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REVIEW

Antidotes for childhood toxidromes

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Abstract

Background: Poisoning causes significant morbidity and sometimes mortality in children worldwide. The clinical skill of toxidrome recognition followed by the timely administration of an antidote specific for the poison is essential for the management of children with suspected poisoning. This is a narrative review on antidotes for toxidromes in paediatric practice.

Methods: A literature search was conducted on PubMed with the keywords "antidote", "poisoning", "intoxication", "children" and "pediatric". The search was customized by applying the appropriate filters (species: humans; age: birth to 18 years) to obtain the most relevant articles for this review article.

Results: Toxidrome recognition may offer a rapid guide to possible toxicology diagnosis such that the specific antidote can be administered in a timely manner. This article summarizes toxidromes and their respective antidotes in paediatric poisoning, with an emphasis on the symptomatology and source of exposure. The antidote and specific management for each toxidrome are discussed. Antidotes are only available for a limited number of poisons responsible for intoxication. Antidotes for common poisonings include N-acetyl cysteine for paracetamol and sodium thiosulphate for poisoning by cyanide.

Conclusion: Poisoning is a common cause of paediatric injury. Physicians should be familiar with the recognition of common toxidromes and promptly use specific antidotes for the management of childhood toxidromes.

Keywords: antidote, extracorporeal treatment, intoxication, paediatric poisoning, toxidrome.

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Introduction

Poisoning is a significant cause of childhood injury that may potentially lead to serious morbidity and even mortality.[1–3] The World Health Organization reported that children and young adults accounted for approximately 13% of global mortality attributed to accidental poisoning.[4] It is estimated that 40% of hospital admissions due to poisoning in children are due to intentional poisoning.[5] Young boys have a greater risk of unintentional ingestion whereas adolescent girls are more often found to intentionally use medications for suicidal intent.[5,6] It is not always necessarily possible to perform a thorough evaluation of a patient with a drug overdose in the emergency setting as the history obtained may not be complete and there may not be adequate time for a comprehensive physical examination. Additionally, the offending agent(s) is/are often not known during the acute and potentially critical phase of management.[7–9] Therefore, the recognition of a toxidrome – a constellation of symptoms and signs caused by an overdose of a specific class of chemicals or drugs – may offer clues to the underlying toxicology diagnosis and help guide the specific management.[10]

The initial management of patients with a drug overdose involves stabilization of the airway, cardiopulmonary system and gastrointestinal decontamination.[11,12] Many specific antidotes for common household poisons can be given in a timely manner if a toxidrome based on the presenting symptomatology can be identified.[13,14] However, it should be noted that polydrug overdose may cause confusing symptoms and the toxic effects of poisons may have delayed manifestations due to delayed absorption, volume distribution effects or time-lag for conversion to an active metabolite.[14,15]

The purpose of this article is to provide an updated narrative review on various toxidromes and their respective antidotes

available in most emergency departments and critical care units for paediatric poisoning.

A literature search was conducted in November 2020 with the keywords "antidote", "toxidrome", "poisoning", "intoxication", "children" and "paediatric". The search was customized by applying the appropriate filters of "age <18 years" and "human" to find the most relevant articles that meet the objective of this review article. Herein, a few commonly used antidotes and their corresponding toxidromes are described.

The antidotes

An antidote is a drug, medicine, chemical or chelating substance given as a remedy that can counteract or neutralize the effects of another drug or a poison. Antidotes for anticoagulants are sometimes referred to as reversal agents such as the box jellyfish venom antidote.[16,17]

Table 1 shows various types of antidotes. Some may only counteract a given drug, whereas others (such as charcoal) may help reduce the toxicity of numerous drugs. Most antidotes are not 100% effective and fatalities may still occur even when an antidote has been given.

Paediatric toxidromes and antidotes

Antidote for anticholinergic toxidrome – physostigmine

Anticholinergics inhibit the binding of the neurotransmitter acetylcholine to the muscarinic receptors in the central nervous system (CNS) and the parasympathetic nervous system. Intoxication with an anticholinergic may cause tachycardia, hyperthermia, non-reactive mydriasis, anhidrosis, dry mucous membranes, skin flushing, decreased bowel sounds and urinary retention. The anticholinergic effects in the CNS include delirium, confusion, anxiety, agitation, mumbling speech, visual hallucination and bizarre behaviour. The duration of the toxic effects in the CNS is usually longer than the peripheral effects due to the lipophilic properties of the causative agents.[14] Anhidrosis, mydriasis, skin flushing, hyperthermia and delirium are important features in anticholinergic poisoning. Paediatric patients are at risk of unintentional poisoning by anticholinergics as many medications used for the symptomatic relief of common paediatric viral illnesses contain anticholinergics.[18]

Physostigmine, a specific antidote for anticholinergic poisoning,[19,20] inhibits acetylcholinesterase and increases the level of acetylcholine in both the CNS and peripheral nervous system. As most patients with anticholinergic toxicity do well with supportive care alone, physostigmine is usually reserved for those who exhibit both peripheral and moderate central anticholinergic toxicity. It can also be used for diagnostic purposes in suspected anticholinergic poisoning.[1] The onset time is of ~5–10 minutes and the suggested dose is 0.5–2 mg for adults or 0.02 mg/kg for children (maximum 0.5 mg) given by slow intravenous push over 5 minutes. Repeated smaller doses may be required and continuous infusion can be used in severe poisoning.[21] The use of physostigmine has been associated with seizures and arrhythmia in patients with tricyclic antidepressant (TCA) overdose.[22,23] Therefore, for patients with existing heart block, prolonged QT interval, suspected TCA overdose or underlying epilepsy disorder, a close monitoring for arrhythmia is needed during the administration of physostigmine, or its use should be avoided.[1]

Antidote for carbon monoxide poisoning – oxygen (100%) and hyperbaric oxygen

Carbon monoxide intoxication is common in those with smoke inhalation injury. Carbon monoxide is a colourless, odourless, non-irritating and tasteless gas produced by the incomplete combustion of carbon-containing fuel or charcoal. Carboxyhaemoglobin (COHb) forms readily in red blood cells when haemoglobin comes into contact with carbon monoxide, reducing the availability of haemoglobin to bind and deliver oxygen at tissue level. Carbon monoxide also causes direct cellular toxicity by binding to cytochromes, myoglobulin and guanylyl cyclase.[24] The symptoms and signs of carbon monoxide poisoning are non-specific and highly variable depending on the blood level of COHb. Children with chronic exposure to carbon monoxide who have low levels of COHb may develop headache, dizziness, malaise and nausea. COHb levels >20% may cause vomiting, visual disturbance, confusion and transient loss of consciousness. Cherry-red lips, coma and seizure usually occur when the COHb level is >50%.[24] The blood COHb level can be used to confirm the diagnosis. Standard pulse oximetry (SpO_2) and arterial partial oxygen pressure (PaO_2) cannot differentiate COHb from normal oxygenated haemoglobin and are hence not useful for diagnosing carbon monoxide poisoning. Complications of carbon monoxide poisoning include ventricular arrhythmias, myocardial ischaemia, pulmonary oedema, marked lactic acidosis and delayed neuropsychiatric syndrome. The neurological or psychological sequelae of carbon monoxide poisoning on a developing child may cause significant morbidity for survivors; hence, active follow-ups should be arranged.[8,25]

Oxygen (100%) is indicated for carbon monoxide poisoning toxidrome. During initial management, patients with carbon monoxide poisoning should be put on 100% oxygen. Intubation with ventilatory support should be considered early. Whether hyperbaric oxygen is useful remains controversial. A Cochrane review on this topic did not demonstrate a significant benefit amongst those who were given hyperbaric oxygen therapy.[26] Nevertheless, hyperbaric oxygen therapy has been found to be effective in reducing the neurological sequelae amongst moderate to high-risk patients with carbon

Table 1. A to Z of selected antidotes.

Antidote	Type of poisoning
Activated charcoal with sorbitol	Many oral toxins
Antimuscarinic drugs (e.g. atropine)	Cholinergic toxidrome Organophosphate and carbamate insecticides, nerve agents, some poisonous mushrooms (see Pralidoxime)
Benzodiazepam ± antipsychotics	Amphetamine/cocaine
Benzodiazepam for seizures + potassium chloride	Theophylline
Beta blocker	Theophylline
Calcium gluconate	Calcium channel blocker, hydrofluoric acid burns
Chelators (e.g. EDTA, dimercaprol, penicillamine and 2,3-dimercaptosuccinic acid (succimer)	Heavy metal
Cyanide antidotes (hydroxocobalamin, amyl nitrite, sodium nitrite or thiosulfate)	Cyanide
Cyproheptadine	Serotonin syndrome
Deferoxamine mesylate	Iron
Digoxin immune fab antibody (Digibind and DigiFab)	Digoxin, Oleander ingestion
Dimercaprol	Arsenic, gold or inorganic mercury
Diphenhydramine hydrochloride and benztropine mesylate	Extrapyramidal reactions associated with antipsychotics
Ethanol (100%) or fomepizole	Ethylene glycol, methanol
Flumazenil	Beware of precipitating seizure in those with proconvulsant overdose Benzodiazepine
Oxygen (100%) or hyperbaric oxygen therapy	Carbon monoxide, cyanide
Idarucizumab	Dabigatran etexilate
Insulin + glucagon	Beta blocker, calcium channel blocker
Intralipid	Local anaesthetic
Leucovorin	Methotrexate, trimethoprim, pyrimethamine
Methylene blue ± ascorbic acid	Contraindicated for children with glucose-6-phosphate dehydrogenase deficiency Acquired methaemoglobinaemia
Naloxone hydrochloride	Opioid
N-acetylcysteine	Paracetamol (acetaminophen)
Nitrites + thiosulphate + hydroxocobalamin	Cyanide
Octreotide	Oral hypoglycaemic agents
Physostigmine sulfate	Anticholinergic toxidrome
Pralidoxime chloride + atropine	Organophosphate insecticides, anticholinesterase nerve agents, some poison mushrooms
Protamine sulfate	Heparin
Prussian blue	Thallium
Pyridoxine	Hydrazine (e.g. from *Gyromitra* mushrooms), ethylene glycol, isoniazid
Sodium bicarbonate	Aspirin, tricyclic antidepressants with a wide QRS
Silibinin (intravenous)	Amatoxin
Succimer (i.e. dimercaptosuccinic acid)	Lead, mercury and arsenic
Vitamin K (phytomenadione)	Warfarin, some (but not all) rodenticides

monoxide poisoning compared to normobaric oxygen therapy.[27] Currently, the exact role and indication of hyperbaric oxygen in the treatment of carbon monoxide poisoning have not been determined[24,26,28] and well-designed, large-scale, randomized, double-blind and placebo-controlled studies are necessary to determine the true efficacy of hyperbaric oxygen for the treatment of carbon monoxide poisoning.

Antidotes for cholinergic toxidrome

Atropine

Acetylcholine is a neurotransmitter acting on the muscarinic and nicotinic receptors in the CNS, autonomic nervous system and neuromuscular junction and is regulated by acetylcholinesterase. Cholinergic toxidromes can be caused by exposure to or ingestion of pesticides containing organophosphates or carbamate, nerve gas, medications such as echothiophate, pyridostigmine, donepezil and tacrine, or mushroom species (e.g. *Inocybe rimosa*, *Clitocybe* species may also cause cholinergic poisoning).[29,30]

Stimulation of the muscarinic receptors may cause bradycardia, bronchorrhea, bronchospasm, lacrimation, miosis, diaphoresis, profuse watery salivation, gastrointestinal hyperactivity with vomiting, abdominal cramps, diarrhoea and involuntary urination. The symptoms caused by muscarinic receptor activation can be summarized by SLUDGE/BBB (**s**alivation, **l**acrimation, **u**rination, **d**efecation, **g**astrointestinal cramping, **e**mesis/**b**radycardia, **b**ronchorrhea, **b**ronchospasm). Activation of the nicotinic receptor may result in muscle fasciculation and flaccid paralysis, bradyarrhythmia, delirium, seizure and coma. However, reports on carbamate and organophosphate poisoning in young children revealed a high proportion of CNS manifestation, including hypotonia, stupor and coma.[31] Therefore, paediatricians should have a high index of suspicion for cholinergic poisoning in children with possible history of exposure.

Atropine is the antidote used for cholinergic poisoning. It acts as a competitive antagonist of acetylcholine at the muscarinic receptors. However, atropine does not have direct action towards the nicotinic receptors. The recommended dose is 1–5 mg given intravenously for adults. For paediatric patients, the usual dosage is 0.01–0.03 mg/kg every 3–5 minutes titrated according to clinical response.[10] The maximum cumulative intravenous dose is 1 mg in children and 2 mg in adolescents.[1,32,33] Atropine can also been given as a continuous infusion.[34] It has been shown that using rapidly incremental doses of atropine followed by infusion results in a lower mortality, lower requirement of respiratory support and a shorter duration to achieve atropinization compared to conventional bolus doses.[35] Atropine can also be used in combination with a benzodiazepine for seizure control in children with cholinergic overdose. As atropine has no nicotinic effect, it is not helpful for symptoms related to nicotinic activation such as muscle fasciculation or paralysis.[10]

Pralidoxime

Pralidoxime is the antidote used for organophosphate poisoning as it cleaves the organophosphate-acetylcholinesterase complex and releases the enzyme to degrade acetylcholine. It is effective for both muscarinic and nicotinic symptoms. However, pralidoxime should only be used as an adjunctive therapy to atropine as monotherapy with pralidoxime may aggravate symptoms due to transient oxime-induced acetylcholinesterase inhibition.[1,10,36] The suggested intravenous dose of pralidoxime is 1–2 g for adults and 25–50 mg/kg for children (maximum 2 g/dose) to be given over 30 minutes. Continuous infusion can also be used and may be associated with better clinical response than bolus doses.[37,38] The adverse events associated with pralidoxime use are not commonly observed in children and include hypertension, headache, blurred vision, nausea and vomiting.[10] Laryngospasm and muscle rigidity have also been reported in those that were given rapid administration of pralidoxime.[10]

Antidotes for cyanide overdose – sodium nitrite, sodium thiosulfate and hydroxocobalamin

Cyanide poisoning can occur through inhalation of the colourless hydrogen cyanide or ingestion of cyanide salts such as sodium cyanide or potassium cyanide. Smoke inhalation is an important source of cyanide toxicity as hydrogen cyanide may be produced through the combustion of substances containing carbon and nitrogen.[39] Other sources of cyanide include natural substances and foods such as cassava or apricot kernels, accidental consumption of chemicals used in the electroplating or mining industry,[40] and prolonged use of sodium nitroprusside in the intensive care unit for the control of hypertension as one molecule of sodium nitroprusside would produce five molecules of cyanides. Cyanide toxicity comes from its binding to the ferric ion of cytochrome oxidase a3, which interferes with oxidative phosphorylation. Cyanide poisoning leads to cellular hypoxia, causing the activation of anaerobic metabolism and the subsequent development of lactic acidosis.[40,41]

The symptoms and signs of cyanide toxicity are often non-specific and clinical manifestations include anxiety, headache, vomiting, abdominal pain, chest pain, confusion, bitter almond odour, cherry-red skin, mydriasis, tachypnoea, tachycardia, arrhythmia, blurred vision, loss of consciousness and seizures.[42] A three-phase change of initial tachycardia and hypertension, followed by tachycardia and hypotension, and eventually hypotension with cardiac arrest has been described.[43] Complications of cyanide poisoning include pulmonary oedema, cardiopulmonary collapse, rhabdomyolysis, acute kidney injury, hepatic necrosis and even death. Neurological deficits and Parkinsonism may be observed amongst the survivors.

Making the diagnosis requires a high index of suspicion as blood cyanide level is usually not readily available in the acute setting to aid diagnosis. Alternatively, a plasma lactate level of ≥10 mmol/L with a suggestive history and presentation may alert the physician to the possibility of cyanide intoxication.[43]

Sodium nitrite, sodium thiosulfate and hydroxocobalamin are antidotes used for cyanide toxicity.[24,44–46] These antidotes can be given simultaneously. Intravenous sodium nitrite 300 mg for adults or 6 mg/kg for children (maximum dose 300 mg) displaces the cyanide from binding cytochrome oxidase in the form of cyanomethaemoglobin, which can further combine with the thiosulfate (250 mg/kg, maximum dose 12.5 g given as slow intravenous infusion following sodium nitrite) to become thiocyanate, which can be excreted by the kidneys. Furthermore, hydroxocobalamin is an alternative antidote, which has a higher affinity for cyanide than cytochrome oxidase and the bound non-toxic complex cyanocobalamin can be excreted through urine. The recommended dose of hydroxocobalamin is 5 g for adults and 70 mg/kg for children (maximum 5 g) to be given intravenously.[47]

Antidote for hypnotic/sedative toxidrome – flumazenil

The manifestation of sedative and hypnotic toxidrome includes slurred speech, ataxia, incoordination and disorientation. In those with severe toxicity, stupor and coma may also be seen. Hypoventilation is rare amongst those who have sedation/hypnotic overdose by the oral form of benzodiazepine. The absence of hypoventilation and miosis can be an indicator to help distinguish sedation/hypnotic overdose from opioid poisoning. The common description of 'coma with normal vitals' is a good illustration of this toxidrome. However, mild bradycardia, hypotension and respiratory depression can still occur in those with intravenous benzodiazepine overdose.[48] Specifically, children with benzodiazepine overdose usually present with ataxia and drowsiness; respiratory depression is less commonly encountered.[49,50] As the continuous infusion of benzodiazepines is a common practice in intensive care units for sedative purposes, the recognition of such a toxidrome is essential, and all medical and nursing staff working in the intensive care units should be familiar with its presentation. Cardiac toxicity leading to dysrhythmia may also be seen in chloral hydrate overdose.

Flumazenil is a competitive benzodiazepine antagonist used for the overdose of benzodiazepine or non-benzodiazepines (e.g. zolpidem), which share the agonistic action at the benzodiazepine receptors. The usual starting dose is 0.2 mg for adults and 0.01 mg/kg for children (maximum 0.2 mg) to be given intravenously. Repeated doses with an increment of dose can be given to titrate against clinical response. The maximum dose is usually 1 mg, though higher doses ranging from 2.5 mg to 10 mg have been reported.[1,51,52] It should be noted that, for those with chronic benzodiazepine abuse, flumazenil may precipitate withdrawal symptoms.

It should be noted that flumazenil can also precipitate seizures in those with a proconvulsant overdose such as TCA. Therefore, flumazenil is not recommended for those with a head injury, underlying epileptic disorder or suspected TCA poisoning[1] to avoid adverse events such as arrhythmia or convulsion.[51] Seizures after flumazenil administration should be treated with benzodiazepines. The onset time is usually within a few minutes and patients that are given flumazenil should be observed for at least few hours.

Antidote for methaemoglobinaemia – methylene blue

Methaemoglobinaemia can be broadly classified into congenital or acquired. Congenital methaemoglobinaemia can be due to the deficiency of cytochrome b5- methaemoglobin (MetHb) reductase or due to a mutant globin that facilitates the spontaneous oxidation of the iron moiety from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state (haemoglobin M disease). Acquired causes include exposure to chemicals (e.g. nitrates, nitrites, aniline, phenylhydroxylamine, aminophenol, acetanilide), foods (e.g. nitrite-containing vegetables or fava beans), herbicides, pesticides, medications (e.g. chloroquine, dapsone), topical anaesthetic agents (e.g. benzocaine, lidocaine) and inhaled nitric oxide.

Methaemoglobinaemia causes cyanosis when the level of MetHb is >1.5 g/dL, that is, equivalent to 8–12% MetHb at normal haemoglobin concentrations.[53] The clinical manifestations of acquired methaemoglobinaemia depend on the level of MetHb. Infants consuming an excessive amount of nitrite causing methaemoglobinaemia may present with marked cyanosis ('blue baby syndrome'). Anxiety, headache and dizziness can occur at MetHb levels of >20%. Fatigue, confusion and tachypnoea can occur at MetHb levels of 30–50%. Arrhythmia, seizure and coma can occur at MetHb levels of >50%.[53]

The diagnosis of methaemoglobinaemia is usually made based on clinical observation. A patient with sudden onset of cyanosis with suggestive symptoms after suspicious exposure that is not responsive to increased oxygen delivery may require the evaluation of methaemoglobinaemia. There is a saturation gap between the reading from the pulse oximeter and the measured value obtained from blood gas analysis. A normal PaO_2 level is usually shown by blood gas analysis. To confirm the diagnosis, a direct measurement of MetHb is required.

Methylene blue is used in the treatment of acquired methaemoglobinaemia. Methylene blue accelerates the NADPH-MetHb reductase pathway to clear MetHb.[1,54,55] The standard dose of methylene blue is 1–2 mg/kg to be given intravenously over 5 minutes and a repeated dose may be needed if symptoms/signs are persistent. The recommended dosage should not be exceeded. Alternative interventions may be required if methaemoglobinaemia does not resolve after two doses. The colour of urine is bluish green after the administration of methylene blue.[55] The monitoring of

MetHb concentration is advised as there may be a rebound phenomenon. Methylene blue is contraindicated in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency as G6PD is required for the NADPH-MetHb reductase pathway. In children with G6PD deficiency, methylene blue may increase the risk of haemolysis. For those children in whom methylene blue is contraindicated, ascorbic acid may be used instead.

Antidote for opioid toxidrome – naloxone

Opioid poisoning may occur in young children who obtain access to pain medications or illicit drugs at home. It has been reported that children who were exposed to >1 mg/kg of codeine may develop toxicity within 1 hour of ingestion.[56] Miosis is a consistent finding in pure opioid overdose; however, it is not a specific sign and the diagnosis of opioid overdose should not be made solely based on this finding. Other clinical manifestations include respiratory depression, CNS depression, hyporeflexia, muscle rigidity, bradycardia, hypotension, flushing, pruritus and decreased or absent bowel sounds.[57] Hypoventilation is the most important complication and may lead to mortality.[58] Other complications include amenorrhea, impaired fertility, non-cardiogenic pulmonary oedema, acute rhabdomyolysis and acute kidney injury.[59] Likewise, seizures can also occur after intravenous sufentanil or fentanyl, prolonged use of meperidine, or ingestion of large amounts of tramadol or propoxyphene. It should be noted that children with opioid overdose may show a delayed onset of toxicity and the clinical effects may be more severe and prolonged than adults.

Naloxone is a synthetic opioid receptor antagonist that is used for both the diagnosis and treatment of opioid poisoning. It has a rapid onset of action and can be given either through intravenous, intramuscular, intranasal or endotracheal route, though the intravenous route is usually preferred.[1] The intranasal route is as effective as intravenous naloxone in reversing the respiratory and CNS depression.[60] The requirement of a rescue dose is higher for intranasal naloxone. The use of naloxone is indicated in those with respiratory depression or a respiratory rate of <12 breaths/minute. The initial intravenous dose is 0.4–2 mg for adolescents and adults and it can be repeated every 3–5 minutes until the desirable clinical response (restoration of respiratory effort) is achieved. The maximum total dose is 10 mg.[58] The recommended initial dose for children is 0.01 mg/kg to be given intravenously. Similarly, the dose can be increased to up to 0.1 mg/kg (maximum 2 mg per dose) until the desired response is obtained. Naloxone may precipitate acute withdrawal, leading to lacrimation, piloerection, diaphoresis, vomiting, diarrhoea and yawning in those with chronic opioid abuse. A longer observation period of at least 24 hours may be required for opioid poisoning in the paediatric populations due to their delayed onset and the prolonged effect of toxicity.[58]

Antidote for paracetamol overdose – N-acetyl cysteine

Paracetamol poisoning in the paediatric population can be caused by both intentional overdose, unintentional consumption or medication error. It has been reported that a single dose of 200 mg/kg may produce acute toxicity and the consumption of more than 75 mg/kg/day in children under 6 years old may also develop toxicity.[61] Children may be relatively asymptomatic at initial presentation and the most concerned toxicity is hepatotoxicity and liver failure. The timing of initiating treatment varies between different international and local guidelines but in general it requires the plotting of paracetamol concentration to the Rumack–Matthew nomogram.[62,63]

N-acetylcysteine is a medication that is used to treat paracetamol (acetaminophen) overdose. In the treatment of acetaminophen overdose, acetylcysteine acts to maintain or replenish depleted glutathione reserves in the liver and enhance the non-toxic metabolism of acetaminophen.[64] As such, acetylcysteine protects liver cells from N-acetyl-p-benzoquinone imine toxicity. This antidote is most effective in preventing or lessening hepatic injury when administered within 8–10 hours after paracetamol overdose.[64,65]

Sodium bicarbonate as an antidote for miscellaneous toxidromes

Sodium bicarbonate infusion is indicated for poisoning with TCA, aspirin or cocaine that presents with a wide QRS. The dose for TCA and cocaine-associated cardiac toxicity is usually 1–2 mmol/kg infused intravenously using 8.4% sodium bicarbonate.[66] Sodium bicarbonate should be titrated up until a urine pH between 7.5 and 8.0 is achieved.[67]

In small children, a small amount of ingestion can be fatal for TCA poisoning.[68] An electrocardiogram should be performed when there is a concern of TCA overdose.[7,69] In TCA overdose, activated charcoal is often recommended.[70] In those who have a wide QRS complex (>100 ms), sodium bicarbonate is recommended in addition to activated charcoal.[69] If seizures occur, benzodiazepines should be given.[69] In those with hypotension, intravenous fluids, norepinephrine and intravenous lipid emulsion may be tried.[70,71]

There is no specific antidote for salicylate poisoning[67,72] and the initial treatment of salicylate overdose involves maintaining an adequate airway and adequate circulation followed by gastric decontamination by administering activated charcoal, which adsorbs the salicylate in the gastrointestinal tract. The alkalinization of the urine and plasma, by giving an intravenous bolus of sodium bicarbonate then adding sodium bicarbonate to maintenance fluids, is an effective method to increase the clearance of salicylates from the body.[67] The alkalinization of urine causes salicylates to be trapped in renal tubules in their ionized form and then readily excreted in the urine. Alkalinization of the plasma decreases the lipid soluble form

of salicylates facilitating movement out of the CNS.[67] Oral sodium bicarbonate is contraindicated in salicylate toxicity as it can cause the dissociation of salicylate tablets in the gastrointestinal tract and subsequent increased absorption.[67] Intravenous fluid containing dextrose, such as dextrose 5% in water with addition of sodium bicarbonate is recommended to keep a urinary output between 1 and 1.5 ml/kg/hour.[67]

Sodium bicarbonate should be given to those with significant aspirin overdose (salicylate level greater than 35 mg/dL 6 hours after ingestion) regardless of the serum pH, as it enhances the elimination of aspirin in the urine. Sodium bicarbonate should be given until a urine pH between 7.5 and 8.0 is achieved.[67]

Cocaine is a stimulant and its overdose may result in a sympathomimetic toxidrome. The clinical manifestations of sympathomimetic toxidromes include mydriasis, hyperthermia, piloerection, diaphoresis, agitation, anxiety, delusion and paranoia. Cardiac toxicity includes hypertension, tachycardia, arrhythmias and myocardial infraction. Rarely, cocaine overdose may induce seizure, cerebral vascular accident, bowel infarction and pulmonary oedema.[73,74] Arrhythmia, especially ventricular tachycardia, ventricular fibrillation or torsade de pointes, can occur with cocaine overdose due to sodium channel blockade, potassium channel blockade, catecholamine excess or myocardial infraction.[66] Apart from the initial stabilization and correction of electrolyte abnormalities, sodium bicarbonate infusion and lidocaine are effective medications to be administered.[66,75] However, there is a lack of data from clinical trials.

Conclusion

The diagnosis and management of childhood poisoning remain challenging and the recognition of toxidromes guided by history and physical findings as well as the results of selected investigations is indispensable. Antidotes can be used for both diagnostic and therapeutic purposes. Physicians should be familiar with some of the specific antidotes as timely administration is crucial to reverse the damage caused by the toxic substances.

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References

1. Betten DP, Vohra RB, Cook MD, Matteucci MJ, Clark RF. Antidote use in the critically ill poisoned patient. *J Intensive Care Med*. 2006;21:255–277. https://doi.org/10.1177/0885066606290386
2. Woolf AD, Lovejoy Jr FH. Epidemiology of drug overdose in children. *Drug Saf*. 1993;9:291–308. https://doi.org/10.2165/00002018-199309040-00007

3. Chiew AL, Buckley NA, Graudins A, Munir VL. Review article: up (to) date for Australian toxicology and toxinology guidelines. *Emerg Med Aust.* 2021;33:6–8. https://doi.org/10.1111/1742-6723.13663
4. Peden M, Oyegbite K, Ozanne-Smith J, et al., eds. *World Report on Child Injury Prevention*. Geneva: World Health Organization World Health Organization, Unicef; 2008:31–56. http://www.who.int/violence_injury_prevention/child/injury/world_report/World_report.pdf. Accessed April 22, 2021.
5. Hon KL, Ho JK, Leung TF, Wong Y, Nelson EA, Fok TF. Review of children hospitalised for ingestion and poisoning at a tertiary centre. *Ann Acad Med Singap.* 2005;34(5):356–361.
6. Hon KL, Leung AKC. Childhood accidents: injuries and poisoning. *Adv Pediatr.* 2010;57(1):33–62. https://doi.org/10.1016/j.yapd.2009.08.010
7. Hon KL, Fung CK, Lee VW, Cheung KL, Wong W, Leung AKC. Neurologic and cardiovascular complications in pediatric life threatening imipramine poisoning. 2015;10(3):261–265. https://doi.org/10.2174/1574886310666150729125149
8. Hon KL Yeung WL, Ho CA, et al. Neurologic and radiologic manifestations of three girls surviving acute carbon monoxide poisoning. *J Child Neurol.* 2006;21(9):737–741. https://doi.org/10.1177/08830738060210090401
9. Hon KL, Ho JK, Hung EC, Cheung KL, Ng PC. Poisoning necessitating pediatric ICU admissions: size of pupils does matter. *J Natl Med Assoc.* 2008;100(8):952–956. https://doi.org/10.1016/s0027-9684(15)31411-5
10. Holstege CP, Borek HA. Toxidromes, 2012;479–498. https://doi.org/10.1016/j.ccc.2012.07.008
11. Boyle JS, Bechtel LK, Holstege CP. Management of the critically poisoned patient. *Scand J Trauma Resusc Emerg Med.* 2009;17:29. https://doi.org/10.1186/1757-7241-17-29
12. Frithsen IL, Simpson WM. Recognition and management of acute medication poisioning. *Am Fam Physician.* 2010;81(3):316–323.
13. Koren G. A primer of paediatric toxic syndromes or "toxidromes." *Paediatr Child Health.* 2007;12(6):457–459. https://doi.org/10.1093/pch/12.6.457a
14. Rasimas JJ, Sinclair CM. Assessment and management of toxidromes in the critical care unit. *Crit Care Clin.* 2017;33(3):521–541. https://doi.org/10.1016/j.ccc.2017.03.002
15. Camidge R, Bateman DN. Self-poisoning in the UK: epidemiology and toxidromes. *Clin Med.* 2003;3(2):111–114. https://doi.org/10.7861/clinmedicine.3-2-111
16. Christos S, Naples R. Anticoagulation reversal and treatment strategies in major bleeding: Update 2016. *West J Emerg Med.* 2016;17:264–270. https://doi.org/10.5811/westjem.2016.3.29294
17. Lau MT, Manion J, Littleboy JB, et al. Molecular dissection of box jellyfish venom cytotoxicity highlights an effective venom antidote. *Nat Commun.* 2019;10(1):1655. https://doi.org/10.1038/s41467-019-09681-1
18. Lee ACW, So KT. Acute anticholinergic poisoning in children. *Hong Kong Med J.* 2005;11(6):520–523.
19. Burns MJ, Linden CH, Graudins A, Brown RM, Fletcher KE. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. *Ann Emerg Med.* 2000;35(4):374–381. https://doi.org/10.1016/S0196-0644(00)70057-6
20. Watkins JW, Schwarz ES, Arroyo-Plasencia AM, Mullins ME, Toxicology Investigators Consortium investigators. The use of physostigmine by toxicologists in anticholinergic toxicity. *J Med Toxicol.* 2015;11(2):179–184. https://doi.org/10.1007/s13181-014-0452-x
21. Phillips MA, Acquisto NM, Gorodetsky RM, Wiegand TJ. Use of a physostigmine continuous infusion for the treatment of severe and recurrent antimuscarinic toxicity in a mixed drug overdose. *J Med Toxicol.* 2014;10(2):205–209. https://doi.org/10.1007/s13181-013-0330-y
22. Pentel P, Peterson CD. Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. *Ann Emerg Med.* 1980;9(11):588–590. https://doi.org/10.1016/s0196-0644(80)80232-0
23. Schneir AB, Offerman SR, Ly BT, et al. Complications of diagnostic physostigmine administration to emergency department patients. *Ann Emerg Med.* 2003;42(1):14–19. https://doi.org/10.1067/mem.2003.232
24. Huzar TF, George T, Cross JM. Carbon monoxide and cyanide toxicity: etiology, pathophysiology and treatment in inhalation injury. *Expert Rev Respir Med.* 2013;7(2):159–170. https://doi.org/10.1586/ers.13.9
25. 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(5):203–210. https://doi.org/10.5694/j.1326-5377.1999.tb140318.x
26. Buckley NA, Juurlink DN, Isbister G, Bennett MH, Lavonas EJ. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev.* 2011;4:CD002041. https://doi.org/10.1002/14651858.CD002041.pub3
27. Casillas S, Galindo A, Camarillo-Reyes LA, Varon J, Surani SR. Effectiveness of hyperbaric oxygenation versus normobaric oxygenation therapy in carbon monoxide poisoning: a systematic review. *Cureus.* 2019;11(10):e5916. https://doi.org/10.7759/cureus.5916
28. Stoller KP. Hyperbaric oxygen and carbon monoxide poisoning: a critical review. *Neurol Res.* 2007;29(2):146–155. https://doi.org/10.1179/016164107X181770

29. Chan CK, Lam HC, Chiu SW, Tse ML, Lau FL. Mushroom poisoning in Hong Kong: a ten-year review. *Hong Kong Med J*. 2016;22(2):124–130. https://doi.org/10.12809/hkmj154706
30. George P, Hegde N. Muscarinic toxicity among family members after consumption of mushrooms. *Toxicol Int*. 2013;20(1):113–115. https://doi.org/10.4103/0971-6580.111559
31. Lifshitz M, Shahak E, Sofer S. Carbamate and organophosphate poisoning in young children. *Pediatr Emerg Care*. 1999; 15(2):102–103. https://doi.org/10.1097/00006565-199904000-00006
32. McLendon K, Preuss CV. Atropine – StatPearls – NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK470551/. Accessed April 22, 2021.
33. Fang LH, Wang JH, Du GH. Atropine. In: *Natural Small Molecule Drugs from Plants*. Springer Singapore; 2018:181–186. https://doi.org/10.1007/978-981-10-8022-7_29
34. Ram JS, Kumar SS, Jayarajan A, Kuppuswamy G. Continuous infusion of high doses of atropine in the management of organophosphorus compound poisoning. *J Assoc Physicians India*. 1991;39(2):190–193.
35. Abedin MJ, Sayeed AA, Basher A, Maude RJ, Hoque G, Faiz MA. Open-Label randomized clinical trial of atropine bolus injection versus incremental boluses plus infusion for organophosphate poisoning in Bangladesh. *J Med Toxicol*. 2012;8(2):108–117. https://doi.org/10.1007/s13181-012-0214-6
36. Calello DP, Osterhoudt KC, Henretig FM. New and novel antidotes in pediatrics. *Pediatric Emerg Care*. 2006;22(7):523–530. https://doi.org/10.1097/01.pec.0000227389.99508.a7
37. Quail MT, Shannon MW. Pralidoxime safety and toxicity in children. *Prehospital Emerg Care*. 2007;11(1):36–41. https://doi.org/10.1080/10903120601023289
38. Liu HX, Liu CF, Yang WH. Clinical study of continuous micropump infusion of atropine and pralidoxime chloride for treatment of severe acute organophosphorus insecticide poisoning. *J Chinese Med Assoc*. 2015;78(12):709–713. https://doi.org/10.1016/j.jcma.2015.08.006
39. Lawson-Smith P, Jansen EC, Hyldegaard O. Cyanide intoxication as part of smoke inhalation--a review on diagnosis and treatment from the emergency perspective. *Scand J Trauma Resusc Emerg Med*. 2011;19:14. https://doi.org/10.1186/1757-7241-19-14
40. Hon KL, Cheung KL. Pink toes and red urine: what is this poison? *Hong Kong Med J*. 2010;16(5):411–412.
41. Connors NJ, Alsakha A, Larocque A, Hoffman RS, Landry T, Gosselin S. Antipsychotics for the treatment of sympathomimetic toxicity: a systematic review. *Am J Emerg Med*. 2019;37(10):1880–1890. https://doi.org/10.1016/j.ajem.2019.01.001
42. Parker-Cote JL, Rizer J, Vakkalanka JP, Rege SV, Holstege CP. Challenges in the diagnosis of acute cyanide poisoning. *Clin Toxicol*. 2018;56(7):609–617. https://doi.org/10.1080/15563650.2018.1435886
43. Baud FJ. Cyanide: critical issues in diagnosis and treatment. *Hum Exp Toxicol*. 2007;26(3):191–201. https://doi.org/10.1177/0960327107070566
44. Geller RJ, Barthold C, Saiers JA, Hall AH. Pediatric cyanide poisoning: causes, manifestations, management, and unmet needs. *Pediatrics*. 2006;118(5):2146–2158. https://doi.org/10.1542/peds.2006-1251
45. Borron S, Baud F. Antidotes for acute cyanide poisoning. *Curr Pharm Biotechnol*. 2012;13(10):1940–1948. https://doi.org/10.2174/138920112802273182
46. Baskin SI, Horowitz AM, Nealley EW. The antidotal action of sodium nitrite and sodium thiosulfate against cyanide poisoning. *J Clin Pharmacol*. 1992;32(4):368–375. https://doi.org/10.1002/j.1552-4604.1992.tb03849.x
47. Borron SW, Baud FJ, Barriot P, Imbert M, Bismuth C. Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. *Ann Emerg Med*. 2007;49(6):P794–801.E2. https://doi.org/10.1016/j.annemergmed.2007.01.026
48. Mendelson N, Gontmacher B, Vodonos A, et al. Benzodiazepine consumption is associated with lower blood pressure in ambulatory blood pressure monitoring (ABPM): retrospective analysis of 4938 ABPMs. *Am J Hypertens*. 2018;31(4):431–437. https://doi.org/10.1093/ajh/hpx188
49. Kang M, Galuska MA, Ghassemzadeh S. Benzodiazepine toxicity. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2021. https://pubmed.ncbi.nlm.nih.gov/29489152/. Accessed April 22, 2021.
50. Wiley CC, Wiley JF. Pediatric benzodiazepine ingestion resulting in hospitalization. *J Clin Toxicol*. 1998;36(3):227–231. https://doi.org/10.3109/15563659809028944
51. Penninga EI, Graudal N, Ladekarl MBB, Jürgens G. Adverse events associated with flumazenil treatment for the management of suspected benzodiazepine intoxication – a systematic review with meta-analyses of randomised trials. *Basic Clin Pharmacol Toxicol*. 2016;118(1):37–44. https://doi.org/10.1111/bcpt.12434
52. Weinbroum A, Rudick V, Sorkine P, et al. Use of flumazenil in the treatment of drug overdose: a double-blind and open clinical study in 110 patients. *Crit Care Med*. 1996;24(2):199–206. https://doi.org/10.1097/00003246-199602000-00004
53. Skold A, Cosco DL, Klein R. Methemoglobinemia: pathogenesis, diagnosis, and management. *South Med J*. 2011;104(11):757–761. https://doi.org/10.1097/SMJ.0b013e318232139f
54. Rutledge C, Brown B, Benner K, Prabhakaran P, Hayes L. A novel use of methylene blue in the pediatric ICU. *Pediatrics*. 2015;136(4):e1030–1034. https://doi.org/10.1542/peds.2014-3722

55. Koratala A, Leghrouz M. Green urine. *Clin Case Rep*. 2017;5(4):549–550. https://doi.org/10.1002/ccr3.891
56. Michael JB, Sztajnkrycer MD. Deadly pediatric poisons: nine common agents that kill at low doses. *Emerg Med Clin North Am*. 2004;22:1019–1050. https://doi.org/10.1016/j.emc.2004.05.004
57. Baldo BA, Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. *Anaesth Intensive Care*. 2012;40(2):216–235. https://doi.org/10.1177/0310057X1204000204
58. Boyer EW. Management of opioid analgesic overdose. *N Engl J Med*. 2012;367:146–155. https://doi.org/10.1056/NEJMra1202561
59. Babak K, Mohammad A, Mazaher G, Samaneh A, Fatemeh T. Clinical and laboratory findings of rhabdomyolysis in opioid overdose patients in the intensive care unit of a poisoning center in 2014 in Iran. *Epidemiol Health*. 2017;39:e2017050. https://doi.org/10.4178/epih.e2017050
60. Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: Intranasal or intravenous? A randomized clinical trial. *Arch Med Sci*. 2014;10(2):309–314. https://doi.org/10.5114/aoms.2014.42584
61. Mund ME, Quarcoo D, Gyo C, Brüggmann D, Groneberg DA. Paracetamol as a toxic substance for children: aspects of legislation in selected countries. *J Occup Med Toxicol*. 2015;10(1):43. https://doi.org/10.1186/s12995-015-0084-3
62. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol*. 2002;40(1):3–20. https://doi.org/10.1081/clt-120002882
63. Chan STB, Chan CK, Tse ML. Paracetamol overdose in Hong Kong: is the 150-treatment line good enough to cover patients with Paracetamol-induced liver injury? *Hong Kong Med J*. 2015;21(5):389–393. https://doi.org/10.12809/hkmj144481
64. Schwarz E, Cohn B. Is intravenous acetylcysteine more effective than oral administration for the prevention of hepatotoxicity in acetaminophen overdose? *Ann Emerg Med*. 2014;63(1):79–80. https://doi.org/10.1016/j.annemergmed.2013.07.002
65. Green JL, Heard KJ, Reynolds KM, Albert D. Oral and intravenous acetylcysteine for treatment of acetaminophen toxicity: a systematic review and meta-analysis. *West J Emerg Med*. 2013;14(3):218–226. https://doi.org/10.5811/westjem.2012.4.6885
66. Hoffman RS. Treatment of patients with cocaine-induced arrhythmias: bringing the bench to the bedside. *Br J Clin Pharmacol*. 2010;69:448–457. https://doi.org/10.1111/j.1365-2125.2010.03632.x
67. Palmer BF, Clegg DJ. Salicylate toxicity. *N Engl J Med*. 2020;382(26):2544–2555. https://doi.org/10.1056/NEJMra2010852
68. Rosenbaum TG, Kou M, Love JN. Are one or two dangerous? Tricyclic antidepressant exposure in toddlers. *J Emerg Med*. 2005;28(2):169–174. https://doi.org/10.1016/j.jemermed.2004.08.018
69. Woolf AD, Erdman AR, Nelson LS, et al. Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol*. 2007;45(3):203–233. https://doi.org/10.1080/15563650701226192
70. Kerr GW, McGuffie AC, Wilkie S. Tricyclic antidepressant overdose: a review. *Emerg Med J*. 2001;18(4):236–241. https://doi.org/10.1136/emj.18.4.236
71. Cao D, Heard K, Foran M, Koyfman A. Intravenous lipid emulsion in the emergency department: a systematic review of recent literature. *J Emerg Med*. 2015;48(3):387–397. https://doi.org/10.1016/j.jemermed.2014.10.009
72. Brookings CH, Ramsey JD. Salicylate removal by charcoal haemoperfusion in experimental intoxication in dogs: an assessment of efficacy and safety. *Arch Toxicol*. 1975;34(3):243–252. https://doi.org/10.1007/BF00353287
73. Mittleman MA, Mintzer D, Maclure M, Tofler GH, Sherwood JB, Muller JE. Triggering of myocardial infarction by cocaine. *Circulation*. 1999;99(21):2737–2741. https://doi.org/10.1161/01.cir.99.21.2737
74. Westover AN, Nakonezny PA, Haley RW. Acute myocardial infarction in young adults who abuse amphetamines. *Drug Alcohol Depend*. 2008;96(1–2):49–56. https://doi.org/10.1016/j.drugalcdep.2008.01.027
75. Wood DM, Dargan PI, Hoffman RS. Management of cocaine-induced cardiac arrhythmias due to cardiac ion channel dysfunction. *Clin Toxicol*. 2009;47:14–23. https://doi.org/10.1080/15563650802339373