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Toxicology

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Toxicology

Abstract

Introduction Poisoning is one of the commonest medical emergencies in the UK and accounts for 10%-20% of acute medical admissions. The most common causes of poisoning in the UK are outlined in Table 13.1. Assessing poisoned patients and managing them is an exciting challenge because they often have complex psychosocial issues, together with general medical problems, and have taken toxins in sizeable doses. They require the best of clinical skills to provide the best outcome. Sadly, poisoned patients do not always meet with the sympathies of admitting doctors because th? ~ay be perceived to have "self-inflicted illness." This is a morally unacceptable view. Self-poisoned patients are most likely to respond to a pragmatlc, non-judgemental approach. Often an overdose is taken at a time of stress, .e.g. due to exams or relationship difficulties. Patients often need a helpful ear, supportive medical care, and follow-up support. Some may need ongoing psychiatric evaluation and support. Some patients, such as those who have taken paracetamol, may need treatment with an antidote. However, in general, the antidotes in toxicology are few (Table 13.2.) and the outcome depends on the ability of the clinincian to deliver meticulous supportive care.

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Chapter 13 Toxicology

Alison Jones

Contents

Introduction

Poisoning is one of the commonest medical emergencies in the UK and accounts for 10%–20% of acute medical admissions. The most common causes of poisoning in the UK are outlined in Table 13.1. Assessing poisoned patients and managing them is an exciting challenge because they often have complex psychosocial issues, together with general medical problems, and have taken toxins in sizeable doses. They require the best of clinical skills to provide the best outcome. Sadly, poisoned patients do not always meet with the sympathies of admitting doctors because they may be perceived to have "self-inflicted illness." This is a morally unacceptable view. Self-poisoned patients are most likely to respond to a pragmatic, non-judgmental approach. Often an overdose is taken at a time of stress, e.g. due to exams or relationship difficulties. Patients often need a helpful ear, supportive medical care, and follow-up support. Some may need on-going psychiatric evaluation and support. Some patients, such as those who have taken paracetamol, may need treatment with an antidote. However, in general, the antidotes in toxicology are few (Table 13.2) and the outcome depends on the ability of the clinician to deliver meticulous supportive care.

How to identify a poisoned patient

Clues that alert us to a toxic exposure having occurred include the following.

- Patient may admit to having taken an overdose.
- Patient may be distressed or tearful.
- Overdose is commoner in younger patients, slightly more common in women than men, but may be of more serious suicidal intent in the elderly.
- Past or current history of depression or other psychiatric diagnoses.
- Past history of overdose or self-harm.
- Past history of personal abuse e.g. victim of sexual abuse as a child.
- Underlying alcohol problem.
- Social problems, e.g. lack of housing, relationship difficulties, social isolation, etc.
- Overdose is more common in lower socioeconomic classes and where there is deprivation.
- Needle marks on arms (men), groins (often women) indicating an injection habit.
- Admission from the workplace (occupational exposure).
- The family or ambulance staff may have brought the patient in with empty packets of drugs.

Assessing a poisoned patient

Substances involved in poisoning vary widely between different countries. The important five for the UK are listed in Table 13.1. In assessing poisoned patients it is important to take a good history and perform a meticulous physical examination. Clinical features of poisoning that identify which toxin may have been taken in a non-comatose patient are shown in Fig. 13.1. How to confirm this diagnosis is then shown in Table 13.3.

When patients are unconscious and no history is available, the diagnosis of the substance causing the poisoning depends on exclusion of other causes of coma and consideration of circumstantial evidence. Figure 13.2 shows how to look out for diagnostic clues. In assessing comatose patients it is vital to remember that other medical causes of coma need to be excluded (see Table 13.4).

Table 13.1. The most common causes of poisoning in the UK

Analgesic drugs, including acetaminophen and non-steroidal anti-inflammatory drugs – these account for half of all poisoning cases
Cardiovascular toxic drugs, especially tricyclic antidepressants – approximately 10% of cases of poisoning
Drugs of misuse
Carbon monoxide – the commonest cause of death by poisoning
Alcohol – the co-ingestant in 50% of cases of self-poisoning

Table 13.2. Common antidotes available for treatment of poisoning

Poison	Antidote
Acetaminophen	*N*-acetylcysteine
Carbon monoxide	Oxygen, hyperbaric oxygen
Tricyclic antidepressants	Sodium bicarbonate
Cyanide	Nitrites, hydroxocobalamin, sodium thiosulphate
Opioids, e.g. heroin, morphine	Naloxone
Iron	Desferrioxamine, deferoxamine
Digoxin	Fab fragments (digibind®)

General management of the poisoned patient

Most require little more than symptomatic and supportive care. First remember to assess:

- Airway
- Breathing
- Circulation

The principles of preventing absorption or enhancing elimination (Table 13.5) depend on to what the patient has been exposed, by what route and how long ago and whether that substance binds to charcoal or not (Table 13.6). Antidotes are few (Table 13.2) but can be life saving. To assess the degree of suicidal intent, prior to formal psychiatric evaluation of the patient, the Beck's depression scale is commonly used (Table 13.7). If the score exceeds 4, the patient requires special nursing to protect against self-harm.

Indications for intubation and assisted ventilation are:

- Glasgow Coma Scale <8, or falling rapidly
- Post-cardio-respiratory arrest
- Recurrent seizures
- Hypoxia – not corrected with oxygen mask and high flow oxygen therapy
- Hypercarbia – p_{CO_2} >6.6 kPa or hypocarbia p_{CO_2} <2.5 kPa
- Inability to protect airway
- Shock, i.e. tachycardia, hypotension, metabolic acidosis.

Optimizing the cardiac output and blood pressure means maintenance of oxygen delivery as well as maintenance of adequate organ perfusion and blood pressure. Hypotension usually responds to filling with IV fluids, then treatment of any cardiac arrhythmia with an inotrope or vasoconstrictor if required. Epinephrine (adrenaline) increases the heart rate and stroke volume. At low doses, the primary effect is to increase cardiac output, while at higher doses there is additional potent vasoconstriction. If, despite adequate filling, the blood pressure remains low then vasoconstrictors should be used, e.g. norepinephrine. This has no effect on cardiac output, but is useful in generating perfusion of the brain, liver, and kidneys. However, it should be used at the lowest possible dose to achieve the desired effect as it reduces renal blood flow, splanchnic blood flow, and impairs peripheral perfusion.

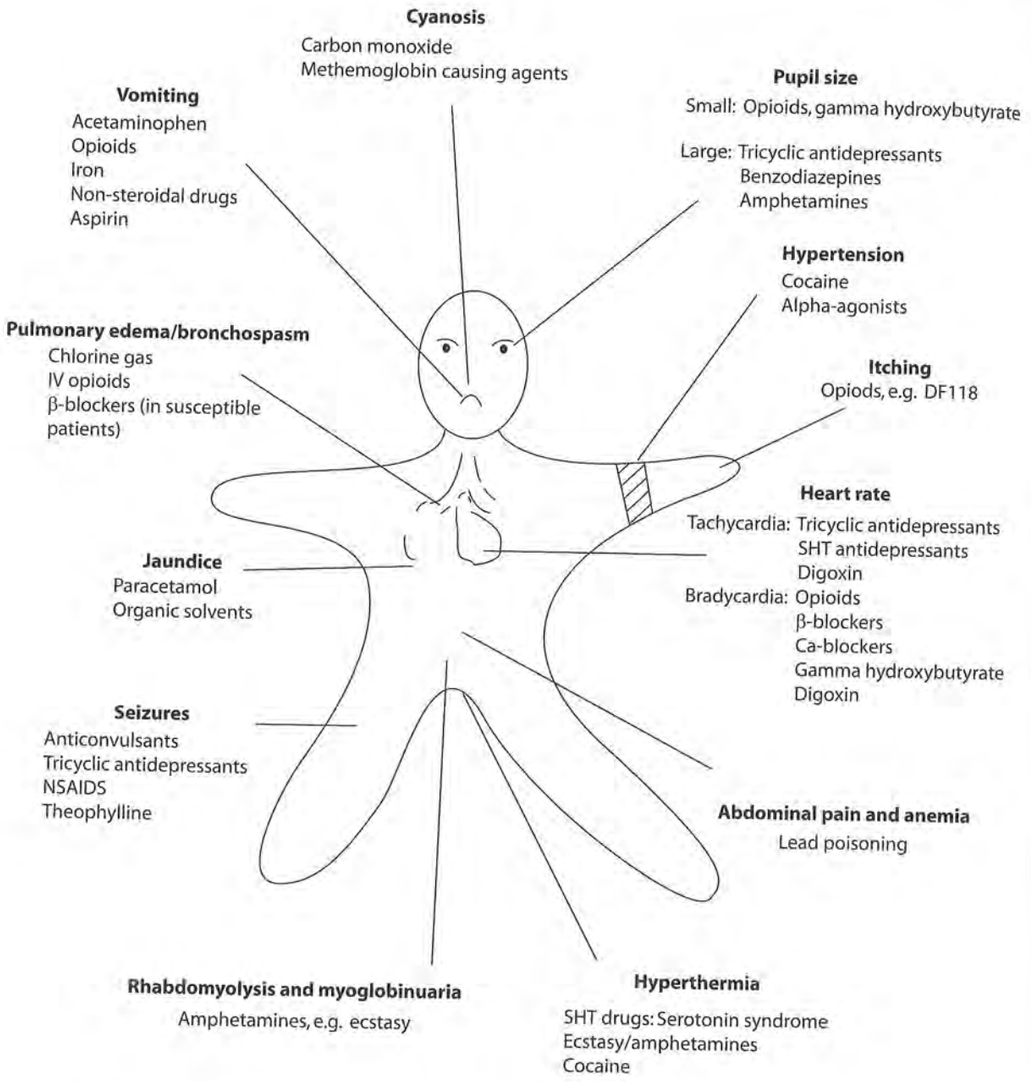
Complications of poisoning and their management

Vomiting

If vomiting fails to respond to simple measures such as sucking ice cubes, metoclopramide 10 mg i.v. or ondansetron 8 mg i.v. by slow injection may be particularly effective, the latter especially in paracetamol or theophylline poisoning.

Agitation

Talk to the patient calmly, and before sedating a patient exclude possible causes of agitation such as hypoglycemia, full bladder, pain, hypoxia. Give diazepam (0.1–0.2 mg/kg) IV, repeated as necessary.



Notes

(1) In mixed overdoses the diagnostic features may become blurred.
(2) In early Acetaminophen poisoning there may be no clinical signs of poisoning.

Fig. 13.1. Diagnostic clues to the poison taken in patients who are not/not yet comatose.

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Table 13.3. Diagnostic tests to confirm the toxin in Fig. 13.1

Possible toxin diagnosis from Fig. 13.1	Associated features	Confirmatory investigation
Acetaminophen	Right upper quadrant tenderness, vomiting, renal angle tenderness	Plasma acetaminophen concentration. If jaundice/ history of ingestion more than 12 hours ago then also do LFTs and PTR or INR
Anticonvulsants	Ataxia, nystagmus, dysarthria, hyponatraemia, heart block	Plasma levels of drug e.g. carbamazepine used for confirmation but there is poor correlation between level and degree of toxicity
Agents causing methemoglobinemia	History of use of "poppers" (amyl nitrite), medication with dapsone	Blood methemoglobin concentration
Tricyclic antidepressants	Cardiac rhythm disturbance, hot dry skin, hypotension, urine retention	ECG shows tachycardia and may show QRS prolongation (>140 ms)
5HT antidepressants	Sometimes may be accompanied by serotonin syndrome characterized by rigidity, hyperthermia, and autonomic instability	ECG shows tachycardia, no QRS prolongation
Drugs of abuse	Agitation/sedation, conjunctival injection with cannabis, cardiac pain/vascular complications	Urine dip test qualitatively confirms presence of amphetamines, benzodiazepines, cannabis, cocaine, or opioids. For legal purposes confirmation by HPLC is needed
Aspirin (salicylate)	Tinnitus, sweating, purpura, respiratory alkalosis, metabolic acidosis	Plasma salicylate concentration
Opioids	Coma, respiratory depression, pin-point pupils	The best diagnostic test is administration of the antidote, naloxone
Lead	Blue line on gums, abdominal pain, anemia	Serum lead concentration, blood film may show basophilic stippling
Carbon monoxide	History of house fire, high serum lactate	COHb – this is good for confirmation but there is poor correlation between level and degree of toxicity
Iron	Metabolic acidosis, vomiting, hepatic injury, rusty colored urine	Serum concentration of iron, abdominal X-ray may reveal radio-opaque iron tablets
Digoxin	Heart block, malignant arrhythmias, reduced cardiac output	Serum digoxin concentration, ECG

Note:
There are no readiliy available diagnostic tests for NSAIDs, gammahydroxybutyrate, beta-blockers, or calcium channel blockers.

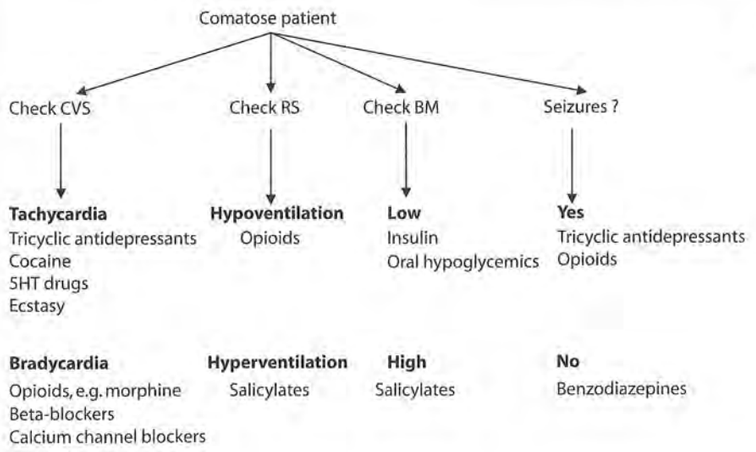

Fig. 13.2. Diagnostic clues to the poison taken in patients who present comatose.

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Table 13.4. Differential diagnosis of common causes of coma

Likely diagnosis		Associated features	Investigations of choice to confirm
Drug overdose	(1) Tricyclic antidepressants	(1) tachycardia, fits, hypotension, warm dry skin, urine retention	(1) ECG – tachycardia and may show QRS prolongation (>140 ms)
	(2) 5HT drugs	(2) serotonergic features – rigidity, autonomic instability, hyperthermia	(2) ECG – tachycardia
	(3) Opioids	(3) pin-point pupils, respiratory depression, coma	(3) Response to naloxone
	(4) Toxic alcohols	(4) profound metabolic acidosis, anion/osmolar gaps	(4) Methanol/ethylene glycol blood concentration
	(5) Hypoglycemic agents and insulin	(5) history of diabetes	(5) Blood glucose
	(6) Benzodiazepines	(6) nil	(6) nil
	(7) Carbon monoxide	(7) evidence of exposure to CO/fire	(7) COHb level in blood
CNS causes	Cerebral contusion	Trauma history	CT head scan, preferably with contrast
	Extradural hematoma	May have focal neurologic signs, trauma history	CT head scan, preferably with contrast
	Subdural hematoma	May have focal neurologic signs	CT head scan, preferably with contrast
	Cerebral infarction or hemorrhage	May have focal neurologic signs	CT head scan, preferably with contrast
	Subarachnoid hemorrhage	May have focal neurologic signs, neck stiffness, photophobia, may have "hit on head with a hammer" history	CT head scan, preferably with contrast and lumbar puncture
	Brainstem infarction/hemorrhage	May have focal neurologic signs	MRI head scan
	Cerebral venous sinus thrombosis	May have focal neurologic signs	CT head scan, preferably with contrast
	Meningitis	Neck stiffness, photophobia, characteristic meningococcal rash	CT and lumbar puncture
	Encephalitis	History of "cold sores" or other viral illness	CT and lumbar puncture, and EEG
	Cerebral abscess	May have history of trauma to the skull, patient may have focal neurologic signs, neck stiffness, other stigmata of infection	CT head scan, preferably with contrast
	Brain tumor	May have history of severe headaches, worse in the morning, focal neurologic signs	CT head scan, preferably with contrast
	Epilepsy (especially post-ictal)	History of epilepsy	CT head scan and EEG
Diabetes	Diabetes mellitus	Hypoglycemia, ketoacidosis, hyperosmolar coma	Blood glucose concentration, arterial blood gases, urea and Electrolytes
Uremia		Often pre-existing history of renal disease or recent exposure to a nephrotoxic drug	Urea and electrolytes, ECG may show tall tented T waves of concurrent hyperkalemia
Hypothermia		Shivering, ECG change (J waves) – history suggestive of lying around for many hours or immersion in cold water etc.	Rectal temperature
Others	Hypothyroidism	May be concurrent goiter, a history of other autoimmune diseases, patient often >40 years of age	Thyroid function tests, thyroid autoantibody tests
	Hyponatremia	Often concurrent hypokalemia	Serum and urine osmolality, urea and electrolytes
	Hepatic failure due to viral agents	Jaundice, renal dysfunction, clotting abnormalities	Liver function tests, ABGs, PTR, hepatitis A,B,C serology, CMV, toxoplasma

Table 13.5. Principles of preventing absorption or enhancing elimination of toxins

Route of exposure	Preventing absorption	Enhanced elimination
Skin	Remove clothing, wash copiously with soap and water	–
Eye	Irrigate with saline for at least 20 minutes, examine under slit lamp for corneal injury	–
Ingestion	If a life-threatening amount of a toxin has been taken within the last hour, consider gastric lavage	If a toxin has a low volume of distribution and low protein binding, it may be effectively cleared by hemodialysis, e.g. salicylates
	If a significant overdose has been taken within the last hour and the substance binds to activated charcoal (AC), give 50 g AC orally. If carbamazepine, dapsone, phenobarbitone, quinine, or theophylline has been taken, give 50 g charcoal every 4 hours with sorbitol/lactulose, i.e. multiple dose activated charcoal	If a toxin binds avidly to charcoal, it may be removed by charcoal hemoperfusion, e.g. carbamazepine
	If a large ingestion of iron, lithium, packets of drugs, or SR preparations such as verapamil or theophylline have been taken, consider whole bowel irrigation with polyethylene glycol	If a toxin is highly protein bound, it may be cleared effectively by MARS (albumin dialysis system)
Inoculation	Local excision and debridement if high pressure injury in a digit	If the toxin is a weak acid, its renal elimination is enhanced by alkaline diuresis, e.g. salicylates
Inhalation	Oxygen – nebulized bronchodilators if wheeze	

Table 13.6. Substances not bound by activated charcoal

- Acids
- Alkalis
- Metals and metallic salts, e.g. Hg and mercuric chloride, lithium
- Toxic alcohols, e.g. methanol, ethylene glycol
- Cyanide

Dystonias

These are common after overdoses with antipsychotic drugs and some anti-emetics. Oculogyric crises, torticollis (wry neck), trismus (jaw clenching) respond to procyclidine (5–10 mg IV) or benztropine (1–2 mg IV).

Seizures

These are common after poisoning with a wide variety of agents. A non-sustained fit does not require pharmacologic intervention. However, persistent (>5 min) and recurrent seizures require treatment. The drug of choice is diazepam (0.1–0.2 mg/kg) repeated as required. If seizures are persistent or recurrent despite adequate doses of benzodiazepines, IV phenytoin should be used (15 mg/kg). Status epilepticus requires paralysis and ventilation with EEG monitoring.

Rhabdomyolysis

Patients with rhabdomyolysis (muscle necrosis) as evidenced by a positive urine dipstick test for blood (cross-reacts with hemoglobin or myoglobin) and a raised serum creatine kinase, should be kept well hydrated with IV fluids to limit the risk of acute renal failure. For severe rhabdomyolysis (serum creatine kinase > several thousands), urinary alkalinization may be considered.

Serotonin syndrome

This is characterized by agitation, hyperreflexia, hypertonia, sweating, tachycardia, and hyperpyrexia. It should be treated by withdrawal of the offending drug, diazepam, application of cooling measures. Rarely, cyproheptadine may be required.

Specific toxins

Acetaminophen

Acetaminophen is frequently taken in overdose, often with another drug or alcohol. After a latent phase, clinical features of poisoning emerge unless the antidote *N*-acetylcysteine has been given within 12 hours of the overdose.

Clinical features

The clinical features include nausea, vomiting, and jaundice. There may be right upper quadrant tenderness from hepatic injury and hepatic failure may occur. More rarely, renal failure may occur.

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Table 13.7. Beck's depression scale

Parameter	Scoring	Beck's score (add up all those relevant below)
0	Isolation	Someone present
1		Someone nearby or in vocal contact
2		No-one nearby in visual/vocal contact
0	Timing	Intervention probable
1		Intervention not likely
2		Intervention highly unlikely
0	Precautions against discovery	None
1		Passive precautions (avoiding others)
2		Active precautions, e.g. locking door
0	Acting to gain help after the attempt	Notified potential helper regarding the attempt
1		Contacted but did not specifically notify helper regarding the attempt
2		Did not contact or notify helper
0	Final acts in the anticipation of death	None
1		Thought about or made some arrangement
2		Definite plans made, e.g. changing will
0	Active preparation for attempt	None
1		Minimal
2		Extensive
0	Suicide note	None
1		None written, written but torn up or thought about
2		Note present
0	Overt communication of intent before attempt	None
1		Equivocal communication
2		Unequivocal communication

Note:
If the sum of all the scores for each parameter is greater than 4, it indicates significant suicidal intent.

Epidemiology

Acetaminophen poisoning is the commonest cause of poisoning in the UK, accounting for up to half of all overdoses. Between 100 and 150 patients die in the UK each year as a result of hepatic injury from acetaminophen.

Pathology

Acetaminophen is converted to the toxic metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which causes hepatic injury (centrilobular necrosis) once protective intracellular glutathione is depleted. If the patient is taking enzyme-inducing agents, more NAPQI is produced, or if they are glutathione depleted (e.g. anorexia), they are at greater risk from acetaminophen. The toxic dose is 150 mg/kg body weight (75 mg/kg for "at-risk" groups).

Investigations

Patients presenting with acetaminophen overdose, or an overdose of white tablets, should have a acetaminophen blood concentration checked. Those presenting late (>15 hours since ingestion) need to have liver function tests, prothrombin time (PTR) or INR, urea and electrolytes, creatinine, and arterial blood gases checked.

Management

The management of a patient with acetaminophen overdose is summarized in Fig. 13.3. If a patient presents within 1 hour of the acetaminophen overdose, activated charcoal can be given in addition to the management shown in the figure. The antidote of choice, *N*-acetylcysteine, provides complete protection against toxicity if given within 10 hours of the overdose; its

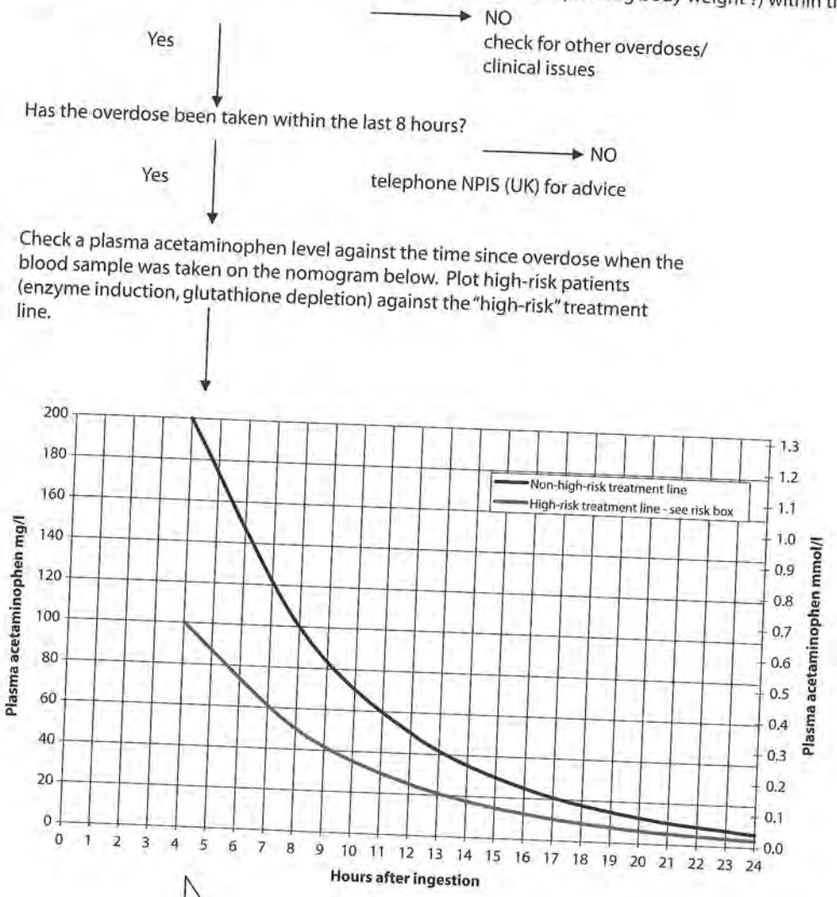

Fig. 13.3. Algorithm for managing an acetaminophen overdose.

efficacy declines thereafter. If a patient presents more than 8 hours after ingestion, *N*-acetylcysteine administration should not be delayed to wait for the result of the acetaminophen blood concentration result but started immediately and the National Poisons Information Service phoned for advice (UK) (see references for the number). Liver transplantation should be considered in individuals who develop acute liver failure due to late acetaminophen poisoning.

If multiple ingestions of acetaminophen have taken place over several hours or days (i.e. a staggered overdose), there is no merit in measuring the plasma acetaminophen concentration as it will be uninterpretable. Such patients should be given *N*-acetylcysteine if the acetaminophen dose exceeds 150 mg/kg body weight in any one 24-hour period, or 75 mg/kg body weight in "high-risk groups."

Outcome

Patients presenting within 10 hours of the overdose who receive the full treatment with IV *N*-acetylcysteine over 20 ¼ hours have complete recovery and can be discharged at the end of the infusion, without further tests, provided any vomiting has settled and there is no abdominal/renal angle tenderness. Patients who present later than this have increasing risk of hepatic injury and developing fulminant hepatic failure. Some survive with ITU level care, but liver transplantation is the preferred option if a suitable donor organ is available.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Mefenamic acid and ibuprofen overdose account for approximately 10% of all overdoses in the UK.

Clinical features

Most overdoses have little more than mild gastro-intestinal upset including mild abdominal pain. Vomiting and diarrhea may occur. Of patients taking a NSAID overdose (particularly mefenamic acid), 10%–20% may have fits, which are usually self-limiting. Renal failure can occur. Acidosis may occur with large ingestions. Drowsiness, lethargy, ataxia, nystagmus, blurred vision, and tachycardia may rarely occur. Serious features including coma, prolonged fits, apnea, and bradycardia are very rare. Deaths have occurred.

Epidemiology

Ingestion is particularly common among young women.

Pathology

Gastro-intestinal effects and renal effects are due to the inhibition of cyclo-oxygenase.

Investigations

Although NSAID concentrations in plasma can be measured, the half-life of the drugs in overdose is so short that it is of no clinical value to measure this. Liver and renal function tests and a full blood count should be checked in large ingestions (>10 tablets) or where there is any clinical concern.

Management

Give 50 g of activated charcoal if >100 mg/kg body weight of ibuprofen or more than 10 tablets of other NSAIDS have been taken in the last hour. Maintain the airway and assist ventilation if necessary. Treat non-self-limiting seizures with diazepam i.v. (0.1–0.2 mg/kg). Oral proton pump inhibitors such as omeprazole may ease symptoms of gastro-intestinal irritation.

Outcome

Most patients do very well and can be discharged within 12 hours. Those with complications need to be admitted for longer than this.

Tricyclic antidepressants

Tricyclic antidepressants such as amitriptyline, imipramine, and dothiepin are still commonly prescribed to depressed patients and are very toxic in overdose, deaths occurring from CVS and CNS features of the drug. Management of tricyclic antidepressant overdose is a good example of meticulous supportive care determining outcome.

Clinical features

Ingestion of more than 10 mg/kg body weight is likely to cause significant toxicity. Features include anticholinergic effects (warm, dry skin, tachycardia, blurred vision, dilated pupils, urine retention, and depressed respiration and level of consciousness), seizures, and arrhythmias. Features of severe poisoning include coma, cardiac arrhythmia, fits, and hypotension due to myocardial depression (Fig. 13.4). ECG abnormalities are common in moderate to severe poisoning, particularly prolongation of the QRS interval. Supra- and ventricular arrhythmias occur and may be the cause of sudden death. Death can occur within a few hours of admission and may result from ventricular fibrillation, intractable cardiogenic shock, or recurrent seizures.

Epidemiology

Tricyclic antidepressant overdose is the second most common overdose in the UK. It is the commonest cause of death in patients who have taken an overdose but reach hospital alive. Those most likely to present are those for whom the drug has been prescribed to treat depression.

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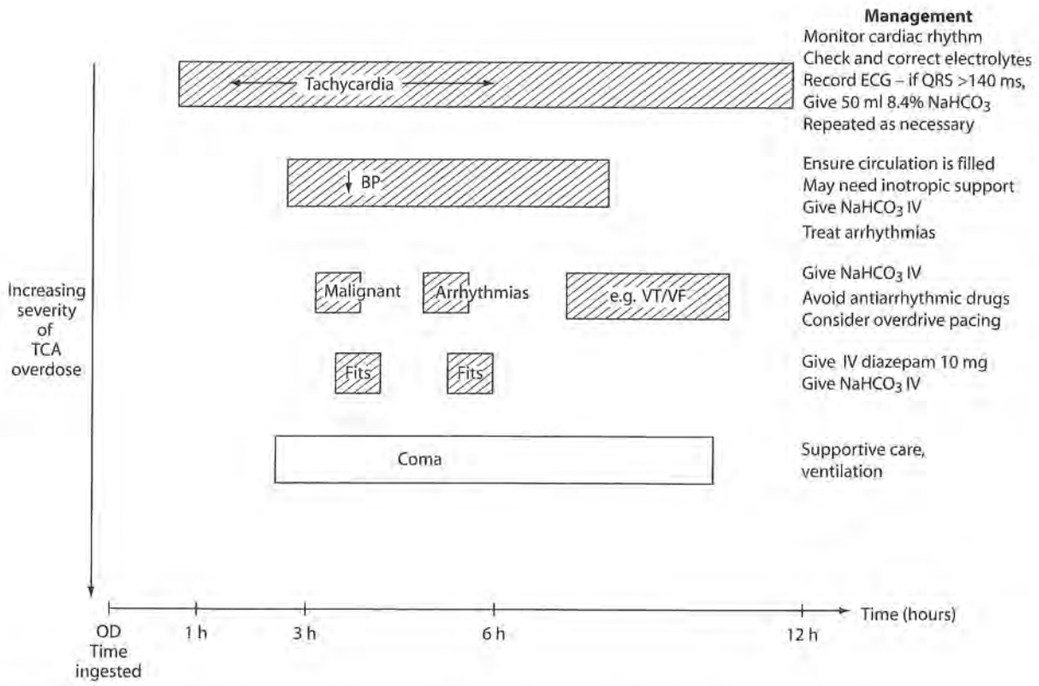

Fig. 13.4. Typical time course, severity, and management of tricyclic antidepressant overdosage.

Pathology
Toxicity is due to the anticholinergic features of the drug, together with alpha-adrenergic effects and direct myocardial depression.

Investigations
Measurement of the plasma level of a tricyclic antidepressant is not helpful in the management of an overdose. An ECG should be performed in all but the most trivial overdose. A QRS interval of >140 ms carries an increased risk of arrhythmias and fits. Arterial blood gas analysis should be performed in patients with marked symptoms and particularly in those with seizures, coma, or a widened QRS complex on ECG.

Management
Maintenance of the airway, breathing, and circulation is critical. Activated charcoal should be given if the patient has ingested more than 10 mg/kg within the last hour.

Cardiac monitoring is essential if significant ingestion (more than five tablets) has taken place and is seldom needed beyond 24 hours post-ingestion. All anti-arrhythmic drugs are arrhythmogenic and should be avoided if possible because the patient already has potential cardiotoxicity from the tricyclic antidepressant.

Sodium bicarbonate (50 ml of 8.4% IV) should be given to all patients with QRS prolongation, arrhythmias, or hypotension (Fig. 13.4). Give repeated doses by bolus, aiming to keep the pH between 7.45 and 7.55. If multiple arrhythmias occur a transvenous pacing wire is required (Fig. 13.4). If ventricular tachycardia occurs and a pacing wire is not *in situ*, give 50–100 ml of 8.4% sodium bicarbonate IV and then lignocaine 100 mg IV.

Outcome
The elderly and those with pre-existing heart disease are at greater risk of toxicity.

5HT drugs or selective serotonin re-uptake inhibitors (SSRIs)
Antidepressant drugs such as fluoxetine, citalopram, and venlafaxine are commonly taken in overdose. They do not have the anticholinergic actions of the tricyclic antidepressants and are thus much less cardiotoxic. In many countries, tricyclic antidepressants are being replaced with the less cardiotoxic selective serotonin re-uptake inhibitors (SSRIs). However, in large doses SSRIs can still cause toxicity.

Clinical features
Drowsiness and sinus tachycardia are the most common effects in overdose, but the extent is much less than in tricyclic antidepressant poisoning. Nausea and diarrhea are common. Seizures can occur, but are more common in venlafaxine overdose. Dizziness, tremor, agitation, bradycardia, and hypertension have been reported. The serotonin syndrome may be caused by the administration of two or more drugs that increase serotonin concentrations in the CNS or by overdose of any drug with serotonergic activity.

Epidemiology
Commonly taken in overdose, especially amongst those who have received prescriptions for the drugs.

Pathology
They act by increasing serotonin (5HT) within the CNS.

Investigations
None, unless level of consciousness is significantly impaired, e.g. Glasgow Coma Scale (GCS) <8.

Management
Supportive and symptomatic measures are required. Give 50 g activated charcoal if an adult has ingested more than 10 tablets within the last 1 hour. Observe for 6 hours. Rarely coma, hypotension, and fits will require treatment.

Outcome
5HT antidepressants cause fewer deaths in overdose than tricyclic antidepressants.

Drugs of abuse
Cannabis
The term "cannabis" refers to all psychoactive substances derived from the dried leaves and flowers of the plant *Cannabis sativa*. Marijuana refers to any part of the plant used to induce effects, and hashish is the dried resin from the flower tops.

Clinical features
When smoked, onset of relaxation and "well-being" occurs within 10–30 minutes; after ingestion the onset is 1–3 hours. The duration of effect is 4–8 hours. Low doses produce euphoria, perceptual alteration, and conjunctival injection, followed by relaxation and drowsiness, hypertension, tachycardia, slurred speech, and ataxia. High doses produce acute paranoid psychosis, anxiety, confusion, hallucinations, and distortion of time and space. Intravenous misuse of the crude extract of cannabis may cause nausea and vomiting, diarrhea, abdominal pain, fever, hypotension, pulmonary edema, acute renal failure, disseminated intravascular coagulation, and death. Psychologic dependence is common but tolerance and withdrawal symptoms are unusual.

Epidemiology
Cannabis is often smoked with tobacco and is very widely used.

Pathology
Cannabis has an active metabolite, delta-9 tetrahydrocannabinoid (Δ9THC), which is responsible for its CNS depressant effect.

Investigations
Most patients have only mild symptoms. Unless severe systemic effects are present, no investigations are needed. Cannabinoid metabolites may be detected in the urine for several days after acute exposure, but urine levels do not correlate with the degree of toxicity.

Management
For patients with drug-induced psychosis, reassurance is usually sufficient but diazepam may be used for sedation. Hypotension usually responds well to intravenous fluids. All patients who have injected cannabis should be admitted, and careful management of fluid and electrolyte balance is essential, owing to the risks of acute renal failure and pulmonary edema, which are managed conventionally.

Outcome
Serious poisoning resulting from ingestion or smoking of cannabis is extremely rare. A few deaths occur either in combination with other drugs or from IV preparations. Most patients with cannabis toxicity do not present to a medical service.

Benzodiazepines
Benzodiazepine (diazepam, clonazepam, temazepam) dependence tends to result from over-prescription. Polydrug abusers also commonly misuse these drugs.

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Clinical features

Drowsiness and mid-position or dilated pupils are common and occur within 3 hours of ingestion. Ataxia, dysarthria, nystagmus, and confusion are also observed. Coma may follow, but in lone benzodiazepine overdose a GCS grade below 10 is very rare. Minor hypotension and respiratory depression may occur. Respiratory arrest is uncommon but can occur after shorter-acting agents such as midazolam.

Epidemiology

Benzodiazepines are taken alone or in combination with other agents in approximately 10% of overdose cases in the UK. Deaths occur only when they are taken with other drugs or alcohol, or if taken by a susceptible population such as the elderly or by patients with respiratory failure.

Pathology

Benzodiazepines bind at a site close to the GABA receptor in the CNS. The depressant effect on the CNS may impair respiration and induce coma.

Investigations

Benzodiazepines in the blood are hardly ever measured. There is a qualitative urine test, which tests for benzodiazepines, but again this is rarely used.

Management

Gastric lavage is not advised in pure benzodiazepine overdose. Activated charcoal, if required, can be given within 1 hour of the overdose, particularly in a mixed overdose. Impaired consciousness is treated conventionally, with particular attention to maintenance of the airway. Observation should be for at least 6 hours after ingestion of the drug, or for 24 hours in more serious cases. Oxygen saturation monitoring using a pulse oximeter is useful for ascertaining the adequacy of ventilation. Flumazenil is a specific benzodiazepine antagonist, but it is not used in the vast majority of cases of poisoning with benzodiazepines. Flumazenil must never be used in patients with a history of convulsions or toxin-induced cardiotoxicity, or in those who have co-ingested tricyclic antidepressants. In such circumstances, seizures and ventricular arrhythmias can be precipitated.

Outcome

In general, lone benzodiazepine overdoses are remarkably safe and near-full recovery takes place within 24 hours. Difficulties occur when other CNS depressants, such as tricyclic antidepressants, opioids, or alcohol, are taken in addition or when an overdose occurs in susceptible groups such as the elderly or those with chronic obstructive pulmonary disease.

Cocaine/crack cocaine

Cocaine (hydrochloride) is usually purchased as a white powder or as colorless crystals and may be sniffed or snorted using a tube into the nose, from which it is rapidly absorbed, or injected intravenously. "Crack" is cocaine that has been separated from its hydrochloride base (free-base), melted, and smoked in a pipe or mixed with tobacco in a cigarette to give a rapid onset of effect similar to intravenous use. Crack is usually sold in "rocks" containing 150 mg of cocaine or as a "line" of cocaine for snorting that contains 20–30 mg of the drug.

Clinical features

After intranasal use, the effects occur within minutes and last 20–90 minutes. Following intravenous use or oral use, the peak "high" occurs within 10 and 45–90 minutes, respectively, and after smoking crack, a peak "high" occurs within 10 minutes. In most cases the effects begin to resolve in about 20 minutes, except when taken intranasally. In fatal poisoning, the onset and progression of symptoms are accelerated and death may occur in minutes. Survival beyond 3 hours indicates that the patient is unlikely to die.

Mild to moderate intoxication with cocaine causes euphoria, agitation, aggression, cerebellar signs, dilated pupils, vomiting, pallor, headache, cold sweats, twitching, pyrexia, tachycardia, hallucinations, and hypertension. Features of severe intoxication are shown in Fig. 13.5. A toxic psychosis occurs with high levels of consumption, and tactile hallucinations (formication) may be prominent.

Epidemiology

One should consider cocaine toxicity in young healthy adults who present with symptoms of ischemic heart disease. It is no longer the pastime of the city rich but can occur in any rural or urban population.

Pathology

Cocaine has alpha activity, which causes profound hypertension. It causes vasospasm which may result in myocardial ischemia or infarction.

Investigations

Patients with features suggestive of cocaine intoxication must have their blood pressure measured early and frequently, and an ECG performed (Fig. 13.5). Those with chest pain should be investigated appropriately

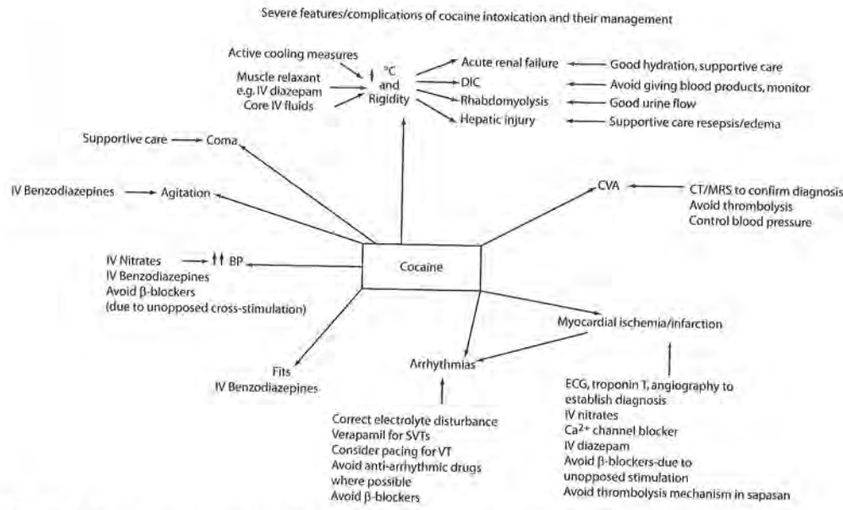

Fig. 13.5. Severe features/complications of cocaine intoxication and their management

(Fig. 13.5). Cocaine can be detected in the urine by simple drug abuse screening tests.

Management

50 g activated charcoal should be given orally to any patient presenting within 1 hour of oral ingestion, irrespective of the amount taken. All patients should be observed with ECG monitoring for a minimum of 2 hours. ECG changes can, however, be misleading in cocaine toxicity. Blood pressure, heart rate, and body temperature should also be monitored and the patient observed carefully for the development of specific complications, which should be managed as shown in Fig. 13.5.

Outcome

The toxic dose is variable and depends on individual tolerance, the presence of other drugs and the route of administration. Ingestion of any amount over 1 g is potentially fatal.

MDMA (ecstasy)

MDMA (3,4-methylenedioxymethamphetamine, ecstasy) is a "designer" amphetamine also known as E, Adam, white dove, white burger, or red and black. It is commonly taken at dance parties because it produces feelings of euphoria and emotional intimacy, together with distorted sensations. Amphetamines and the newer designer amphetamines are virtually indistinguishable in their clinical effects. There is no evidence that they are addictive.

Clinical features

Effects occur within 1 hour of ingestion and last 4–6 hours following doses of 75–150 mg but up to 48 hours after the ingestion of 100–300 mg. However, tolerance is common, and most regular users need to take considerably higher doses. Agitation or drowsiness is also common. The majority of patients who have taken ecstasy become profoundly dehydrated, but a small proportion develop hyponatremia, usually through drinking excessive amounts of water in the absence of sufficient exertion to sweat off the fluid. Antidiuretic hormone secretion may also contribute to the development of hyponatremia. Other features of intoxication with amphetamines or ecstasy include nausea, hyperreflexia, muscle pain, trismus (jaw-clenching), dilated pupils, blurred vision, sweating, dry mouth, agitation, visual hallucinations, paranoid psychosis, and anxiety. Severe intoxication is characterized by the same features as cocaine toxicity (Fig. 13.5) with perhaps less propensity for myocardial ischaemia. A serotonin-like syndrome can also be caused by ecstasy.

Epidemiology

Use of ecstasy and other amphetamines remains common in the UK. Only a small proportion of users develop problems with the drug, perhaps due to dehydration, hyperthermia, or some sort of genetic susceptibility such as a metabolic myopathy.

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Pathology
Ecstasy and other amphetamines cause serotonergic neurons in the CNS to release 5HT.

Investigations
It is important to measure serum urea and electrolytes, creatine kinase, and blood glucose, a full blood count and liver function tests, and observe all symptomatic cases with ECG, blood pressure, and temperature monitoring for at least 6 hours post-exposure. A 12-lead ECG is required.

Management
The complications described above should be treated as for cocaine (see Fig. 13.5). Selective serotonergic antagonists (e.g. cyproheptadine/ketanserin) may be used to reduce temperature and rigidity by central mechanisms in those with a 5HT-like syndrome.

Outcome
Several tens of deaths have occurred from ecstasy in the UK between 2000 and 2005. Some have been due to hepatic injury, others to cerebral edema.

Opioids
These include heroin, morphine, methadone, codeine, pethidine, dihydrocodeine, and dextropropoxyphene. They give a rapid, intensely pleasurable experience, often accompanied by heightened sexual arousal. Physical dependence occurs within a few weeks of regular high-dose injection and, as a result, the dose is escalated and the addict's life becomes increasingly centered upon obtaining and taking the drug.

Clinical features of opioid overdose
Accidental overdose is common. The hallmarks of opioid analgesic poisoning are:

- depressed respiration
- pinpoint or small pupils
- depressed consciousness level
- signs of intravenous drug misuse (e.g. needle track marks)

Severe poisoning is indicated by respiratory depression, hypotension, non-cardiogenic pulmonary edema, and hypothermia. Death occurs by respiratory arrest or from aspiration of gastric contents. Poisoning with dextropropoxyphene (the opioid moiety of co-proxamol) may also result in cardiac conduction effects, particularly QRS prolongation, ventricular arrhythmias, and heart block. Symptoms of opioid poisoning can be prolonged for up to 48 hours, particularly after ingestion of methadone, which has a long half-life.

Epidemiology
Accidental overdose is common. Opioids are beginning to overtake carbon monoxide as the commonest cause of death by poisoning in the UK.

Pathology
Opioids bind to receptors in the CNS (μ and κ amongst others) and periphery, causing CNS depression, analgesia, and respiratory depression.

Investigations
Unconscious patients should always have their acetaminophen concentration checked because of the prevalence of combination opioid/acetaminophen drugs. Oxygen saturation and arterial blood gases demonstrate the adequacy of ventilation in those whose respiration has been compromised. Qualitative screening of the urine is an effective way to confirm recent use. Occasionally, measuring opioids and their metabolites in blood is required for medicolegal purposes, particularly when there is a fatality.

Management
Steps should be taken to ensure a clear airway and, if necessary, provide respiratory support. Supplementary high-flow oxygen should be administered. The need for endotracheal intubation can often be avoided by prompt administration of adequate doses of the opioid antagonist naloxone (see Fig. 13.6). Oxygen saturation monitoring and arterial blood gases demonstrate the adequacy of ventilation in those whose respiration has been compromised. The treatment of coma, fits, and hypotension is detailed elsewhere. Non-cardiogenic pulmonary edema in severe cases does not usually respond to diuretic therapy, and non-invasive ventilatory support with continuous positive airway pressure (CPAP) may be required.

Naloxone is a specific opioid antagonist that reverses the above features of opioid toxicity. Its use is shown in Fig. 13.6. Administration of too much naloxone should be avoided as it can precipitate a withdrawal reaction, characterized by gastro-intestinal effects, sweating, and fits. After the initial IV bolus, an infusion of naloxone may be needed because the half-life of the antidote is much shorter than the half-lives of most opioids. Naloxone has been reported to cause pulmonary edema and ventricular arrhythmias, but such events are infrequent and not enough to outweigh its use.

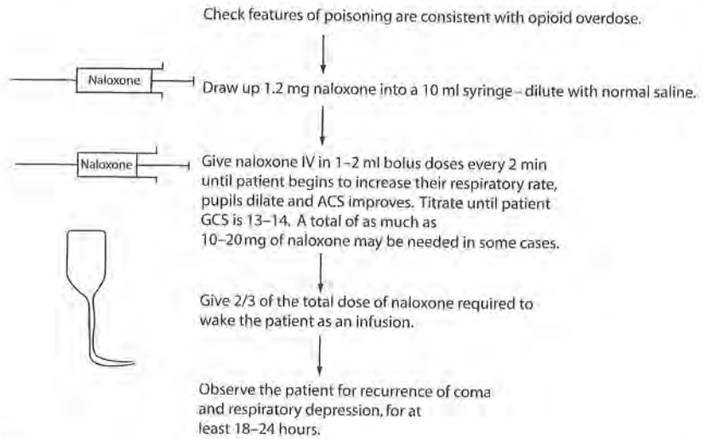

Fig. 13.6. How to give naloxone in opioid poisoning

Note:
(1) IV is the prefered method for naloxone administration.
(2) It can be given undiluted down an endotracheal tube in emergencies.
(3) Administration of too much naloxone should be avoided because it can precipitate a withdrawal reaction, characterized by sweating and seizures.

Outcome
Most deaths occur in the community. Those reaching hospital alive usually survive.

Carbon monoxide and smoke
Carbon monoxide is a colorless, non-irritant, odorless gas; sources include smoke from fires, car exhausts, and the incomplete burning of gas fires or cookers.

Clinical features
Clinical effects from carbon monoxide exposure range from the more subtle cardiovascular and neurobehavioral effects at low ambient concentrations to unconsciousness and death after exposure to high concentrations. The early clinical features of acute carbon monoxide poisoning are headache, nausea, and vomiting (often mistaken for "gastric flu"), ataxia, and nystagmus. Later features are drowsiness, hyperventilation, hyper-reflexia, and shivering. Central and peripheral cyanosis occur. Some patients are disinhibited, agitated, or aggressive rather than drowsy. In severe cases (Fig. 13.7) convulsions, coma, hypotension, respiratory depression, ECG changes (ST segment depression, T-wave abnormalities, ventricular tachycardia, or ventricular fibrillation), and cardiovascular arrest may occur. Cerebral edema is common and focal neurologic signs can be present. Significant abnormalities on physical examination include impaired short-term memory and cerebellar signs (past-pointing and unsteadiness of gait, particularly heel–toe walking). Any one of these signs would classify the episode as severe. Rigidity, hyper-reflexia, and an extensor plantar response may occur in mild, moderate, or severe cases. Carbon monoxide poisoning in pregnancy is likely to cause miscarriage or premature labor due to fetal hypoxia. Patients recovering from carbon monoxide poisoning may suffer neurologic sequelae including tremor, personality changes, memory impairment, visual loss, inability to concentrate, and Parkinsonian features. Chronic ("low level") carbon monoxide poisoning causes symptoms which are difficult to distinguish from influenza, i.e. nausea, vomiting, headache, lethargy, and aches and pains. Angina may become more severe. Neurobehavioral effects may be seen, especially in the aged. Behavior that requires sustained attention or performance is most sensitive to disruption by carbon monoxide.

Epidemiology
The risk of carbon monoxide poisoning is greatest where surrounding air ventilation is poor, particularly in the home. As well as carbon monoxide, smoke produced in house fires contains a mixture of soot and organic particles, together with other gases such as hydrogen sulfide. Carbon monoxide is the most common cause of death by poisoning in the UK and many other countries.

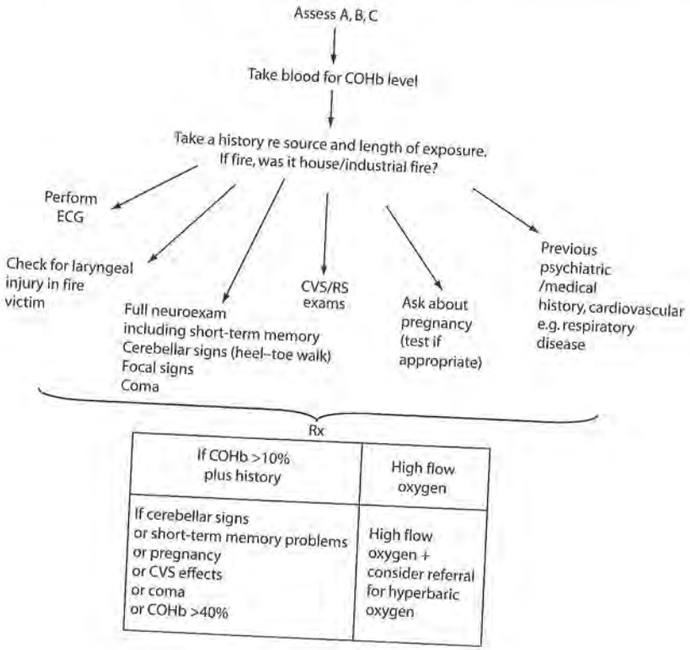

Fig. 13.7. Assessing and managing a carbon monoxide poisoned patient.

Pathology

Carbon monoxide reduces the oxygen-carrying capacity of the blood by binding to hemoglobin to form carboxyhemoglobin (COHb), and impairs the function of cytochrome oxidases. This impairs oxygen delivery from blood to tissues and its utilization within tissues. It acts as a chemical asphyxiant.

Investigations

The carboxyhemoglobin (COHb) concentration is of value in confirming the diagnosis of acute carbon monoxide poisoning, although it may not be elevated sufficiently to be diagnostic in chronic cases. However, the degree of COHb elevation measured at hospital does not correlate well with the severity of poisoning, even acutely. This is because blood COHb concentrations fall rapidly on cessation of exposure and patients may also receive oxygen therapy in ambulances whilst being transferred to hospitals. Normal values are up to 3%–5% and can be as high as 6%–10% in smokers; COHb levels below 10% are not usually associated with symptoms. An ECG should be performed in anyone with acute poisoning, especially in patients with pre-existing heart disease. Serious poisoning also requires arterial blood gas analysis. Oxygen saturation readings by pulse oximetry are misleading (see below).

Management

The most important first step in treating carbon monoxide poisoning is to move the patient away from the source of exposure. It is vital to ensure that the airway, breathing, and circulation are adequately maintained and give supplementary oxygen as soon as possible. The half-life of COHb whilst breathing air ranges from 4–6 hours. On 100% oxygen at ambient pressure, the half-life of COHb is reduced to approximately 40 min. Thus, oxygen should be given in high flow, e.g. 12 liters per minute, ideally through a tightly fitting facemask such as a CPAP mask. It should be continued until the COHb is less than 5% and for at least 6 hours after exposure. Sometimes 12–20 hours are required for this to take place. Unfortunately, pulse oximeters measure both carboxyhemoglobin and oxyhemoglobin and so a normal saturation value does not give grounds for reassurance. Care should be taken to avoid excessive intravenous fluid administration, particularly in the elderly, because of the risk of pulmonary edema. Most deaths occur in those who have arrested at the scene or who are unconscious on arrival at hospital. Blood pressure should be monitored and convulsions controlled with diazepam.

The use of hyperbaric oxygen is controversial; Figure 13.7 lists the current indications for considering such therapy. The theoretical value of hyperbaric oxygen is that at 2.5 atmospheres the half-life of COHb is reduced to 20 minutes and it also increases the amount of dissolved oxygen by about ten times. The logistic difficulties of transporting sick patients to hyperbaric chambers should not be under-estimated.

Outcome

Carbon monoxide remains the commonest cause of death by poisoning in the UK. Both acute and chronic exposure can result in serious neurologic sequelae.

Alcohol/ethanol

Ethanol is found not just in alcoholic drinks but in many household preparations, e.g. mouthwash and antiseptics.

Clinical features

The fatal dose of absolute ethanol is 6–10 ml/kg body weight. Ethanol is rapidly absorbed and generally absorption is 80%-90% complete in 1 hour. Mild effects (blood alcohol <1.5 g/l) include impaired co-ordination and reaction time. Moderate effects (blood alcohol 1.5–3 g/l) include dysarthria, ataxia, diplopia, flushing, sweating, and tachycardia. Severe effects (blood alcohol 3–5 g/l) include hypothermia, drowsiness progressing to coma and metabolic acidosis, and respiratory or circulatory arrest. Severe hypoglycemia may lead to convulsions.

Epidemiology

Ethanol is commonly taken with other drugs in overdose.

Pathology

Ethanol has a CNS depressant effect. Its effect is additive with other CNS depressant drugs.

Investigations

Blood or breath alcohol level should be determined if the patient is symptomatic. At blood alcohol levels of >1.5 g/l all patients should have urea and electrolytes, glucose, and ABGs performed.

Management

Gastric lavage is not useful as ethanol is rapidly absorbed and activated charcoal does not absorb alcohol. Observation is recommended for at least 4 hours post-ingestion, or until the patient is asymptomatic. Protect the airway to prevent aspiration. Intubation and ventilation may be required for respiratory depression. Ensure the patient is well hydrated. Acidosis will usually respond to correction of the hypoglycemia and hypovolemia but additional sodium bicarbonate may occasionally be required. Convulsions usually respond to the correction of hypoglycemia. Diazepam 10 mg IV may occasionally be necessary. Supportive care is usually enough and hemodialysis should be reserved for life-threatening cases. It should be considered if the blood ethanol level is >5 g/l or arterial pH <7.0.

Outcome

With supportive care, most ethanol poisoned patients recover within 12 hours.

Further reading

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UK National Poisons Information Service 0870 600 6266; database TOXBASE®.

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