

Case based review: Toxicology on the Acute Medical Unit

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Abstract

Accidental and intentional poisoning from prescribed, illicit and organic substances remains a major cause of morbidity and mortality worldwide and accounts for just under 1% of the total number of NHS hospital admissions, or around 170,000, a year in the UK1. A knowledge of the constellation of signs and symptoms that constitute specific poisonings (referred to as toxidromes) may enable early empirical decontamination, antidote administration, enhanced elimination and supportive care, and may also help to predict the clinical course. This paper presents a series of clinical vignettes to demonstrate emerging presentations in toxicology to help inform the practice of Acute Physicians, who alongside colleagues in Emergency Medicine and Critical Care, are at the front line of diagnosing and treating poisoned patients.

Keywords

toxicology, toxidrome, poisoning, overdose

Key points

- Toxicological presentations are broad and heterogeneous and the mainstay of management is supportive.
- Toxidrome thinking may enable early decontamination, antidote administration, enhanced elimination and improved supportive care. Consider calling the NPIS to discuss features, possible causes and treatment options.
- A proportion of patients, particularly those with low conscious level and refractory shock, will require critical care support, for which there are emerging supportive treatment options.
- Acute physicians deliver front line care to toxicology patients and must remain vigilant to changing threats (e.g. NPS, nerve agents) and therapeutic options and protocols (e.g. staggered paracetamol overdose).

Introduction

Poisoning encompasses a broad and heterogeneous group of presentations that may pose several challenges for the treating clinician. Patients may be unable or unwilling to reveal what they have consumed. Laboratory tests such as drug screening and drug levels are often not rapidly available and are unhelpful in the acute situation. Patients may present in extremis and require targeted treatment despite incomplete or uncertain information. Calls to the National Poisons Information Service (NPIS), although not an exact surrogate for clinical harm, have revealed changes in poisoning exposures over time. Although cocaine, MDMA and cannabis remain the most common drugs of abuse in telephone enquiries to the NPIS, the last few years have seen ‘branded products’ (novel psychoactive substances) and synthetic cannabinoids (considered as a separate entity in the NPIS reports) amongst the top ten reasons for telephone contact with the NPIS.¹ Combined with an increase in established risks including fire smoke as tragically demonstrated by the Grenfell Tower disaster and acts of terrorism as recently described in the Skripal poisonings, this article provides a reminder of toxidrome presentations within these emerging settings whilst discussing newer supportive therapies. Local guidelines, The National Poisons

Information Service (NPIS) and its primary clinical toxicology database TOXBASE[®] should always be consulted in suspected cases of poisoning.²

Case 1

A man in his 20s was brought to the Emergency Department in the early hours of the morning with marked agitation, hallucinations and dystonic movements. He had no past medical history, took no prescription drugs and had no known allergies. His observations revealed hypertension of 190/118 mmHg, tachycardia of 130/min and a temperature of 38.9°C. He had no clear focus of infection, his cardiorespiratory examination was normal and whilst neurological examination was challenging he appeared ataxic and had slurred speech but no obvious meningitic features. His friends revealed that they had been to a club where they had smoked and ingested substances given to them by a stranger. His bloods showed a mild leucocytosis (WCC 13.1 $\times 10^9/L$) whilst biochemistry including urea and electrolytes, thyroid function and CRP were normal and urine toxicology screen was negative.

What is the differential diagnosis?

It is important to consider sepsis in a patient with fever and the neurological features may raise suspicion of meningoencephalitis in particular. Thyrotoxicosis is easily excluded with normal serum markers. Toxidromes such as that relating

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Figure 1. Examples of novel psychoactive substance packaging
<https://www.talkingdrugs.org/drug-alert-dangerous-synthetic-cannabinoid-mmb-chminaca-causing-hospitalizations-deaths-in-europe>

to sympathomimetics and the serotonin syndrome are favoured given the history. The unusual nature of ingestion raises suspicion of novel psychoactive substance toxicity.

What are Novel Psychoactive Substances (NPS)?

NPS are derived from parent compounds whose chemical structure has been manipulated, hence the nickname ‘designer drugs’, designed to mimic the effects of conventional drugs of abuse. They may be referred to as ‘legal highs’ although the Psychoactive Substances Act (PSA) renders this terminology inaccurate. 1 in 40 (2.6%), or 162,000 young adults took an NPS in the last year, particularly young men³. They are often distributed in packaging with distinctive branding¹ (picture 1). Common examples are synthetic cannabinoids (e.g. ‘K2’ and ‘spice’), synthetic cathinones (e.g. mephedrone, often known as ‘bath salts’), other stimulants such as BZP and depressants such as GHB and synthetic opioids.^{3,4}

How may NPS toxicity present?

The severity of presentation varies from mild agitation to life-threatening organ dysfunction requiring critical care support. Neuropsychiatric effects are common, often manifesting as hyperactive delirium and hallucinations. Dystonic reactions and seizures may develop, particularly in synthetic cannabinoid and cathinone ingestion. Cardiovascular effects include tachycardia, arrhythmias and hypertension. Myocardial ischaemia and myocarditis have been reported.^{5,6} Hyperpyrexia (>40°C) is life-threatening and may precipitate rhabdomyolysis causing acute tubular necrosis, extreme electrolyte imbalance and disseminated intravascular coagulation.^{6,7}

Whilst not the focus of this case, NPS also includes depressant substances such as GHB and fentanyl analogues. These typically present with depressed conscious levels and bradypnoea and there is a risk of respiratory arrest.³

What are the general management priorities?

Management is largely supportive. In severe intoxication an A to E approach must identify and manage any life-threatening features. In agitated states the sympathetic response can be blunted with benzodiazepines (e.g. IV lorazepam 0.05 to 0.1mg/kg), whilst dehydration and fever should be managed with active cooling and restoration of circulatory volume. Beta-blockade may lead to unopposed alpha-mediated hypertension and should generally be avoided. Toxidrome recognition is helpful as there are specific therapies to consider such as cyproheptadine if Hunter’s criteria are met (PO 12 mg initially, then 2 mg every 2 hours until signs abate), indicating serotonin syndrome (table 1). Dystonic reactions should be managed with benzodiazepines rather than anticholinergic

Table 1. Hunter’s criteria for diagnosing serotonin syndrome. ⁴⁹
Ingestion of a serotonergic agent AND
Spontaneous clonus OR
Inducible clonus AND agitation OR diaphoresis
Ocular clonus AND agitation OR diaphoresis
Tremor AND hyperreflexia
Hypertonic AND temperature >38oC AND ocular clonus OR inducible clonus

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medications, which may exacerbate agitation and delirium.⁹ Enhanced elimination options may be limited but activated charcoal should be administered if there is documented gastrointestinal ingestion within the preceding hour.²

A friend brings in a packet of powder labelled 'K2', a known synthetic cannabinoid. The patient is noted to be bleeding from venipuncture sites. What features might indicate synthetic cannabinoid toxicity over another compound?

In mild cannabinoid toxicity nausea, vomiting, nystagmus, ataxia and slurred speech feature commonly. As many substances are inhaled, respiratory symptoms may coexist, particularly in patients with underlying airways disease.⁷

A coagulopathy caused by contamination of synthetic cannabinoids with the vitamin K antagonist brodifacoum, a common rat poison, has been reported.¹⁰ If this is suspected vitamin K can be administered and significant bleeding may require resuscitation and blood product support with Haematology input. A deranged coagulation profile without bleeding rarely requires routine correction.

In spite of receiving 30 mg IV diazepam alongside paracetamol and external cooling his temperature rises to 41°C. How should this be managed?

Hyperpyrexia is life-threatening and should be managed emergently. Paracetamol has no role as the underlying mechanism is muscle overactivity, not a change in hypothalamic temperature set-point.⁷ External methods of cooling such as removing clothing, moistening skin, ice packs and fans should be initiated. Invasive methods include cool intravenous fluids (4°C), although the volumes required (30ml/kg over 30 minutes) may be problematic in disorders of sodium homeostasis, which is common in amphetamine toxicity⁶. Gastric, bladder and peritoneal lavage can be considered, although a temperature of greater than 40°C that does not settle quickly should prompt rapid sequence intubation.⁸ Invasive cooling devices, extracorporeal circuits and ongoing paralysis may be required on critical care for refractory hyperpyrexia.

What other challenges are associated with NPS poisoning?

One of the compelling features of NPS for those who use them is their ability to evade detection using conventional point of care testing. Synthetic cannabinoids and their metabolites do not cross-react with delta-9 tetrahydrocannabinol (THC), which explains why the screen in this scenario was negative.¹¹ The diagnosis is clinical, which is why toxidrome recognition is vital (table 2).

Slower absorption of some substances, particularly synthetic cathinones, has led consumers to take repeated doses believing they have consumed a low potency batch, often resulting in more extreme symptoms at presentation.³ Unexpected symptoms and signs should prompt consideration of contamination, co-ingestion or an alternative diagnosis.

Case 2

A woman in her 40s was brought in to the Emergency Department after a friend informed emergency services that she had taken an overdose. She had a history of depression and hypertension and took Amlodipine and Ramipril. She was orientated but tearful, stating that she had ingested an entire box of medication around 90 minutes previously. Her initial observations appeared stable; BP 111/56 mmHg, heart rate 68/min, SpO2 98% in air, respiratory rate 20 breaths per minute, and her bloods and ECG were initially unremarkable except for an elevated blood glucose of 12 mmol/L. She was considered to be outside the window for activated charcoal and was admitted for observation. After an hour she became obtunded with a blood pressure of 70/32 mmHg and heart rate 40/min. She demonstrated a poor response to volume loading, atropine and peripheral vasopressor therapy and was admitted to critical care.

What forms of poisoning can lead to refractory shock?

Many medications in overdose are associated with cardiovascular toxicity although severe refractory hypotension is most associated with calcium channel blockers (CCB), beta-blockers, tricyclic antidepressants (TCA) and to a lesser extent chloroquine and colchicine. Blood sugar may help to discriminate between beta-blocker and CCB overdose; typically hypoglycaemia is associated with beta-blocker toxicity whereas CCB toxicity is associated with hyperglycaemia.⁸

What are the early management priorities and challenges associated with these medications?

The patient should be assessed and managed according to an A to E approach. Patients often appear surprisingly well until the moment they become unstable, by which point they are often refractory to conventional treatment.⁸ This is particularly true for CCB.

With the exception of chloroquine, these drugs have no antidote so management is largely supportive. Calcium is not a specific antidote to CCB overdose but must be replaced alongside deficiencies of other electrolytes, particularly in patients with prolonged QTc on their ECG, which can cause Torsades de Pointes. 1–2 g (10–20 ml) of calcium chloride or 3–6 g (30–60 ml) of calcium gluconate can be

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Table 2. Common toxidromes associated with conventional and novel psychoactive substances (* refers to NPS).

Toxidrome & common examples	Signs of toxicity				Antidote
	Neurological	Vital signs	Pupils	Other hallmarks	
Sympathomimetic MDMA, ecstasy, mephedrone*, BZP*	Agitation Paranoia Seizures	Hyperthermia Tachycardia Hypertension	Dilated	Piloerection Sweating Hyperactive bowel sounds	None
Serotonin syndrome SSRIs, TCAs, synthetic cathinones*, synthetic cannabinoids*	Hunter's criteria (table 3)	Hyperthermia Tachycardia Hypertension	Dilated	Quick onset (<24 hours) Diarrhoea	Cyproheptadine
Anticholinergic Antihistamines, antiparkinsonians	Agitation Paranoia Seizures	Hyperthermia Tachycardia Hypertension	Dilated	Dry skin No bowel sounds Urinary retention	Physostigmine
Psychedelic / dissociative LSD, PCP, ketamine, methoxetamine*	Hallucinations Synesthesia	Hypertension Tachycardia	Dilated	Severe vital sign derangement is rare	None
Cannabinoid Cannabis, synthetic cannabinoids*	Agitation Paranoia Seizures*	Tachycardia Orthostatic hypotension	Variable	Red eye Dystonia* Coagulopathy*	None
Sedative-hypnotic Benzodiazepines, barbiturates, GHB*, GBL*	Sedation Ataxia Confusion	Bradycardia Hypotension Bradypnoea/apnoea	Variable		None
Opioid Fentanyl, heroin, MT-45*	Depressed conscious level	Bradycardia Hypotension Bradypnoea/apnoea	Pinpoint	Constipation Pulmonary oedema (rarely)	Naloxone
Cholinergic Pyridostigmine, nerve agents, organophosphates	Confusion Weakness Fasciculations Seizures	Bradycardia, labile BP, bradypnoea/apnoea	Pinpoint	Salivation Lacrimation Urination Diarrhoea GI discomfort Emesis	Atropine Pralidoxime

administered intravenously over 5–10 minutes and may be repeated every 20 minutes up to a maximum of 3 doses.²

Enhanced elimination techniques such as multiple dose activated charcoal (50g every 4 hours), which aims to interrupt enterohepatic circulation and absorb intraluminal toxin, should be considered particularly in overdose of modified release preparations. Plasma alkalinisation (1–2 ml/kg boluses of 8.4% sodium bicarbonate, through a central line wherever possible, to achieve a plasma pH of 7.55 to 7.6) reduces cardiac toxicity associated with sodium channel blockade in TCA overdose and should be given where the QRS duration on ECG exceeds 100 ms or there is ventricular arrhythmia. Extracorporeal elimination is generally ineffective as these medications are highly protein bound and have a large volume of distribution.¹²

She is diagnosed with suspected calcium channel blocker toxicity. She is intubated and receives activated charcoal, glucagon, High-dose Insulin Euglycaemia Therapy (HIET) and lipid rescue alongside dobutamine for bradycardia and noradrenaline for hypotension.

How can HIET help?

Shock in CCB is largely due to a loss of inotropy, chronotropy and vascular tone caused by blocked L-type calcium channels. As well as supporting cardiac myocytes and vascular smooth muscle these channels are also instrumental in pancreatic beta islet cell function.^{13,14} Insulin promotes glucose uptake by cardiac myocytes and enhances calcium uptake by mitochondria, which serves to improve excitation–contraction coupling and contractility. This is particularly helpful in the stressed myocardium where carbohydrate metabolism is favoured over resting state free fatty acid metabolism.¹⁴ HIET effectively functions as an inotrope.

The Western Australian Toxicology Service devised the first widely used protocol in 2009 with doses of insulin up to 5 units/kg/hr, although higher doses are now commonly used.¹³ This therapy requires close monitoring, particularly for hypoglycaemia and hypokalaemia. Observational series have demonstrated improved haemodynamic parameters and lower mortality, particularly when it is employed early rather than as a rescue therapy,

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although the quality of evidence is low.¹⁵ As well as CCB toxicity, the use of HIET has been described in beta-blocker toxicity and severe sepsis.^{15,16}

What is lipid rescue therapy?

Lipid rescue therapy uses an intravenous fat emulsion which is most commonly available as 20% intralipid. It was first utilised for systemic local anaesthetic toxicity and has an Association of Anaesthetists of Great Britain and Ireland (AAGBI) protocol for its use. In recent years it has gained interest as an antidote of last resort in cardiotoxic overdoses of lipophilic agents, which include CCBs, beta-blockers and TCAs.¹⁷

Lipid therapy appears to exert its effects at a membrane level by blocking lipophilic toxin receptor binding and as an inotrope by promoting calcium entry via voltage-dependent calcium channels, thereby increasing contractility.¹⁸ Both the AAGBI and LipidRescue™ protocols include an initial loading dose of 1.5mL/kg and differ slightly in the subsequent infusion rate.^{17,19} Evidence for its efficacy is confined to multiple case reports.

What other options exist for patients refractory to this treatment?

Mechanical cardiac support may be considered where other measures have failed.⁸ Veno-Arterial Extra-Corporeal Membrane Oxygenation (VA-ECMO) is an invasive treatment that allows blood to be oxygenated through an extra-corporeal circuit and provides direct cardiovascular support by returning blood to the arterial system. Its use as a salvage treatment option for many causes of cardiovascular collapse is growing, although the number of patients treated in the context of toxicology is small, there is limited evidence of its efficacy and as many 50% will experience complications including acute kidney injury, sepsis and bleeding.^{20, 21} Lipid rescue therapy may interfere with the extra-corporeal circuit so ideally a decision to proceed with VA-ECMO should be made before lipid rescue is administered.

Alternative invasive mechanical cardiac support exists in the form of an Intra-Aortic Balloon Pump. This is a large bore catheter with a balloon at its distal end that is passed through the femoral artery into the aorta between the left subclavian artery and renal arteries. It typically uses the patient's ECG to inflate during diastole, thereby providing diastolic augmentation and enhanced coronary perfusion, and deflate in systole, thereby reducing left ventricular afterload. Major vascular complications including limb ischaemia should be considered alongside disappointing data regarding its efficacy in various populations.^{22,23} Its use in calcium channel blocker toxicity is limited to case reports.²⁴

Case 3

A man in his 70s with a history of depression and a recent diagnosis of Alzheimer's dementia presented to the Emergency Department after his son discovered that he had taken more than the recommended dose of paracetamol. He had bought the packet for him the previous day and 14 x 500 mg tablets were missing. The patient could not reliably say when and how many of these tablets he had taken, although the last ingested dose of 1g was witnessed by his son 2 hours earlier. The patient appeared well and clinical examination was unremarkable, in particular he had no abdominal tenderness. His observations were normal. As it was not clear whether his presentation represented therapeutic excess or staggered overdose he was managed according to guidelines for the latter and an infusion of intravenous N-acetylcysteine (NAC) was commenced.

What paracetamol dose is associated with toxicity?

Serious toxicity is usually associated with ingestion of more than 150 mg/kg in any 24-hour period, although rarely toxicity can occur with ingestions between 75 and 150 mg/kg within any 24-hour period. Doses consistently less than 75 mg/kg in any 24-hour period are very unlikely to be toxic.² Symptoms commonly include nausea, vomiting and abdominal pain, or coma in patients with extremely high plasma paracetamol concentrations, although the absence of symptoms does not exclude toxicity.

What is the latest nomenclature in paracetamol overdose?

Therapeutic Excess (previously referred to as repeated supratherapeutic ingestion) constitute ingestions of excessive paracetamol (>4g in any 24h period) with therapeutic intent and without intent of self-harm.

Staggered Overdose constitutes non-therapeutic ingestions of excessive paracetamol over a period of greater than one hour.

Acute Overdose is the ingestion of excessive paracetamol over a period of less than or equal to one hour, usually, but not always, in the context of self-harm.

If there is any uncertainty about whether a patient's presentation is due to therapeutic excess or staggered overdose, the patient should be managed according to guidelines for staggered paracetamol overdose.²

Four hours following his last ingestion of paracetamol the patient has a blood test, showing a paracetamol level of 6 mg/L and normal urea and electrolytes, liver function and coagulation profiles. NAC is discontinued and he is discharged.

How is staggered overdose now managed?

NAC should be immediately administered as before, but where the guidelines previously mandated treatment for at least 21 hours pending blood

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Table 3. Factors that increase risk of hepatotoxicity in paracetamol overdose (forms part of the guideline for therapeutic excess)

Concomitant drug therapy	Carbamazepine
	Phenobarbital
	Phenytoin
	Primidone
	Rifampicin
	St John's Wort
	Other enzyme inducing medications
Alcohol	In excess of recommended amounts
Risk of glutathione depletion	Eating disorders
	Cystic fibrosis
	HIV
	Starvation
	Cachexia

results, TOXBASE® now states that NAC can now discontinued if 4 or more hours have passed since the last paracetamol ingestion and if the following features are present:

- Paracetamol concentration less than 10 mg/L **AND**
- ALT within the normal range **AND**
- INR 1.3 or less **AND**
- Patient has no symptoms suggesting liver damage

If the patient also has a normal serum creatinine, they can be discharged.²

What is the relevance of serum creatinine?

Acute kidney injury as a result of hepatorenal syndrome can ensue in severe hepatotoxicity but isolated renal dysfunction is also a recognised complication of paracetamol overdose, thought to be a consequence of glutathione depletion causing apoptosis and tubular damage through increased reactive oxygen radicals.²⁵ There is no evidence that NAC mitigates against this but if there is evidence of renal dysfunction the patient should be admitted for surveillance and TOXBASE® recommends discussion with the NPIS. Patients who go on to require RRT need their NAC prescription amended (typically doubled).²

Have there been other changes to paracetamol guidelines?

The guidance for therapeutic excess in adults has also changed and only mandates referral for clinical assessment and blood tests in patients with symptoms **or** in ingestion of ≥ 75 mg/kg in any 24 hour period

or < 75 mg/kg/24 hours over the preceding 2 or more days if the total dose was greater than 4 g a day.

If the patient has symptoms NAC should be commenced and bloods taken (paracetamol concentration, LFTs, INR, U&Es and FBC) and analysed according to the guidance for staggered overdose, stated in the previous question. Where the dose has exceeded 75 mg/kg in a 24 hour period but there are no symptoms bloods should be taken at least 4 hours after the last paracetamol ingestion. Where less than 75 mg/kg/24 hours has been ingested for the preceding 2 or more days the risk is very low, but NAC should be commenced and bloods taken only if there are other factors present that may increase the risk of hepatotoxicity (table 3).²

What is the next step for patients requiring ongoing treatment with NAC?

Bloods should be repeated at the end, or just before the 21 hour infusion finishes. Patients can be discharged if they meet the following criteria:

- INR 1.3 or less **AND**
- ALT less than two times the upper limit of normal **AND**
- ALT not more than double the admission measurement

If these criteria are not satisfied NAC should be continued at the dose and infusion rate used in the 3rd treatment bag and bloods repeated in 8–16 hours. If there are features of liver failure or acute kidney injury, these should be managed conventionally.²

Is this guidance likely to change again?

The current 21-hour dosing regimen based on bodyweight may underdose patients who have taken larger doses and expose low-risk patients to an unnecessary hospital stay. A trial investigating a 12-hour regimen demonstrated less vomiting, fewer anaphylactoid reactions and reduced incidence of treatment interruption (although it was underpowered to detect non-inferiority of this protocol versus the existing model).²⁶

Individualising the timing and dosing of NAC is an area of research interest and a number of biomarkers of liver damage, including miR-122 and HMGB1, are being developed with good early results of specificity and sensitivity.²⁷ New therapies for liver damage that ensues despite NAC treatment are also being investigated.

Case 4

A 36 year old lady presented to the Emergency Department after being rescued from a house fire, which had started in an adjacent room, but from which she had significant smoke exposure. At presentation she was haemodynamically stable

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and peripheral oxygen saturations were 99% in air, but she had an elevated respiratory rate of 26/min. She was drowsy but able to tell the team that she had no medical history, took no medications and had no allergies. Some soot was visible around her nose but she did not have a hoarse voice or stridor. An arterial blood gas was taken in view of her dyspnoea and revealed a low partial pressure of oxygen (6 kPa), a carboxyhaemoglobin level of 26% and an elevated lactate of 6 mmol/L. She was diagnosed with carbon monoxide poisoning and treated with high flow oxygen through a non-rebreather mask and intravenous fluid.

What types of poisoning can fire smoke cause?

Each fire generates its particular composition of chemicals depending on the combusting materials.²⁸ It is estimated that between 50–75% of fire-related injuries have a component of carbon monoxide poisoning, and cyanide poisoning in house fires is becoming increasingly relevant due to current trends of using synthetic building compounds that release cyanide on combustion e.g. polyurethane, polyacrylonitriles, and synthetic rubber.²⁹

What are the features of carbon monoxide (CO) poisoning and how are they caused?

The most common features of acute CO poisoning are headache, nausea and vomiting, dizziness and lethargy. More severe exposure can cause confusion, syncope and seizures and may be fatal.³⁰ Late features can develop over 2 to 40 days post-exposure and include delayed neurological symptoms (DNS). These often last for a year or longer with symptoms including loss of memory, disorders of movement, low mood, dementia and psychosis.³¹ CO produces its effects through tissue ischaemia and cellular apoptosis as it binds to haemoglobin with an affinity of over 200 times that of oxygen, displacing the oxygen dissociation curve to the left thereby reducing peripheral oxygen offloading, and disrupts mitochondrial oxygen utilisation by inhibiting cytochrome C oxidase.³⁰

How is CO poisoning diagnosed?

Diagnosis of acute CO poisoning is made through measurement of carboxyhaemoglobin (HbCO) levels in blood. Normal values are <5% in non-smokers and 5–13% in smokers.³² Arterial blood gas analysis is helpful in the first instance to detail the degree of hypoxia, but for subsequent HbCO monitoring venous samples are adequate. Table 4 outlines the correlation between HbCO levels and symptoms/signs, although this is approximate and should only be used as a guide.

How is CO poisoning treated?

HbCO dissociation increases as the Fraction of Inspired Oxygen (FiO₂) increases and current

treatment guidelines recommend administration of 100% oxygen, which reduces the half-life from 320 minutes to 74 minutes.³³ Hyperbaric oxygen (HBO) may be considered if there are markers of severity, such as HbCO >30%, ECG evidence of infarction or persistent acidosis. HBO increases blood dissolved-oxygen content, speeds elimination of CO and preserves ATP level in tissues exposed to CO, however, randomised trials have failed to establish any improvement in long term outcomes.³⁴

The patient received 3 L of a balanced crystalloid in boluses due to hypotension. Her GCS reduced to 11/15 and she began to vomit. Venous blood gas analysis revealed that her lactate had risen to 11 mmol/L. She was diagnosed with concomitant inhalational cyanide poisoning of moderate severity, for which treatment was commenced.

What are the features of cyanide poisoning and how is severity classified?

Symptoms from inhalational cyanide poisoning result from tissue hypoxia, which ensues due to inhibition of cytochrome C oxidase, which inhibits mitochondrial function.³⁵ Early symptoms include headache, dizziness and nausea followed by confusion, palpitations and tachypnoea. In moderate toxicity the patient may have brief episodes of loss of consciousness, seizures, vomiting, hypotension and typically a lactate concentration of 10 – 15 mmol/L. Severe toxicity is indicated by coma, fixed pupils, arrhythmia, AV block or cardiovascular collapse and typically a lactate concentration of >15 mmol/L². The cardinal feature of moderate to severe inhalational cyanide poisoning is lactic acidosis causing a high anion gap metabolic acidosis.³⁶

What antidotes are available for inhalational cyanide poisoning?

Only a small number of laboratories are able to measure cyanide concentration in blood and it cannot

Table 4. Symptoms according to carboxyhaemoglobin levels (shading indicates higher levels and risk of death).

HbCO %	Symptoms / signs
<10	Typically asymptomatic
10-20	Mild headache, reduced exercise tolerance
20-30	Moderate headache, nausea, difficulty concentrating
30-40	Severe headache, nausea and vomiting, impaired cognition
40-50	Increasing confusion, reduced conscious level
>50	Coma, seizures, increasing risk of death

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be performed rapidly so electing to give antidotal treatment must be made on the basis of the clinical features described above. These treatments may be hazardous, although in moderate to severe toxicity the potential benefit is considered to outweigh this risk.

In mild or moderate poisoning 12.5 g of sodium thiosulphate (25 mL of 50%) should be administered intravenously over 10 minutes.

In moderate poisoning hydroxocobalamin 200 mL of 25 mg/mL (5 g) intravenously over 15 minutes **or** dicobalt edetate 20 mL of 1.5% solution (300 mg) intravenously over 1 minute (followed immediately by 50 mL of 50% dextrose) may be used instead.²

In severe poisoning dicobalt edetate (as for moderate poisoning) **or** hydroxycarbamide (as for moderate poisoning) are preferred. If these two agents are unavailable an alternative is 3% sodium nitrite 10 mL of solution (300 mg) intravenously over 5 – 20 minutes and sodium thiosulphate (as for mild to moderate poisoning).²

Hydroxocobalamin has been associated with acute kidney injury due to tubular necrosis and can cause skin discolouration and hypertension.³⁷ Dicobalt edetate can be extremely toxic in the absence of cyanide toxicity so clinical suspicion should be high when using this treatment.³⁸ Sodium nitrite works by inducing methaemoglobinaemia as methaemoglobin binds cyanide which is potentially hazardous, in particular where there is concomitant CO poisoning, as it may aggravate tissue hypoxia.³⁹

What else needs to be considered?

Managing patients who have been exposed to fire is complex, requiring a dedicated multidisciplinary team and a structured A to E approach to management. Patients with a hoarse voice, soot in the mouth, facial burns or stridor usually require immediate tracheal intubation as laryngeal oedema tends to progress rapidly over the first 24 hours. Peripheral burns may require input from plastic surgery teams. The National Network for Burn Care (NNBC) have produced a guideline describing the criteria for referral to a specialist burns centre.⁴⁰ It is important to remember to ask about prehospital treatment for suspected cyanide toxicity, as repeated doses of the antidotes described may be dangerous.²

Case 5

A 45 year old gentleman was admitted to the Emergency Department after a sudden onset of headache, dyspnoea, nausea, vomiting, weakness and cough, which he reported a short time after handling a leaking package. He had no past medical history, took no regular medications and had no known drug allergies. He was initially confused and taking rapid shallow breaths. The use of a nerve agent had been suspected at the scene and he had undergone spot

decontamination. His initial observations revealed his blood pressure to be 98/52 mmHg, heart rate 55/min, respiratory rate 24/min and SpO2 90% in room air. On examination he had audible upper airway secretions, miosis and mild symmetrical limb weakness. He was treated with an atropine bolus and pralidoxime chloride as a bolus and then infusion, and oxygen was administered. He was re-treated with atropine every 5 minutes until secretions ceased and was admitted to a high-dependency ward.

What types of agent may be used in a chemical attack?

Mass production of chemical agents was first seen during World War One where agents such as phosgene, toxic mustard and lewisites were used. In World War Two the Nazis murdered millions of civilians using Zyklon B gas.⁴¹ Since then there have been at least two well documented cases of chemical attacks including the use of the nerve agent Sarin, first in Tokyo (1995), then in Syria (2013).^{42,43} Recently, more advanced agents have been used including VX in the assassination of Kim Jong Nam in Malaysia and most recently a Novichok agent has been implicated in the poisoning of Sergei Skripal and his daughter in Salisbury.^{44,45}

What are the challenges when dealing with suspected chemical attacks?

Detection is a particular challenge. Although the risk of further attacks appears to have increased, they are still very rare events and as such, responding medical staff may not be trained in their recognition or treatment. The concurrent use of conventional weapons such as firearms may cause distraction to the possibility of chemical agents also being used.⁴⁶ Injuries not fully explained by conventional weapons, a large number of casualties, and the development of symptoms in first responders all point towards the use of a chemical agent. Portable handheld devices which give rapid results with reliable sensitivity and specificity are not in widespread use and devices using aerosol sampling and biosensing technologies are being developed.⁴⁷

Attending medical personnel are at risk, particularly from nerve agents displaying high persistence, meaning that they evaporate and disperse at a slower rate. Sulfur mustard and nerve agent VX are particularly persistent, whilst sarin is semi persistent. Medical personnel should wear appropriate personal protective equipment, although this may not always be readily available.⁴⁸

How can we use toxidrome recognition in a chemical attack?

Toxidrome thinking is particularly helpful in this setting given the lack of reliable chemical agent

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detection and is best undertaken as a stepwise approach to rapid triage. The fastest lethal agents which necessitate emergency antidotes and treatment should be considered first, which include nerve agents, asphyxiants, and opioids. Next, toxidromes requiring decontamination prior to or alongside treatment should be evaluated, for instance anaesthetic (e.g. nitrous oxide, halothane), riot control (e.g. chloroacetophenone), caustic (e.g. hydrochloric acid), anticholinergic (e.g. atropine) and vesicant agents (e.g. mustards).⁴⁶

What pharmacological management is available for nerve agent poisoning?

Nerve agents cause inactivation of acetylcholinesterase, leading to excess acetylcholine at nerve synapses.⁴⁶ Increased acetylcholine leads to the typical nerve agent toxidrome of fasciculations, weakness and increased secretions. Atropine is a competitive, reversible antagonist of muscarinic acetylcholine receptors and should be administered if the patient develops rhinorrhoea or bronchorrhoea at a dose of 2–4 mg intravenously, repeated at 5 minute intervals until the patient is considered appropriately ‘atropinised’ – that is when the lungs are clear, heart rate is greater than 80/min and blood pressure is reasonable.² It will not improve muscle weakness. All patients requiring atropine should receive pralidoxime chloride 30 mg/kg intravenously over 30 minutes followed by an infusion of 8 mg/kg/h, which regenerates acetylcholinesterase by displacing nerve agents.⁴⁶ After 12–24 hours this can be stopped and restarted if there is clinical deterioration.

What pharmacological management is available for opioid poisoning?

Features of respiratory depression, vomiting with low GCS or airway obstruction associated with an opioid toxidrome produced by an agent such as fentanyl should be treated immediately with 200–400 mcg intramuscular or intravenous naloxone. If there is no response after 60 seconds 800 mcg should be given and this can be repeated up to 2 mg in total (4mg in severe overdose). The initial aim is reversal of respiratory depression rather than a return to normal GCS. If the patient is still symptomatic during reversal or has required repeat dosing an infusion should be started with 60% of the initial dose required infused per hour and patients should be admitted to at least a level 2 environment for close monitoring. Care should be taken with patients who are believed to be chronic opioid users or where pain control is required.²

What pharmacological management is available for poisoning with an asphyxiant agent?

Suspicion of an asphyxiant toxidrome implicating the potential use of cyanide requires the administration of cyanide antidotes, discussed in the previous case. Anaesthetic, riot control, caustic, anticholinergic and vesicant agents do not require specific antidotes. Decontamination, supportive care, close airway monitoring, eye irrigation, and frequent assessment constitute the mainstay of supportive care.⁴⁶

Conflict of interest

None

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