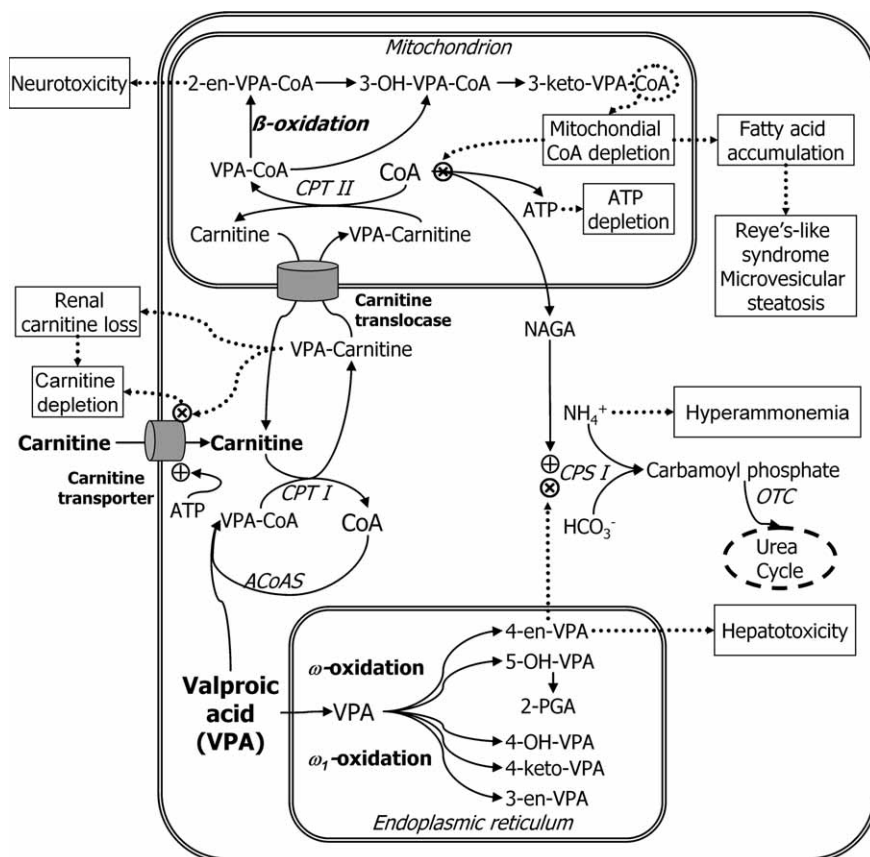
Figure 3. Valproic acid (VPA) metabolism and toxic mechanisms (see text for details). Several additional valproate metabolites are omitted. Enzymes (*italicized*): ACoAS, acyl-CoA synthetase; CPS I, carbamoyl-phosphate synthetase 1; CPT I, carnitine palmitoyltransferase I (reaction occurs on mitochondrial outer membrane); CPT II, carnitine palmitoyltransferase II (reaction occurs on mitochondrial inner membrane); and OTC, ornithine transcarbamylase. Substances: ATP, adenosine triphosphate; 2-, 3-, or 4-en-VPA, 2-propyl-2-, 3-, or 4-pentenoic acid; 3-, 4- or 5-OH-VPA, 3-, 4- or 5-hydroxy-2-propylpentanoic acid; 3-keto-VPA, 3-oxo-2-propylpentanoic acid; 2-PGA, 2-polyglutaric acid; 4-keto-VPA, 4-oxo-2-propylpentanoic acid; and NAGA, *N*-acetylglutamate. Symbols: ⊕, agonism or co-factor; ⊗, antagonism. Data used can be found in [201, 202, 204, 212, 482].

from case reports also suggest that reversal of metabolic derangements and improvement in clinical symptoms occurs when carnitine is provided [219–221]. A single large retrospective analysis showed a significant survival benefit with i.v. carnitine supplementation (with VPA cessation) in patients with valproate-induced hepatotoxicity [222].

L-Carnitine dosing for cases of overdose is not currently evidence based. An oral or i.v. dose of 100 mg/kg per day, divided and given every 6 hours (maximum daily dose 3 g), is provided to those patients with acute overdose and

asymptomatic hyperammonemia or hepatotoxicity in the absence of CNS depression or metabolic derangement [211]. Symptomatic patients with hyperammonemia or symptomatic hepatotoxicity should receive 100 mg/kg L-carnitine i.v. over 30 min (maximum 6 g), followed by 15 mg/kg every 4 hours over 10–30 min until clinical improvement occurs [211, 223]. Others have supplemented at the higher dosing strategy when VPA concentrations exceed 450 mg/L [224]. In addition, given the decrease in protein binding that occurs, hemodialysis or hemoperfusion is recommended for patients with VPA concentrations exceeding 850–1000 mg/L or with severe clinical symptoms [202].

L-Carnitine is generally well tolerated. Side effects associated with carnitine supplementation are nausea, abdominal discomfort, dose-related diarrhea, and fishy body odor [223]. A small retrospective chart review found no adverse effects or allergic reactions in VPA overdose patients administered carnitine [225]. The current L-carnitine package inserts have no warnings or contraindications, but note that seizures have been reported to occur in patients, with or without pre-existing seizure activity, who received either oral or i.v. L-carnitine [226]. Up to 600 mg/kg per day for 5 days has been provided without complications [227]. The D-isomer and the racemate (D,L-carnitine) are contraindicated. Historic use of racemic D,L-carnitine was associated with myasthenia-like syndromes and cardiac dysrhythmias, which disappeared after L-carnitine administration [228]. D-Carnitine also competitively depletes cardiac and skeletal muscles and kidneys of L-carnitine [229].

Antihyperglycemic antidotes

Dextrose

Dextrose (D-glucose) is indicated to rapidly reverse organic or toxin-induced hypoglycemia (e.g., from sulfonylureas, insulin, ethanol, salicylates, β-adrenergic antagonists, quinolines, pentamidine, ritodrine, and disopyramide) [230, 231]. Hypoglycemia onset may be significantly delayed with certain agents (e.g., long-acting insulin or sulfonylureas). Limited CNS glycogen stores (in astrocytes) and the inability to acutely use free fatty acids make the CNS particularly vulnerable to hypoglycemia [232]. Patients (and providers) may be unaware of hypoglycemia in the absence of objective testing; both the counter-regulatory autonomic response and overt neurological deficit may be absent [233, 234]. Additionally, significant neuroglycopenia and hypoglycemia-associated delirium (particularly in salicylism) may occur despite a "normal" peripheral blood glucose [235]. A wide range of clinical presentations have been described, including diaphoresis, nausea, tachycardia, tremor, hypothermia, focal neurological deficits, and CNS agitation, confusion, or depression. These are generally reversible upon prompt treatment. Untreated hypoglycemia may result in seizure, coma, and death. Hypoglycemic seizures increase cerebral metabolic rate, contribute to ATP depletion, and produce irre-

versible brain damage [236, 237]. For these reasons, when bedside testing is unavailable, a risk-benefit calculation has generally favored empiric dextrose administration in the absence of a very clear alternative history or explanation for altered mental status.

Following a determination of absolute or relative hypoglycemia, 0.5–1.0 g/kg i.v of age-appropriate dextrose containing solutions should be provided immediately – D50W (50 g/100 mL) in adults, D25W (25 g/100 mL) in children, and D10W (10 g/100 mL) in neonates. Frequent re-evaluation of response to therapy is required. Glucose uptake and distribution, hyperglycemia-induced insulin secretion in those with a competent pancreas, and ongoing toxin exposure may cause recurrent hypoglycemia and necessitate repeat dosing. Feeding, which provides significantly more calories than each 50 mL ampule of D50W (85 kcal according to one manufacturer [238]), should be commenced as soon as practicable. While D10W "maintenance" solutions may be subsequently required, at an infusion rate of 100 mL/h, this concentration only provides 34 kcal per hour. Continuous infusion of more concentrated solutions (e.g., D20W) requires a central venous catheter for administration. Only the D-isomer is clinically useful. Most glucose transporters (GLUTs) and the specific transporter required for facilitated diffusion of glucose across the blood-brain barrier, GLUT1 (SLC2A1), have a high affinity for D-glucose and negligible affinity for L-glucose [236, 239]. D-Glucose is also generally favored over other D-glucose epimers such as D-mannose or D-galactose.

D50W is hypertonic and may cause phlebitis or thrombosis at the site of injection. Extravasations of solutions containing as low as 10% dextrose have caused significant tissue injury and necrosis, particularly in young children [240]. Pseudoagglutination of red blood cells may occur if concentrated dextrose solutions without electrolytes are administered simultaneously with blood through the same infusion set [238]. Hypertonic dextrose administration may also induce generally clinically irrelevant hypophosphatemia [241].

Octreotide

Octreotide acetate, a synthetic somatostatin analogue, is now favored in cases of refractory hypoglycemia due to sulfonylureas or quinine. It is FDA approved for treatment of acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors [242]. It is a more potent inhibitor of insulin secretion than the natural hormone [242]. In pancreatic β-islet cells, ATP generated from glucose uptake and subsequent metabolism normally induces closure of the ATP-dependent potassium channel by binding to its pore subunit (Fig. 4). Sulfonylureas similarly induce channel closure after binding to a regulatory (SUR1) subunit. Increased intracellular potassium triggers calcium entry through voltage-dependent calcium channels, leading to increased cytosolic calcium and insulin exocytosis [243, 244]. Additionally, ATP contributes to
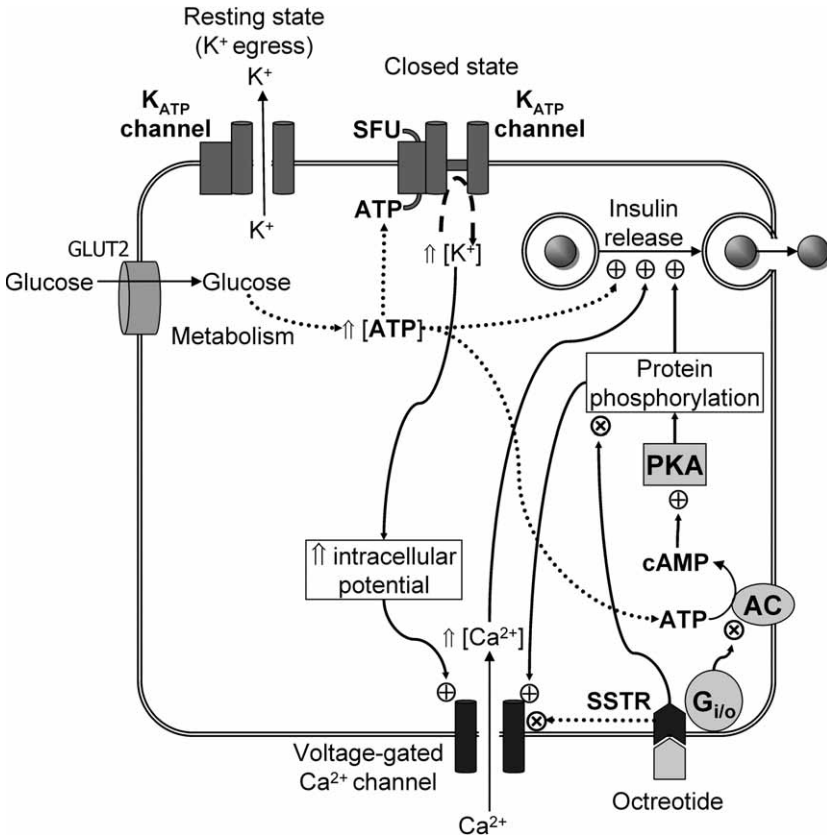
Figure 4. Pancreatic β-islet cell mechanisms of insulin release and octreotide action (see text for details). Enzymes and substances: AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GLUT2, glucose transporter 2; PKA, protein kinase A; SFU, sulfonylurea; SSTR, somatostatin receptor. Symbols: ⊕, agonism or co-factor; ⊗, antagonism. Data used can be found in [243–246].

insulin vesicles movement and provides a substrate for protein kinase A (PKA)-mediated phosphorylation. Octreotide binds to the somatostatin receptor (primarily SSTR$_5$) [243]. The subsequent effects continue to be explored and include inhibitory calcium channel effects, inhibition of adenylyl cyclase, and dephosphorylation of specific proteins required for movement and/or docking of vesicles [243, 245, 246]. Octreotide effectively suppresses endogenous insulin release in controlled studies in diabetics and in cases of sulfonylurea overdose, but does not (and would not be expected to have) an effect on exogenously administered insulin [247–249].

Several factors support octreotide usage following failure of initial dextrose administration and feeding. Bolused dextrose may produce hyperglycemia and thus subsequently stimulate an exaggerated insulin response, particularly when

sulfonylureas persist. This contributes to recurrent (sometimes more significant) hypoglycemia. A vicious cycle of serum glucose concentrations is described in case reports and controlled trials following dextrose administration after sulfonylurea exposure [249–251]. Additionally, as has been demonstrated, classic neuroglycopenic symptoms may not be present, and patients may need to be admitted during periods when circadian sleep patterns would complicate assessment. Octreotide administration also obviates the concern of excess water administration in pediatric patients receiving i.v. dextrose solutions.

Relatively few trials are available to judge the efficacy of octreotide for sulfonylurea-induced hypoglycemia. In one study, glipizide was used to induce induced hypoglycemia (50 mg/dL) in eight healthy volunteers, who were then resuscitated with dextrose infusion, diazoxide, or octreotide [251]. Dextrose requirements were markedly less in patients provided octreotide and hypoglycemic events were markedly attenuated after all therapies were stopped. One retrospective chart review of nine patients demonstrated that octreotide significantly reduced the number of recurrent hypoglycemic events and dextrose requirement [252]. One prospective randomized controlled trial in 40 poisoned patients, despite a failure to control for carbohydrate intake and having an unusual dosing strategy (a single octreotide 75 µg dose subcutaneously), demonstrated consistently higher glucose values for the duration for which octreotide would be expected to be effective (6–8 hours) [253]. Controlled animal studies with 25–100 µg octreotide demonstrated a similar decrease in hypoglycemic events [254]. The remainder of human clinical experience of the effectiveness of octreotide in sulfonylurea overdose comes from abstracts, case reports, and case series (e.g., [249, 250, 255–257]).

Pediatric experience in sulfonylurea overdose comes only in the form of limited abstracts and case reports in children aged 12 months to 17 years [248, 258–260]. However, octreotide has been used for prolonged periods to treat persistent hyperinsulinemic hypoglycemia of infancy [261, 262].

Two human studies examined the effectiveness of octreotide in quinine-induced hypoglycemia. In one study of nine healthy volunteers, 50 µg/hour octreotide as a continuous i.v. infusion abolished quinine-induced insulin release [263]. The authors reported resolution of hypoglycemia in an additional patient being treated with quinine for *Plasmodium falciparum* malaria. A subsequent study in eight patients with *P. falciparum* malaria confirmed octreotide suppression of quinine-induced hyperinsulinemia [264].

Optimal dosing of octreotide has not been definitively determined. Initial doses of 40–100 µg subcutaneously in adults have been reported, although 50 µg every 6–8 hours is commonly provided [256, 265]. In children, an initial dose of 1.0–1.25 µg/kg is used, although up to 2.5 µg/kg (or more) has been reported [258, 260]. Peak serum concentrations are achieved within 30 min after subcutaneous administration and within 4 min after a short (3 min) i.v. infusion [266]. The elimination half-life (by either route of administration) is approximately 1.5 hours. In patients with severe renal impairment (which may have contributed to sulfonylurea-induced hypoglycemia in the

first place), the plasma clearance is reduced by 50% [266]. The subcutaneous route is recommended due to longer duration of effect, as i.v. administration has resulted in treatment failure [267]. Side effects are generally minimal. Octreotide does inhibit gallbladder contractility and decreases bile secretion in normal volunteers [242]. When octreotide has been used to reverse sulfonyl-urea-induced hypoglycemia, bradycardia, hypokalemia, anaphylactoid reaction, and hypertension and apnea have been reported [257, 259]. Other adverse events include nausea, abdominal cramps, diarrhea, fat malabsorption and flatulence [268]. Octreotide also suppresses glucagon release, although hypoglycemia has been a concern only in patients on long-term therapy for organic hyperinsulinemia [269].

Glucagon is not generally recommended to correct hypoglycemia. Glycogen stores are frequently depleted by the time toxin-induced hypoglycemia manifests; glucagon's half-life (less than 20 min) is inadequate given the prolonged duration of the effect of sulfonylureas; and glucagon may exacerbate hyperinsulinemia [258]. Diazoxide, an antihypertensive agent, which reduces insulin release by opening the ATP-dependent potassium channel, is now of historical interest due to associated hypotension, reflex tachycardia, nausea and vomiting, and fluid retention [243, 265].

Antimicrobial antidotes

Pyridoxine

Since its introduction in 1952, isoniazid (INH, isonicotinic hydrazide, pyridine-4-carbohydrazide) has remained a mainstay for treatment and prophylaxis of mycobacterial infections [270]. The adult single tablet, 300 mg daily dose (4.3 mg/kg in a 70 kg individual) targets a peak plasma concentration of 3–5 μg/mL [271]. Acute INH toxicity may occur following ingestion of 20 mg/kg INH; it is common above 35–40 mg/kg [272]. The relatively narrow therapeutic window poses a significant risk for those with suicidal intent and for those who ingest extra pills to "catch up" after a brief period of incomplete compliance [273]. Historically, death rates of 21% were reported [274]. Seizures refractory to typical therapy, severe metabolic lactic acidosis, and coma may occur as early as 30 min post ingestion due to the rapid and nearly complete absorption of INH from the gastrointestinal tract. Seizures may occur at lower doses in those with pre-existing susceptibility. Associated respiratory failure, hypotension, and rhabdomyolysis may ensue. In patients provided 2.1–3.9 g (64–83 mg/kg) INH due to medication error, all experienced nausea or vomiting, vertigo, and coma within 30 min to 6 hours after ingestion [275]. Abnormal generalized discharges as sharp and slow waves were seen on EEG in all patients. Chronic INH toxicity may present with nausea, vomiting, hepatitis, hemolytic anemia, and neurological findings (restlessness, neuropathy, cerebellar findings, and psychosis).

The acute clinical effects are a product of the multiple biochemical actions of INH, which lead to pyridoxine depletion and subsequent neuronal hyperexcitability (Fig. 5) [272, 276–278]. INH hydrazones inhibit pyridoxine phosphokinase, which activates pyridoxine. INH hydrazines and hydrazides inactivate active pyridoxal 5-phosphate. INH metabolites also complex with pyridoxal 5-phosphate, leading to increased urinary elimination. Glutamic acid decarboxylase (GAD) and GABA transaminase (GABA-T) both require pyridoxal 5-phosphate as a co-factor. Inhibition of GAD exceeds that of GABA-T [279]. The resulting GABA depletion and loss of neuronal inhibition is thought to underlie seizure activity. Metabolic acidosis may be profound – survival has been reported with a pH of 6.49 [280]. Seizure-associated lactate generation is substantial; INH-induced metabolic acidosis does not develop in paralyzed dogs (despite EEG evidence of seizure) [281]. Importantly, merely correcting the acidosis (e.g., by bicarbonate) does not prevent additional seizures or terminate INH toxicity [281, 282]. INH also impairs lactate conversion to pyruvate (Fig. 5). Increased metabolism of fatty acids due to impaired glucose metabolism with hyperglycemia and ketonuria has been reported [272, 283]. INH also impairs cellular reduction-oxidation capacity *via* competitive inhibition of NAD [284, 285]. Pyridoxine deficiency also appears to play a role in INH-induced mental status changes (coma and lethargy) [275, 282, 286].

Appropriately dosed pyridoxine (vitamin B6) has been the mainstay of antidotal therapy for INH intoxication since the early reports of benefit *versus* his-
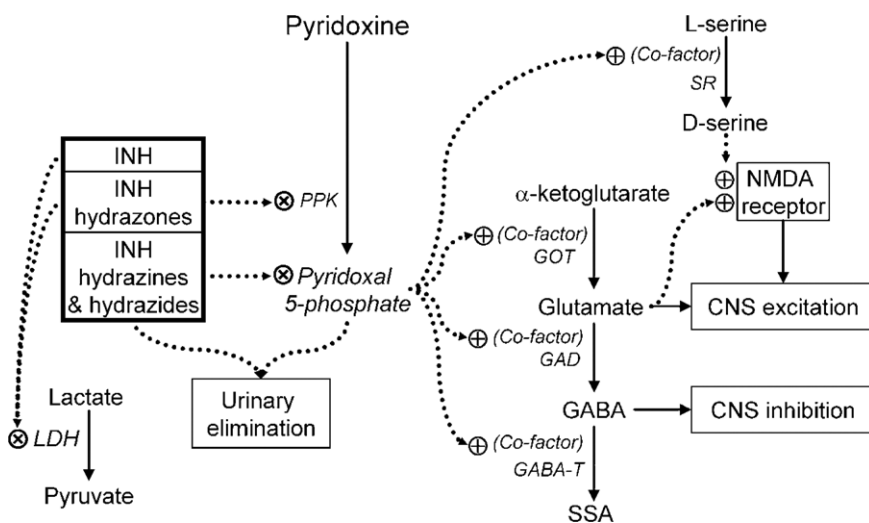

Figure 5. Mechanisms of isoniazid (INH) toxicity (see text for details). Enzymes (*italicized*): GABA-T, GABA transaminase; GAD, glutamic acid decarboxylase; GOT, glutamic-oxaloacetic transaminase; LDH, lactate dehydrogenase; PPK, pyridoxine phosphokinase; and SR, serine racemase. Substances: GABA, γ-aminobutyric acid; and SSA, succinic semi-aldehyde. Symbols: ⊕, agonism or co-factor; ⊗, antagonism. Data used can be located in [272, 276–278, 483].

torical controls [282]. Exogenous vitamin B6 provides the necessary precursor for the co-factor for GABA regeneration. Clinical experience with pyridoxine comes from case series, case reports, and animal data [273, 275, 281, 282, 287–289]. Clinical trials are absent due to ethical considerations. Vitamin B6 (as pyridoxine hydrochloride) is provided on a gram per gram basis for each gram of INH ingested, to a maximum of 5 g or 70 mg/kg (the empiric dose in ingestions of unknown quantity) [272, 282, 287]. A repeat dose can be provided if necessary. Due to the large amount of pyridoxine required, inadequate stocking and depletion of institutional and entire regional supplies have been widely reported [287, 290, 291]. In the convulsing patient, pyridoxine is administered i.v. at 0.5 g/min (5 g maximum) until seizure termination, with the remainder over 4–6 hours. Pediatric dosing should not exceed 70 mg/kg (5 g maximum). Large doses of pyridoxine have been safely administered; however, sensory neuropathy may occur with massive acute doses (>100 g) or chronic large daily doses [292]. Co-administration of benzodiazepines is synergistic in controlling seizures [288, 289]. Massive INH ingestion may require additional sedative hypnotics or anesthetic agents to suppress seizures [293]. INH is dialyzable, and hemodialysis has been used successfully in cases refractory to antidotal treatment, in those with extremely high plasma INH concentrations, and in patients with renal failure [283, 293].

Pyridoxine also appears to rapidly reverse the impaired consciousness seen in INH overdose [282, 286]. The CNS excitatory neurotransmitters include glutamate and D-serine, which with glutamate is a co-agonist of the NMDA receptor [278]. Examination of the metabolic pathways affected by pyridoxal 5-phosphate depletion (Fig. 5) suggests that inadequate stores of these neurotransmitters (due to inadequate co-factors for glutamic-oxaloacetic transaminase and serine racemase) might be contributory, in addition to general substrate or catecholamine deficiency.

Pyridoxine therapy is also recommended for poisoning through other hydrazines or hydrazine precursors (e.g., *Gyrometra* mushrooms, monomethylhydrazine, and unsymmetrical dimethylhydrazine fuel). Pyridoxine is effective in treating the chronic INH-associated neuropathy, particularly in patients with renal failure. Doses of 10–50 mg pyridoxine/day have typically been used in the chronic setting [271]. Pyridoxine has no effect in prevention or treatment of INH-associated hepatic injury.

Antineoplastic antidotes

Antineoplastic agents are used for the treatment of a variety of benign and malignant neoplasms. Some antineoplastic agents (such as the antifolates) have an expanded spectrum that includes use in rheumatology, dermatology, and obstetrics and gynecology. Toxicity may be due to the agent itself or delivery of the agent to an unintended target (e.g., extravasation). Several antidotes are used in a prophylactic fashion or on chronic basis. Amifostine (WR-2721) –

which is dephosphorylated by alkaline phosphatase to an activated, protective thiol form – is approved to decrease toxicity associated with radiotherapy and renal injury associated with cisplatin [294]. It has also been used to reduce chemotherapy-induced neutropenia; genitourinary injury associated with cyclophosphamide; and transfusion requirements, gastrointestinal and hepatic toxicity in pediatric patients [295, 296]. Cyclophosphamide and ifosfamide induce bladder toxicity (hemorrhagic cystitis) *via* their metabolite acrolein. Mesna (2-mercaptoethane sulfonate), a thiol agent that complexes with and inactivates acrolein, is provided orally or i.v. as prophylaxis [294]. Diethyldithiocarbamate (DDTC), the major metabolite of disulfiram, is an investigational agent for prevention of neuropathy from cisplatin and its analogs; it increased nephrotoxicity in one study [297]. Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (hemopoietin) and its derivatives, oprelvekin (recombinant interleukin-11), and other stimulating factors are employed as adjuvants to reconstitute various hematopoietic lines damaged by chemotherapy and radiation [298, 299]. Palifermin (recombinant truncated human keratinocyte growth factor) is used to prevent severe mucositis in patients receiving stem-cell transplantation with a total body irradiation conditioning regimen [294]. The remaining section focuses on antineoplastic antidotes used in the acute setting.

Dexrazoxane

A dreaded complication of administration of vesicant chemotherapeutic agents is extravasation. Risk factors for extravasation include small, fragile, or sclerosed veins, obesity, comorbid conditions (diabetes, circulatory disorders, impaired sensory perception), use of rigid i.v. catheters, and clinicians' lack of knowledge and skills [300]. Redness, burning pain, and swelling may portend later blistering, ulceration, and necrosis. Dexrazoxane is U.S. FDA approved for treatment of extravasation resulting from i.v. anthracycline chemotherapy, to diminish tissue damage and the need for surgical excision of necrotic tissue [301]. Clinical efficacy data comes from two simultaneously reported openlabel, single-arm, prospective multicenter studies in which only 1 out of 54 patients with biopsy-proven extravasation required surgical debridement [302]. Additional instances of successful dexrazoxane treatment of anthracycline extravasation are provided as case reports ([303] and others). Dexrazoxane is provided once daily for 3 consecutive days, with the first infusion initiated as soon as possible. Daily doses are as follows: day 1, 1000 mg/m^2 (maximum 2000 mg); day 2, 1000 mg/m^2 (maximum 2000 mg); day 3, 500 mg/m^2 (maximum 1000 mg) [301]. The dose is reduced by 50% in patients with creatinine clearance of less than 40 mL/min. In mice, efficacy rapidly decreased when dexrazoxane was provided beyond 6 hours after extravasation [304]. Dexrazoxane's mechanism of action appears to involve reversible inhibition of topoisomerase II and inhibition by its metabolite, an ethylenediamintetraacetic

acid (EDTA) analogue, of free radical formation *via* iron removal from the iron-doxorubicin complex [305]. Topoisomerase II-independent effects have also been described [306]. In contrast, some authors have encouraged the non-concurrent, off-label use of topical dimethyl sulfoxide (DMSO) for anthracycline extravasation because of the risk of infection, neutropenia, and thrombocytopenia associated with dexrazoxane [307]. Dexrazoxane is also used prophylactically to limit anthracycline-associated cardiomyopathy [294].

Leucovorin

In 1950, methotrexate (MTX) joined the oncological armamentarium for leukemia [308]. MTX treatment of solid cancers was reported in 1956, and it gained FDA approval for psoriasis in 1971 [309, 310]. MTX is now used intramuscularly, intrathecally, i.v., and orally for a range of dermatological, rheumatological, obstetric, and gynecological conditions. The dose ranges from 7.5–30 mg orally once weekly for psoriasis or rheumatoid arthritis to 8–12 g/m^2 or more for osteosarcoma, leukemia, and lymphoma [311–313]. MTX poisoning may result from intentional overdose; unintentional ingestion, prescription, dispensing, administration, and patient errors; or renal insufficiency leading to persistent MTX in patients receiving high-dose chemotherapy regimens [314, 315]. MTX antagonizes folate metabolism (and rapidly proliferating cells) *via* multiple mechanisms. Dihydrofolate reductase inhibition by MTX and its polyglutamated metabolites ensures that neither dihydrofolate nor active tetrahydrofolate can be generated from folate, nor can existing dihydrofolate be recycled. Thymidylate synthase inhibition compromises thymidine synthesis. Purine ring synthesis is impaired by inhibition of the participating enzymes amidophospho-ribosyltransferase (PPAT) and 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (AICART) [316, 317].

Maintenance of brisk urinary elimination with i.v. hydration and urinary alkalinization are standard therapies for patients receiving MTX. MTX is ten times more soluble in alkalinized urine (i.e., pH 7.5) than at pH 5.5 [318]. Folate (folic acid) is an ineffective therapy for MTX poisoning. While folate will inhibit renal resorption of MTX, persistent dihydrofolate reductase inhibition by MTX inhibits folate's activation. Leucovorin (folinic acid, 5-formyltetrahydrofolic acid, citrovorum factor) sustains the folate cycle by bypassing the blocked dihydrofolate reductase pathways. Addition of leucovorin "rescue" permitted the administration of very-high-dose MTX chemotherapy [319]. However, in patients receiving MTX chemotherapy, 24-hour MTX concentrations greater than 1×10^{-5} M (10 μmol/L), 48-hour concentrations greater than 1×10^{-6} M (1 μmol/L), or 72-hour concentrations greater than 1×10^{-7} M (0.1 μmol/L, 100 nM), or those with evidence of renal dysfunction are considered at high risk for toxicity [320]. In the setting of MTX persistence or toxicity, leucovorin i.v. doses are increased to 100 mg/m^2 or 1000 mg/m^2 every 6 hours according to established nomograms; doses and as high as 10 g/day

have been used [319, 321]. Leucovorin therapy continues until MTX concentration are less than 0.5×10^{-7}–1.0×10^{-7} M (0.05–0.1 μmol/L, 50–100 nM) [319]. However, adequate leucovorin concentrations cannot be achieved for competitive reversal of MTX toxicity when MTX concentrations are persistently above 10–100 μmol/L; other antidotal strategies are then considered [313].

Treatment of patients ingesting MTX should not be delayed pending MTX concentrations. Inhibition of DNA synthesis is nearly complete when MTX plasma concentrations are greater than 1×10^{-8} M (0.01 μmol/L, 10 nmol/L) [322]. Therefore, leucovorin is provided until MTX concentrations are less than 1×10^{-8} M in patients receiving MTX for non-oncological indications or in patients not receiving MTX therapeutically [311]. Only leucovorin's *S*-form [levoleucovorin, (6*S*)-leucovorin] is active and rapidly metabolized to usable, reduced folates; the inactive isomer is slowly eliminated by renal excretion during i.v. administration [323]. Leucovorin was available in the U.S. only as a racemate until 2008, when levoleucovorin received FDA approval. Levoleucovorin at one-half of the usual racemic dose (as it is entirely active) appears to provide similar rescue therapy in high-dose MTX chemotherapy [324]. Oral rescue is not routinely recommended as leucovorin's bioavailability is poor above 40 mg due to saturation of active intestinal transport [323]. The calcium content of leucovorin (0.004 mEq calcium/mg leucovorin) mandates that infusion should not exceed 160 mg/min. Intrathecal administration of leucovorin is contraindicated, as death may result [325].

Glucarpidase

Glucarpidase (carboxypeptidase G_2, $CPDG_2$) is undergoing evaluation as an additional antidote for MTX toxicity. U.S. or European marketing approval for glucarpidase has not been granted at the time of writing. Competitive and complete reversal of MTX toxicity by leucovorin may not be possible at MTX concentrations above 100 μmol/L (and perhaps even lower) [313, 326, 327]. Patients with systemic MTX toxicity (significant mucositis, gastrointestinal distress, myelosuppression, hepatitis, or neurotoxicity), persistent serum MTX, and renal impairment following high-dose MTX have been considered for glucarpidase therapy in addition to leucovorin. Recommendations for glucarpidase above certain MTX concentrations have varied by malignancy, degree of renal impairment, initial MTX dose, and serum MTX concentration (e.g., Clinical Trials NCT00424645, NCT00481559, and [313, 328–330]).

Purification of "carboxypeptidase G", a pseudomonad zinc-dependent enzyme capable of MTX cleavage, was reported in 1967 [331]. Its antidotal potential was suggested in 1972. In mice injected with lethal MTX doses, carboxypeptidase G_1 rapidly decreased MTX concentrations and improved survival [332]. $CPDG_1$ selectively eliminated systemic MTX in patients treated with high dosages targeting CNS malignancy, and rescued a patient receiving MTX with renal failure in 1978 [333, 334]. After the original enzyme source

of CPDG$_1$ was lost, a revived recombinant CPDG$_2$ product demonstrated success in both i.v. and intrathecal rescue of MTX overdose in non-human primates [335–337]. Successful use in multiple case reports and human trials in adult and pediatric patients with i.v. and intrathecal MTX overdose emerged [313, 315, 328, 329, 337–339].

Glucarpidase is a dimerized protein with two domains – a zinc-dependent catalytic domain that removes C-terminal glutamate residues of folate and folate analogues and a β-sheet interaction site [340]. Glucarpidase splits MTX and its 7-hydroxy-MTX metabolite into inactive 4-{[2,4-diamino-6-(pteridinyl)methyl]-methylamino}-benzoic acid (DAMPA) and hydroxy-DAMPA plus glutamate [341, 342]. MTX serum concentrations decline by 71–99% within minutes after glucarpidase [313, 315, 326, 330, 343, 344]. Intracellular, intraluminal (gastrointestinal tract) and intracerebral MTX is unaffected, creating the potential for rebound concentrations and persistent cytotoxicity [317, 328, 332, 345–347]. Leucovorin therapy must continue after carboxypeptidase administration. DAMPA's poor urinary solubility also requires ongoing alkalinization and saline diuresis to prevent renal precipitation [315, 348].

Anti-glucarpidase antibodies have been detected in patients receiving glucarpidase, although patients have been successfully treated with additional doses of glucarpidase for persistently elevated MTX concentrations [313, 326, 328, 337, 339, 342, 345]. HPLC must be used to determine actual MTX concentrations after glucarpidase as both MTX metabolites, 7-hydroxy-MTX and DAMPA, interfere with immunoassay techniques [349]. Glucarpidase has an affinity for MTX approximately 10- to 15-fold higher than it does for leucovorin; however, its affinity for folate and 5-methyltetrahydrofolate are similar [350, 351]. Glucarpidase eliminates active *levo*-(*6S*)-leucovorin about 50% faster than nonphysiological *dextro*-(*6R*)-leucovorin [348]. A study to address the clinical consequence is ongoing. Because of the stereoselective destruction of active leucovorin and its metabolites, many protocols attempt to separate leucovorin administration from glucarpidase administration by 2–4 hours. Administration of glucarpidase more proximate to leucovorin administration, and which antidote to provide should glucarpidase become available at a leucovorin dosing interval, requires a thoughtful benefit-risk assessment. Country-specific information on obtaining glucarpidase, institutional review board protocol, and consent issues have been made available online (www.btgplc.com/BTGPipeline/273/Voraxaze.html; and www.fda.gov/cder/cancer/singleIND.htm).

Cardiovascular antidotes

Cardiovascular pharmaceuticals comprise a wide variety of agents including anti-dysrhythmics, β-adrenergic antagonists (β-blockers, BBs), angiotensin antagonists, calcium channel antagonists (CCBs), cardioactive glycosides, and imidazoline derivatives. Overdose of these agents alone or in combination can

generate potentially lethal combinations of impaired conduction, dysrhythmia, vasodilatation, and negative inotropy. Management of severe cases may necessitate diagnostic adjuncts such as echocardiography and right heart catheterization (Swan-Ganz measurements). In cases refractory to routine supportive care, vigorous gastrointestinal decontamination, and pharmacological intervention, aggressive measures including cardiac pacing, intra-aortic balloon counter-pulsation, or extracorporeal circulation (cardiopulmonary bypass) may be required until toxin elimination can be achieved [352]. Cardiac pacing may improve heart rate without increasing cardiac output if inotropy is compromised. Use of naloxone in the management of overdose of clonidine and angiotensin receptor antagonists and angiotensin converting enzyme inhibitors is provided in the opioid antagonists section. Strategies to mitigate the anticoagulant toxicity of vitamin K antagonists (i.e., coumadin) including exogenous oral or i.v. vitamin K, fresh frozen plasma, prothrombin concentrates, and recombinant factor VII are detailed in the 2008 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [353]. The Guidelines also address protamine sulfate for reversal of heparin anticoagulation and use of nonheparin anticoagulants for treatment and prevention of heparin-induced thrombocytopenia [354, 355].

Atropine

Atropine (D,L-hyoscyamine) is familiar to clinicians due to its use in several advanced cardiac life support (ACLS) algorithms [356]. Atropine is a central-acting, competitive antagonist of muscarinic acetylcholine receptors (M_1–M_5) [357]. It is used to counteract bradycardia from BBs, CCBs, cardioactive glycosides, and clonidine. Atropine increases basal heart rate; it does not affect the basal force of contraction [357]. Positive chronotropy alone may not produce systemic benefit in severe poisoning, and conduction system poisoning may limit responsiveness to atropine [358]. For symptomatic bradycardia, atropine 0.5–1.0 mg (pediatric dose: 0.02 mg/kg) i.v. is provided every 2–3 min to a maximum dose of 3 mg. Paradoxical parasympathetic response may occur during slow infusions or doses less then 0.5 mg (0.1 mg minimum in children) [356]. In slowing gastrointestinal motility, atropine may impair decontamination with WBI or AC.

Calcium

CCBs antagonize L-type calcium channels, slowing entry of calcium ions during myocyte depolarization; however, intracellular calcium release is not directly affected. This disrupts calcium-mediated excitation-contraction coupling, action potential generation and conduction, and vascular smooth muscle tone [359]. Exogenous i.v. calcium is indicated in cases of CCB and BB toxi-

city [352]. In animal models, calcium salts reverse CCB-induced deficits in contractility, blood pressure, and cardiac output [352]. Multiple uncontrolled cases reports document the effectiveness of calcium salts; however, interpretation of effectiveness is complicated by the co-administration of other modalities. Some authors advocate aggressive high-dose calcium therapy, providing large amounts of calcium without apparent ill effect [358]. This approach does carry a risk of death from hypercalcemia [reported concentration, 32.3 mg/dL (8.07 mmol/L) after 38 g calcium] [360]. Others recommend a bolus dose followed by continuous infusion to maintain physiological calcium levels [361]. Peripheral administration as calcium gluconate decreases the risk of extravasation and tissue necrosis. A standard container of 10 mL of 10% calcium gluconate provide 4.65 mEq (93 mg) elemental Ca^{2+}; 10 mL of 10% calcium chloride (1 g total $CaCl_2$) yields 13.6 mEq elemental Ca^{2+} [362]. A suggested approach is to initially administer a 0.6 mL/kg (0.28 mEq/kg) bolus of 10% calcium gluconate (0.2 mL/kg 10% $CaCl_2$) over 5–10 min [359, 361]. Empirically, this is roughly one vial (1 g) of 10% $CaCl_2$ or three vials (3 g) of 10% calcium gluconate i.v. The bolus may be repeated several times. Due to bolus dissipation, most patients are placed on an infusion of 10% calcium gluconate at 0.6–1.5 mL/kg per hour (0.28–0.7 mEq/kg per hour) or 0.2–0.5 mL/kg per hour [359, 361]. Serum phosphate, calcium, and hydration status should be closely monitored. Calcium administration for hyperkalemia has been generally contraindicated in cases of cardioactive glycoside toxicity, out of concern for dysrhythmias or systolic arrest (also known as "stone heart") [363]. While more recent studies have challenged this assertion, it is advisable to withhold calcium until the definitive cardiac glycoside antidote, digoxin-specific Fab fragments, has been provided [364].

Digoxin-specific antibody fragments (Fab)

Digoxin and cardioactive glycosides inhibit the cardiac sodium-potassium ATPase. The subsequent accumulation of sodium in the cytoplasm dissipates the driving force for calcium expulsion *via* the sodium-calcium exchanger. Increased intracellular calcium enhances actin-myosin coupling, myocyte contraction, and inotropy. In overdose, the excess calcium may result in membrane hyperexcitability and delayed after-depolarizations. Increased vagal tone decreases conduction through the AV node. The combination of increased automaticity and vagotonicity may yield lethal ventricular escape rhythms.

Digoxin-specific antibody fragments bind free digoxin in serum to decrease digoxin serum concentrations to undetectable levels within minutes [365]. Successful reversal of digoxin toxicity with digoxin-specific Fab was first reported in 1976 [366]. The results of a prospective multicenter study demonstrated significant effectiveness in reversing life-threatening digitalis toxicity, and more recent studies confirm ongoing Fab fragment utility [367, 368]. Digoxin-specific Fab were also shown to be effective in children [369].

Digoxin-specific Fab are produced from purified ovine-derived immunoglobulin G. Cleaving the Fc antibody portion significantly improves renal excretion of the complex, decreases immunogenicity, and facilitates diffusion of remaining free Fab into tissue [370]. Reflecting digoxin redistribution from target organs of toxicity, the initial response to digoxin-specific Fab was 19 min (0–60 min), and complete reversal of systemic toxicity occurred on average by 88 min (30–360 min) [367].

Indications for therapy include life-threatening or progressive dysrhythmia or shock; potassium greater than 5.0 mEq/L (acute poisoning); chronic poisoning with other end-organ manifestations such as altered mental status, significant gastrointestinal symptoms or renal impairment; or serum digoxin concentration >15 ng/mL or greater than 10 ng/mL beyond 6 hours after ingestion. Hyperkalemia is rapidly reversed by digoxin-specific Fab [365]. One vial neutralizes approximately 0.5 mg of digoxin (or digitoxin). Dosing is based either on amount ingested [number of vials = amount ingested (in mg) × 0.8 (oral bioavailability) / 0.5], or a serum concentration [number of vials = serum digoxin concentration (ng/mL) × patient weight (kg) / 100]. The number of vials is rounded up and administered i.v. over 30 min. Empiric therapy is 10–20 vials for adult or pediatric patients in acute poisoning or 3–6 vials (1–2 vials in children) in chronic poisoning. Partial reversal is recommended by some authors [371], but is not common U.S. practice due in part to concern for recrudescent toxicity with inadequate therapy [370].

Following treatment, free digoxin concentrations may rebound upwards within 12–24 hours, most likely reflecting tissue redistribution into the vascular space [372]. This provides a measure of protection against development of significant congestive heart failure (CHF) in patients dependent upon digoxin for inotropy, although exacerbation of CHF may occur [370]. Clinically significant late rebound of digoxin concentrations and toxicity have occurred in patients with marked renal dysfunction [373]. Immunogenicity from repeat digoxin-specific Fab has generally not been significant, although allergic reactions have been infrequently reported with administration [374]. Digoxin-specific Fab has been used clinically or experimentally to treat poisoning by other cardiac glycosides – yellow oleander (*Thevetia peruviana*), *Nerium oleander*, *Chan Su* and "Love Stone" (extract of the *Bufo bufo gargarizans* toad) [375, 376]. Higher dosing may be required due to poor binding affinity.

Glucagon

BBs competitively antagonize catecholamine effects at cardiac β-receptors, leading to decreased inotropy and slowed conduction through the AV node. Bradycardia, conduction delay, hypotension, and decreased cardiac output may accompany significant poisoning. BB interference with gluconeogenesis and glycogenolysis may lead to hypoglycemia, as well as blunt the catecholamine response that is important in its recognition.

Glucagon, a 29-amino acid peptide hormone secreted by pancreatic α-cells, counteracts hypoglycemia and the actions of insulin; regulates gastrointestinal motility; and mediates the rate of renal filtration, urea excretion, and water resorption [377]. The current glucagon product is now produced in non-pathogenic *E. coli* by recombinant techniques [378]. Myocardial binding occurs at a distinct glucagon receptor (GCGR) coupled with the β-agonist binding site. Antidotal (off-label) use of glucagon thus bypasses β-receptor blockade to directly induce G-protein-mediated stimulation of adenylate cyclase to convert ATP to cAMP [379]. cAMP, in turn, activates protein kinase A (PKA), which promotes the phosphorylation and opening of dormant L-type calcium channels to improve calcium-dependent excitation-contraction coupling [361]. Another proposed mechanism is C-terminal cleavage of glucagon to mini-glucagon, which has a direct effect on sarcoplasmic reticulum calcium stores *via* arachidonic acid [380].

In human volunteers evaluated by cardiac catheterization, glucagon increased heart rate, cardiac index, and mean atrial pressure, but not left ventricular end-diastolic pressure (EDP) or systemic vascular resistance (SVR) [381]. Clinical experience in overdose consists primarily of case reports [382, 383]. Due to the complex nature of overdose, glucagon is often used in combination with other agents in severe BB overdose. Additionally, several *ex vivo* experiments, controlled animal studies, and uncontrolled case reports have demonstrated that glucagon can be beneficial in CCB exposure [384–386]. The recommended initial bolus dose of glucagon is 50–150 µg/kg, which may be repeated after 3–5 min [359]. A continuous infusion corresponding to the total effective bolus reversal dose is then provided per hour (e.g., if clinical response was observed following administration of 2 mg, 3 mg, and finally 5 mg, the hourly infusion would be 10 mg/hour). The effects of glucagon administered i.v. begin within 1–3 min, peak at 5–7 min and last for approximately 15 min [381]. Nausea and vomiting are common and should be anticipated. This may complicate management of patients with depressed mental status or airway concerns. Flushing, transient hyperglycemia, and smooth muscle relaxation, and ileus may also occur.

High-dose insulin euglycemia therapy

Since CCBs antagonize the L-type calcium channel in pancreatic islet cells, a subsequent decreased insulin production can produce hyperglycemia [361]. Animals poisoned by CCBs have impaired myocardial fatty acid uptake (leaving them dependent upon carbohydrate metabolism), impaired uptake of glucose, and myocardial insulin resistance [387, 388]. In humans, intracoronary verapamil increased glucose release and altered myocardial lactate use from consumption to release [389].

Decades ago, glucose-insulin-potassium (GIK) was proposed as adjuvant therapy for acute myocardial infarction, with the intent of suppressing uptake

of free fatty acids, improve myocardial energy production, and stabilize intra-cellular potassium [390]. Randomized trials of GIK therapy in patients with acute myocardial infarction (AMI) have not shown benefit, although the insulin doses tend to be low (in general, ≤0.075 U/kg) [390]. Experience in the surgical literature in cases where much higher insulin doses have been used has been somewhat different [391]. Patients undergoing aortic valve replacement and coronary artery bypass who received high-dose insulin at 1 unit/kg per hour demonstrated more rapid lactate clearance, lower glucose, lower dobutamine requirements, a trend for improved cardiac indices, and potential anti-inflammatory benefit (lower C-reactive protein and free fatty acid levels) [392]. Insulin doses of 2.5 units/kg were tolerated without excess increase of insulin-induced potassium elimination [393]. In combination with dopamine, insulin 7 units/kg was used to significantly augment cardiac output and decrease systemic vascular resistance in post-coronary artery bypass graft (CABG) patients without generating excess in oxygen demand [394]. Additional benefits of high-dose insulin included overcoming insulin resistance, increased expression of glucose transporters, and improved turnover of sodium-potassium-ATPases [391].

The basis for high-dose insulin euglycemia therapy (HIET) (off-label) in overdose has been explored in a series of animal models of CCB and BB toxicity [387, 388, 395–397]. HIET increased myocardial lactate uptake and improved systolic and diastolic heart function. Insulin outperformed epinephrine and glucagon [395–397]. Multiple human cases of successful management of CCB overdose with HIET have been described [359, 398]. Because the beneficial cardiovascular effects of HIET are not seen for 15–60 min after initiation, it must be considered early, before patients become unsalvageable [359]. A proposed dosing scheme includes a bolus dose of regular insulin of 1.0 units/kg, followed by an infusion of 0.5–1.0 units/kg per hour, titrated upwards as necessary [359]. A dextrose bolus is also provided unless significant hyperglycemia exists, followed by an infusion of 0.5–1.0 g/kg per hour to maintain blood glucose between 100 and 250 mg/dL.

Persistent physician reticence to utilizing the high-dose insulin out of concern for excess hypoglycemia presents an obstacle for implementation of adequate HIET [399]. This ignores a body of physiological data that demonstrate that the insulin transport follows saturation kinetics [400, 401]. Alternatively, it has also been demonstrated that insulin-stimulated glucose clearance reaches a maximum in both lean and obese subjects [402]. Taken together, this suggests that, from a therapeutic standpoint, since insulin effect *via* insulin receptors appears saturable, additional mechanisms must be at work. The effects of HIET may include counteracting CCB-mediated insulin impairment or shock-induced hyperglycemia, improving myocardial substrate utilization, and improving myocardial metabolism [359]. From an adverse-effects standpoint, once adequate and ongoing glucose has been provided, hypoglycemia should not present an excessive risk [398], although frequent serum glucose and potassium evaluation are obvious components of HIET therapy. Due to the

high dosing, insulin may persist after the infusion cessation and necessitate ongoing supplemental dextrose beyond insulin infusion. As hypokalemia is an intracellular result of shift, it is supplemented cautiously.

Lipid emulsion (20%)

During administration of local anesthetics, severe toxicity may result from systemic absorption or unintended intravascular administration. Loss of consciousness, dysrhythmia, cardiovascular collapse, seizures, and lactate-associated acidemia may rapidly ensue [403]. Furthermore, in animal models, for some of the local anesthetics (bupivacaine, levobupivacaine, and ropivacaine), treatment with "standard" advanced cardiac life support (ACLS) drugs such as epinephrine may precipitate ventricular dysrhythmia [404].

Following a serendipitous observation that pretreatment with a lipid emulsion altered the dose-response to bupivacaine-induced asystole, murine and canine studies provided evidence of survival benefit with lipids in bupivacaine toxicity [405, 406]. Case reports of successful resuscitation of patients severely affected by bupivacaine, levobupivacaine, mepivacaine, prilocaine and ropivacaine (alone or in combination) followed [403, 407–409]. Pediatric experience is limited to a case of successful resuscitation following lidocaine/ropivacaine toxicity from a posterior lumbar plexus block [410]. Lipid therapy has been successfully applied in human bupropion toxicity and combined quetiapine and sertraline overdose [411, 412]. Animal models have suggested a possible benefit in clomipramine, propranolol, thiopentone, and verapamil poisoning [413–416]. An understanding of lipid's mechanism of action is incomplete. It may act as a "circulating lipid sink" in which excess lipophilic drug may dissolve; modulate intracellular processes; or provide an alternative myocardial energy supply [411]. Presumably due to central sympathetic activation, human volunteers given a 4-hour lipid emulsion (20%) infusion had increased systemic vascular resistance, blood pressure, muscle sympathetic nerve activity, and concentrations of insulin and aldosterone, without increased cardiac output [417]. Lipid emulsion increased inotropy in both spontaneously beating and paced isolated rat hearts poisoned with levobupivacaine [418].

Dosing guidelines for the off-label use of lipid emulsion in resuscitation are provisional, as optimal bolus and continuous infusion therapy and timing are still being explored. The Association of Anaesthetists of Great Britain and Ireland recommends an i.v. bolus of 1.5 mL/kg Intralipid® (20%) over 1 min, which may be repeated twice at 5-min intervals if an adequate circulation has not been restored [419]. Following the initial bolus, an infusion is commenced at 0.25 mL/kg per min (which may be increased to 0.5 mL/kg per min in inadequate circulation). Propofol is an inadequate substitute [419, 420]. Ongoing lipid therapy may be required as recrudescence may occur [421]. Hyperamylasemia may be anticipated. Additional concerns include pancreatitis,

allergic reactions, acute myocardial infarction, fat embolism, and altered coagulation [420]. In lapine and porcine models of asphyxial cardiac collapse (pulseless electrical activity or arrest), lipid emulsion was markedly ineffective [422, 423]. *In vitro*, lipid affinity for both bupivacaine and ropivacaine is also adversely affected by low pH (by a factor of 1.68 in a pH drop from 7.40 to 7.00) [424]. These data suggest that ventilatory status must be aggressively addressed early in toxicity.

Magnesium

Due to their physicochemical characteristics and structure, many non-antiarrhythmic drugs are able to antagonize or alter expression of the myocardial potassium delayed rectifier channel (hERG, KCNH2, LQT2). With channel block, potassium efflux is compromised, and the repolarizing cardiac I_{Kr} current is impaired. The surface ECG reflects this as QT prolongation. Age, female gender, comorbidities such as structural heart disease, electrolyte disturbances such as hypokalemia, and heart rate (bradycardia) may provide additional risk. Certain antibiotics, antihistamines, antipsychotics, antidepressants, and methadone are prone to induce QT prolongation. QT prolongation is associated with torsade de pointes, a polymorphic ventricular arrhythmia that can degenerate into ventricular fibrillation, cardiac arrest and sudden death [425]. If significant QT prolongation (QTc >500 ms) is detected, administration of 1–2 g magnesium sulfate i.v. (pediatric dose, 25–50 mg/kg) over 5 to 60 min (depending on urgency of presentation), followed by an infusion of 2–4 mg/min is suggested [426]. Rapid infusion may cause hypotension, and magnesium should be administered cautiously in renal failure. A second bolus can be provided 5–15 min later [427]. Magnesium sulfate i.v. is effective in arrhythmias occurring due to early or delayed depolarization-induced triggered activity [427]. Acceleration of the heart rate with isoproterenol or transvenous pacing (overdrive pacing) may be needed to preclude recurrence of torsade de pointes while correction of underlying risk factors (hypokalemia and hypocalcemia) ensues. Immediate non-synchronized defibrillation is required for unstable polymorphic ventricular tachycardia or ventricular fibrillation.

Sodium bicarbonate

Severe cardiovascular toxicity may result from blockade of cardiac sodium channels by tricyclic antidepressants (TCAs) – leading to conduction delays, dysrhythmias, and myocardial depression. TCAs adversely affect maximum upstroke velocity (V_{max}), which approximates the magnitude of sodium entry [428]. The sodium channel blockade displays rate dependence. At slow rates the TCA has time to disassociate, allowing channel recovery. At faster rates, block progressively worsens. Given the anticholinergic effects of TCAs that

speed the heart rate, this is a significant concern. However, attempts to decrease heart rate with propranolol produced hypotension and lethality in canine studies [429, 430].

With progressive sodium channel block, ventricular impulse propagation becomes delayed. Sodium channel blockade manifests on the surface ECG as QRS widening. A QRS equal or greater than 100 ms is a significant predictor of seizure; a QRS ≥160 ms predicts ventricular dysrhythmia [431]. The right bundle branch has a relatively longer refractory period, and it is affected disproportionately by impaired intraventricular conduction delay. Rightward terminal axis shift or outright bundle branch block may be present [432]. These rightward terminal forces may also produce terminal R waves in leftward-directed leads [433]. Acidemia secondary to hypoperfusion or seizure may generate progressively worsened block. In an acidemic environment, free TCA concentrations increase as binding to α-1 acid glycoprotein decreases, the TCA ionized fraction increases, and sodium channel blockade worsens [434]. Seizures are severe and consequential, leading to QRS widening and hypotension [435].

Administration of sodium bicarbonate improves V_{max} and action potential amplitude by increasing extracellular pH and sodium concentration [428]. Consequentially, compromised myocardial inotropy, conduction aberrations, and dysrhythmia are reversed. Several animal studies have demonstrated these beneficial effects [429, 430]. Both the sodium and alkalemia induced by sodium bicarbonate improve cardiac performance [429]. The enhanced inotropy with sodium bicarbonate is independent of and additive to vasopressor treatment [436]. Hyperventilation-induced alkalinization similarly narrows the QRS [437]. Sodium bicarbonate outperformed hyperventilation in a swine model, although hypertonic saline was superior to both [438]. This approach has been reported clinically [439]. While sodium bicarbonate is recommended for QRS widening in TCA evidence-based consensus guidelines for out-of-hospital management, actual human studies are not as extensive as one might suspect [440, 441].

Initially, hypertonic sodium bicarbonate 1–2 mEq/kg i.v. is provided, preferably with continued ECG monitoring of the QRS. Institutions usually stock either an 8.4% solution (1 mEq/mL sodium and bicarbonate ions) or a 7.5% solution (0.892 mEq/mL sodium and bicarbonate ions). Rarely, a 5% solution may be encountered (0.595 mEq/mL). A "standard" 50-mL ampule of 8.4% or 7.5% solutions would deliver 50 or 44.6 mEq of $NaHCO_3$. Several boluses may be required, either initially or as the bolus effect declines due to redistribution [429]. Ongoing alkalinization should be provided as discussed previously, with a goal of serum pH 7.55. If sodium bicarbonate administration is problematic due to fluid load, hyperventilation and/or hypertonic saline may be required [437, 439].

Due to mechanistic similarities, sodium bicarbonate has been recommended for QRS widening seen in poisoning by Vaughn-Williams Class IA and IC antidysrhythmics, cocaine, diphenhydramine, carbamazepine, and propoxy-

phene [442–445]. Treatment of bupropion-induced QRS widening with sodium bicarbonate has met with both success and failure [446]. Sodium bicarbonate has also been suggested to treat QRS widening from venlafaxine; similar effects seen with lamotrigine might also be amenable [447, 448]. Sodium bicarbonate therapy may have a role in *Taxus* species (yew berry) toxicity [449]. Treatment of amantadine-induced QRS widening with sodium bicarbonate may be complicated by concurrent profound hypokalemia [450].

Opioid antidotes

Naloxone

Naloxone is a competitive opioid antagonist at all receptor subtypes [451]. It can prevent or reverse the effects of opioids, notably CNS and respiratory depression. Massive doses of naloxone (5.4 mg/kg with 4.0 mg/kg per hour infusion) have been administered safely in non-opioid tolerant individuals suffering from spinal cord injury [452]. However, indiscriminate use of naloxone in opioid-tolerant individuals can precipitate acute opioid withdrawal, with attendant acute lung injury, seizure, hypertension, or cardiac dysrhythmia [453]. These are likely associated with the abrupt, significant, and sustained increases in plasma catecholamine concentrations (epinephrine and norepinephrine) that accompany narcotic reversal, particularly in the setting of hypercapnia [454]. Withdrawal-induced vomiting may compromise the airway in patients with concomitant sedative-hypnotic ingestion. Precipitated withdrawal-associated agitation and violent behavior may require chemical restraint, leading to a vicious cycle of compromised CNS and cardiopulmonary function as naloxone wears off. Self-release and relapse following naloxone administration is also a concern in opioids with prolonged duration of effect (methadone, controlled-release oxycodone hydrochloride, etc.). Naloxone is no longer recommended as the initial resuscitation of newborns with respiratory depression in the delivery room; precipitation of acute neonatal opioid withdrawal may produce severe consequences [455]. Sudden cardiac arrest has occurred in preterm neonates given naloxone to reverse opioid overdose [456].

Naloxone is utilized in those individuals with clear evidence of the opioid toxidrome. Those with a respiratory rate ≤12 or hypopnea are likely to benefit [457]. The goal of therapy is titration to adequate ventilatory status without withdrawal. After normocapnia is achieved by supported ventilation, this can be done with i.v. administration of 0.04–0.05 mg initially (e.g., 1 mL of 0.4 mg naloxone in 10 mL diluent or 1 mg naloxone in 20 mL diluent). Due to rapid onset, effectiveness can be assessed, and if required, the dose can be titrated upwards incrementally to 0.4 mg, 2 mg, or even 10 mg. Patients without response to 10 mg naloxone are unlikely to have opioid-induced respiratory depression. Nonopioid-dependent adults are administered 0.4–2 mg i.v.

Pediatric dosing for infants and children from birth to 5 years of age or less than 20 kg body weight is 0.1 mg/kg; children older than 5 years of age or weighing more than 20 kg are provided 2 mg [455]. For longer acting opioids, following adequate initial opioid antagonism, two-thirds of the initial naloxone reversal bolus is provided as a continuous i.v. infusion [458].

Naloxone can successfully antagonize buprenorphine overdose in children, although prolonged therapy and monitoring may be required [459]. Higher doses may be required due to reverse buprenorphine effects because of its high affinity for opioid receptors [460]. Naloxone has also been used to reverse clonidine toxicity, although this is not always the case [461]. It has been postulated that patients with higher hyperadrenergic tone (who have higher concentrations of endogenous opioids) or those in whom clonidine induces more endogenous opioid release may respond best to naloxone [462]. Mental status, blood pressure, and heart rate may respond differently.

Naloxone has been employed in angiotensin converting enzyme inhibitor overdose. One author reported that a 1.6 mg bolus of naloxone followed by repeat 2 mg bolus reversed hypotension due to overdose with 500 mg captopril [463]. Naloxone has been ineffective in reversing hypotension in other cases complicated by co-ingestants [464]. The mechanism may relate to antagonism of endogenous opioids [465]. Co-administration of 0.2 mg/kg naloxone mitigated captopril-related decreases in systolic and diastolic blood pressure in healthy volunteers [465]. A placebo-controlled study of healthy men found that naloxone pretreatment with 10 mg followed by 2.46 mg/hour infusion precluded systolic blood pressure decrease induced by captopril (50 mg) [466]. Under different experimental conditions [naloxone, 0.4 mg bolus and a 2-hour continuous infusion (4.0 mg/hour), and captopril (25 mg)], no difference was observed [467].

Sedative-hypnotic antidotes

Flumazenil

Analogous to naloxone antagonism at opioid receptors, flumazenil competitively antagonizes benzodiazepine receptors – allosteric sites located at the macromolecular $GABA_A$ receptor complex, which regulate chloride ion flux within the associated ion channel [468]. Flumazenil reverses the sedative, psychomotor, and amnestic effects of benzodiazepines [469]. Flumazenil's effectiveness depends upon the number of benzodiazepine receptors that can be occupied according to the mass-action law, the affinity of a particular benzodiazepine for the receptor, and the free benzodiazepine concentration near the receptor [470]. In contrast, antagonism of benzodiazepine-induced respiratory depression is inconsistent, and acute tolerance may develop to large doses [471–473]. Flumazenil administration can reverse bispectral index (BIS) depression and permit earlier emergence from anesthesia in patients provided

non-benzodiazepine anesthesia (propofol/remifentanil) [474]. Postulated mechanisms included intrinsic CNS stimulant activity or antagonism of endogenous benzodiazepine-like ligands (endozepines). Under certain experimental conditions, flumazenil may also demonstrate partial agonist or even inverse agonist activity [475, 476].

The appropriate utilization of flumazenil as an antidote in patients with benzodiazepine overdose is still a matter of debate. Patients who ingest benzodiazepines alone or in combination generally have acceptable outcomes with supportive care alone. Proponents argue that awakening is therapeutic and diagnostic, obviates requirements for investigatory procedures, and limits complications of sedation. Opponents point to the low risk of mortality with benzodiazepine ingestion, frequent co-ingestants for which flumazenil is ineffective or contraindicated, relapse, and risks of reversal. While flumazenil can be administered safely, indiscriminate flumazenil administration may produce an acute withdrawal syndrome in benzodiazepine-dependent patients, seizures, dysrhythmias, vomiting, and agitation [477–480].

Flumazenil is not recommended in cases complicated by co-ingestants capable of inducing seizures or dysrhythmias (e.g., bupropion, carbamazepine, chloral hydrate, chlorinated hydrocarbons, chloroquine, cocaine, cyclic antidepressants, cyclosporine, isoniazid, lithium, methylxanthines, monoamine oxidase inhibitors, phenothiazines, and propoxyphene) [477, 479, 481]. As might be anticipated with an antidote of lesser half-life than many benzodiazepines, clinical condition may deteriorate following initial improvement, mandating ongoing monitoring. In one study, patients with primarily benzodiazepines ingestion remained awake for 72 ± 37 min following flumazenil; this was markedly decreased to 18 ± 7 min with co-ingestants [478]. This may be problematic in patients who, once aroused, demand release from medical care. After excluding co-ingestants of concern, vital sign abnormalities, and an aberrant ECG, and considering the risk-benefit ratio, flumazenil is administered slowly i.v., titrated to clinical effect (0.1 mg/min, max ≤1 mg) [481]. Off-label continuous infusions of 0.3–0.5 mg/hour have been provided to preclude relapse.

Conclusions

Patients poisoned by pharmaceuticals present many challenges to the treating clinicians. They generally benefit from aggressive support of vital functions, a careful history and physical examination, specific laboratory analyses, and a thoughtful consideration of the risks and benefits of decontamination and enhanced elimination. Data on the effectiveness of certain antidotes ranges from isolated case reports to robust clinical trials. Clinicians are encouraged to liberally utilize consultation with regional poison centers or those with toxicology training to assist with diagnosis, management, and administration of antidotes, particularly in unfamiliar cases.

References

1 Wax PM (1997) Analeptic use in clinical toxicology: A historical appraisal. *J Toxicol Clin Toxicol* 35: 203–209
2 Jones AW, Dooley J, Murphy JR (1950) Treatment of choice in barbiturate poisoning; series of twenty-nine cases of barbiturate poisoning treated with pentylenetetrazole (metrazol) and supportive therapy. *J Am Med Assoc* 143: 884–888
3 Orwin A, Sim M, Waterhouse JAH (1965) A study of the anti-barbiturate effects of bemegride. *Br J Psychiatry* 111: 531–533
4 Hirsh K, Wang SC (1975) Respiratory stimulant effects of ethamivan and picrotoxin. *J Pharmacol Exp Ther* 193: 657–663
5 Bickerman HA, Chusid EL (1970) The case against the use of respiratory stimulants. *Chest* 58: 53–56
6 Wolfson B, Siker ES, Ciccarelli HE (1965) A double blind comparison of doxapram, ethamivan and methylphenidate. *Am J Med Sci* 249: 391–398
7 Rappolt RT S, Gay GR, Decker WJ, Inaba DS (1980) NAGD regimen for the coma of drug-related overdose. *Ann Emerg Med* 9: 357–363
8 Nattel S, Bayne L, Ruedy J (1979) Physostigmine in coma due to drug overdose. *Clin Pharmacol Ther* 25: 96–102
9 Zvosec DL, Smith SW, Litonjua R, Westfal RE (2007) Physostigmine for γ-hydroxybutyrate coma: Inefficacy, adverse events, and review. *Clin Toxicol* 45: 261–265
10 Hoffman RS, Goldfrank LR (1995) The poisoned patient with altered consciousness. Controversies in the use of a 'coma cocktail'. *J Am Med Assoc* 274: 562–569
11 Anonymous (1915) Practical pharmacology. XXIV. *J Am Med Assoc* 64: 2063–2067
12 Temple WA, Smith NA, Beasley M (1991) Management of oil of citronella poisoning. *J Toxicol Clin Toxicol* 29: 257–262
13 Sheffield P (2008) Emetics, cathartics, and gastric lavage. *Pediatr Rev* 29: 214–215
14 Fantus B (1915) Fullers earth; its absorptive power, and its antidotal value for alkaloids. *J Am Med Assoc* 64: 1838–1845
15 Alpert JJ, Lovejoy FH Jr (1971) Management of acute childhood poisoning. *Curr Probl Pediatr* 1: 1–40
16 Clemmesen C, Nilsson E (1961) Therapeutic trends in the treatment of barbiturate poisoning. The Scandinavian method. *Clin Pharmacol Ther* 2: 220–229
17 Lawson AA, Mitchell I (1972) Patients with acute poisoning seen in a general medical unit (1960–71). *Br Med J* 4: 153–156
18 Beaubien AR, Carpenter DC, Mathieu LF, MacConaill M, Hrdina PD (1976) Antagonism of imipramine poisoning by anticonvulsants in the rat. *Toxicol Appl Pharmacol* 38: 1–6
19 Callaham M, Schumaker H, Pentel P (1988) Phenytoin prophylaxis of cardiotoxicity in experimental amitriptyline poisoning. *J Pharmacol Exp Ther* 245: 216–220

20 Sechi G, Serra A (2007) Wernicke's encephalopathy: New clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 6: 442–455

21 Sporer KA, Khayam-Bashi H (1996) Acetaminophen and salicylate serum levels in patients with suicidal ingestion or altered mental status. *Am J Emerg Med* 14: 443–446

22 Ashbourne JF, Olson KR, Khayam-Bashi H (1989) Value of rapid screening for acetaminophen in all patients with intentional drug overdose. *Ann Emerg Med* 18: 1035–1038

23 Cooper GM, Le Couteur DG, Richardson D, Buckley NA (2005) A randomized clinical trial of activated charcoal for the routine management of oral drug overdose. *QJM* 98: 655–660

24 Karim A, Ivatts S, Dargan P, Jones A (2001) How feasible is it to conform to the European guidelines on administration of activated charcoal within one hour of an overdose? *Emerg Med J* 18: 390–392

25 Krenzelok EP, McGuigan M, Lheur P (1997) Position statement: Ipecac syrup. *J Toxicol Clin Toxicol* 35: 699–709

26 Saetta JP, March S, Gaunt ME, Quinton DN (1991) Gastric emptying procedures in the self-poisoned patient: Are we forcing gastric content beyond the pylorus? *J R Soc Med* 84: 274–276

27 Saetta JP, Quinton DN (1991) Residual gastric content after gastric lavage and ipecacuanha-induced emesis in self-poisoned patients: An endoscopic study. *J R Soc Med* 84: 35–38

28 Saincher A, Sitar DS, Tenenbein M (1997) Efficacy of ipecac during the first hour after drug ingestion in human volunteers. *J Toxicol Clin Toxicol* 35: 609–615

29 Lapatto-Reiniluoto O, Kivisto KT, Neuvonen PJ (2000) Gastric decontamination performed 5 min after the ingestion of temazepam, verapamil and moclobemide: Charcoal is superior to lavage. *Br J Clin Pharmacol* 49: 274–278

30 Grierson R, Green R, Sitar DS, Tenenbein M (2000) Gastric lavage for liquid poisons. *Ann Emerg Med* 35: 435–439

31 Tenenbein M, Cohen S, Sitar DS (1987) Efficacy of ipecac-induced emesis, orogastric lavage, and activated charcoal for acute drug overdose. *Ann Emerg Med* 16: 838–841

32 Vale JA, Kulig K (2004) Position paper: Gastric lavage. *J Toxicol Clin Toxicol* 42: 933–943

33 Sato RL, Wong JJ, Sumida SM, Marn RY, Enoki NR, Yamamoto LG (2003) Efficacy of superactivated charcoal administered late (3 hours) after acetaminophen overdose. *Am J Emerg Med* 21: 189–191

34 Christophersen AB, Levin D, Hoegberg LC, Angelo HR, Kampmann JP (2002) Activated charcoal alone or after gastric lavage: A simulated large paracetamol intoxication. *Br J Clin Pharmacol* 53: 312–317

35 Alaspaa AO, Kuisma MJ, Hoppu K, Neuvonen PJ (2005) Out-of-hospital administration of activated charcoal by emergency medical services. *Ann Emerg Med* 45: 207–212

36 Adams BK, Mann MD, Aboo A, Isaacs S, Evans A (2004) Prolonged gastric emptying half-time and gastric hypomotility after drug overdose. *Am J Emerg Med* 22: 548–554

37 Green R, Sitar DS, Tenenbein M (2004) Effect of anticholinergic drugs on the efficacy of activated charcoal. *J Toxicol Clin Toxicol* 42: 267–272

38 Auerbach PS, Osterloh J, Braun O, Hu P, Geehr EC, Kizer KW, McKinney H (1986) Efficacy of gastric emptying: Gastric lavage *versus* emesis induced with ipecac. *Ann Emerg Med* 15: 692–698

39 Albertson TE, Derlet RW, Foulke GE, Minguillon MC, Tharratt SR (1989) Superiority of activated charcoal alone compared with ipecac and activated charcoal in the treatment of acute toxic ingestions. *Ann Emerg Med* 18: 56–59

40 Kulig K, Bar-Or D, Cantrill SV, Rosen P, Rumack BH (1985) Management of acutely poisoned patients without gastric emptying. *Ann Emerg Med* 14: 562–567

41 Comstock EG, Boisaubin EV, Comstock BS, Faulkner TP (1982) Assessment of the efficacy of activated charcoal following gastric lavage in acute drug emergencies. *J Toxicol Clin Toxicol* 19: 149–165

42 Pond SM, Lewis-Driver DJ, Williams GM, Green AC, Stevenson NW (1995) Gastric emptying in acute overdose: A prospective randomised controlled trial. *Med J Aust* 163: 345–349

43 Bosse GM, Barefoot JA, Pfeifer MP, Rodgers GC (1995) Comparison of three methods of gut decontamination in tricyclic antidepressant overdose. *J Emerg Med* 13: 203–209

44 Kirshenbaum LA, Mathews SC, Sitar DS, Tenenbein M (1989) Whole-bowel irrigation *versus* activated charcoal in sorbitol for the ingestion of modified-release pharmaceuticals. *Clin Pharmacol Ther* 46: 264–271

45 Mayer AL, Sitar DS, Tenenbein M (1992) Multiple-dose charcoal and whole-bowel irrigation do

not increase clearance of absorbed salicylate. *Arch Intern Med* 152: 393–396

46 Lee MR (2008) Ipecacuanha: The South American vomiting root. *J R Coll Physicians Edinb* 38: 355–360

47 Manno BR, Manno JE (1977) Toxicology of ipecac: A review. *Clin Toxicol* 10: 221–242

48 Krenzelok EP, Dean BS (1987) Effectiveness of 15-mL *versus* 30-mL doses of syrup of ipecac in children. *Clin Pharm* 6: 715–717

49 Yamashita M, Yamashita M, Azuma J (2002) Urinary excretion of ipecac alkaloids in human volunteers. *Vet Hum Toxicol* 44: 257–259

50 Anonymous (2004) Position paper: Ipecac syrup. *J Toxicol Clin Toxicol* 42: 133–143

51 Garrison J, Shepherd G, Huddleston WL, Watson WA (2003) Evaluation of the time frame for home ipecac syrup use when not kept in the home. *J Toxicol Clin Toxicol* 41: 217–221

52 American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention (2003) Poison treatment in the home. *Pediatrics* 112: 1182–1185

53 Bond GR (2003) Home syrup of ipecac use does not reduce emergency department use or improve outcome. *Pediatrics* 112: 1061–1064

54 MacLean WC Jr (1973) A comparison of ipecac syrup and apomorphine in the immediate treatment of ingestion of poisons. *J Pediatr* 82: 121–124

55 Dorrington CL, Johnson DW, Brant R (2003) The frequency of complications associated with the use of multiple-dose activated charcoal. *Ann Emerg Med* 41: 370–377

56 Caravati EM, Knight HH, Linscott MS Jr, Stringham JC (2001) Esophageal laceration and charcoal mediastinum complicating gastric lavage. *J Emerg Med* 20: 273–276

57 Mofredj A, Rakotondreantoanina JR, Farouj N (2000) Severe hypernatremia secondary to gastric lavage. *Ann Fr Anesth Reanim* 19: 219–220

58 Roberts JR, Gracely EJ, Schoffstall JM (1997) Advantage of high-surface-area charcoal for gastrointestinal decontamination in a human acetaminophen ingestion model. *Acad Emerg Med* 4: 167–174

59 Chyka PA, Seger D, Krenzelok EP, Vale JA (2005) Position paper: Single-dose activated charcoal. *Clin Toxicol* 43: 61–87

60 Neuvonen PJ (1982) Clinical pharmacokinetics of oral activated charcoal in acute intoxications. *Clin Pharmacokinet* 7: 465–489

61 Spiller HA, Winter ML, Klein-Schwartz W, Bangh SA (2006) Efficacy of activated charcoal administered more than four hours after acetaminophen overdose. *J Emerg Med* 30: 1–5

62 Buckley NA, Whyte IM, O'Connell DL, Dawson AH (1999) Activated charcoal reduces the need for *N*-acetylcysteine treatment after acetaminophen (paracetamol) overdose. *J Toxicol Clin Toxicol* 37: 753–757

63 Berg MJ, Berlinger WG, Goldberg MJ, Spector R, Johnson GF (1982) Acceleration of the body clearance of phenobarbital by oral activated charcoal. *N Engl J Med* 307: 642–644

64 Berlinger WG, Spector R, Goldberg MJ, Johnson GF, Quee CK, Berg MJ (1983) Enhancement of theophylline clearance by oral activated charcoal. *Clin Pharmacol Ther* 33: 351–354

65 Levy G (1982) Gastrointestinal clearance of drugs with activated charcoal. *N Engl J Med* 307: 676–678

66 American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists (1999) Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 37: 731–751

67 Campbell JW, Chyka PA (1992) Physicochemical characteristics of drugs and response to repeat-dose activated charcoal. *Am J Emerg Med* 10: 208–210

68 Pond SM, Olson KR, Osterloh JD, Tong TG (1984) Randomized study of the treatment of phenobarbital overdose with repeated doses of activated charcoal. *J Am Med Assoc* 251: 3104–3108

69 Swartz CM, Sherman A (1984) The treatment of tricyclic antidepressant overdose with repeated charcoal. *J Clin Psychopharmacol* 4: 336–340

70 De Silva HA, Fonseka MM, Pathmeswaran A, Alahakone DG, Ratnatilake GA, Gunatilake SB, Ranasinha CD, Lalloo DG, Aronson JK, de Silva HJ (2003) Multiple-dose activated charcoal for treatment of yellow oleander poisoning: A single-blind, randomised, placebo-controlled trial. *Lancet* 361: 1935–1938

71 Eddleston M, Juszczak E, Buckley NA, Senarathna L, Mohamed F, Dissanayake W, Hittarage A, Azher S, Jeganathan K, Jayamanne S, Sheriff MR, Warrell DA (2008) Multiple-dose activated charcoal in acute self-poisoning: A randomised controlled trial. *Lancet* 371: 579–587

72 Olkkola KT (1985) Effect of charcoal-drug ratio on antidotal efficacy of oral activated charcoal in

man. *Br J Clin Pharmacol* 19: 767–773

73 Hoegberg LC, Angelo HR, Christophersen AB, Christensen HR (2003) The effect of food and ice cream on the adsorption capacity of paracetamol to high surface activated charcoal: *In vitro* studies. *Pharmacol Toxicol* 93: 233–237

74 McLuckie A, Forbes AM, Ilett KF (1990) Role of repeated doses of oral activated charcoal in the treatment of acute intoxications. *Anaesth Intensive Care* 18: 375–384

75 Pollack MM, Dunbar BS, Holbrook PR, Fields AI (1981) Aspiration of activated charcoal and gastric contents. *Ann Emerg Med* 10: 528–529

76 Osterhoudt KC, Durbin D, Alpern ER, Henretig FM (2004) Risk factors for emesis after therapeutic use of activated charcoal in acutely poisoned children. *Pediatrics* 113: 806–810

77 Mariani PJ, Pook N (1993) Gastrointestinal tract perforation with charcoal peritoneum complicating orogastric intubation and lavage. *Ann Emerg Med* 22: 606–609

78 Watson WA, Cremer KF, Chapman JA (1986) Gastrointestinal obstruction associated with multiple-dose activated charcoal. *J Emerg Med* 4: 401–407

79 Menzies DG, Busuttil A, Prescott LF (1988) Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 297: 459–460

80 Gades NM, Chyka PA, Butler AY, Virgous CK, Mandrell TD (2003) Activated charcoal and the absorption of ferrous sulfate in rats. *Vet Hum Toxicol* 45: 183–187

81 Rangan C, Nordt SP, Hamilton R, Ingels M, Clark RF (2001) Treatment of acetaminophen ingestion with a superactivated charcoal-cola mixture. *Ann Emerg Med* 37: 55–58

82 Stewart JJ (1983) Effects of emetic and cathartic agents on the gastrointestinal tract and the treatment of toxic ingestion. *J Toxicol Clin Toxicol* 20: 199–253

83 Barceloux D, McGuigan M, Hartigan-Go K (1997) Position statement: Cathartics. *J Toxicol Clin Toxicol* 35: 743–752

84 Smilkstein MJ, Smolinske SC, Kulig KW, Rumack BH (1988) Severe hypermagnesemia due to multiple-dose cathartic therapy. *West J Med* 148: 208–211

85 Beloosesky Y, Grinblat J, Weiss A, Grosman B, Gafter U, Chagnac A (2003) Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. *Arch Intern Med* 163: 803–808

86 McNamara RM, Aaron CK, Gemborys M, Davidheiser S (1988) Sorbitol catharsis does not enhance efficacy of charcoal in a simulated acetaminophen overdose. *Ann Emerg Med* 17: 243–246

87 al-Shareef AH, Buss DC, Allen EM, Routledge PA (1990) The effects of charcoal and sorbitol (alone and in combination) on plasma theophylline concentrations after a sustained-release formulation. *Hum Exp Toxicol* 9: 179–182

88 Allerton JP, Strom JA (1991) Hypernatremia due to repeated doses of charcoal-sorbitol. *Am J Kidney Dis* 17: 581–584

89 Martin RR, Lisehora GR, Braxton M Jr, Barcia PJ (1987) Fatal poisoning from sodium phosphate enema. Case report and experimental study. *J Am Med Assoc* 257: 2190–2192

90 Korkis AM, Miskovitz PF, Yurt RW, Klein H (1992) Rectal prolapse after oral cathartics. *J Clin Gastroenterol* 14: 339–341

91 Ly BT, Schneir AB, Clark RF (2004) Effect of whole bowel irrigation on the pharmacokinetics of an acetaminophen formulation and progression of radiopaque markers through the gastrointestinal tract. *Ann Emerg Med* 43: 189–195

92 Tenenbein M (1997) Position statement: Whole bowel irrigation. *J Toxicol Clin Toxicol* 35: 753–762

93 Lapatto-Reiniluoto O, Kivisto KT, Neuvonen PJ (2001) Activated charcoal alone and followed by whole-bowel irrigation in preventing the absorption of sustained-release drugs. *Clin Pharmacol Ther* 70: 255–260

94 Everson GW, Bertaccini EJ, O'Leary J (1991) Use of whole bowel irrigation in an infant following iron overdose. *Am J Emerg Med* 9: 366–369

95 Smith SW, Ling LJ, Halstenson CE (1991) Whole-bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med* 20: 536–539

96 Roberge RJ, Martin TG (1992) Whole bowel irrigation in an acute oral lead intoxication. *Am J Emerg Med* 10: 577–583

97 Hendrickson RG, Horowitz BZ, Norton RL, Notenboom H (2006) "Parachuting" meth: A novel delivery method for methamphetamine and delayed-onset toxicity from "body stuffing". *Clin Toxicol* 44: 379–382

98 Scharman EJ, Lembersky R, Krenzelok EP (1994) Efficiency of whole bowel irrigation with and without metoclopramide pretreatment. *Am J Emerg Med* 12: 302–305

99 Langdon DE (1996) Colonic perforation with volume laxatives. *Am J Gastroenterol* 91: 622–623

100 Narsinghani U, Chadha M, Farrar HC, Anand KS (2001) Life-threatening respiratory failure following accidental infusion of polyethylene glycol electrolyte solution into the lung. *J Toxicol Clin Toxicol* 39: 105–107

101 Hoffman RS, Chiang WK, Howland MA, Weisman RS, Goldfrank LR (1991) Theophylline desorption from activated charcoal caused by whole bowel irrigation solution. *J Toxicol Clin Toxicol* 29: 191–201

102 Ng HW, Tse ML, Lau FL, Chu W (2008) Endoscopic removal of iron bezoar following acute overdose. *Clin Toxicol* 46: 913–915

103 Hojer J, Personne M (2008) Endoscopic removal of slow release clomipramine bezoars in two cases of acute poisoning. *Clin Toxicol* 46: 317–319

104 Wells CD, Luckritz TC, Rady MY, Zornik JM, Leighton JA, Patel BM (2006) Bezoar formation requiring endoscopic removal after intentional overdose of extended-release nifedipine. *Pharmacotherapy* 26: 1802–1805

105 Choudhary AM, Taubin H, Gupta T, Roberts I (1998) Endoscopic removal of a cocaine packet from the stomach. *J Clin Gastroenterol* 27: 155–156

106 Clifton JC 2nd, Sigg T, Burda AM, Leikin JB, Smith CJ, Sandler RH (2002) Acute pediatric lead poisoning: Combined whole bowel irrigation, succimer therapy, and endoscopic removal of ingested lead pellets. *Pediatr Emerg Care* 18: 200–202

107 Foxford R, Goldfrank L (1985) Gastrotomy – A surgical approach to iron overdose. *Ann Emerg Med* 14: 1223–1226

108 Lapostolle F, Finot MA, Adnet F, Borron SW, Baud FJ, Bismuth C (2000) Radiopacity of clomipramine conglomerations and unsuccessful endoscopy: Report of 4 cases. *J Toxicol Clin Toxicol* 38: 477–482

109 de Prost N, Lefebvre A, Questel F, Roche N, Pourriat JL, Huchon G, Rabbat A (2005) Prognosis of cocaine body-packers. *Intensive Care Med* 31: 955–958

110 Schaper A, Hofmann R, Bargain P, Desel H, Ebbecke M, Langer C (2007) Surgical treatment in cocaine body packers and body pushers. *Int J Colorectal Dis* 22: 1531–1535

111 Bodenham A, Shelly MP, Park GR (1988) The altered pharmacokinetics and pharmacodynamics of drugs commonly used in critically ill patients. *Clin Pharmacokinet* 14: 347–373

112 Proudfoot AT, Krenzelok EP, Vale JA (2004) Position Paper on urine alkalinization. *J Toxicol Clin Toxicol* 42: 1–26

113 Jaing TH, Hung IJ, Chung HT, Lai CH, Liu WM, Chang KW (2002) Acute hypermagnesemia: A rare complication of antacid administration after bone marrow transplantation. *Clin Chim Acta* 326: 201–203

114 Scharman EJ (1997) Methods used to decrease lithium absorption or enhance elimination. *J Toxicol Clin Toxicol* 35: 601–608

115 Kleinman GE, Rodriquez H, Good MC, Caudle MR (1991) Hypercalcemic crisis in pregnancy associated with excessive ingestion of calcium carbonate antacid (milk-alkali syndrome): Successful treatment with hemodialysis. *Obstet Gynecol* 78: 496–499

116 Birrer RB, Shallash AJ, Totten V (2002) Hypermagnesemia-induced fatality following epsom salt gargles. *J Emerg Med* 22: 185–188

117 Bailey CS, Weiner JJ, Gibby OM, Penney MD (2008) Excessive calcium ingestion leading to milk-alkali syndrome. *Ann Clin Biochem* 45: 527–529

118 Chatterjee M, Speiser PW (2007) Pamidronate treatment of hypercalcemia caused by vitamin D toxicity. *J Pediatr Endocrinol Metab* 20: 1241–1248

119 Grunfeld JP, Rossier BC (2009) Lithium nephrotoxicity revisited. *Nat Rev Nephrol* 5: 270–276

120 Majumdar SR, Kjellstrand CM, Tymchak WJ, Hervas-Malo M, Taylor DA, Teo KK (2009) Forced euvolemic ciuresis with mannitol and furosemide for prevention of contrast-induced nephropathy in patients with CKD undergoing coronary angiography: A randomized controlled trial. *Am J Kidney Dis*, in press

121 Eyer F, Pfab R, Felgenhauer N, Lutz J, Heemann U, Steimer W, Zondler S, Fichtl B, Zilker T (2006) Lithium poisoning: Pharmacokinetics and clearance during different therapeutic measures. *J Clin Psychopharmacol* 26: 325–330

122 Van Bommel EF, Kalmeijer MD, Ponssen HH (2000) Treatment of life-threatening lithium toxicity with high-volume continuous venovenous hemofiltration. *Am J Nephrol* 20: 408–411

123 Bressolle F, Kinowski JM, de la Coussaye JE, Wynn N, Eledjam JJ, Galtier M (1994) Clinical pharmacokinetics during continuous haemofiltration. *Clin Pharmacokinet* 26: 457–471

124 Meyer LM, Miller FR, Rowen MJ, Bock G, Rutzky J (1950) Treatment of acute leukemia with amethopterin (4-amino, 10-methyl pteroyl glutamic acid). *Acta Haematol* 4: 157–167

125 Goldfarb DS, Matalon D (2006) Principles and techniques applied to enhance elimination. In: NE Flomenbaum, LR Goldfrank, RS Hoffman, MA Howland, NA Lewin, and LS Nelson (eds): *Goldfrank's Toxicologic Emergencies*, 8th edn., McGraw-Hill, New York, 160–72.

126 Johnson LZ, Martinez I, Fernandez MC, Davis CP, Kasinath BS (1999) Successful treatment of valproic acid overdose with hemodialysis. *Am J Kidney Dis* 33: 786–789

127 Lalau JD, Andrejak M, Moriniere P, Coevoet B, Debussche X, Westeel PF, Fournier A, Quichaud J (1989) Hemodialysis in the treatment of lactic acidosis in diabetics treated by metformin: a study of metformin elimination. *Int J Clin Pharmacol Ther Toxicol* 27: 285–288

128 Tapolyai M, Campbell M, Dailey K, Udvari-Nagy S (2002) Hemodialysis is as effective as hemoperfusion for drug removal in carbamazepine poisoning. *Nephron* 90: 213–215

129 Carlsson M, Cortes D, Jepsen S, Kanstrup T (2008) Severe iron intoxication treated with exchange transfusion. *Arch Dis Child* 93: 321–322

130 Shannon M, Wernovsky G, Morris C (1992) Exchange transfusion in the treatment of severe theophylline poisoning. *Pediatrics* 89: 145–147

131 Manikian A, Stone S, Hamilton R, Foltin G, Howland MA, Hoffman RS (2002) Exchange transfusion in severe infant salicylism. *Vet Hum Toxicol* 44: 224–227

132 Katz BE, Carver MW (1956) Acute poisoning with isoniazid treated by exchange transfusion. *Pediatrics* 18: 72–76

133 Sancak R, Kucukoduk S, Tasdemir HA, Belet N (1999) Exchange transfusion treatment in a newborn with phenobarbital intoxication. *Pediatr Emerg Care* 15: 268–270

134 Kosmidis HV, Bouhoutsou DO, Varvoutsi MC, Papadatos J, Stefanidis CG, Vlachos P, Scardoutsou A, Kostakis A (1991) Vincristine overdose: Experience with 3 patients. *Pediatr Hematol Oncol* 8: 171–178

135 Coleman MD, Coleman NA (1996) Drug-induced methaemoglobinaemia. Treatment issues. *Drug Saf* 14: 394–405

136 Kwon SU, Lim SH, Rhee I, Kim SW, Kim JK, Kim DW, Jeon ES (2006) Successful whole blood exchange by apheresis in a patient with acute cyclosporine intoxication without long-term sequelae. *J Heart Lung Transplant* 25: 483–485

137 Camerino DC, Desaphy JF, Tricarico D, Pierno S, Liantonio A (2008) Therapeutic approaches to ion channel diseases. *Adv Genet* 64: 81–145

138 Diaz-Sylvester PL, Porta M, Copello JA (2008) Halothane modulation of skeletal muscle ryanodine receptors: Dependence on Ca^{2+}, Mg^{2+}, and ATP. *Am J Physiol Cell Physiol* 294: C1103–1112

139 Smith FA, Wittmann CW, Stern TA (2008) Medical complications of psychiatric treatment. *Crit Care Clin* 24: 635–656

140 Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM (2003) The Hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. *QJM* 96: 635–642

141 Sternbach H (1991) The serotonin syndrome. *Am J Psychiatry* 148: 705–713

142 Boyer EW, Shannon M (2005) The serotonin syndrome. *N Engl J Med* 352: 1112–1120

143 Rusyniak DE, Sprague JE (2005) Toxin-induced hyperthermic syndromes. *Med Clin North Am* 89: 1277–1296

144 Ioos V, Das V, Maury E, Baudel JL, Guechot J, Guidet B, Offenstadt G (2008) A thyrotoxicosis outbreak due to dietary pills in Paris. *Ther Clin Risk Manag* 4: 1375–1379

145 Redahan C, Karski JM (1994) Thyrotoxicosis factitia in a post-aortocoronary bypass patient. *Can J Anaesth* 41: 969–972

146 Hsiao AL, Santucci KA, Seo-Mayer P, Mariappan MR, Hodsdon ME, Banasiak KJ, Baum CR (2005) Pediatric fatality following ingestion of dinitrophenol: Postmortem identification of a "dietary supplement". *Clin Toxicol* 43: 281–285

147 Argaud L, Ferry T, Le QH, Marfisi A, Ciorba D, Achache P, Ducluzeau R, Robert D (2007) Short- and long-term outcomes of heatstroke following the 2003 heat wave in Lyon, France. *Arch Intern Med* 167: 2177–2183

148 Dematte JE, O'Mara K, Buescher J, Whitney CG, Forsythe S, McNamee T, Adiga RB, Ndukwu IM (1998) Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med* 129:

173–181

149 Marzuk PM, Tardiff K, Leon AC, Hirsch CS, Portera L, Iqbal MI, Nock MK, Hartwell N (1998) Ambient temperature and mortality from unintentional cocaine overdose. *J Am Med Assoc* 279: 1795–1800

150 Bowyer JF, Davies DL, Schmued L, Broening HW, Newport GD, Slikker W Jr, Holson RR (1994) Further studies of the role of hyperthermia in methamphetamine neurotoxicity. *J Pharmacol Exp Ther* 268: 1571–1580

151 Ferris EB, Blankenhorn MA, Robinson HW, Cullen GE (1938) Heat stroke: Clinical and chemical observations on 44 cases. *J Clin Invest* 17: 249–262

152 Bouchama A, Dehbi M, Chaves-Carballo E (2007) Cooling and hemodynamic management in heatstroke: Practical recommendations. *Crit Care* 11: R54

153 Armstrong LE, Crago AE, Adams R, Roberts WO, Maresh CM (1996) Whole-body cooling of hyperthermic runners: Comparison of two field therapies. *Am J Emerg Med* 14: 355–358

154 Costrini A (1990) Emergency treatment of exertional heatstroke and comparison of whole body cooling techniques. *Med Sci Sports Exerc* 22: 15–18

155 Nisijima K, Shioda K, Yoshino T, Takano K, Kato S (2003) Diazepam and chlormethiazole attenuate the development of hyperthermia in an animal model of the serotonin syndrome. *Neurochem Int* 43: 155–164

156 Derlet RW, Albertson TE, Rice P (1990) Antagonism of cocaine, amphetamine, and methamphetamine toxicity. *Pharmacol Biochem Behav* 36: 745–749

157 Laorden ML, Carrillo E, Miralles FS, Puig MM (1990) Effects of diltiazem on hyperthermia induced seizures in the rat pup. *Gen Pharmacol* 21: 313–315

158 Kobayashi S, Bannister ML, Gangopadhyay JP, Hamada T, Parness J, Ikemoto N (2005) Dantrolene stabilizes domain interactions within the ryanodine receptor. *J Biol Chem* 280: 6580–6587

159 Cherednichenko G, Ward CW, Feng W, Cabrales E, Michaelson L, Samso M, Lopez JR, Allen PD, Pessah IN (2008) Enhanced excitation-coupled calcium entry in myotubes expressing malignant hyperthermia mutation R163C is attenuated by dantrolene. *Mol Pharmacol* 73: 1203–1212

160 Reulbach U, Dutsch C, Biermann T, Sperling W, Thuerauf N, Kornhuber J, Bleich S (2007) Managing an effective treatment for neuroleptic malignant syndrome. *Crit Care* 11: R4

161 Sakkas P, Davis JM, Janicak PG, Wang ZY (1991) Drug treatment of the neuroleptic malignant syndrome. *Psychopharmacol Bull* 27: 381–384

162 Massicotte A (2008) Contrast medium-induced nephropathy: Strategies for prevention. *Pharmacotherapy* 28: 1140–1150

163 Rumack BH (2002) Acetaminophen hepatotoxicity: The first 35 years. *J Toxicol Clin Toxicol* 40: 3–20

164 Laine JE, Auriola S, Pasanen M, Juvonen RO (2009) Acetaminophen bioactivation by human cytochrome P450 enzymes and animal microsomes. *Xenobiotica* 39: 11–21

165 Heard KJ (2008) Acetylcysteine for acetaminophen poisoning. *N Engl J Med* 359: 285–292

166 Lauterburg BH, Corcoran GB, Mitchell JR (1983) Mechanism of action of *N*-acetylcysteine in the protection against the hepatotoxicity of acetaminophen in rats *in vivo*. *J Clin Invest* 71: 980–991

167 Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, Williams R (1991) Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: A prospective controlled trial. *BMJ* 303: 1026–1029

168 Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R (1991) Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med* 324: 1852–1857

169 Devlin J, Ellis AE, McPeake J, Heaton N, Wendon JA, Williams R (1997) *N*-Acetylcysteine improves indocyanine green extraction and oxygen transport during hepatic dysfunction. *Crit Care Med* 25: 236–242

170 Rank N, Michel C, Haertel C, Lenhart A, Welte M, Meier-Hellmann A, Spies C (2000) *N*-Acetylcysteine increases liver blood flow and improves liver function in septic shock patients: Results of a prospective, randomized, double-blind study. *Crit Care Med* 28: 3799–3807

171 Wong BK, Chan HC, Corcoran GB (1986) Selective effects of *N*-acetylcysteine stereoisomers on hepatic glutathione and plasma sulfate in mice. *Toxicol Appl Pharmacol* 86: 421–429

172 Wong BK, Galinsky RE, Corcoran GB (1986) Dissociation of increased sulfation from sulfate replenishment and hepatoprotection in acetaminophen-poisoned mice by *N*-acetylcysteine

stereoisomers. *J Pharm Sci* 75: 878–880

173 Tsai CL, Chang WT, Weng TI, Fang CC, Walson PD (2005) A patient-tailored *N*-acetylcysteine protocol for acute acetaminophen intoxication. *Clin Ther* 27: 336–341

174 Betten DP, Cantrell FL, Thomas SC, Williams SR, Clark RF (2007) A prospective evaluation of shortened course oral *N*-acetylcysteine for the treatment of acute acetaminophen poisoning. *Ann Emerg Med* 50: 272–279

175 Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA (2008) Guidelines for the management of paracetamol poisoning in Australia and New Zealand – Explanation and elaboration. *Med J Aust* 188: 296–301

176 Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH (1988) Efficacy of oral *N*-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985) *N Engl J Med* 319: 1557–1562

177 Bridger S, Henderson K, Glucksman E, Ellis AJ, Henry JA, Williams R (1998) Deaths from low dose paracetamol poisoning. *BMJ* 316: 1724–1725

178 Rumack BH (2004) Acetaminophen misconceptions. *Hepatology* 40: 10–15

179 Pakravan N, Waring WS, Sharma S, Ludlam C, Megson I, Bateman DN (2008) Risk factors and mechanisms of anaphylactoid reactions to acetylcysteine in acetaminophen overdose. *Clin Toxicol* 46: 697–702

180 Hayes BD, Klein-Schwartz W, Doyon S (2008) Frequency of medication errors with intravenous acetylcysteine for acetaminophen overdose. *Ann Pharmacother* 42: 766–770

181 Sung L, Simons JA, Dayneka NL (1997) Dilution of intravenous *N*-acetylcysteine as a cause of hyponatremia. *Pediatrics* 100: 389–391

182 Yarema MC, Johnson DW, Berlin RJ, Sivilotti ML, Nettel-Aguirre A, Brant RF, Spyker DA, Bailey B, Chalut D, Lee JS, Plint AC, Purssell RA, Rutledge T, Seviour CA, Stiell IG, Thompson M, Tyberg J, Dart RC, Rumack BH (2009) Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. *Ann Emerg Med* 54: 606–614

183 Doyon S, Klein-Schwartz W (2009) Hepatotoxicity despite early administration of intravenous *N*-acetylcysteine for acute acetaminophen overdose. *Acad Emerg Med* 16: 34–39

184 Smith SW, Howland MA, Hoffman RS, Nelson LS (2008) Acetaminophen overdose with altered acetaminophen pharmacokinetics and hepatotoxicity associated with premature cessation of intravenous *N*-acetylcysteine therapy. *Ann Pharmacother* 42: 1333–1339

185 Halcomb SE, Sivilotti ML, Goklaney A, Mullins ME (2005) Pharmacokinetic effects of diphenhydramine or oxycodone in simulated acetaminophen overdose. *Acad Emerg Med* 12: 169–172

186 Cetaruk EW, Dart RC, Hurlbut KM, Horowitz RS, Shih R (1997) Tylenol extended relief overdose. *Ann Emerg Med* 30: 104–108

187 Fraser TR (1863) On the characters, actions, and therapeutic uses of the bean of Calabar. *Edin Med J* 9: 36–56; 123–132; 235–248

188 Nickalls RW, Nickalls EA (1988) The first use of physostigmine in the treatment of atropine poisoning. A translation of Kleinwachter's paper entitled 'Observations on the effect of Calabar bean extract as an antidote to atropine poisoning'. *Anaesthesia* 43: 776–779

189 Atack JR, Yu QS, Soncrant TT, Brossi A, Rapoport SI (1989) Comparative inhibitory effects of various physostigmine analogs against acetyl- and butyrylcholinesterases. *J Pharmacol Exp Ther* 249: 194–202

190 Brossi A, Schonenberger B, Clark OE, Ray R (1986) Inhibition of acetylcholinesterase from electric eel by (–)- and (+)-physostigmine and related compounds. *FEBS Lett* 201: 190–192

191 Barak D, Ordentlich A, Stein D, Yu QS, Greig NH, Shafferman A (2009) Accommodation of physostigmine and its analogues by acetylcholinesterase is dominated by hydrophobic interactions. *Biochem J* 417: 213–222

192 Pereira EF, Hilmas C, Santos MD, Alkondon M, Maelicke A, Albuquerque EX (2002) Unconventional ligands and modulators of nicotinic receptors. *J Neurobiol* 53: 479–500

193 Pentel P, Peterson CD (1980) Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. *Ann Emerg Med* 9: 588–590

194 Suchard JR (2003) Assessing physostigmine's contraindication in cyclic antidepressant ingestions. *J Emerg Med* 25: 185–191

195 Ago J, Ishikawa T, Matsumoto N, Ashequr Rahman M, Kamei C (2006) Mechanism of imipramine-induced seizures in amygdala-kindled rats. *Epilepsy Res* 72: 1–9

196 Fleck C, Braunlich H (1982) Failure of physostigmine in intoxications with tricyclic antidepres-

sants in rats. *Toxicology* 24: 335–344

197 Burns MJ, Linden CH, Graudins A, Brown RM, Fletcher KE (2000) A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. *Ann Emerg Med* 35: 374–381

198 Frascogna N (2007) Physostigmine: Is there a role for this antidote in pediatric poisonings? *Curr Opin Pediatr* 19: 201–205

199 Claessens YE, Cariou A, Monchi M, Soufir L, Azoulay E, Rouges P, Goldgran-Toledano D, Branche F, Dhainaut JF (2003) Detecting life-threatening lactic acidosis related to nucleoside-analog treatment of human immunodeficiency virus-infected patients, and treatment with L-carnitine. *Crit Care Med* 31: 1042–1047

200 Delaney CE, Hopkins SP, Addison CL (2007) Supplementation with L-carnitine does not reduce the efficacy of epirubicin treatment in breast cancer cells. *Cancer Lett* 252: 195–207

201 Lheureux PE, Penaloza A, Zahir S, Gris M (2005) Science review: Carnitine in the treatment of valproic acid-induced toxicity – What is the evidence? *Crit Care* 9: 431–440

202 Katiyar A, Aaron C (2007) Case files of the Children's Hospital of Michigan Regional Poison Control Center: The use of carnitine for the management of acute valproic acid toxicity. *J Med Toxicol* 3: 129–138

203 Loscher W (2002) Basic pharmacology of valproate: A review after 35 years of clinical use for the treatment of epilepsy. *CNS Drugs* 16: 669–694

204 Silva MF, Aires CC, Luis PB, Ruiter JP, Ijlst L, Duran M, Wanders RJ, Tavares de Almeida I (2008) Valproic acid metabolism and its effects on mitochondrial fatty acid oxidation: A review. *J Inherit Metab Dis*, *in press*

205 Ingels M, Beauchamp J, Clark RF, Williams SR (2002) Delayed valproic acid toxicity: A retrospective case series. *Ann Emerg Med* 39: 616–621

206 Eyer F, Felgenhauer N, Gempel K, Steimer W, Gerbitz KD, Zilker T (2005) Acute valproate poisoning: Pharmacokinetics, alteration in fatty acid metabolism, and changes during therapy. *J Clin Psychopharmacol* 25: 376–380

207 Sztajnkrycer MD (2002) Valproic acid toxicity: Overview and management. *J Toxicol Clin Toxicol* 40: 789–801

208 Riva R, Albani F, Gobbi G, Santucci M, Baruzzi A (1993) Carnitine disposition before and during valproate therapy in patients with epilepsy. *Epilepsia* 34: 184–187

209 Okamura N, Ohnishi S, Shimaoka H, Norikura R, Hasegawa H (2006) Involvement of recognition and interaction of carnitine transporter in the decrease of L-carnitine concentration induced by pivalic acid and valproic acid. *Pharm Res* 23: 1729–1735

210 Spahr L, Negro F, Rubbia-Brandt L, Marinescu O, Goodman K, Jordan M, Frossard JL, Hadengue A (2001) Acute valproate-associated microvesicular steatosis: Could the [^{13}C]methionine breath test be useful to assess liver mitochondrial function? *Dig Dis Sci* 46: 2758–2761

211 Russell S (2007) Carnitine as an antidote for acute valproate toxicity in children. *Curr Opin Pediatr* 19: 206–210

212 De Vivo DC, Bohan TP, Coulter DL, Dreifuss FE, Greenwood RS, Nordli DR Jr, Shields WD, Stafstrom CE, Tein I (1998) L-carnitine supplementation in childhood epilepsy: Current perspectives. *Epilepsia* 39: 1216–1225

213 Anil M, Helvaci M, Ozbal E, Kalenderer O, Anil AB, Dilek M (2009) Serum and muscle carnitine levels in epileptic children receiving sodium valproate. *J Child Neurol* 24: 80–86

214 Zelnik N, Isler N, Goez H, Shiffer M, David M, Shahar E (2008) Vigabatrin, lamotrigine, topiramate and serum carnitine levels. *Pediatr Neurol* 39: 18–21

215 Verrotti A, Greco R, Morgese G, Chiarelli F (1999) Carnitine deficiency and hyperammonemia in children receiving valproic acid with and without other anticonvulsant drugs. *Int J Clin Lab Res* 29: 36–40

216 Bohles H, Sewell AC, Wenzel D (1996) The effect of carnitine supplementation in valproate-induced hyperammonaemia. *Acta Paediatr* 85: 446–449

217 Gidal BE, Inglese CM, Meyer JF, Pitterle ME, Antonopolous J, Rust RS (1997) Diet- and valproate-induced transient hyperammonemia: Effect of L-carnitine. *Pediatr Neurol* 16: 301–305

218 Van Wouwe JP (1995) Carnitine deficiency during valproic acid treatment. *Int J Vitam Nutr Res* 65: 211–214

219 Ishikura H, Matsuo N, Matsubara M, Ishihara T, Takeyama N, Tanaka T (1996) Valproic acid overdose and L-carnitine therapy. *J Anal Toxicol* 20: 55–58

220 Romero-Falcon A, de la Santa-Belda E, Garci-Contreras R, Varela JM (2003) A case of valproate-

associated hepatotoxicity treated with L-carnitine. *Eur J Intern Med* 14: 338–340

221 Wadzinski J, Franks R, Roane D, Bayard M (2007) Valproate-associated hyperammonemic encephalopathy. *J Am Board Fam Med* 20: 499–502

222 Bohan TP, Helton E, McDonald I, Konig S, Gazitt S, Sugimoto T, Scheffner D, Cusmano L, Li S, Koch G (2001) Effect of L-carnitine treatment for valproate-induced hepatotoxicity. *Neurology* 56: 1405–1409

223 Raskind JY, El-Chaar GM (2000) The role of carnitine supplementation during valproic acid therapy. *Ann Pharmacother* 34: 630–638

224 Beauchamp J, Olson K (1999) Valproic acid overdoses: A retrospective study comparing serum drug levels and the incidence of adverse outcomes. *J Toxicol Clin Toxicol* 37: 637–638

225 LoVecchio F, Shriki J, Samaddar R (2005) L-Carnitine was safely administered in the setting of valproate toxicity. *Am J Emerg Med* 23: 321–322

226 Sigma-Tau Pharmaceuticals Inc (2006) CARNITOR® (levocarnitine) Tablets (330 mg). CARNITOR® (levocarnitine) Oral Solution (1 g per 10 mL multidose). CARNITOR® SF (levocarnitine) Sugar-Free Oral Solution (1 g per 10 mL multidose). Sigma-Tau Pharmaceuticals Inc., Gaithersburg, MD

227 Jung J, Eo E, Ahn KO (2008) A case of hemoperfusion and L-carnitine management in valproic acid overdose. *Am J Emerg Med* 26: 388.e3–4

228 Rossini PM, Marchionno L, Gambi D, Pirchio M, Del Rosso G, Albertazzi A (1981) EMG changes in chronically dialyzed uraemic subjects undergoing D,L-carnitine treatment. *Ital J Neurol Sci* 2: 255–262

229 Tsoko M, Beauseigneur F, Gresti J, Niot I, Demarquoy J, Boichot J, Bezard J, Rochette L, Clouet P (1995) Enhancement of activities relative to fatty acid oxidation in the liver of rats depleted of L-carnitine by D-carnitine and a γ-butyrobetaine hydroxylase inhibitor. *Biochem Pharmacol* 49: 1403–1410

230 Seltzer HS (1989) Drug-induced hypoglycemia. A review of 1418 cases. *Endocrinol Metab Clin North Am* 18: 163–183

231 Chan JC, Cockram CS, Critchley JA (1996) Drug-induced disorders of glucose metabolism. Mechanisms and management. *Drug Saf* 15: 135–157

232 Wender R, Brown AM, Fern R, Swanson RA, Farrell K, Ransom BR (2000) Astrocytic glycogen influences axon function and survival during glucose deprivation in central white matter. *J Neurosci* 20: 6804–6810

233 Boyle PJ, Kempers SF, O'Connor AM, Nagy RJ (1995) Brain glucose uptake and unawareness of hypoglycemia in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 333: 1726–1731

234 Dalan R, Leow MK, George J, Chian KY, Tan A, Han HW, Cheow SP (2009) Neuroglycopenia and adrenergic responses to hypoglycaemia: Insights from a local epidemic of serendipitous massive overdose of glibenclamide. *Diabet Med* 26: 105–109

235 Kuzak N, Brubacher JR, Kennedy JR (2007) Reversal of salicylate-induced euglycemic delirium with dextrose. *Clin Toxicol (Phila)* 45: 526–529

236 Abdelmalik PA, Shannon P, Yiu A, Liang P, Adamchik Y, Weisspapir M, Samoilova M, Burnham WM, Carlen PL (2007) Hypoglycemic seizures during transient hypoglycemia exacerbate hippocampal dysfunction. *Neurobiol Dis* 26: 646–660

237 Auer RN, Wieloch T, Olsson Y, Siesjo BK (1984) The distribution of hypoglycemic brain damage. *Acta Neuropathol* 64: 177–191

238 Hospira, Inc (2004) Concentrated Dextrose for Intravenous Administration. Hospira Inc., Lake Forest, IL

239 Cunningham P, Afzal-Ahmed I, Naftalin RJ (2006) Docking studies show that D-glucose and quercetin slide through the transporter GLUT1. *J Biol Chem* 281: 5797–5803

240 Yosowitz P, Ekland DA, Shaw RC, Parsons RW (1975) Peripheral intravenous infiltration necrosis. *Ann Surg* 182: 553–556

241 MacLeod DB, Montoya DR, Fick GH, Jessen KR (1994) The effect of 25 grams i.v. glucose on serum inorganic phosphate levels. *Ann Emerg Med* 23: 524–528

242 Novartis Pharma Stein AG (2008) Sandostatin® octreotide acetate Injection Prescribing Information. Novartis Pharma Stein AG, Stein, Switzerland

243 Doyle ME, Egan JM (2003) Pharmacological agents that directly modulate insulin secretion. *Pharmacol Rev* 55: 105–131

244 Gerich JE (1989) Oral hypoglycemic agents. *N Engl J Med* 321: 1231–1245

245 Hansen JB, Arkhammar PO, Bodvarsdottir TB, Wahl P (2004) Inhibition of insulin secretion as a new drug target in the treatment of metabolic disorders. *Curr Med Chem* 11: 1595–1615

246 Lahlou H, Guillermet J, Hortala M, Vernejoul F, Pyronnet S, Bousquet C, Susini C (2004) Molecular signaling of somatostatin receptors. *Ann NY Acad Sci* 1014: 121–131

247 Di Mauro M, Papalia G, Le Moli R, Nativo B, Nicoletti F, Lunetta M (2001) Effect of octreotide on insulin requirement, hepatic glucose production, growth hormone, glucagon and c-peptide levels in type 2 diabetic patients with chronic renal failure or normal renal function. *Diabetes Res Clin Pract* 51: 45–50

248 Mordel A, Sivilotti MLA, Old AC, Ferm RP (1998) Octreotide for pediatric sulfonylurea poisoning. *J Toxicol Clin Toxicol* 36: 437

249 Skugor M, Siraj ES (2003) A diabetic woman with worsening heart failure, hunger, and tremor. *Cleve Clin J Med* 70: 882–888

250 Green RS, Palatnick W (2003) Effectiveness of octreotide in a case of refractory sulfonylurea-induced hypoglycemia. *J Emerg Med* 25: 283–287

251 Boyle PJ, Justice K, Krentz AJ, Nagy RJ, Schade DS (1993) Octreotide reverses hyperinsulinemia and prevents hypoglycemia induced by sulfonylurea overdoses. *J Clin Endocrinol Metab* 76: 752–756

252 McLaughlin SA, Crandall CS, McKinney PE (2000) Octreotide: An antidote for sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 36: 133–138

253 Fasano CJ, O'Malley G, Dominici P, Aguilera E, Latta DR (2008) Comparison of octreotide and standard therapy *versus* standard therapy alone for the treatment of sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 51: 400–406

254 Gul M, Cander B, Girisgin S, Ayan M, Kocak S, Unlu A (2006) The effectiveness of various doses of octreotide for sulfonylurea-induced hypoglycemia after overdose. *Adv Ther* 23: 878–884

255 Fleseriu M, Skugor M, Chinnappa P, Siraj ES (2006) Successful treatment of sulfonylurea-induced prolonged hypoglycemia with use of octreotide. *Endocr Pract* 12: 635–640

256 Carr R, Zed PJ (2002) Octreotide for sulfonylurea-induced hypoglycemia following overdose. *Ann Pharmacother* 36: 1727–1732

257 Tenenbein MS, Tenenbein M (2006) Anaphylactoid reaction to octreotide. *Clin Toxicol* 44: 707

258 Calello DP, Kelly A, Osterhoudt KC (2006) Case files of the Medical Toxicology Fellowship Training Program at the Children's Hospital of Philadelphia: A pediatric exploratory sulfonylurea ingestion. *J Med Toxicol* 2: 19–24

259 Curtis JA, Greenberg MI (2006) Bradycardia and hyperkalemia associated with octreotide administration. *Clin Toxicol* 44: 498

260 Rath S, Bar-Zeev N, Anderson K, Fahy R, Roseby R (2008) Octreotide in children with hypoglycaemia due to sulfonylurea ingestion. *J Paediatr Child Health* 44: 383–384

261 Al-Shanafey S, Habib Z, AlNassar S (2009) Laparoscopic pancreatectomy for persistent hyperinsulinemic hypoglycemia of infancy. *J Pediatr Surg* 44: 134–138

262 Ferraz DP, Almeida MA, Mello BF (2005) Octreotide therapy for persistent hyperinsulinemic hypoglycemia of infancy. *Arq Bras Endocrinol Metabol* 49: 460–467

263 Phillips RE, Warrell DA, Looareesuwan S, Turner RC, Bloom SR, Quantrill D, Moore AR (1986) Effectiveness of SMS 201–995, a synthetic, long-acting somatostatin analogue, in treatment of quinine-induced hyperinsulinaemia. *Lancet* 1: 713–716

264 Phillips RE, Looareesuwan S, Molyneux ME, Hatz C, Warrell DA (1993) Hypoglycaemia and counterregulatory hormone responses in severe falciparum malaria: Treatment with sandostatin. *Q J Med* 86: 233–240

265 Lheureux PE, Zahir S, Penaloza A, Gris M (2005) Bench-to-bedside review: Antidotal treatment of sulfonylurea-induced hypoglycaemia with octreotide. *Crit Care* 9: 543–549

266 Harris AG (1994) Somatostatin and somatostatin analogues: Pharmacokinetics and pharmacodynamic effects. *Gut* 35: S1–4

267 Kalman SD, Rogers R, Barrueto F Jr (2006) Glyburide sold as "Street Steroid" causes hypoglycemia complicated by inappropriate IV administration of octreotide. *Clin Toxicol* 44: 713–714

268 Lamberts SW, van der Lely AJ, de Herder WW, Hofland LJ (1996) Octreotide. *N Engl J Med* 334: 246–254

269 Mohnike K, Blankenstein O, Pfuetzner A, Potzsch S, Schober E, Steiner S, Hardy OT, Grimberg A, van Waarde WM (2008) Long-term non-surgical therapy of severe persistent congenital hyperinsulinism with glucagon. *Horm Res* 70: 59–64

270 Garibaldi RA, Drusin RE, Ferebee SH, Gregg MB (1972) Isoniazid-associated hepatitis. Report

of an outbreak. *Am Rev Respir Dis* 106: 357–365

271 Peloquin CA (2002) Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs* 62: 2169–2183

272 Lheureux P, Penaloza A, Gris M (2005) Pyridoxine in clinical toxicology: A review. *Eur J Emerg Med* 12: 78–85

273 Sullivan EA, Geoffroy P, Weisman R, Hoffman R, Frieden TR (1998) Isoniazid poisonings in New York City. *J Emerg Med* 16: 57–59

274 Brown CV (1972) Acute isoniazid poisoning. *Am Rev Respir Dis* 105: 206–216

275 Agrawal RL, Dwivedi NC, Agrawal M, Jain S, Agrawal A (2008) Accidental isoniazid poisoning – A report. *Indian J Tuberc* 55: 94–96

276 Handbook of Anti-Tuberculosis Agents (2008) Isoniazid *Tuberculosis* 88: 112–116

277 Dunlop DS, Neidle A (1997) The origin and turnover of D-serine in brain. *Biochem Biophys Res Commun* 235: 26–30

278 Mustafa AK, van Rossum DB, Patterson RL, Maag D, Ehmsen JT, Gazi SK, Chakraborty A, Barrow RK, Amzel LM, Snyder SH (2009) Glutamatergic regulation of serine racemase *via* reversal of PIP2 inhibition. *Proc Natl Acad Sci USA* 106: 2921–2926

279 Wood JD, Peesker SJ (1972) The effect on GABA metabolism in brain of isonicotinic acid hydrazide and pyridoxine as a fuction of time after administration. *J Neurochem* 19: 1527–1537

280 Hankins DG, Saxena K, Faville RJ Jr, Warren BJ (1987) Profound acidosis caused by isoniazid ingestion. *Am J Emerg Med* 5: 165–166

281 Chin L, Sievers ML, Herrier RN, Picchioni AL (1979) Convulsions as the etiology of lactic acidosis in acute isoniazid toxicity in dogs. *Toxicol Appl Pharmacol* 49: 377–384

282 Wason S, Lacouture PG, Lovejoy FH Jr (1981) Single high-dose pyridoxine treatment for isoniazid overdose. *J Am Med Assoc* 246: 1102–1104

283 Terman DS, Teitelbaum DT (1970) Isoniazid self-poisoning. *Neurology* 20: 299–304

284 Jen M, Shah KN, Yan AC (2008) Cutaneous changes in nutritional disease. In: K Wolff, LA Goldsmith, SI Katz, BA Gilchrest, AS Paller, DJ Leffell (eds): *Fitzpatrick's Dermatology in General Medicine*, 7th edn., The McGraw-Hill Companies Inc. (http://www.accessmedicine. com/content.aspx?aID=2964061, accessed April 6, 2009)

285 Miller J, Robinson A, Percy AK (1980) Acute isoniazid poisoning in childhood. *Am J Dis Child* 134: 290–292

286 Brent J, Vo N, Kulig K, Rumack BH (1990) Reversal of prolonged isoniazid-induced coma by pyridoxine. *Arch Intern Med* 150: 1751–1753

287 Shah BR, Santucci K, Sinert R, Steiner P (1995) Acute isoniazid neurotoxicity in an urban hospital. *Pediatrics* 95: 700–704

288 Alvarez FG, Guntupalli KK (1995) Isoniazid overdose: Four case reports and review of the literature. *Intensive Care Med* 21: 641–644

289 Chin L, Sievers ML, Laird HE, Herrier RN, Picchioni AL (1978) Evaluation of diazepam and pyridoxine as antidotes to isoniazid intoxication in rats and dogs. *Toxicol Appl Pharmacol* 45: 713–722

290 Morrow LE, Wear RE, Schuller D, Malesker M (2006) Acute isoniazid toxicity and the need for adequate pyridoxine supplies. *Pharmacotherapy* 26: 1529–1532

291 Scharman EJ, Rosencrane JG (1994) Isoniazid toxicity: A survey of pyridoxine availability. *Am J Emerg Med* 12: 386–388

292 Schaumburg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ (1983) Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. *N Engl J Med* 309: 445–448

293 Bredemann JA, Krechel SW, Eggers GW Jr (1990) Treatment of refractory seizures in massive isoniazid overdose. *Anesth Analg* 71: 554–557

294 Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, Cohen GI, Emami B, Gradishar WJ, Mitchell RB, Thigpen JT, Trotti A 3rd, von Hoff D, Schuchter LM (2009) American Society of Clinical Oncology 2008 clinical practice guideline update: Use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 27: 127–145

295 Cetingul N, Midyat L, Kantar M, Demirag B, Aksoylar S, Kansoy S (2009) Cytoprotective effects of amifostine in the treatment of childhood malignancies. *Pediatr Blood Cancer* 52: 829–833

296 Batista CK, Mota JM, Souza ML, Leitao BT, Souza MH, Brito GA, Cunha FQ, Ribeiro RA (2007) Amifostine and glutathione prevent ifosfamide- and acrolein-induced hemorrhagic cystitis. *Cancer Chemother Pharmacol* 59: 71–77

297 Gandara DR, Nahhas WA, Adelson MD, Lichtman SM, Podczaski ES, Yanovich S, Homesley HD, Braly P, Ritch PS, Weisberg SR (1995) Randomized placebo-controlled multicenter evaluation of diethyldithiocarbamate for chemoprotection against cisplatin-induced toxicities. *J Clin Oncol* 13: 490–496

298 Crawford J, Armitage J, Balducci L, Bennett C, Blayney DW, Cataland SR, Dale DC, Demetri GD, Erba HP, Foran J, Freifeld AG, Goemann M, Heaney ML, Htoy S, Hudock S, Kloth DD, Kuter DJ, Lyman GH, Michaud LB, Miyata SC, Tallman MS, Vadhan-Raj S, Westervelt P, Wong MK (2009) Myeloid growth factors. *J Natl Compr Canc Netw* 7: 64–83

299 Wyeth Pharmaceuticals Inc (2009) NEUMEGA® [nu-meg<a] (oprelvekin). Wyeth Pharmaceuticals Inc., Philadelphia, PA

300 Wengstrom Y, Margulies A (2008) European Oncology Nursing Society extravasation guidelines. *Eur J Oncol Nurs* 12: 357–361

301 TopoTarget USA Inc (2007) Totect™ (Dexrazoxane) for injection. Totect™ Package Insert. Distributed by Integrated Commercialization Solutions. Manufactured by Ben Venue Laboratories Inc., and Hameln Pharmaceuticals GmbH for TopoTarget A/S. Marketed by TopoTarget USA Inc., Rockaway, NJ

302 Mouridsen HT, Langer SW, Buter J, Eidtmann H, Rosti G, de Wit M, Knoblauch P, Rasmussen A, Dahlstrom K, Jensen PB, Giaccone G (2007) Treatment of anthracycline extravasation with Savene (dexrazoxane): Results from two prospective clinical multicentre studies. *Ann Oncol* 18: 546–550

303 Frost A, Gmehling D, Azemar M, Unger C, Mross K (2006) Treatment of anthracycline extravasation with dexrazoxane – Clinical experience. *Onkologie* 29: 314–318

304 Kane RC, McGuinn WD Jr, Dagher R, Justice R, Pazdur R (2008) Dexrazoxane (Totect): FDA review and approval for the treatment of accidental extravasation following intravenous anthracycline chemotherapy. *Oncologist* 13: 445–450

305 Reeves D (2007) Management of anthracycline extravasation injuries. *Ann Pharmacother* 41: 1238–1242

306 Yan T, Deng S, Metzger A, Godtel-Armbrust U, Porter AC, Wojnowski L (2009) Topoisomerase IIα-dependent and -independent apoptotic effects of dexrazoxane and doxorubicin. *Mol Cancer Ther*, in press

307 Dexrazoxane: New indication. Anthracycline extravasation: Continue using dimethyl sulfoxide (2009) *Prescrire Int* 18: 6–8 (http://www.find-health-articles.com/rec_pub_19382398-dexrazoxane-new-indication-anthracycline-extravasation-continue-using.htm)

308 Sacks MS, Bradford GT, Schoenbach EB (1950) The response of acute leukemia to the administration of the folic acid antagonists, aminopterin and a-methopterin; Report of 14 cases. *Ann Intern Med* 32: 80–115

309 Li MC, Hertz R, Spencer DB (1956) Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma. *Proc Soc Exp Biol Med* 93: 361–366

310 Abel EA (2000) Immunosuppressant and cytotoxic drugs: Unapproved uses or indications. *Clin Dermatol* 18: 95–101

311 Roenigk HH Jr, Auerbach R, Maibach H, Weinstein G, Lebwohl M (1998) Methotrexate in psoriasis: Consensus conference. *J Am Acad Dermatol* 38: 478–485

312 Borchers AT, Keen CL, Cheema GS, Gershwin ME (2004) The use of methotrexate in rheumatoid arthritis. *Semin Arthritis Rheum* 34: 465–483

313 Buchen S, Ngampolo D, Melton RG, Hasan C, Zoubek A, Henze G, Bode U, Fleischhack G (2005) Carboxypeptidase G_2 rescue in patients with methotrexate intoxication and renal failure. *Br J Cancer* 92: 480–487

314 Moisa A, Fritz P, Benz D, Wehner HD (2006) Iatrogenically-related, fatal methotrexate intoxication: A series of four cases. *Forensic Sci Int* 156: 154–157

315 Widemann BC, Balis FM, Kempf-Bielack B, Bielack S, Pratt CB, Ferrari S, Bacci G, Craft AW, Adamson PC (2004) High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. *Cancer* 100: 2222–2232

316 Dervieux T, Furst D, Lein DO, Capps R, Smith K, Walsh M, Kremer J (2004) Polyglutamation of methotrexate with common polymorphisms in reduced folate carrier, aminoimidazole carboxamide ribonucleotide transformylase, and thymidylate synthase are associated with methotrexate effects in rheumatoid arthritis. *Arthritis Rheum* 50: 2766–2774

317 Genestier L, Paillot R, Quemeneur L, Izeradjene K, Revillard JP (2000) Mechanisms of action of methotrexate. *Immunopharmacology* 47: 247–257

318 Sasaki K, Tanaka J, Fujimoto T (1984) Theoretically required urinary flow during high-dose methotrexate infusion. *Cancer Chemother Pharmacol* 13: 9–13

319 Bleyer WA (1977) Methotrexate: Clinical pharmacology, current status and therapeutic guidelines. *Cancer Treat Rev* 4: 87–101

320 Nirenberg A, Mosende C, Mehta BM, Gisolfi AL, Rosen G (1977) High-dose methotrexate with citrovorum factor rescue: Predictive value of serum methotrexate concentrations and corrective measures to avert toxicity. *Cancer Treat Rep* 61: 779–783

321 Flombaum CD, Meyers PA (1999) High-dose leucovorin as sole therapy for methotrexate toxicity. *J Clin Oncol* 17: 1589–1594

322 Chabner BA, Young RC (1973) Threshold methotrexate concentration for *in vivo* inhibition of DNA synthesis in normal and tumorous target tissues. *J Clin Invest* 52: 1804–1811

323 Schilsky RL, Ratain MJ (1990) Clinical pharmacokinetics of high-dose leucovorin calcium after intravenous and oral administration. *J Natl Cancer Inst* 82: 1411–1415

324 Goorin A, Strother D, Poplack D, Letvak LA, George M, Link M (1995) Safety and efficacy of L-leucovorin rescue following high-dose methotrexate for osteosarcoma. *Med Pediatr Oncol* 24: 362–367

325 Jardine LF, Ingram LC, Bleyer WA (1996) Intrathecal leucovorin after intrathecal methotrexate overdose. *J Pediatr Hematol Oncol* 18: 302–304

326 Krause AS, Weihrauch MR, Bode U, Fleischhack G, Elter T, Heuer T, Engert A, Diehl V, Josting A (2002) Carboxypeptidase-G_2 rescue in cancer patients with delayed methotrexate elimination after high-dose methotrexate therapy. *Leuk Lymphoma* 43: 2139–2143

327 Pinedo HM, Zaharko DS, Bull JM, Chabner BA (1976) The reversal of methotrexate cytotoxicity to mouse bone marrow cells by leucovorin and nucleosides. *Cancer Res* 36: 4418–4424

328 Schwartz S, Borner K, Muller K, Martus P, Fischer L, Korfel A, Auton T, Thiel E (2007) Glucarpidase (carboxypeptidase G_2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. *Oncologist* 12: 1299–1308

329 Widemann BC, Balis FM, Shalabi A, Boron M, O'Brien M, Cole DE, Jayaprakash N, Ivy P, Castle V, Muraszko K, Moertel CL, Trueworthy R, Hermann RC, Moussa A, Hinton S, Reaman G, Poplack D, Adamson PC (2004) Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G_2. *J Natl Cancer Inst* 96: 1557–1559

330 Widemann BC, Adamson PC (2006) Understanding and managing methotrexate nephrotoxicity. *Oncologist* 11: 694–703

331 Goldman P, Levy CC (1967) Carboxypeptidase G: Purification and properties. *Proc Natl Acad Sci USA* 58: 1299–1306

332 Chabner BA, Johns DG, Bertino JR (1972) Enzymatic cleavage of methotrexate provides a method for prevention of drug toxicity. *Nature* 239: 395–397

333 Abelson HT, Ensminger W, Rosowsky A, Uren J (1978) Comparative effects of citrovorum factor and carboxypeptidase G1 on cerebrospinal fluid-methotrexate pharmacokinetics. *Cancer Treat Rep* 62: 1549–1552

334 Howell SB, Blair HE, Uren J, Frei E 3rd (1978) Hemodialysis and enzymatic cleavage of methotrexate in man. *Eur J Cancer* 14: 787–792

335 Adamson PC, Balis FM, McCully CL, Godwin KS, Poplack DG (1992) Methotrexate pharmacokinetics following administration of recombinant carboxypeptidase-G_2 in rhesus monkeys. *J Clin Oncol* 10: 1359–1364

336 Adamson PC, Balis FM, McCully CL, Godwin KS, Bacher JD, Walsh TJ, Poplack DG (1991) Rescue of experimental intrathecal methotrexate overdose with carboxypeptidase-G_2. *J Clin Oncol* 9: 670–674

337 Zoubek A, Zaunschirm HA, Lion T, Fischmeister G, Vollnhofer G, Gadner H, Pillwein K, Schalhorn A, Bode U (1995) Successful carboxypeptidase G_2 rescue in delayed methotrexate elimination due to renal failure. *Pediatr Hematol Oncol* 12: 471–477

338 O'Marcaigh AS, Johnson CM, Smithson WA, Patterson MC, Widemann BC, Adamson PC, McManus MJ (1996) Successful treatment of intrathecal methotrexate overdose by using ventriculolumbar perfusion and intrathecal instillation of carboxypeptidase G_2. *Mayo Clin Proc* 71: 161–165

339 Peyriere H, Cociglio M, Margueritte G, Vallat C, Blayac JP, Hillaire-Buys D (2004) Optimal management of methotrexate intoxication in a child with osteosarcoma. *Ann Pharmacother* 38: 422–427

340 Rowsell S, Pauptit RA, Tucker AD, Melton RG, Blow DM, Brick P (1997) Crystal structure of carboxypeptidase G$_2$, a bacterial enzyme with applications in cancer therapy. *Structure* 5: 337–347

341 Widemann BC, Sung E, Anderson L, Salzer WL, Balis FM, Monitjo KS, McCully C, Hawkins M, Adamson PC (2000) Pharmacokinetics and metabolism of the methotrexate metabolite 2,4-diamino-N^{10}-methylpteroic acid. *J Pharmacol Exp Ther* 294: 894–901

342 Widemann BC, Hetherington ML, Murphy RF, Balis FM, Adamson PC (1995) Carboxy-peptidase-G$_2$ rescue in a patient with high dose methotrexate-induced nephrotoxicity. *Cancer* 76: 521–526

343 Widemann BC, Balis FM, Murphy RF, Sorensen JM, Montello MJ, O'Brien M, Adamson PC (1997) Carboxypeptidase-G$_2$, thymidine, and leucovorin rescue in cancer patients with methotrexate-induced renal dysfunction. *J Clin Oncol* 15: 2125–2134

344 Schwartz S, Müller K, Fischer L, Korfel A, Jahnke K, Auton T, Thiel E (2005) Favorable out-come in excessive methotrexate (MTX) intoxication after high-dose (HD) MTX therapy by early use of carboxypeptidase G$_2$ (CPG$_2$). *J Clin Oncol* 23(16S): 8255

345 DeAngelis LM, Tong WP, Lin S, Fleisher M, Bertino JR (1996) Carboxypeptidase G$_2$ rescue after high-dose methotrexate. *J Clin Oncol* 14: 2145–2149

346 Abelson HT, Ensminger W, Rosowsky A, Uren J (1978) Comparative effects of citrovorum fac-tor and carboxypeptidase G1 on cerebrospinal fluid-methotrexate pharmacokinetics. *Cancer Treat Rep* 62: 1549–1552

347 Widemann BC, Balis FM, Shalabi A, Boron M, O'Brien M, Cole DE, Jayaprakash N, Ivy P, Castle V, Muraszko K, Moertel CL, Trueworthy R, Hermann RC, Moussa A, Hinton S, Reaman G, Poplack D, Adamson PC (2004) Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G$_2$. *J Natl Cancer Inst* 96: 1557–1559

348 Hempel G, Lingg R, Boos J (2005) Interactions of carboxypeptidase G$_2$ with 6*S*-leucovorin and 6*R*-leucovorin *in vitro*: Implications for the application in case of methotrexate intoxications. *Cancer Chemother Pharmacol* 55: 347–353

349 Fotoohi K, Skarby T, Soderhall S, Peterson C, Albertioni F (2005) Interference of 7-hydroxy-methotrexate with the determination of methotrexate in plasma samples from children with acute lymphoblastic leukemia employing routine clinical assays. *J Chromatogr B Analyt Technol Biomed Life Sci* 817: 139–144

350 European Medicines Agency (2008) Pre-authorisation Evaluation of Medicines for Human Use. Withdrawal Assessment Report for Voraxaze. EMEA/CHMP/171907/2008. European Medicines Agency (EMEA), London, UK

351 Sherwood RF, Melton RG, Alwan SM, Hughes P (1985) Purification and properties of car-boxypeptidase G$_2$ from *Pseudomonas* sp. strain RS-16. Use of a novel triazine dye affinity method. *Eur J Biochem* 148: 447–453

352 Albertson TE, Dawson A, de Latorre F, Hoffman RS, Hollander JE, Jaeger A, Kerns WR 2nd, Martin TG, Ross MP (2001) TOX-ACLS: Toxicologic-oriented advanced cardiac life support. *Ann Emerg Med* 37: S78–90

353 Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G (2008) Pharmacology and man-agement of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th edn. *Chest* 133: 160S–198S

354 Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI (2008) Parenteral anticoagu-lants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th edn. *Chest* 133: 141S–159S

355 Warkentin TE, Greinacher A, Koster A, Lincoff AM (2008) Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th edn. *Chest* 133: 340S–380S

356 Dager WE, Sanoski CA, Wiggins BS, Tisdale JE (2006) Pharmacotherapy considerations in advanced cardiac life support. *Pharmacotherapy* 26: 1703–1729

357 Dhein S, van Koppen CJ, Brodde OE (2001) Muscarinic receptors in the mammalian heart. *Pharmacol Res* 44: 161–182

358 Howarth DM, Dawson AH, Smith AJ, Buckley N, Whyte IM (1994) Calcium channel blocking drug overdose: An Australian series. *Hum Exp Toxicol* 13: 161–166

359 Kerns W 2nd (2007) Management of β-adrenergic blocker and calcium channel antagonist toxi-city. *Emerg Med Clin North Am* 25: 309–331

360 Sim MT, Stevenson FT (2008) A fatal case of iatrogenic hypercalcemia after calcium channel

blocker overdose. *J Med Toxicol* 4: 25–29

361 Salhanick SD, Shannon MW (2003) Management of calcium channel antagonist overdose. *Drug Saf* 26: 65–79

362 APP (2007) Calcium Gluconate Injection, USP 10%. APP Pharmaceuticals, LLC, Schaumburg, IL

363 Nola GT, Pope, S, Harrison, DC (1970) Assessment of the synergistic relationship between serum calcium and digitalis. *Am Heart J* 79: 499

364 Ericksona CP, Olson KR (2008) Case files of the medical toxicology fellowship of the California poison control system-San Francisco: Calcium plus digoxin-more taboo than toxic? *J Med Toxicol* 4: 33–39

365 Wenger TL, Butler VP Jr, Haber E, Smith TW (1985) Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. *J Am Coll Cardiol* 5: 118A–123A

366 Smith TW, Haber E, Yeatman L, Butler VP Jr (1976) Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *N Engl J Med* 294: 797–800

367 Antman EM, Wenger TL, Butler VP Jr, Haber E, Smith TW (1990) Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. *Circulation* 81: 1744–1752

368 Lapostolle F, Borron SW, Verdier C, Taboulet P, Guerrier G, Adnet F, Clemessy JL, Bismuth C, Baud FJ (2008) Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Crit Care Med* 36: 3014–3018

369 Woolf AD, Wenger T, Smith TW, Lovejoy FH Jr (1992) The use of digoxin-specific Fab fragments for severe digitalis intoxication in children. *N Engl J Med* 326: 1739–1744

370 Smith TW (1991) Review of clinical experience with digoxin immune Fab (ovine). *Am J Emerg Med* 9: 1–6

371 Bateman DN (2004) Digoxin-specific antibody fragments: How much and when? *Toxicol Rev* 23: 135–143

372 Ujhelyi MR, Robert S (1995) Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 28: 483–493

373 Mehta RN, Mehta NJ, Gulati A (2002) Late rebound digoxin toxicity after digoxin-specific antibody Fab fragments therapy in anuric patient. *J Emerg Med* 22: 203–206

374 Bosse GM, Pope TM (1994) Recurrent digoxin overdose and treatment with digoxin-specific Fab antibody fragments. *J Emerg Med* 12: 179–185

375 Camphausen C, Haas NA, Mattke AC (2005) Successful treatment of oleander intoxication (cardiac glycosides) with digoxin-specific Fab antibody fragments in a 7-year-old child: Case report and review of literature. *Z Kardiol* 94: 817–823

376 Brubacher JR, Lachmanen D, Ravikumar PR, Hoffman RS (1999) Efficacy of digoxin specific Fab fragments (Digibind) in the treatment of toad venom poisoning. *Toxicon* 37: 931–942

377 Ali S, Drucker DJ (2009) Benefits and limitations of reducing glucagon action for the treatment of type 2 diabetes. *Am J Physiol Endocrinol Metab* 296: E415–421

378 Eli Lilly and Company (2005) Information for the Physician. Glucagon for Injection (rDNA origin). Eli Lilly and Company, Indianapolis, IN

379 Shepherd G (2006) Treatment of poisoning caused by β-adrenergic and calcium-channel blockers. *Am J Health Syst Pharm* 63: 1828–1835

380 Sauvadet A, Rohn T, Pecker F, Pavoine C (1997) Arachidonic acid drives mini-glucagon action in cardiac cells. *J Biol Chem* 272: 12437–12445

381 Parmley WW, Glick G, Sonnenblick EH (1968) Cardiovascular effects of glucagon in man. *N Engl J Med* 279: 12–17

382 Boyd R, Ghosh A (2003) Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Glucagon for the treatment of symptomatic β blocker overdose. *Emerg Med J* 20: 266–267

383 Lee J (2004) Glucagon use in symptomatic β blocker overdose. *Emerg Med J* 21: 755

384 Stone CK, May WA, Carroll R (1995) Treatment of verapamil overdose with glucagon in dogs. *Ann Emerg Med* 25: 369–374

385 Walter FG, Frye G, Mullen JT, Ekins BR, Khasigian PA (1993) Amelioration of nifedipine poisoning associated with glucagon therapy. *Ann Emerg Med* 22: 1234–1237

386 Zaritsky AL, Horowitz M, Chernow B (1988) Glucagon antagonism of calcium channel blocker-induced myocardial dysfunction. *Crit Care Med* 16: 246–251

387 Kline JA, Leonova E, Williams TC, Schroeder JD, Watts JA (1996) Myocardial metabolism dur-

ing graded intraportal verapamil infusion in awake dogs. *J Cardiovasc Pharmacol* 27: 719–726

388 Kline JA, Leonova E, Raymond RM (1995) Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. *Crit Care Med* 23: 1251–1263

389 Oldenburg O, Eggebrecht H, Gutersohn A, Schaar J, Brauck K, Haude M, Erbel R, Baumgart D (2001) Myocardial lactate release after intracoronary verapamil application in humans: Acute effects of intracoronary verapamil on systemic and coronary hemodynamics, myocardial metabolism, and norepinephrine levels. *Cardiovasc Drugs Ther* 15: 55–61

390 Puskarich MA, Runyon MS, Trzeciak S, Kline JA, Jones AE (2009) Effect of glucose-insulin-potassium infusion on mortality in critical care settings: A systematic review and meta-analysis. *J Clin Pharmacol* 49: 758–767

391 Schipke JD, Friebe R, Gams E (2006) Forty years of glucose-insulin-potassium (GIK) in cardiac surgery: A review of randomized, controlled trials. *Eur J Cardiothorac Surg* 29: 479–485

392 Koskenkari JK, Kaukoranta PK, Rimpilainen J, Vainionpaa V, Ohtonen PP, Surcel HM, Juvonen T, Ala-Kokko TI (2006) Anti-inflammatory effect of high-dose insulin treatment after urgent coronary revascularization surgery. *Acta Anaesthesiol Scand* 50: 962–969

393 Doenst T, Bothe W, Beyersdorf F (2003) Therapy with insulin in cardiac surgery: Controversies and possible solutions. *Ann Thorac Surg* 75: S721–728

394 Svedjeholm R, Ekroth R, Joachimsson PO, Tyden H (1991) High-dose insulin improves the efficacy of dopamine early after cardiac surgery. A study of myocardial performance and oxygen consumption. *Scand J Thorac Cardiovasc Surg* 25: 215–221

395 Kline JA, Raymond RM, Leonova ED, Williams TC, Watts JA (1997) Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. *Cardiovasc Res* 34: 289–298

396 Kerns W 2nd, Schroeder D, Williams C, Tomaszewski C, Raymond R (1997) Insulin improves survival in a canine model of acute β-blocker toxicity. *Ann Emerg Med* 29: 748–757

397 Holger JS, Engebretsen KM, Fritzlar SJ, Patten LC, Harris CR, Flottemesch TJ (2007) Insulin *versus* vasopressin and epinephrine to treat β-blocker toxicity. *Clin Toxicol* 45: 396–401

398 Greene SL, Gawarammana I, Wood DM, Jones AL, Dargan PI (2007) Relative safety of hyper-insulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: A prospective observational study. *Intensive Care Med* 33: 2019–2024

399 Cohen V, Jellinek SP, Fancher L, Sangwan G, Wakslak M, Marquart E, Farahani C (2009) Tarka(R) (trandolapril/verapamil hydrochloride extended-release) overdose. *J Emerg Med*, *in press*

400 Prigeon RL, Roder ME, Porte D Jr, Kahn SE (1996) The effect of insulin dose on the measurement of insulin sensitivity by the minimal model technique. Evidence for saturable insulin transport in humans. *J Clin Invest* 97: 501–507

401 Mokshagundam SP, Peiris AN, Stagner JI, Gingerich RL, Samols E (1996) Interstitial insulin during euglycemic-hyperinsulinemic clamp in obese and lean individuals. *Metabolism* 45: 951–956

402 Natali A, Gastaldelli A, Camastra S, Sironi AM, Toschi E, Masoni A, Ferrannini E, Mari A (2000) Dose-response characteristics of insulin action on glucose metabolism: A non-steady-state approach. *Am J Physiol Endocrinol Metab* 278: E794–801

403 Foxall G, McCahon R, Lamb J, Hardman JG, Bedforth NM (2007) Levobupivacaine-induced seizures and cardiovascular collapse treated with Intralipid. *Anaesthesia* 62: 516–518

404 Groban L, Deal DD, Vernon JC, James RL, Butterworth J (2001) Cardiac resuscitation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs. *Anesth Analg* 92: 37–43

405 Weinberg G, Ripper R, Feinstein DL, Hoffman W (2003) Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. *Reg Anesth Pain Med* 28: 198–202

406 Weinberg GL, Di Gregorio G, Ripper R, Kelly K, Massad M, Edelman L, Schwartz D, Shah N, Zheng S, Feinstein DL (2008) Resuscitation with lipid *versus* epinephrine in a rat model of bupivacaine overdose. *Anesthesiology* 108: 907–913

407 Warren JA, Thoma RB, Georgescu A, Shah SJ (2008) Intravenous lipid infusion in the successful resuscitation of local anesthetic-induced cardiovascular collapse after supraclavicular brachial plexus block. *Anesth Analg* 106: 1578–1580

408 Litz RJ, Popp M, Stehr SN, Koch T (2006) Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia* 61: 800–801

409 Litz RJ, Roessel T, Heller AR, Stehr SN (2008) Reversal of central nervous system and cardiac toxicity after local anesthetic intoxication by lipid emulsion injection. *Anesth Analg* 106:

1575–1577

410 Ludot H, Tharin JY, Belouadah M, Mazoit JX, Malinovsky JM (2008) Successful resuscitation after ropivacaine and lidocaine-induced ventricular arrhythmia following posterior lumbar plexus block in a child. *Anesth Analg* 106: 1572–1574

411 Finn SD, Uncles DR, Willers J, Sable N (2009) Early treatment of a quetiapine and sertraline overdose with Intralipid. *Anaesthesia* 64: 191–194

412 Sirianni AJ, Osterhoudt KC, Calello DP, Muller AA, Waterhouse MR, Goodkin MB, Weinberg GL, Henretig FM (2008) Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. *Ann Emerg Med* 51: 412–415

413 Harvey M, Cave G (2007) Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. *Ann Emerg Med* 49: 178–185

414 Harvey MG, Cave GR (2008) Intralipid infusion ameliorates propranolol-induced hypotension in rabbits. *J Med Toxicol* 4: 71–76

415 Bania TC, Chu J, Perez E, Su M, Hahn IH (2007) Hemodynamic effects of intravenous fat emulsion in an animal model of severe verapamil toxicity resuscitated with atropine, calcium, and saline. *Acad Emerg Med* 14: 105–111

416 Cave G, Harvey MG, Castle CD (2005) Intralipid ameliorates thiopentone induced respiratory depression in rats: Investigative pilot study. *Emerg Med Australas* 17: 180–181

417 Florian JP, Pawelczyk JA (2009) Non-esterified fatty acids increase arterial pressure *via* central sympathetic activation in humans. *Clin Sci* 118: 61–69

418 Stehr SN, Ziegeler JC, Pexa A, Oertel R, Deussen A, Koch T, Hubler M (2007) The effects of lipid infusion on myocardial function and bioenergetics in L-bupivacaine toxicity in the isolated rat heart. *Anesth Analg* 104: 186–192

419 The Association of Anaesthetists of Great Britain & Ireland (2007) Guidelines for the Management of Severe Local Anaesthetic Toxicity (http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf, accessed May 19, 2009)

420 Felice K, Schumann H (2008) Intravenous lipid emulsion for local anesthetic toxicity: A review of the literature. *J Med Toxicol* 4: 184–191

421 Marwick PC, Levin AI, Coetzee AR (2009) Recurrence of cardiotoxicity after lipid rescue from bupivacaine-induced cardiac arrest. *Anesth Analg* 108: 1344–1346

422 Harvey M, Cave G, Kazemi A (2009) Intralipid infusion diminishes return of spontaneous circulation after hypoxic cardiac arrest in rabbits. *Anesth Analg* 108: 1163–1168

423 Mayr VD, Mitterschiffthaler L, Neurauter A, Gritsch C, Wenzel V, Muller T, Luckner G, Lindner KH, Strohmenger HU (2008) A comparison of the combination of epinephrine and vasopressin with lipid emulsion in a porcine model of asphyxial cardiac arrest after intravenous injection of bupivacaine. *Anesth Analg* 106: 1566–1571

424 Mazoit JX, Le Guen R, Beloeil H, Benhamou D (2009) Binding of long-lasting local anesthetics to lipid emulsions. *Anesthesiology* 110: 380–386

425 De Bruin ML, Langendijk PN, Koopmans RP, Wilde AA, Leufkens HG, Hoes AW (2007) In-hospital cardiac arrest is associated with use of non-antiarrhythmic QTc-prolonging drugs. *Br J Clin Pharmacol* 63: 216–223

426 Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG (2007) Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J* 153: 891–899

427 Khan IA, Gowda RM (2004) Novel therapeutics for treatment of long-QT syndrome and torsade de pointes. *Int J Cardiol* 95: 1–6

428 Sasyniuk BI, Jhamandas V (1984) Mechanism of reversal of toxic effects of amitriptyline on cardiac Purkinje fibers by sodium bicarbonate. *J Pharmacol Exp Ther* 231: 387–394

429 Sasyniuk BI, Jhamandas V, Valois M (1986) Experimental amitriptyline intoxication: Treatment of cardiac toxicity with sodium bicarbonate. *Ann Emerg Med* 15: 1052–1059

430 Brown TC (1976) Tricyclic antidepressant overdosage: Experimental studies on the management of circulatory complications. *Clin Toxicol* 9: 255–272

431 Boehnert MT, Lovejoy FH Jr (1985) Value of the QRS duration *versus* the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med* 313: 474–479

432 Niemann JT, Bessen HA, Rothstein RJ, Laks MM (1986) Electrocardiographic criteria for tricyclic antidepressant cardiotoxicity. *Am J Cardiol* 57: 1154–1159

433 Liebelt EL, Francis PD, Woolf AD (1995) ECG lead aVR *versus* QRS interval in predicting seizures and arrhythmias in acute tricyclic antidepressant toxicity. *Ann Emerg Med* 26: 195–201

434 Pentel PR, Keyler DE (1988) Effects of high dose α-1-acid glycoprotein on desipramine toxicity in rats. *J Pharmacol Exp Ther* 246: 1061–1066

435 Taboulet P, Michard F, Muszynski J, Galliot-Guilley M, Bismuth C (1995) Cardiovascular repercussions of seizures during cyclic antidepressant poisoning. *J Toxicol Clin Toxicol* 33: 205–211

436 Knudsen K, Abrahamsson J (1997) Epinephrine and sodium bicarbonate independently and additively increase survival in experimental amitriptyline poisoning. *Crit Care Med* 25: 669–674

437 Bessen HA, Niemann JT (1985) Improvement of cardiac conduction after hyperventilation in tricyclic antidepressant overdose. *J Toxicol Clin Toxicol* 23: 537–546

438 McCabe JL, Cobaugh DJ, Menegazzi JJ, Fata J (1998) Experimental tricyclic antidepressant toxicity: A randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate, and hyperventilation. *Ann Emerg Med* 32: 329–333

439 McKinney PE, Rasmussen R (2003) Reversal of severe tricyclic antidepressant-induced cardiotoxicity with intravenous hypertonic saline solution. *Ann Emerg Med* 42: 20–24

440 Brown TC (1976) Sodium bicarbonate treatment for tricyclic antidepressant arrhythmias in children. *Med J Aust* 2: 380–382

441 Woolf AD, Erdman AR, Nelson LS, Caravati EM, Cobaugh DJ, Booze LL, Wax PM, Manoguerra AS, Scharman EJ, Olson KR, Chyka PA, Christianson G, Troutman WG (2007) Tricyclic antidepressant poisoning: An evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol* 45: 203–233

442 Sharma AN, Hexdall AH, Chang EK, Nelson LS, Hoffman RS (2003) Diphenhydramine-induced wide complex dysrhythmia responds to treatment with sodium bicarbonate. *Am J Emerg Med* 21: 212–215

443 Stork CM, Redd JT, Fine K, Hoffman RS (1995) Propoxyphene-induced wide QRS complex dysrhythmia responsive to sodium bicarbonate – A case report. *J Toxicol Clin Toxicol* 33: 179–183

444 Kalimullah EA, Bryant SM (2008) Case files of the medical toxicology fellowship at the toxikon consortium in Chicago: Cocaine-associated wide-complex dysrhythmias and cardiac arrest – Treatment nuances and controversies. *J Med Toxicol* 4: 277–283

445 Mailloux D, Adar E, Su M (2005) Acute carbamazepine toxicity associated with a widened QRS interval treated with intravenous sodium bicarbonate. *Clin Toxicol* 43: 505–506

446 Wills BK, Zell-Kanter M, Aks SE (2009) Bupropion-associated QRS prolongation unresponsive to sodium bicarbonate therapy. *Am J Ther* 16: 193–196

447 Bosse GM, Spiller HA, Collins AM (2008) A fatal case of venlafaxine overdose. *J Med Toxicol* 4: 18–20

448 Buckley NA, Whyte IM, Dawson AH (1993) Self-poisoning with lamotrigine. *Lancet* 342: 1552–1553

449 Pierog J, Kane B, Kane K, Donovan JW (2009) Management of isolated yew berry toxicity with sodium bicarbonate: A case report in treatment efficacy. *J Med Toxicol* 5: 84–89

450 Schwartz M, Patel M, Kazzi Z, Morgan B (2008) Cardiotoxicity after massive amantadine overdose. *J Med Toxicol* 4: 173–179

451 Clarke SF, Dargan PI, Jones AL (2005) Naloxone in opioid poisoning: Walking the tightrope. *Emerg Med J* 22: 612–616

452 Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, Eisenberg HM, Flamm E, Leo-Summers L, Maroon J (1990) A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med* 322: 1405–1411

453 Buajordet I, Naess AC, Jacobsen D, Brors O (2004) Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *Eur J Emerg Med* 11: 19–23

454 Mills CA, Flacke JW, Flacke WE, Bloor BC, Liu MD (1990) Narcotic reversal in hypercapnic dogs: Comparison of naloxone and nalbuphine. *Can J Anaesth* 37: 238–244

455 International Liaison Committee on Resuscitation (2006) The ILCOR consensus on science with treatment recommendations for pediatric and neonatal patients: Neonatal resuscitation. *Pediatrics* 117: e978–988

456 Deshpande G, Gill A (2009) Cardiac arrest following naloxone in an extremely preterm neonate. *Eur J Pediatr* 168: 115–117

457 Hoffman JR, Schriger DL, Luo JS (1991) The empiric use of naloxone in patients with altered mental status: A reappraisal. *Ann Emerg Med* 20: 246–252

458 Goldfrank L, Weisman RS, Errick JK, Lo MW (1986) A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med* 15: 566–570

459 Geib AJ, Babu K, Ewald MB, Boyer EW (2006) Adverse effects in children after unintentional buprenorphine exposure. *Pediatrics* 118: 1746–1751

460 Van Dorp E, Yassen A, Sarton E, Romberg R, Olofsen E, Teppema L, Danhof M, Dahan A (2006) Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology* 105: 51–57

461 Horowitz R, Mazor SS, Aks SE, Leikin JB (2005) Accidental clonidine patch ingestion in a child. *Am J Ther* 12: 272–274

462 Seger DL (2002) Clonidine toxicity revisited. *J Toxicol Clin Toxicol* 40: 145–155

463 Varon J, Duncan SR (1991) Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med* 20: 1125–1127

464 Barr CS, Payne R, Newton RW (1991) Profound prolonged hypotension following captopril overdose. *Postgrad Med J* 67: 953–954

465 Millar JA, Sturani A, Rubin PC, Lawrie C, Reid JL (1983) Attenuation of the antihypertensive effect of captopril by the opioid receptor antagonist naloxone. *Clin Exp Pharmacol Physiol* 10: 253–259

466 Ajayi AA, Campbell BC, Rubin PC, Reid JL (1985) Effect of naloxone on the actions of captopril. *Clin Pharmacol Ther* 38: 560–565

467 Bernini G, Taddei S, Graziadei L, Pedrinelli R, Salvetti A (1985) Naloxone does not modify the antihypertensive effect of captopril in essential hypertensive patients. *J Hypertens Suppl* 3: S117–119

468 Lopez-Romero B, Evrard G, Durant F, Sevrin M, George P (1998) Molecular structure and stereoelectronic properties of sarmazenil – A weak inverse agonist at the omega modulatory sites (benzodiazepine receptors): Comparison with bretazenil and flumazenil. *Bioorg Med Chem* 6: 1745–1757

469 Dunton AW, Schwam E, Pitman V, McGrath J, Hendler J, Siegel J (1988) Flumazenil: US clinical pharmacology studies. *Eur J Anaesthesiol* 2: 81–95

470 Amrein R, Hetzel W, Hartmann D, Lorscheid T (1988) Clinical pharmacology of flumazenil. *Eur J Anaesthesiol Suppl* 2: 65–80

471 Mora CT, Torjman M, White PF (1995) Sedative and ventilatory effects of midazolam infusion: Effect of flumazenil reversal. *Can J Anaesth* 42: 677–684

472 Flogel CM, Ward DS, Wada DR, Ritter JW (1993) The effects of large-dose flumazenil on midazolam-induced ventilatory depression. *Anesth Analg* 77: 1207–1214

473 Shalansky SJ, Naumann TL, Englander FA (1993) Effect of flumazenil on benzodiazepine-induced respiratory depression. *Clin Pharm* 12: 483–487

474 Dahaba AA, Bornemann H, Rehak PH, Wang G, Wu XM, Metzler H (2009) Effect of flumazenil on bispectral index monitoring in unpremedicated patients. *Anesthesiology* 110: 1036–1040

475 Polc P (1988) Electrophysiology of benzodiazepine receptor ligands: Multiple mechanisms and sites of action. *Prog Neurobiol* 31: 349–423

476 Morgan MM, Levin ED, Liebeskind JC (1987) Characterization of the analgesic effects of the benzodiazepine antagonist, Ro 15-1788. *Brain Res* 415: 367–370

477 Gueye PN, Hoffman JR, Taboulet P, Vicaut E, Baud FJ (1996) Empiric use of flumazenil in comatose patients: Limited applicability of criteria to define low risk. *Ann Emerg Med* 27: 730–735

478 Weinbroum A, Rudick V, Sorkine P, Nevo Y, Halpern P, Geller E, Niv D (1996) Use of flumazenil in the treatment of drug overdose: A double-blind and open clinical study in 110 patients. *Crit Care Med* 24: 199–206

479 Spivey WH (1992) Flumazenil and seizures: Analysis of 43 cases. *Clin Ther* 14: 292–305

480 Anonymous (1992) Treatment of benzodiazepine overdose with flumazenil. The Flumazenil in Benzodiazepine Intoxication Multicenter Study Group. *Clin Ther* 14: 978–995

481 Weinbroum AA, Flaishon R, Sorkine P, Szold O, Rudick V (1997) A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. *Drug Saf* 17: 181–196

482 Nau H, Loscher W (1984) Valproic acid and metabolites: Pharmacological and toxicological studies. *Epilepsia* 25 Suppl 1: S14–22

483 Weber WW, Hein DW (1979) Clinical pharmacokinetics of isoniazid. *Clin Pharmacokinet* 4: 401–422