Disorders of Consciousness Induced by Intoxication

Peter De Paepe, MD, PhD[a,b,*], Sabine Lemoyne, MD[a], Walter Buylaert, MD, PhD[a]

KEYWORDS

• Coma • Delirium • Consciousness • Intoxication

Xenobiotics that induce alterations in mental status or consciousness can be divided into two groups.[1] The first group includes agents that produce neuroexcitation resulting in confusion, agitation, hallucinations, or seizures. The second group consists of agents producing neuroinhibition leading to decreased consciousness and coma. Intoxication is a frequent cause of coma accounting for approximately 30% of all patients presenting to an emergency department with coma of unknown origin.[2]

The prognosis of patients with altered consciousness is mainly determined by early diagnosis and appropriate therapeutic interventions and by the type of toxin. The potential causes of altered consciousness are many and may reflect systemic illness, isolated organ system dysfunction, drug intoxications or withdrawal, psychiatric illness, or neurologic disease. In this article, a comprehensive approach to patients with altered consciousness and suspected poisoning is discussed. This survey, however, does not intend to be a substitute for the need for consultation with a clinical toxicologist qualified in the diagnosis and treatment of poisoned patients.

PATHOPHYSIOLOGY

Neuroexcitatory agents enhance neurotransmission of excitatory amino acids or diminish inhibitory input from γ-aminobutyric acid (GABA) neurons.[2] A non limitative list of agents inducing agitation and/or delirium is shown in **Box 1**. Enhanced transmission can occur through inhibition of presynaptic metabolism (monoamine oxidase

No financial disclosures and/or conflicts of interest.

[a] Department of Emergency Medicine, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium
[b] Heymans Institute of Pharmacology, Ghent University, De Pintelaan 185, B-9000 Ghent, Belgium
* Corresponding author. De Pintelaan 185, B-9000 Ghent, Belgium.
E-mail address: peter.depaepe@ugent.be

Neurol Clin 30 (2012) 359–384
doi:10.1016/j.ncl.2011.10.003 **neurologic.theclinics.com**
0733-8619/12/$ – see front matter

Box 1
Nonlimitative list of agents that may induce agitation and/or delirium

Alcohols

Amantadine

Anticholinergics (eg, antihistamines, atropine, scopolamine, antiparkinson agents, antispasmodics, phenothiazines, and tricyclic antidepressants)

Carbon monoxide (CO)

Drug withdrawal states

Hallucinogens (eg, lysergic acid diethylamide [LSD], phencyclidine, mescaline, psilocybin, ketamine, and designer amphetamines)

Heavy metals

Hypoglycemic agents

Lithium

Local anesthetics

Salicylates

Sympathomimetics (eg, amphetamines, cocaine, caffeine, phenylpropanolamine, and theophylline)

inhibitors [MAOIs]), stimulation of neurotransmitter release (amphetamines), impairment of neurotransmitter reuptake (cocaine), or inhibition of synaptic degradation (acetylcholinesterase inhibitors). Central nervous system (CNS) excitation after anticholinergic poisoning is caused predominantly by blockade of central G protein–linked muscarinic receptors resulting in disinhibition. Methylxanthines, such as caffeine and theophylline, act in the CNS as adenosine antagonists as well as inhibitors of phosphodiesterase C, allowing an increased and prolonged response to other stimulatory hormones. Withdrawal states may also cause excitation. Chronic presence of ethanol causes increased numbers of *N*-methyl-d-aspartate (NMDA) receptors as well as increased sensitivity of NMDA receptors to glutamate, which explains the overexcitation of the CNS when alcohol is withdrawn. Withdrawal of ethanol is also associated with a decrease in GABAergic activity because persistent stimulation of the inhibitory GABA receptor-chloride channel complex by ethanol leads to down-regulation of the complex. Similar to frequent ethanol and benzodiazepine use, chronic γ-hydroxybutyric acid (GHB) use is believed to lead to tolerance associated with down-regulation of inhibitory GABA and GHB receptors. Subsequent decreased GHB consumption results in decreased GABA-mediated and GHB-mediated neuroinhibition, resulting in unopposed excitatory neurotransmission (glutamate, norepinephrine, and dopamine systems) and the onset of a withdrawal syndrome.[3] Neuroexcitation may also be caused by agents inducing metabolic derangements, such as hypoglycemia and hypoxia (discussed later).

Many substances are capable of producing coma and they can be classified into two groups: agents that produce coma through a direct effect on brain cells and agents for which coma is an indirect result of derangements involving other organ systems (**Table 1**).[4,5]

Examples of direct-acting neurotoxins include agents that increase GABA effects, such as benzodiazepines, alcohols, barbiturates, and GHB.[6] $GABA_A$ receptors are the primary mediators of inhibitory neurotransmission in the brain. The $GABA_A$ receptor is a pentameric structure composed of varying polypeptide subunits

Table 1
Non limitative list of substances that may be involved in coma due to poisoning classified according to their mechanism

Direct Effect on the Brain	Indirect Effect on the Brain
Anticholinergic agents	Antiarrhythmics
Barbiturates	Antihypertensives
Benzodiazepines	CO
Carbamazepine	Gases and fumes
CO	Insulin
Cyanide	Methemoglobin-forming agents
Ethanol	Oral hypoglycemic drugs
Ethylene glycol	
GHB	
Glutethimide	
H_1-antihistamines	
Hydrogen sulfide	
Lithium	
MAOIs	
Methanol	
Neuroleptics	
Opioids	
Organophosphates	
Phenytoin	
Presynaptic α2-receptor agonists	
Salicylates	
Selective serotonin reuptake inhibitors	
Trichloroethanol	
Tricyclic antidepressants	
Valproic acid	

associated with a chloride channel on the postsynaptic membrane. Sedative-hypnotics alter the function of the chloride channel by increasing either its frequency or duration of opening. Indirect-acting agonists, such as benzodiazepines, require the presence of GABA to affect the channel. Other agents, such as barbiturates, can directly open the channel at high doses without the presence of GABA. This may explain the high lethality seen with barbiturate overdoses as compared with benzodiazepine overdoses. Many sedative hypnotics, such as barbiturates, alcohols, and trichloroethanol, also decrease the effects of glutamate-mediated excitatory neurotransmission by interaction with the NMDA receptors.[7] GHB also has affinity for inhibitory presynaptic $GABA_B$ and opioid receptors. In addition, there is evidence to suggest that there are also specific GHB receptor sites.[8] Agents with anticholinergic properties like H1-antihistamines, tricyclic antidepressants and neuroleptics induce coma by antagonism at the central muscarinic acetylcholine receptors. H1-antihistamines and neuroleptics also produce central nervous system depression due to central histamine H1 receptor inhibition.[9–11]

Opioids produce sedation by their effect on μ receptors and κ receptors, which belong to the family of G protein–coupled receptors and inhibit adenylate cyclase, reducing the intracellular cyclic adenosine monophosphate content.[12] These receptors also exert effects on ion channels through a direct G protein coupling to the channel. By these means, opioids promote the opening of potassium channels and inhibit the opening of voltage-gated calcium channels. These membrane effects reduce both neuronal excitability and transmitter release, resulting in an overall inhibitory effect at the cellular level.

Cyanide causes direct neurotoxicity by binding to the ferric ions of cytochrome a_3, an integral component of the third and final cytochrome oxidase enzyme in the mitochondrial electron transport chain.[13] Once bound, the enzyme becomes inactivated and oxidative phosphorylation is blocked. Cells are thus deprived of their major energy source. The inhibition of oxidative phosphorylation results in widespread metabolic derangements. ATP is consumed by active cells, but little can be produced. Tissues quickly exhaust their supply of ATP. Furthermore, hydrogen ions that are generated by ATP hydrolysis begin to accumulate because they can no longer be recycled into the process of ATP formation resulting in metabolic acidosis. The result of these intracellular derangements is cellular dysfunction and ultimately cell death if cytochrome inhibition persists. Cyanide also induces cellular oxidative stress possibly through inhibition of antioxidant enzymes, such as catalase, glutathione dehydrogenase, glutathione reductase, or superoxide dismutase. Cyanide-induced lipid peroxidation occurs to the greatest extent in the brain, which explains the predominance of neurologic findings in patients with cyanide poisoning. There is also compelling evidence that cyanide neurotoxicity is mediated by glutamate release, leading to increased cytosolic calcium and cell death.

Hydrogen sulfide's toxicity results from its potent inhibition of cytochrome oxidase, thereby interrupting oxidative phosphorylation. Like cyanide, hydrogen sulfide binds to the ferric moiety of cytochrome a_3 oxidase complex. The resulting inhibition of oxidative phosphorylation produces cellular hypoxia.[14]

The second group of agents are those for which coma is an indirect result of derangements involving other organ systems. Examples of indirect agents include those causing hypoxia, such as methemoglobin-forming agents, or agents that decrease oxygen delivery to cells via hypoperfusion, such as antiarrhythmic and antihypertensive drugs.

CO is an example of a substance-producing coma via a combination of systemic effects and direct cellular toxicity.[15] CO's most obvious effect is binding to hemoglobin, rendering it incapable of delivering oxygen to the cells because the affinity for hemoglobin is 200 to 250 times greater than that of oxygen. Direct cellular toxicity is caused by cytochrome oxidase inactivation accompanied by ischemic-reperfusion injury. Animal studies suggest that CO poisoning may also cause glutamate increases in the brain, resulting in intracellular calcium release and neuronal cell death.

PRIMARY ASSESSMENTS

Safety

Before any rescue attempts are undertaken, the rescuer's safety should be guaranteed. This is especially important for gas intoxications (eg, CO and hydrogen sulfide) because there still may be gas present in the air. Some toxic agents, for instance, organophosphates, may be absorbed through the skin and mucosa and may intoxicate a health care provider when in contact with a patient without taking protective measures. In cases of an illegal drug overdose, the rescuer should always be alert for the presence of intravenous needles to avoid stick injuries. Managing patients with aggressive behavior due to altered consciousness may also pose a risk to the personal safety of health care professionals and may lead to mistakes in the assessment of a patient's presenting illness. Successful management of aggression requires an interdisciplinary management plan with an underlying philosophy that all health professionals accept responsibility for assessing, responding to, and managing aggression.

Primary Assessment and Resuscitation

Irrespective of the cause of altered consciousness, primary assessment requires identification and treatment of life-threatening conditions.[16–22] The primary assessment should be repeated after emergency treatment and with any further deterioration in the patient's condition. The importance of these measures cannot be overemphasized. In many cases, altered mental status induced by poisoning has a good prognosis provided secondary damage due to hypoxia, hypoperfusion, and sepsis is avoided.

In order not to overlook life-threatening conditions, a structured approach to patients with altered consciousness is provided. As discussed later, however, management is often also guided by the underlying cause. The aim of the primary assessment is to identify and treat all immediately life-threatening conditions.

Key components of the primary assessment (ABCDE) are
- A—Airway and oxygen administration
- B—Breathing
- C—Circulation
- D—Disability
- E—Exposure

A—Airway and oxygen administration

All agents causing CNS depression may compromise airway patency. Improper or nonaggressive airway management may lead to anoxic brain injury and/or aspiration. Airway patency may be assessed by evaluating a patient's verbal response to questions. A patient answering appropriately indicates an open airway, the presence of breathing, and adequate cerebral perfusion. If a patient remains unresponsive, the airway should be opened with the head tilt–chin lift maneuver. If a neck injury cannot be excluded (discussed later), however, cervical immobilization should be maintained; the jaw thrust technique is then the safest approach to control the airway. The mouth should be inspected for foreign bodies. Removing liquid (blood, saliva, and gastric contents) from the upper airway using a suction device may be necessary to clear the airway. This should be done cautiously, however, if a patient has an intact gag reflex because the suction device can provoke vomiting. Oropharyngeal airway cannulas are curved plastic tubes that fit between the tongue and the hard palate and are often helpful to improve or maintain airway patency in an unconscious patient. These devices should not be used in patients with preserved glossopharyngeal and laryngeal reflexes because insertion may cause vomiting and laryngospasm.[20,21] The recovery position may be used in unresponsive and spontaneously breathing patients to avoid airway obstruction by the tongue or mucus and vomit. Indications for orotracheal intubation in comatose patients are the presence of apnea and bradypnea related to deep coma and/or vomiting.[21] Deep coma, often defined as the presence of a Glasgow Coma Scale (GCS) score lower than 8, is not an absolute criterion for intubation (see examples later) and the score intended for head trauma has never been validated in intoxications.[23] Clinical assessment by experienced medical staff rather than physiologic variables is the key to determining intubation requirements in poisoned patients with a reduced GCS score. GCS score alone is not a good predictor of intubation.[24] Once control of the airway has been achieved, supplemental oxygen should be delivered.

B—Breathing

To assess breathing, an open airway should be maintained and chest movements subsequently looked for, breathing sounds listened for, and expired air felt for.

If there are signs of inadequacy, ventilation through a mask and an orotracheal tube is needed.[16] Respiratory depression and bradypnea may occur in opiate and sedative-hypnotic overdose. Hyperventilation is observed in poisoning with salicylates and during the initial stage of any cause of hypoxia, such as CO and cyanide poisoning; if left untreated, these ultimately result in respiratory failure. Cheyne-Stokes respiration, defined as alternating hyperpnea and apnea, is rarely observed in poisoned patients; rather, it indicates the presence of a structural lesion at the level of the midbrain, infection, cardiopulmonary disease, or other metabolic disorders.

Hypoxemia can easily be detected with pulse oximetry. Pulse oxymeters, however, are unable to detect hypercarbia, which may result from hypoventilation. Pulse oxymeters are also totally unreliable in CO poisoning because the apparatus cannot distinguish between oxyhemoglobin and carboxyhemoglobin (COHb). Newer devices, called pulse CO-oximeters, allow immediate noninvasive COHb measurement.

C—Circulation

A patient's hemodynamic status should be assessed by checking for an arterial pulse, ideally the carotid, for rate, rhythm, and character. Blood pressure should be measured and peripheral perfusion should be assessed using capillary refill time. Patients should be connected to a cardiac monitor, and urinary catheterization is necessary for all unconscious patients to follow urine output.

In cases of cardiac arrest, resuscitation should be started at once. Cardiac arrest may be due to a direct toxic effect on the heart or a severe metabolic disturbance or may be secondary to a respiratory arrest. Examples of drugs that can cause a cardiac arrest through a direct effect on the heart include the tricyclic antidepressants, chloral hydrate, and the phenothiazines. Calcium antagonists, β-adrenergic antagonists, vasodilators and any negative inotropic drug in overdose may also cause cardiovascular collapse, leading to cardiac arrest. Resuscitation for a prolonged period should be considered because the poison may be metabolized or excreted during extended life-support measures.[21]

Hemodynamic shock can impair consciousness due to reduced cerebral perfusion. Malignant tachyarrhythmias resulting in hypotension may be observed in intoxications with tricyclic antidepressants or theophylline. Bradyarrhythmias and hypotension may result from an overdose of β-adrenoceptor antagonists, digoxin, and clonidine. Intravenous access has to be established and shock should be treated appropriately with, for instance, intravenous fluids and vasopressors to prevent secondary brain injury and other organ failures. Cardiovascular collapse after overdose with β-adrenergic or calcium antagonists requires specific antidote therapy (eg, glucagon and calcium).[25]

D—Disability

The initial neurologic assessment should be a rapid evaluation of the GCS score and the pupils (size, equality, and reaction to light). The alert/verbal/painful/unresponsive (AVPU) responsiveness scale provides a more rapid and simple alternative to the GCS score in assessing consciousness level in most poisoned patients.[26] Both scales are difficult to use in uncooperative patients (eg, ethanol-intoxicated patients).

During this phase, the crucial question should arise if the altered consciousness is really due to intoxication. Causes of altered consciousness may be of toxicologic, metabolic, infectious, neurologic with structural changes, or psychiatric nature. Life-threatening conditions should be looked for, such as hypoglycemia, meningitis, epilepsy, and opiate poisoning, and treated appropriately. Hypoglycemia may result

not only from insulin and oral hypoglycemic poisoning but also from intoxication with ethanol (more common in young children), paracetamol (acetaminophen), and salicylates. Confirming hypoglycemia can easily be done and should be routine in every comatose patient. Rapid bedside tests are available but the apparatus may not always be accurate, with falsely elevated glucose levels. Furthermore, diabetic patients may experience glycopenic symptoms at lower but still normal glucose levels.[27] The treatment of hypoglycemia is discussed later.

Signs of recent head trauma (eg, abrasions, contusions, and hematoma) or the presence of lateralizing or asymmetric neurologic findings should prompt an immediate search for a structural lesion. Bilateral orbital hematoma (raccoon eyes) and ecchymosis behind the ear (Battle sign) may indicate a skull fracture. Focal findings on examination greatly reduce the likelihood of toxic etiology alone. Patients may have more than one cause of coma. For instance, poisoning with CNS depressants may result in a fall leading to a traumatic subdural hematoma.

The pupils may provide important information in establishing a diagnosis. Many medical textbooks state that in coma caused by a toxic-metabolic process, the integrity of the pupillary light reflex remains intact. Exceptions include anoxia, hypothermia, and intoxication with anticholinergics, barbiturates, cholinergics, glutethimide, or opioids.[5] In a prospective study, the loss of the light reflex and anisocoria were independent predictors for structural causes of coma, with sensitivity and specificity for loss of light reflex of 83% and 77%, respectively (likelihood ratio 3.56) and for anisocoria 39% and 96%, respectively (likelihood ratio 9); this means, however, that in 23% of patients with coma of metabolic-toxic origin light reflex was absent.[28] Pupils that are equal, pinpoint, and fixed may be observed in intoxications with opioids and organophosphates and should be differentiated from pontine lesions. Equal, dilated, and reactive pupils can be seen in methylenedioxymethamphetamine (MDMA) and amphetamine users but may also result from metabolic disturbances or midbrain lesions. Equal, dilated, and fixed pupils may occur in anticholinergic poisoning and also in hypoxemia, hypothermia, and in the peri-ictal phase. Meningeal irritation should be checked if there are no contraindications to mobilization of the spine.

E—Exposure

Patients must be fully exposed to allow complete assessment, and body temperature must be measured. Hypothermia is an important cause of coma. Factors predisposing to hypothermia are CNS depression and immobilization, which may be observed after an overdose with, for instance, sedatives. In an urban setting, alcohol intoxication is the most common predisposing factor to hypothermia. The mechanism by which ethanol predisposes to hypothermia is probably based on its depressive effects on the CNS, vasodilation, and blunting of behavioral responses to cold. Hyperthermia may indicate the presence of a serotonergic syndrome, a neuroleptic malignant syndrome, an anticholinergic syndrome, or intoxication with CNS stimulants (eg, cocaine and amphetamines). Important information can be obtained by contacting relatives and friends and by searching the patient's clothes for useful information, such as medical cards and drugs. Environmental manipulation (eg, quiet room and calm conversation) is important in patients with agitation.

At the end of the primary assessment, the potential lethality of the overdose should be assessed. This requires knowledge of the substance, the time of intake, and the dose. It often happens, however, that information about these 3 key elements is not available or not reliable; in these cases there should be a high suspicion of a potentially lethal intoxication.

Etiology-Oriented Approach

In comatose patients with respiratory depression, etiologic clues of a heroin overdose should immediately alert the rescuer to watch carefully for needles to avoid stick injuries. Initial airway management consists of oxygenation and bag mask ventilation followed by administration of the antidote naloxone rather than immediately performing an orotracheal intubation (discussed later).

A comatose, spontaneously breathing patient with a history of insulin-dependent diabetes mellitus should immediately prompt the rescuer to exclude hypoglycemia and, if needed, the intravenous administration of glucose (discussed later). Except for providing a patent airway, additional airway management maneuvers usually are not needed.

Respiratory insufficiency in patients with an organophosphate poisoning must be managed by immediate orotracheal intubation and appropriate antidotal treatment. Protective safety measures for the rescuer are important because organophosphates may be absorbed through the skin.

CO poisoning poses an important safety risk to the rescuers. Carrying CO detectors by rescuers is an important safety measure. The mainstay of treatment of comatose patients from CO poisoning is attention to the airway and oxygenation. As soon as possible, 100% oxygen should be provided by mask reservoir followed, if necessary, by endotracheal tube, and the patient should be transferred to a hospital with hyperbaric oxygen (HBO) therapy facilities (discussed later).

Most patients comatose from barbiturate poisoning require definite airway protection by orotracheal intubation and ventilatory support due to the expected prolonged, profound coma. Conversely, uncomplicated coma induced by benzodiazepines and/or alcohol can often be managed by providing oxygen, free airway, and positioning of patients in the recovery position under close monitoring. For benzodiazepines, the use of the antidote flumazenil can be considered under certain and rare conditions (discussed later).

SECONDARY ASSESSMENTS

The secondary assessment should only be done once the immediately life-threatening conditions have been treated. In most cases, a complete history taking and thorough clinical examination result in identification of the substance taken.[29] Important information can also be obtained by anamnesis of the patient's surroundings and by searching, for example, (empty) drug blisters. Identifying the toxic substance by clinical examination requires profound knowledge of the different toxidromes.

Neurologic Examination

Trying to determine the cause of altered consciousness should be part of the primary assessment, because a rapid diagnosis may be important for prognosis of a patient's neurologic outcome. Subsequently, during the secondary assessment, a careful neurologic assessment should be performed to further distinguish between a toxic-metabolic cause for altered consciousness and structural neurologic causes, for instance, a cerebrovascular accident or an epidural or subdural hematoma. At this stage, the role of a thorough neurologic clinical examination is of pivotal importance. Examination of pupillary reactivity, motor responses to noxious stimuli, and ocular movements is of paramount importance to differentiate between these two entities.[2,5,30]

As discussed previously, pupil size and reaction to light may provide valuable information. Dysconjugate gaze in the horizontal plane is normally observed in drowsiness

and in various sedated states, including alcohol intoxication, with parallel ocular axes re-emerging when a patient awakens or slips deeper into coma. Dysconjugate gaze in the vertical plane, called skew deviation, generally results from pontine or cerebellar lesions. Sustained conjugate upward gaze is usually the result of hypoxic encephalopathy.

Focal or asymmetric findings in motor responses to a noxious stimulus should invoke a search for a structural lesion. There are, however, exceptions to this generalization. For instance, mass lesions of the brain may cause compression of the brainstem bilaterally resulting in bilateral and symmetric neurologic deficit. Some toxic-metabolic conditions, such as hyperosmolar nonketotic hyperglycemia or hypoglycemia, may produce focal deficits. Different metabolic demands in different brain regions and circulation defects have been suggested as the causes of hypoglycemia-related stroke-like episodes.[31] Focal neurologic signs observed in hyperosmolar nonketotic hyperglycemia have been hypothesized as secondary to effects of hyperosmolality on the brain, resulting in focal regions of brain edema and reactivation of previously resolved neurologic deficits.

The presence of oculocephalic and oculovestibular reflexes also helps in differentiating toxic from structural causes of coma. The oculocephalic reflex (doll's eye movements) implies conjugate eye movement away from the direction of rotation. This maneuver is strictly contraindicated when there is a possibility of cervical instability. The oculovestibular reflex, which involves cold-water irrigation of the tympanic membrane, produces transient conjugate slow deviation of gaze toward the side of the stimulus (brainstem mediated) followed by a quick saccadic correction back to midline (cortically mediated). Because the hallmark of a toxic-metabolic coma is a dissociation of findings, these reflexes should be paired with other findings, such as pupillary reactivity. For instance, with respect to pupillary reactivity, this means that pupillary reactivity is dissociated from other neuraxis dysfunction in a fashion that is not characteristic of structural brain disease. Thus, in addition to symmetric findings, patients whose coma originates from a toxicologic or metabolic cause typically have an intact and equal pupillary light reflex that may be paired with an absent oculovestibular response, an absent motor response to noxious stimuli, or hypoventilation requiring ventilatory support. This phenomenon of dissociation occurs with toxic-metabolic coma because other brainstem functions tend to be far more vulnerable to toxic and metabolic insult than are the pupillary light reflexes. In contrast with coma caused by structural disease, in coma caused by a toxic-metabolic process there is symmetry in either response or nonresponse to provocative maneuvers.

Seizures caused by drugs and toxins are mostly of the generalized tonic-clonic variety unless there is underlying focal neurologic disease or epilepsy. Seizures may result from a direct reduction of seizure threshold or from secondary events, such as hypoxia. Toxin-induced seizures are most commonly caused by tricyclic antidepressants or sympathomimetic or anticholinergic agents. Seizures as part of an alcohol or benzodiazepine withdrawal syndrome are also frequently observed.[32,33]

Clonus is caused by a variety of substances, most commonly sedative-hypnotics and anticonvulsants. Rigidity, clonus, hyperreflexia, and tremor are seen with lithium poisoning.

Serotonin syndrome and neuroleptic malignant syndrome typically have a motor component combined with altered mental status and hyperthermia. The key differences between the two syndromes are shown in **Table 2**. The serotonin syndrome is an adverse drug reaction resulting from excessive serotonergic neurotransmission after therapeutic drug use (rare when only one serotonergic drug is used), intentional self-poisoning, or inadvertent interactions between drugs, such as selective serotonin

Table 2
Key differences between serotonin and neuroleptic malignant syndrome

Feature	Serotonin Syndrome	Neuroleptic Malignant Syndrome
Neuroleptic drugs	0	+++
Serotonergic drugs	+++	0
Hyperactivity	+++	0
Clonus	+++	0
Tremor	+++	+
Shivering	+++	0
Hyperreflexia	+++	0
Rapid onset	+++	0
Leaden rigidity	0	+++
Bradykinesia	0	+++
Stupor/mutism	0	+++
Creatine kinase activity	++	+++
Hallucinations	+	++
Hyperthermia	++	++

Data from Richards D, Aronson J. Oxford handbook of practical drug therapy. Oxford: Oxford University Press; 2005.

reuptake inhibitors; serotonin precursors, such as tryptophan and serotonin agonists, such as the triptans; serotonin releasers, such as amphetamines; tricyclic antidepressants; and MAOIs.[34] Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction to antipsychotic agents. There are also case reports of other medications causing NMS, including venlafaxine, promethazine, metoclopramide, and prochlorperazine. NMS is believed to result from CNS dopamine receptor blockade or withdrawal of exogenous dopaminergic agonists. NMS can develop in patients with Parkinson disease after withdrawal of levodopa therapy. The probability of developing NMS is directly related to the antidopaminergic potency of the neuroleptic agent.

Toxidromes

The identification of specific toxidromes may be helpful in establishing a diagnosis when the exposure is not well defined.[18] These are grouped physiologically based on abnormalities of vital signs, general appearance, skin, eyes, mucous membranes, and pulmonary, cardiovascular, gastrointestinal, and neurologic systems, that are known to occur with specific classes of substances, such as anticholinergic, cholinergic, sympathomimetic, and opioid agents (**Table 3**). The list of representative agents in the table is not limitative. The actual clinical manifestations of an ingestion or exposure are far more variable than the syndromes described in the table.

Odors and Skin

Odors can provide useful hints. An odor of alcohol may indicate ethanol intoxication. An odor of acetone may accompany diabetic ketoacidosis, chloral hydrate, or isopropyl alcohol poisoning; the scent of bitter almonds with cyanide; and a garlic-like odor with organophosphates and arsenic.

Central cyanosis is a sign of hypoxia, but methemoglobinemia may also cause a similar color. The cherry pink skin color of COHb is not always obvious, and its absence does not exclude serious CO poisoning. Anticholinergics, alcohol, cocaine,

cyanide, and borates may produce a flushed pink skin. The presence of track marks is often indicative of intravenous drug use and resultant opiate or sympathomimetic toxicity. Cutaneous bullae (coma blisters) may be found not only in barbiturate, glutethimide, and other sedative overdoses but also in tricyclic antidepressant and CO poisoning.

Bruises and hematoma indicate a traumatic injury, which may be due to violence. In this context, some drugs (eg, GHB, flunitrazepam, and ketamine) may be used to assist a sexual assault because of their sedative, muscle relaxant, and amnestic properties and are, therefore, called date rape drugs.

Patients who have been lying in coma for a long time on a hard surface may develop cutaneous bullae and rhabdomyolysis due to pressure necrosis of the skin and muscles. This particularly affects muscles in compartments leading to compartment syndrome and renal failure. The agents most often implicated are CO, alcohol, opioids, barbiturates, or other CNS depressants. Therefore, all extremities of coma patients should be inspected for edema, color change, or vascular deficit. Diagnosis of a compartment syndrome can be established by measuring compartment pressures. Some agents, such as cocaine and ethanol, may induce rhabdomyolysis by direct toxic effects on the sarcoplasmic reticulum.

DECONTAMINATION PROCEDURES

Decontamination procedures have to be considered in the treatment of poisoned patients. These procedures are discussed briefly based on the guidelines published by the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists.

In cases of a potentially lethal overdose or if the exact nature of the overdose is not known, measures to prevent or reduce toxic drug levels should always be considered. This may be achieved by reducing drug absorption and/or by enhancing drug elimination. Methods used to decrease drug absorption in the gastrointestinal tract are activated charcoal, gastric lavage, whole-bowel irrigation, and therapeutic emesis. Procedures enhancing drug elimination include multiple doses of activated charcoal, therapeutic diuresis, urinary alkalinization, hemoperfusion, and hemodialysis.

Before initiating these procedures, consultation with a clinical toxicologist is advisable. In comatose patients, emesis is prohibited, and gastric lavage and the administration of activated charcoal are contraindicated unless a patient has a secured airway by means of an orotracheal tube with inflated cuff.

Reducing Absorption

Skin decontamination

Skin decontamination should always be considered on toxic exposure of the skin.[35] Removal of the clothes is an important measure to prevent direct effects and systemic absorption of certain toxins (eg, organophosphates). In general, a copious amount of water is the decontamination agent of choice for skin irrigation. Soap should be added when adherent materials are involved.

Gastrointestinal decontamination

Activated charcoal Charcoal works by adsorbing ingested drugs onto its large surface area and adsorbs 10% of its own weight. In most instances, 0.5 g/kg to 1 g/kg is an appropriate initial dose of activated charcoal; doses of 1.5 g/kg to 2 g/kg should be used after particularly massive or dangerous ingestions. In vitro studies show that ideal activated charcoal-to-drug ratios vary widely, but 10:1 is a representative value for many typical drugs and is, therefore, useful in theoretic consideration of optimal

Table 3
Toxidromes

Toxidrome	Mental Status	Pupils	Vital Signs	Other Symptoms	Representative Agents
Sympathomimetic	Hyperalertness Agitation Hallucinations Paranoia	Mydriasis	Hyperthermia Tachycardia Hypertension Tachypnea Hyperpnea	Diaphoresis Tremor Hyperreflexia Seizures	Cocaine Amphetamines Ephedrine Pseudoephedrine Phenylpropanolamine Theophylline Caffeine
Anticholinergic	Hyperalertness Agitation Hallucinations Delirium Mumbling speech Coma	Mydriasis	Hyperthermia Tachycardia Hypertension Tachypnea	Flushing Dry skin Dry mucosa Blurred vision Decreased bowel sounds Urinary retention Myoclonus Choreoathetosis Seizures	H_1-antihistamines Tricyclic antidepressants Antiparkinson drugs Antispasmodic drugs Phenothiazines Atropine Scopolamine Belladonna alkaloids
Hallucinogenic	Hallucinations Distortion of perception Depersonalization Agitation	Mydriasis (usually)	Hyperthermia Tachycardia Hypertension Tachypnea	Nystagmus	Phencyclidine LSD Mescaline Psilocybin Amphetamines (eg, 3, 4-Methylenedioxy-N-ethylamphetamine and *N*-methyldiethanolamine)
Opiates	CNS depression Coma	Miosis	Hypothermia Bradycardia Hypotension Hypopnea Bradypnea	Hyporeflexia Lung edema Decreased bowel sounds Needle track marks	Opiates (eg, heroin, morphine, methadone, oxycodone, and hydromorphone) Diphenoxylate

Sedative/ Hypnotic	Confusion Sedation Stupor Coma Slurred speech Ataxia	Miosis (usually)	Hypothermia Bradycardia Hypotension Hypopnea Bradypnea	Hyporeflexia	Benzodiazepines Zolpidem Barbiturates Alcohol
	Combativeness interspersed with obtundation Sudden awakening	Variable			GHB
Cholinergic	Confusion Coma	Miosis	Bradycardia (initially tachycardia) Hypertension or hypotension Tachypnea or bradypnea	Salivation Urination Defecation (diarrhea) Diaphoresis Lacrimation Abdominal cramps Bronchoconstriction Bronchorrhea Muscle weakness and fasciculations Seizures	Organophosphates Nerve agents Nicotine Pilocarpine Physostigmine Edrophonium Bethanechol Urecholine
Serotonin syndrome	Confusion Agitation Coma	Mydriasis	Hyperthermia Tachycardia Hypertension Tachypnea	Tremor Myoclonus Hyperreflexia Clonus Diaphoresis Flushes Jaw stiffness Muscle stiffness Diarrhea	Selective serotonin reuptake inhibitors, serotonin precursors (tryptophan), serotonin agonists (eg, triptans), serotonin releasers (eg, MDMA), MAOIs, tricyclic antidepressants, others (eg, dextromethorphan and lithium)
Tricyclic antidepressants	Confusion Agitation Coma	Mydriasis	Hyperthermia Tachycardia Hypertension followed by hypotension Hypopnea	Seizures Myoclonus Choreoathetosis Arrhythmia Conduction disorders	Amitriptyline Nortriptyline Imipramine Clomipramine Desipramine Doxepin

Data from Burns MJ, Schwartzstein RM. General approach to drug poisoning in adults. UpToDate online 19.2; 2011.

activated charcoal dosing. Substances, such as toxic alcohols, lithium, and iron, are not effectively adsorbed by activated charcoal. Based on volunteer studies, the administration of activated charcoal should be considered if a patient has ingested a potentially toxic amount of a poison (which is known to be adsorbed to charcoal) up to 1 hour previously.[36,37] Although volunteer studies demonstrate that the reduction of drug absorption decreases to values of questionable clinical importance when charcoal is administered at times greater than 1 hour, the potential for benefit after 1 hour cannot be excluded, and it should therefore still be considered in intoxications where delayed gastrointestinal absorption is possible (eg, tricyclic antidepressants causing delayed gastric emptying due to anticholinergic effect or sustained-release preparations). In this respect, unless a patient has an intact or protected airway, the administration of charcoal is contraindicated because of the risk of lung aspiration. Activated charcoal is also contraindicated if its use increases the risk and severity of aspiration (eg, ingestion of a hydrocarbon with a high aspiration potential). Patients who are at risk of gastrointestinal hemorrhage or perforation due to medical conditions or recent surgery of the gastrointestinal tract could be further compromised by single-dose activated charcoal. Presence of activated charcoal in the gastrointestinal tract may obscure endoscopic visualization, but intoxication with a corrosive is not a contraindication for activated charcoal when it is administered for co-ingested agents that are systemic toxins.

Multiple-dose activated charcoal therapy involves the repeated administration (more than 2 doses) of oral activated charcoal to enhance the elimination of drugs already absorbed into the body. Multiple-dose activated charcoal is thought to produce its beneficial effect by interrupting the enteroenteric and, in some cases, the enterohepatic and the enterogastric circulation of drugs.[38] Based on experimental and clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. The use of multiple-dose charcoal in salicylate poisoning is controversial.

Finally when weighing the advantages of activated charcoal against its disadvantages, it should be stressed that there is no evidence from randomized controlled trials that the administration of activated charcoal improves clinical outcome.

Gastric lavage Gastric lavage should not be used routinely, if ever, in the management of poisoned patients.[39] The results of clinical outcome studies in overdose patients are weighted heavily on the side of showing a lack of beneficial effect. Serious risks of the procedure include hypoxia, arrhythmias, laryngospasm, perforation of the gastrointestinal tract or pharynx, fluid and electrolyte abnormalities, and aspiration pneumonitis. In comatose patients without a gag reflex, endotracheal or nasotracheal intubation should always precede gastric lavage. Contraindications for gastric lavage include ingestion of a strong acid or alkali, ingestion of a hydrocarbon with a high aspiration potential, or risk of gastrointestinal hemorrhage due to an underlying medical or surgical condition. In situations where the procedure may be a reasonable treatment option (eg, recent overdose with a life-threatening toxin, such as tricyclic antidepressants, lithium, and organophosphates), the clinician should carefully examine the risk-benefit ratio. Gastric lavage is usually followed by the administration of activated charcoal.

Whole-bowel irrigation Whole-bowel irrigation cleanses the bowel by the enteral administration of large amounts of an osmotically balanced polyethylene glycol electrolyte solution, which induces a liquid stool. It reduces drug absorption by

decontaminating the entire gastrointestinal tract by physically expelling intraluminal contents. Whole-bowel irrigation should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs, particularly for those patients presenting more than 2 hours after drug ingestion.[40] It should also be considered for the removal of ingested packets of illicit drugs in body packers. In cases of a ruptured cocaine packet, however, emergency surgery is required whereas in cases of a ruptured heroin packet, patients may be treated by a continuous naloxone infusion awaiting spontaneous elimination. Whole-bowel irrigation is contraindicated in patients with bowel obstruction, perforation, or ileus and in patients with hemodynamic instability or compromised unprotected airways. The concurrent administration of activated charcoal and whole-bowel irrigation may decrease the effectiveness of the charcoal.

Emesis Apomorphine and saltwater are outdated and dangerous emetics and should no longer be used.

Syrup of ipecac has been used to promote active vomiting.[41] There is, however, no evidence from clinical studies that ipecac improves the outcome of poisoned patients and its routine administration in the emergency department should be abandoned. Ipecac may delay the administration or reduce the effectiveness of activated charcoal, oral antidotes, and whole-bowel irrigation. Ipecac should not be administered to patients who have a decreased level or impending loss of consciousness or who have ingested a corrosive substance or hydrocarbon with high aspiration potential.

Increasing Elimination

Measures to increase elimination include therapeutic diuresis, urinary alkalinization, hemoperfusion, and hemodialysis.

Forced diuresis by administration of large volumes of isotonic fluids and diuretics to increase renal excretion of a drug or metabolite is of limited clinical value. It is not recommended because of potential volume overload and electrolyte abnormalities.

Urinary alkalinization to enhance excretion of weak acids is achieved by the administration of intravenous sodium bicarbonate to produce urine with a pH greater than or equal to 7.5 and may be beneficial for compounds, such as salicylates and phenobarbital/primidone.[42] Side effects of urinary alkalinization are alkalemia and electrolyte disturbances, such as hypokalemia and hypocalcemia.

Invasive techniques, such as hemodialysis and hemoperfusion, are reserved for elimination of specific life-threatening toxins.[43] Hemodialysis is particularly suited for drugs or metabolites that are water soluble, have a low volume of distribution, have a molecular weight less than 500 Da, and have low plasma protein binding (eg, methanol, ethylene glycol, lithium, and salicylates). Hemoperfusion involves the passage of blood through an adsorptive-containing cartridge (usually resin or charcoal). This technique removes substances that have a high degree of plasma protein binding. Charcoal hemoperfusion may be indicated for intoxications with carbamazepine, phenobarbital, phenytoin, and theophylline. There are limited data available on drug removal by continuous arteriovenous or continuous venovenous hemofiltration. Hemofiltration has been used to enhance elimination of aminoglycosides, vancomycin, and metal chelate complexes, but the technique does not remove highly protein-bound drugs effectively. It may also be of benefit for intoxications with drugs that have a large volume of distribution, tight tissue binding, or slow intercompartmental transfer.

FURTHER DIAGNOSTIC APPROACH

ECG

A 12-lead ECG should be recorded in all patients with a potential risk of cardiac effects from their overdose or if rhythm disturbances are observed on cardiac monitoring. The ECG should be examined for rate and rhythm disturbance, ST changes indicative of ischemia, atrioventricular(AV) block, QRS and QT interval prolongation, and right axis deviation. For instance, prolongation of the QRS duration greater than100 milliseconds and/or right axis deviation of the terminal 40 milliseconds of the QRS complex (terminal S wave in lead I and elevated R wave in lead aVR) after tricyclic antidepressant intoxication is a sign of potential cardiac toxicity.[44] Poisoning with cardiac glycosides can present with almost any type of rhythm disturbance but frequently express a bradycardic rhythm with AV block similar to intoxication with calcium channel or β-blocking agents. Cocaine use may be associated with myocardial ischemia and dysrhythmias. Unfortunately, in the setting of cocaine-associated chest pain, the ECG has neither the sensitivity nor the specificity necessary to permit exclusion or confirmation of cardiac injury.

Blood and Urine Analysis

A glucose level should be obtained during the primary assessment to rule out hypoglycemia. Blood should be taken for complete blood count, renal and liver function, electrolyte tests, clotting studies, and osmolality. Cardiac markers are always required when considering myocardial ischemia after cocaine use. A creatine kinase level should be obtained when rhabdomyolysis is suspected. The possibility of pregnancy should be ruled out in every woman presenting with coma. Hypokalemia may indicate salbutamol, theophylline, or salicylate poisoning. Raised osmolality suggests ethanol, methanol, ethylene glycol, or isopropanol poisoning. Arterial blood gases help with quantifying any respiratory compromise and also indicate an acid-base disturbance. If an acidosis is present, a serum lactate level and calculation of the serum anion gap (anion gap = sodium − [chloride + bicarbonate], normal value 13 $\pm$ 4 meq/L) help assess the type of acid-base disorder. Metabolic acidosis may result from poisoning with, for example, salicylates, paracetamol (acetaminophen), ethanol, methanol, and ethylene glycol or also from circulatory shock. Any poison causing seizure, hypoxemia, shock (hypotension), cellular anoxia, or rhabdomyolysis results in a high anion gap metabolic acidosis from increased lactic acid concentrations. Poisoning with CO or the presence of methemoglobin can be ruled out by measuring COHb and methemoglobin levels, respectively. As discussed previously, pulse oximetry is unable to distinguish between oxyhemoglobin and COHb because of their spectrophotometric similarities. Urinalysis can assist in the evaluation of ketosis, hemolysis, and renal injury. Microscopy of urine may reveal calcium oxalate crystals, suggesting ethylene glycol poisoning.

Toxicologic Testing

Toxicology screening on blood and/or urine may be ordered depending on the clinical picture.[45,46] It is obvious that when clinically indicated, therapy for patients with suspected poisoning should never be postponed until the toxicologic results are known. In practice, however, many clinicians, emergency physicians, and neurologists believe that toxicologic testing is useful. When, for instance, in patients with altered consciousness, doubt remains about the cause, toxicologic data are of great help even when they are negative. This aspect is rarely studied. Furthermore, identifying the toxic substance influences therapy and prevents morbidity and mortality in

a few percentages of patients. For instance, knowing that a coma is due to lithium poisoning may point to the necessity of hemodialysis. Finally for documentation and liability concerns, confirmation of a suspected poisoning with a toxicologic analysis is preferred by most clinicians. A more important issue than whether or not to order tests is how to order the tests. Clinicians treating patients with altered consciousness and suspected poisoning should know the limitation of a "comprehensive tox-screen." The number of drugs detected in a screen varies from laboratory to laboratory and can be falsely negative or reassuring. Moreover a comprehensive screen demands a lot of work in a laboratory and may not be cost effective. To increase efficiency and reduce the cost of toxicologic analysis, it is important that clinicians provide information on the suspected drugs and consult with a clinical toxicologist.

The possibility of (co-)intoxication with paracetamol (acetaminophen) and salicylate poisoning should always be considered in patients presenting with an overdose because these drugs are widely available, potentially lethal, and treatable in the early phase of intoxication.[47] Salicylates by themselves can cause coma through cerebral edema, and paracetamol (acetaminophen) and combination preparations, for instance, paracetamol (acetaminophen) and codeine, in massive overdose have been associated with coma.[48,49]

For some drugs and poisons, quantitative concentration measurements may be useful because they may guide treatment (**Box 2**). For some coma-inducing substances, such as anticonvulsants, lithium, and methemoglobin, there is a good correlation between the concentration and the clinical symptoms. Levels of alcohol and benzodiazepines usually do not correlate well with depth of coma due to the large interindividual variability; chronic users, for instance, exhibit CNS depression at significantly higher blood concentrations than nontolerant individuals. The problem with using COHb levels is that there is wide variation in clinical manifestations with identical COHb levels and that particular COHb levels are not predictive of symptoms or final outcome.[50] Also for salicylates, the severity of toxicity poorly correlates with serum levels. Quantitative levels of tricyclic antidepressants also have little correlation with clinical symptoms and fail to predict the risk of seizures or ventricular dysrhythmias

Box 2
Some examples of compounds for which quantitative analysis may be useful in guiding treatment

Antiepileptics: carbamazepine, phenytoin, and valproic acid

COHb

Digoxin

Ethylene glycol

Heavy metals: iron, lead, and mercury

Lithium

Methanol

Methemoglobin

Paracetamol

Paraquat

Salicylates

Theophylline

and are therefore rarely indicated. Timing of measuring blood concentrations may be important; for example, concentrations measured during the absorption phase may lead to underestimation of the risk and to potentially fatal errors. Sometimes repeated drug concentrations should be determined to look for trends, because drug absorption in overdose may be delayed or erratic.

Radiography

A chest radiograph is indicated in patients presenting with coma to evaluate for an infectious source of coma or aspiration pneumonia. All suspected body packers should undergo radiographic evaluation of the abdomen; packets can be visualized as multiple radiodense foreign bodies.

Cranial CT should be performed if a concern for an intracranial lesion exists or if cerebral edema is suspected (eg, in acetaminophen-induced liver failure). If indicated, a lumbar puncture should be considered to rule out subarachnoid bleed, meningitis, or encephalitis.

URGENT SPECIFIC ANTIDOTES

Some of the most frequently used antidotes that may be considered during initial management of patients with altered consciousness are reviewed. Antidotes for cyanides, organophosphates, tricyclic antidepressants, and methemoglobin-forming agents are not discussed and readers are referred to specialized textbooks in toxicology.[51] Normobaric oxygen (NBO) should be delivered to all comatose patients and in cases of CO poisoning the administration of HBO may be considered. The value of the antidotes dextrose and thiamine and the opiate antagonist naloxone used as a "coma cocktail" is discussed later.[52] More recently, the benzodiazepine receptor antagonist flumazenil has also been considered an urgent antidote. Benzodiazepines have an important role in the treatment of substance-induced agitation.

Hyperbaric Oxygen

HBO involves exposing patients to 100% oxygen under supra-atmospheric conditions. This results in a decrease in the half-life of carboxyhemoglobin (COHb), from 40 to 80 minutes on 100% NBO to 15 to 30 minutes during HBO. HBO may be beneficial in preventing the late neurocognitive deficits associated with severe CO poisoning; however, the quality and results of clinical trials have varied widely.[53–55]

A well-designed double-blind controlled trial randomly assigned 152 patients with symptomatic CO intoxication within 24 hours of presentation to HBO or NBO.[56] Treatment was administered during 3 sessions in a hyperbaric chamber. Six weeks after presentation, cognitive sequelae were more common in the group treated with NBO (46 vs 25%). This advantage of HBO was maintained at 1 year after initial presentation. In 31% of the patients in the study by Weaver and colleagues,[56] CO intoxication was related to a suicide attempt.

Another study randomly assigned 343 patients without initial impairment of consciousness in a nonblinded way to either 6 hours of NBO or 2 hours of HBO at 2 atm plus 4 hours of NBO.[57] No difference in mortality or in the incidence of delayed neurologic sequelae was observed. Critics of the study noted, however, that many patients in the HBO group did not receive treatment until more than 6 hours from the time of poisoning and that patients were treated with only one HBO session.

Similar findings were noted in a double-blind randomized trial of 191 patients with CO poisoning referred to a tertiary center, which failed to document benefit for patients who received HBO.[58] On the contrary, delayed neurologic sequelae and

poor performance on neuropsychiatric tests after 1 month were significantly more common among HBO-treated patients. In this study, although people with all levels of CO were included, a high proportion (73%) of patients with severe CO poisoning was presented. Moreover, cluster randomization was used for patients presenting simultaneously, which may have engendered the risk of bias. Also, mean time interval to treatment was high (>6 hours), and it is therefore possible that a significant proportion of the patients were treated at a time after CO exposure when HBO is unlikely to be effective. Annane and colleagues[59] randomized patients with transient loss of consciousness due to CO poisoning to HBO (2 ATA for 2 hours followed by 100% oxygen at atmospheric pressure for 4 hours) versus NBO; no benefit from HBO over NBO was found. The investigators, however, only permitted less severely poisoned patients to be randomized to HBO or NBO. Because interventions are, in general, most likely to show benefit in patients with more severe disease, the possibility of type II error in these trials is high. Consequently, this trial does not disprove a benefit of HBO, particularly in more severely poisoned patients.

Despite the uncertainty in identifying patients who will benefit from HBO therapy, most authorities favor HBO in the presence of COHb greater than 25%, metabolic acidosis, a history of loss of consciousness, or neurologic or cardiovascular dysfunction or in pregnant women with COHb greater than 15% or evidence of fetal distress. All patients selected to receive HBO should have at least 1 treatment at 2.5 atm to 3.0 atm as soon as possible to reverse the acute effects of CO intoxication, possibly with additional hyperbaric sessions directed toward limitation or prevention of delayed neurologic sequelae.

Glucose and Glucagon

Any patients with an altered mental status should be suspected of hypoglycemia. Clinical diagnosis of hypoglycemia is not easy. Symptoms may range from agitation to deep coma with diaphoresis and tachycardia. Other neurologic symptoms, however, such as decerebrate and decorticate posturing may occur and even focal signs with, for instance, hemiplegia. In most cases a glucose dose of 10 g to 15 g in adults (as hypertonic glucose 50%) is sufficient to reverse hypoglycemic coma; however, in some cases doses as high as 0.5 g/kg to 1 g/kg are needed (for instance in deliberate insulin overdose). Glucagon (adult dose 1–2 mg) may be used as a temporizing measure in patients who have no intravenous access because it can be administered intramuscularly.

Thiamine

Although Wernicke encephalopathy is rare, thiamine (100 mg intravenously or intramuscularly) should be given in any patient with an altered mental state.[60] Adverse effects seldom occur after administration of thiamine, but hypersensitivity reactions have occurred, mainly after parenteral administration ranging in severity from very mild to, rarely, fatal anaphylactic shock. It only rarely immediately improves the mental state but its routine use reminds us of potential nutritional deficiencies in many patients, especially chronic alcoholics who are at risk of Wernicke encephalopathy. Administration of intravenous glucose to severely malnourished patients can exhaust their supply of thiamine and precipitate Wernicke-Korsakoff syndrome. Therefore, glucose and thiamine should be given as a cocktail for comatose patients.

Naloxone

Naloxone is an antagonist with a high affinity for μ, κ, and σ opioid receptors.[61] It antagonizes, therefore, the opiate effects, such as sedation and the life-threatening

respiratory depression, which makes it of great value in cases of intoxication. It is less effective in poisoning with d-propoxyphene, pentazocine, and buprenorphine. It is a pure antagonist, which means that it does not produce opiate effects by itself and is specific for opiate poisoning.

Naloxone is a competitive antagonist, which implies that the dose needed to reverse the opiate effects depends on the amount of the opiate present in a poisoned patient, which is of course rarely known in acute poisoning.

Initially, and especially in the United States, naloxone was propagated in the coma cocktail for diagnostic and therapeutic use in any patient with decreased consciousness. This indiscriminate use is questioned now, however, because of the poor yield of beneficial effects (only in approximately 3% of comatose patients) and because studies indicate that clinical diagnosis of opiate poisoning based on respiratory rate and pupil size is reliable.[62] Therefore, naloxone is only indicated now in coma and/or respiratory depression (rate <12/min) in patients showing signs of opiate poisoning. The side effects, such as pulmonary edema, are rare.

Potentially severe withdrawal problems may occur in opiate addicts. Therefore, when naloxone is used in potentially dependent patients, the use of incremental doses intravenously is recommended based on the clinical response, such as reversal of respiratory depression and decreased consciousness. A practical starting dose in most adult patients is 0.05 mg, increasing to 0.4 mg, then to 2 mg, and finally to 10 mg.[61] If there is no response to 10 mg, then an opioid is unlikely responsible for the coma and/or respiratory depression.

Recurrent toxicity is common after an initial good response because the half-life of naloxone is short (20–30 minutes), which obviates a continuous infusion or a repeat bolus administration (eg, after 15 minutes). Naloxone can also be administered by the intramuscular, subcutaneous, intralingual, and intratracheal route.

Flumazenil

Flumazenil is a competitive antagonist of the benzodiazepine receptor in the CNS, which facilitates gabaminergic transmission, giving rise to the classical effects of benzodiazepines, such as sedation, anxiolytic, anticonvulsive, and hypnotic properties.[63] Flumazenil reverses the effects, such as sedation, and also the anticonvulsant properties of the benzodiazepines. Although the use of flumazenil is well established to counteract the effects of benzodiazepines used in diagnostic procedures, such as endoscopy, where benzodiazepines are used for sedation, its use in patients with acute poisoning is still the subject of debate.

Opponents of the use of flumazenil in patients with benzodiazepine poisoning stress that benzodiazepines rarely cause morbidity and mortality. The latter is often not due to respiratory depression (which is not always reversed by flumazenil) but to aspiration pneumonia, which already occurred before admission to the hospital. They emphasize the importance of the risk of inducing seizures, which can be due to co-ingested drugs (eg, tricyclic antidepressants) or to the acute withdrawal provoked in patients chronically taking benzodiazepines.

Proponents of the use of flumazenil stress the benefit of avoiding procedures carrying their own risks in the diagnostic work-up of a coma patient. Furthermore, they mention the benefits of avoiding the risks of endotracheal intubation and ventilation.[64]

Flumazenil is better avoided, or even contraindicated, in patients with a history of seizures or current treatment for seizures. History of intake or ingestion of substances capable of provoking seizures or provoking cardiac arrhythmias (eg, tricyclic antidepressants, theophylline, carbamazepine, chloroquine, and chlorinated hydrocarbons)

is also a contraindication. Long-term use of benzodiazepines is also a contraindication. Finally flumazenil should never be used in patients with abnormal vital signs.

If needed, flumazenil should be given slowly and by titration (0.1 mg/min in adults) without exceeding a total dose of 1 mg. Relapse of the sedation may occur after 20 or more minutes due to the short half-life of flumazenil.

In summary, many investigators agree that the indications for flumazenil in the overdose setting are pure benzodiazepine poisoning in individuals who are not tolerant to benzodiazepines, who have CNS depression, normal vital signs, normal ECG, otherwise normal neurologic examination, and no history of epilepsy.[65] Such cases are rare in adults with benzodiazepine poisoning.

Benzodiazepines

Benzodiazepines are used as first-line anticonvulsants for virtually all xenobiotic-induced seizures; as the sedatives of choice for most forms of xenobiotic-induced agitation and for withdrawal from ethanol, GHB, and a variety of sedatives; and as muscle relaxant for disorders, such as serotonin syndrome and NMS.[66] Cocaine-associated myocardial ischemia and infarction are also indications for benzodiazepines. For the treatment of agitation induced by xenobiotics, it is important to titrate the benzodiazepines until the patient is calm. Cumulative benzodiazepine dosages required in the initial 30 minutes to achieve adequate sedation frequently exceed 100 mg of diazepam or its equivalent. Antipsychotics are not recommended for the treatment of xenobiotic-induced agitation because they may lower the seizure threshold, alter temperature regulation, and cause acute dystonia and cardiac dysrhythmias.

DISPOSITION

All patients with altered consciousness should be closely observed with frequent controls of blood pressure, heart rate, respiratory rate, body temperature, GCS score, and pupils. ECG monitoring is required in all patients intoxicated with potential cardiotoxic agents. Continuous pulse oximetry is recommended in comatose patients because all agents causing CNS depression may compromise airway patency. Depending on end-organ toxicity, toxin characteristics, requirements for physiologic monitoring and specialized treatment, and patient factors, admission to an intensive care unit is indicated.

In a retrospective study, a set of criteria was established to identify those poisoned patients needing intensive care unit admission without taking into account the specific toxin ingested.[67] Criteria defining high-risk patients were need for intubation, unresponsiveness to verbal stimuli, seizures, P_{CO_2} greater than 45 mm Hg, systolic blood pressure less than 80 mm Hg, QRS duration greater than 0.12 seconds, or any cardiac rhythm except normal sinus rhythm, sinus tachycardia, or sinus bradycardia.

Intensive care unit admission is always warranted for patients with expected serious toxic effects from an ingested poison. This is especially true for those toxins known to be deadly, such as calcium channel blockers, cocaine, cyanide, cyclic antidepressants, and salicylates. Indicators of toxicity should be identified for individual toxins so that high-risk patients may be closely monitored and aggressively treated.

The intensive care unit setting provides a nurse-to-patient ratio that allows for frequent or continuous monitoring of basic physiologic parameters. The intensive care units are also most equipped to provide supportive care measures to treat respiratory failure and hemodynamic shock. Extracorporeal methods for eliminating toxins and most antidotal therapy are also best performed in the intensive care unit.

Pre-existing medical conditions increase a patient's risk for developing toxicity and may, therefore, require intensive care unit admission. For instance, patients with underlying cardiac disease are more susceptible to myocardial ischemia from CO poisoning. Renal and hepatic disease may alter drug metabolism and elimination resulting in prolonged toxicity.

PSYCHOSOCIAL APPROACH

Most intoxications presenting to the emergency department result from autointoxication. Therefore, psychosocial factors are significant in the evaluation and treatment of patients with toxicologic emergencies.[68] The acute event of an intoxication offers opportunity to initiate well-coordinated care management with particular attention to continuity and follow-up. Integrated health care systems include formal and informal linkages to community-based health, mental health, substance abuse treatment, and social service agencies, all of which interact with interdisciplinary teams in their management of toxicologic emergencies. Even with the highest levels of clinical and technologic expertise applied in the diagnosis and treatment of poisoned or overdosed patients, successful outcomes may be compromised by inadequacies in aftercare and follow-up. Therefore, it is important to identify and cultivate appropriate referral resources for a wide range of continuing-care services.

Self-poisoning prompts immediate referral for further psychosocial, social, and psychiatric assessment and poses unique problems for clinicians who must make appropriate assessment and management decisions.[68–70] The assessor should at least have received specific training and have access to support from a psychiatrist.[71] Identifying risk factors for suicide can aid clinicians in using preventive or early intervention strategies. Important risk factors for suicidal behavior include past history of suicide attempts, comorbid mental illness, substance intoxication, young age groups, and absence of a social/family support network. Mental status examination for suicidal risk should focus on extrinsic factors, such as current ideation, intent, lethality of the plan, and current life stressors as well as intrinsic vulnerability factors, such as comorbid mental illness, feelings of hopelessness, and impulsivity. Early detection and rapid intervention for patients at risk for suicide are the best means for preventing injury or death.[72]

Appropriate interventions should also be offered to patients with hazardous or harmful alcohol drinking.[73] In general, health care providers tend to have an overly pessimistic view of the benefits of treating alcoholism. This view is not in line with psychosocial interventional strategies, however, which have proved effective.

Optimal psychosocial care of patients with substance abuse is also challenging. A compassionate and nonjudgmental approach is important to gain their confidence and enhance the care rendered. Providing access to programs that support detoxification is essential.

SUMMARY

Patients with altered consciousness and suspected poisoning are a challenge to the clinicians involved in the management of these patients. The approach of these patients should start with stabilization of vital parameters and the judicious use of antidotes. Clinicians should be alert not only for specific clinical signs of acute poisoning but also for other causes of decreased consciousness. They should always be suspicious for associated traumatic injuries in poisoned patients. Thorough knowledge of toxidromes, clinical neurologic examination, decontamination procedures, and toxicologic testing are of major importance in the management of these patients.

Therefore, early consultation between the neurologist and the clinical toxicologist is of utmost importance as is communication with the toxicology laboratory. Attention should be paid to optimal psychosocial support of poisoned patients, especially in autointoxications.

REFERENCES

1. Meehan TJ, Bryant SM, Aks SE. Drugs of abuse: the highs and lows of altered mental states in the emergency department. Emerg Med Clin North Am 2010; 28:663–82.
2. Rao RB. Neurologic principles. In: Nelson LS, Lewin NA, Howland MA, et al, editors. Goldfrank's toxicologic emergencies. 9th edition. New York: McGraw-Hill; 2011. p. 275–84.
3. Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. Ann Emerg Med 2001;37:147–53.
4. De Paepe P, Calle PA, Buylaert WA. Coma induced by intoxication. Handb Clin Neurol 2008;90:175–91.
5. Kostic MA, Dart RC. Coma of unclear etiology. In: Dart RC, editor. Medical toxicology. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 66–8.
6. Chebib M, Johnston GA. The 'ABC' of GABA receptors. A brief review. Clin Exp Pharmacol Physiol 1999;26:937–40.
7. Zhu H, Cottrell JE, Kass IS. The effect of thiopental and propofol on NMDA- and AMPA-mediated glutamate excitotoxicity. Anesthesiology 1997;87:944–51.
8. Wong CG, Chan KF, Gibson KM, et al. Gamma-hydroxybutyric acid: neurobiology and toxicology of a recreational drug. Toxicol Rev 2004;23:3–20.
9. Simons FE, Simons KJ. The pharmacology and use of H1-receptor-antagonist drugs. N Engl J Med 1994;330:1663–70.
10. Parsons M, Buckley NA. Antipsychotic drugs in overdose: practical management guidelines. CNS Drugs 1997;6:427–41.
11. Bateman DN. Tricyclic antidepressant poisoning: central nervous system effects and management. Toxicol Rev 2005;24:181–6.
12. Dhawan BN, Cesselin F, Raghubir R, et al. Classification of opioid receptors. Pharmacol Rev 1996;48:567–92.
13. Gracia R, Shepherd G. Cyanide poisoning and its treatment. Pharmacotherapy 2004;24:1358–65.
14. Smith RP, Gosselin RE. Hydrogen sulfide poisoning. J Occup Med 1979;21:93–7.
15. Jaffe FA. Pathogenicity of carbon monoxide. Am J Forensic Med Pathol 1997;18: 406–10.
16. Advanced Life Support Group. Acute medical emergencies. London: BMJ Books; 2010.
17. Greene SL, Dargan PI, Jones AL. Acute poisoning: understanding 90% of cases in a nutshell. Postgrad Med J 2005;81:204–16.
18. Hack JB, Hoffman RS. General management of poisoned patients. In: Tintinalli JE, Kelen GD, Stapczynski JS, editors. Emergency medicine. A comprehensive study guide. New York: McGraw-Hill; 2004. p. 1015–22.
19. Huff JS. Altered mental status and coma. In: Tintinalli JE, Kelen GD, Stapczynski JS, editors. Emergency medicine. A comprehensive study guide. New York: McGraw-Hill; 2004. p. 1390–7.
20. Koster RW, Baubin MA, Bossaert LL, et al. European Resuscitation Council Guidelines for Resuscitation 2010. Section 2. Adult basic life support and use of automated external defibrillators. Resuscitation 2010;81:1277–92.

21. Deakin CD, Nolan JP, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2010. Section 4. Adult advanced life support. Resuscitation 2010;81:1305–52.
22. Mokhlesi B, Leiken JB, Murray P, et al. Adult toxicology in critical care. Part I: general approach to the intoxicated patient. Chest 2003;123:577–92.
23. Chan B, Gaudry P, Grattan-Smith TM, et al. The use of Glasgow Coma Scale in poisoning. J Emerg Med 1993;11:579–82.
24. Donald C, Duncan R, Thakore S. Predictors of the need for rapid sequence intubation in the poisoned patient with reduced Glasgow coma score. Emerg Med J 2009;26:510–2.
25. Dewitt CR, Waksman JC. Pharmacology, pathophysiology and management of calcium channel blocker and beta-blocker toxicity. Toxicol Rev 2004;23:223–38.
26. Kelly CA, Upex A. Comparison of consciousness level assessment in the poisoned patient using the alert/verbal/painful/unresponsive scale and the Glasgow Coma Scale. Ann Emerg Med 2004;44:108–13.
27. Boyle PJ, Schwartz NS, Shah SD, et al. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 1988;318:1487–92.
28. Tokuda Y, Nakazato N, Stein GH. Pupillary evaluation for differential diagnosis of coma. Postgrad Med J 2003;79:49–51.
29. Olson KR, Pentel PR, Kelley MT. Physical assessment and differential diagnosis of the poisoned patient. Med Toxicol 1987;2:52–81.
30. Cooke JL. Depressed consciousness and coma. In: Marx JA, Hockberger RS, Walls RM, et al, editors. Rosen's emergency medicine. Concepts and clinical practice. St Louis (MO): Mosby; 2010. p. 106–12.
31. Gold AE, Marshall SM. Cortical blindness and cerebral infarction associated with severe hypoglycemia. Diabetes Care 1996;19:1001–3.
32. Pétursson H. The benzodiazepine withdrawal syndrome. Addiction 1994;89: 1455–9.
33. Schuckit MA, Tipp JE, Reich T, et al. The histories of withdrawal convulsions and delirium tremens in 1648 alcohol dependent subjects. Addiction 1995;90:1335–47.
34. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352: 1112–20.
35. Lewin NA, Nelson LS. Dermatologic principles. In: Nelson LS, Lewin NA, Howland MA, et al, editors. Goldfrank's toxicologic emergencies. 9th edition. New York: McGraw-Hill; 2011. p. 410–22.
36. American Academy of Clinical Toxicology, European Association of Poison Centres, Clinical Toxicologists. Position paper: single-dose activated charcoal. Clin Toxicol 2005;43:61–87.
37. Isbister GK, Kumar VV. Indications for single-dose activated charcoal administration. Curr Opin Crit Care 2011;17:351–7.
38. American Academy of Clinical Toxicology, European Association of Poison Centres, Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. Clin Toxicol 1999;37:731–51.
39. American Academy of Clinical Toxicology, European Association of Poison Centres, Clinical Toxicologists. Position paper: gastric lavage. Clin Toxicol 2004;42:933–43.
40. American Academy of Clinical Toxicology, European Association of Poison Centres, Clinical Toxicologists. Position paper: whole bowel irrigation. Clin Toxicol 2004;42:843–54.

41. American Academy of Clinical Toxicology, European Association of Poison Centres, Clinical Toxicologists. Position paper: ipecac syrup. Clin Toxicol 2004; 42:133–43.
42. Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. Clin Toxicol 2004;42:1–26.
43. Cutler RD, Forland SC, Hammond PG. Extracorporeal removal of drugs and poisons by hemodialysis and hemoperfusion. Annu Rev Pharmacol Toxicol 1987;27:169–91.
44. Liebelt EL. Cyclic antidepressants. In: Nelson LS, Lewin NA, Howland MA, et al, editors. Goldfrank's toxicologic emergencies. 9th edition. New York: McGraw-Hill; 2011. p. 1049–59.
45. Rainey PM. Laboratory principles and techniques for evaluation of the poisoned or overdosed patient. In: Nelson LS, Lewin NA, Howland MA, et al, editors. Goldfrank's toxicologic emergencies. 9th edition. New York: McGraw-Hill; 2011. p. 70–89.
46. Wu AH, McKay C, Broussard LA, et al. National academy of clinical biochemistry laboratory medicine practice guidelines: recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem 2003;49:357–79.
47. Hartington K, Hartley J, Clancy M. Measuring plasma paracetamol concentrations in all patients with drug overdoses; development of a clinical decision rule and clinicians willingness to use it. Emerg Med J 2002;19:408–11.
48. Schiodt FV, Rochling FA, Casey DL, et al. Acetaminophen toxicity in an urban county hospital. N Engl J Med 1997;337:1112–7.
49. Yip L, Dart RC, Gabow PA. Concepts and controversies in salicylate toxicity. Emerg Med Clin North Am 1994;12:351–64.
50. Myers RA. Carbon monoxide poisoning. J Emerg Med 1984;1:245–8.
51. Nelson LS, Lewin NA, Howland MA, et al, editors. Goldfrank's toxicologic emergencies. 9th edition. New York: McGraw-Hill; 2011.
52. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness. Controversies in the use of a 'coma cocktail'. JAMA 1995;274:562–9.
53. Clardy P, Manaker S, Perry H. Carbon monoxide poisoning. UpToDate online 19.2; 2011.
54. Phin N. Carbon monoxide poisoning (acute). Clin Evid 2010;10:2103.
55. Buckley NA, Juurlink DN, Isbister G, et al. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev 2011;4:CD002041.
56. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002;347:1057–67.
57. Raphael JC, Elkharrat D, Jars-Guincestre MC, et al. Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. Lancet 1989;19: 414–9.
58. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial. Med J Aust 1999;170:203–10.
59. Annane D, Chadda K, Gajdos P, et al. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. Intensive Care Med 2011;37:486–92.
60. Zubaran C, Fernandes JG, Rodnight R. Wernicke-Korsakoff syndrome. Postgrad Med J 1997;73:27–31.
61. Howland MA, Nelson LS. Antidotes in depth—opioid antagonists. In: Nelson LS, Lewin NA, Howland MA, et al, editors. Goldfrank's toxicologic emergencies. 9th edition. New York: McGraw-Hill; 2011. p. 579–85.

62. Hoffman JR, Schriger DL, Luo JS. The empiric use of naloxone in patients with altered mental status: a reappraisal. Ann Emerg Med 1991;20:246–52.
63. Howland MA. Antidotes in depth—flumazenil. In: Nelson LS, Lewin NA, Howland MA, et al, editors. Goldfrank's toxicologic emergencies. 9th edition. New York: McGraw-Hill; 2011. p. 1072–7.
64. Höjer J, Baehrendtz S, Matell G, et al. Diagnostic utility of flumazenil in coma with suspected poisoning: a double blind, randomised controlled study. BMJ 1990; 301:1308–11.
65. Gueye PN, Hoffman JR, Taboulet P, et al. Empiric use of flumazenil in comatose patients: limited applicability of criteria to define low risk. Ann Emerg Med 1996; 27:730–5.
66. Hoffman RS, Nelson LS, Howland MA. Antidotes in depth. Benzodiazepines. In: Nelson LS, Lewin NA, Howland MA, et al, editors. Goldfrank's toxicologic emergencies. 9th edition. New York: McGraw-Hill; 2011. p. 1109–14.
67. Brett A, Rothchild N, Gray R, et al. Predicting the clinical course in intentional drug overdose: implications for use of the intensive care unit. Arch Intern Med 1987;147:133–7.
68. National Institute for Health, Clinical Excellence. Self-harm. The short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care. London: NICE; 2004.
69. Hawton K, Arensman E, Townsend E, et al. Deliberate self harm: systematic review of efficacy of psychosocial and pharmacological treatments in preventing repetition. BMJ 1998;317:441–7.
70. Sinclair J, Green J. Understanding resolution of deliberate self harm: qualitative interview study of patients' experiences. BMJ 2005;330:1112–5.
71. Skegg K. Self-harm. Lancet 2005;366:1471–83.
72. Gunnell D, Ho D, Murray V. Medical management of deliberate drug overdose: a neglected area for suicide prevention? Emerg Med J 2004;21:35–8.
73. Ritson B. Treatment for alcohol related problems. BMJ 2005;330:139–41.