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Small dose...

Big poison

Background
It is not possible to identify all toxic substances in a single journal article. However, there are some exposures that in small doses are potentially fatal. Many of these exposures are particularly toxic to children. Using data from poison control centres, it is possible to recognise this group of exposures.

Objective
This article provides information to assist the general practitioner to identify potential toxic substance exposures in children.

Discussion
In this article the authors report the signs and symptoms of toxic exposures and identify the time of onset. Where clear recommendations on the period of observation and known fatal dose are available, these are provided. We do not discuss management or disposition, and advise readers to contact the Poison Information Service or a toxicologist for this advice.

Keywords: poisons; toxicology; poison control centres

All substances are poisons;
There is none which is not a poison.
The right dose differentiates a poison from a remedy.

Paracelsus (1493–1541)[1]

Poisoning is a frequent occurrence with a low fatality rate. In 2008, almost 2.5 million human exposures were reported to the National Poison Data System (NPDS) in the United States, of which only 1315 were thought to contribute to fatality.[2] The most common poisons associated with fatalities are shown in *Figure 1*. Polypharmacy (the ingestion of more than one drug) is far more common.

Substances most frequently involved in human exposure are shown in *Figure 2*. In paediatric exposures there is an over-representation of personal care products, cleaning solutions and other household products, with ingestions peaking in the toddler age group. This reflects the acquisition of developmental milestones and subsequent behaviours while 'exploring' their environment.[3] Younger children are also more likely to move objects into their mouths.[4] The majority of paediatric medication errors occur in the home (98.2%) with close family members being involved (83.1%).[5] Poor administration factors also lead to the majority of errors.[6]

Bar-Oz et al[7] identified medications that could kill a toddler weighing 10 kg on ingestion of 1–2 units. This information is reproduced in *Table 1* using Australian dose preparations.

Medications toxic to children

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are cardiotoxic in overdose and may cause serious problems in toddlers who accidentally ingest small amounts. Toxic effects include:

- cardiac sodium channel blocking effects leading to a widening of the QRS interval on electrocardiogram (ECG)
- ventricular arrhythmias
- hypotension
- central nervous system (CNS) depression
- seizures, and
- anticholinergic toxicity.

Patients should be admitted if more than 6 mg/kg of a TCA is ingested, if there are abnormalities on ECG, or if the patient is

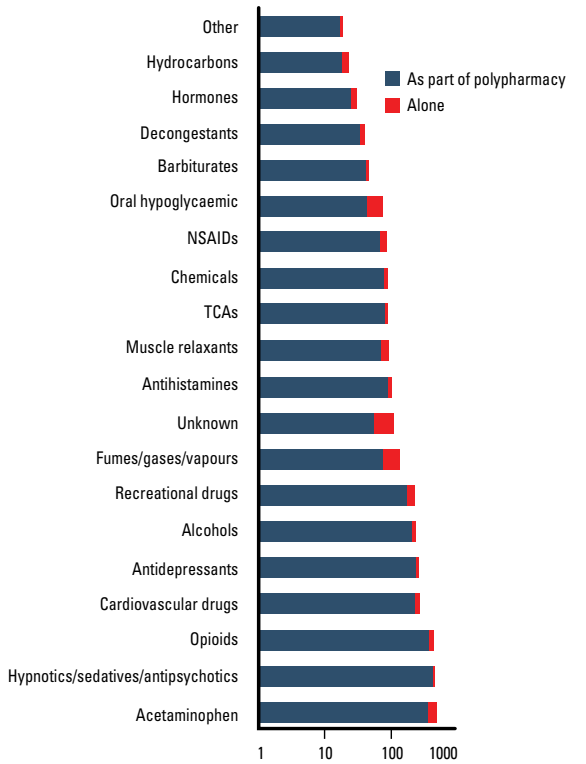

Figure 1. Substances associated with the largest number of fatalaties[2]

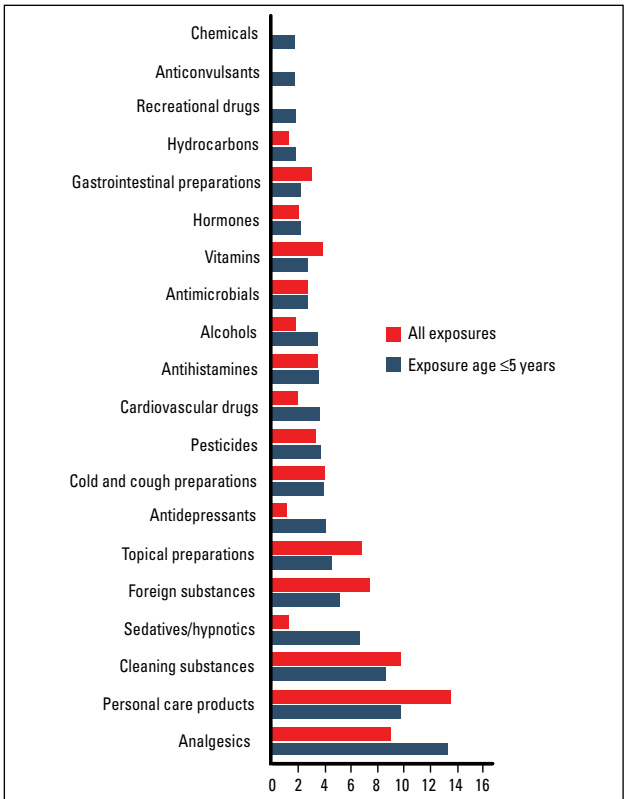

Figure 2. Substances most frequently involved in human exposures (%)[2]

symptomatic. Asymptomatic patients can be discharged after 6 hours of observation.[8]

There has been a decrease in the prescribing of TCAs in recent years following the introduction of selective serotonin re-uptake inhibitors (SSRIs).[2,9]

Calcium channel antagonists

The number of exposures to calcium channel antagonists (CCAs) has increased since the 1990s. Bradycardia and hypotension are the most common manifestations of poisoning with these agents, and deaths of children have occurred from low dose exposures. Nifedipine and verapamil are most closely associated with severe toxicity.[10]

Following a toxic ingestion of regular release CCA formulations, symptoms develop within 6 hours and death may occur within 12 hours.[11] Amlodipine, which has a half-life of over 24 hours, has the potential to delay the onset of symptoms. However, a recent study [10] reported that all patients who ingested amlodipine became symptomatic within 3 hours. Ingestion of sustained release preparations had a more variable time to symptomatology, ranging from 2–14 hours. This likely reflects variation in absorption. Hence, 24 hours of observation is recommended for sustained release medications.[8]

Beta blockers

The bradycardia and hypotension associated with beta-adrenergic receptor antagonists is generally well tolerated in children. However, an underappreciated toxicity of beta blockers that primarily affects children is hypoglycaemia. Hypoglycaemic seizures and coma have been observed in both accidental ingestion and with therapeutic use. Beta-adrenergic blockades may blunt objective signs of hypoglycaemia.[12]

Lipophilic beta-adrenergic blocking drugs, such as propranolol, possess tricyclic-like sodium channel blocking effects that can lead to seizures (ingestion of more than 2 g) and cardiac arrhythmias associated with a widened QRS interval.[12] Sotalol, a beta blocker with type 3 anti-arrhythmic activity, causes dose dependent prolongation of the QT interval, and young children may be susceptible to torsades de pointes after an accidental overdose.[13] Patients who ingest slow release preparations should be observed for 24 hours.

Flecainide

Flecainide acetate is a class 1C anti-arrhythmic used to treat supraventricular and ventricular arrhythmias. It also blocks sodium channels causing a marked depression of the conduction pathways. As a class, 1C anti-arrhythmics have a case fatality rate of 22.5% compared to 1% for all overdoses.[14] Flecainide overdose symptoms include:

- nausea
- vomiting
- hypotension
- bradycardia
- varying degrees of atrioventricular block, and
- tachyarrhythmia.[15]

Symptom onset is rapid, occurring within 30 minutes of ingestion, with serious cardiac conduction disturbances manifesting within 30–120 minutes.[14,16] In one case report a boy, aged 2 years, who was mistakenly given five times his prescribed dose of 5 mg/kg, had a cardiac arrest 3 hours later.[17]

Clonidine

Clonidine, an imidazoline and alpha-2 receptor agonist, is prescribed for the treatment of hypertension, opiate withdrawal and attention deficit hyperactivity syndrome. Toxicity can occur after ingesting 1–2 tablets. Of particular concern are clonidine patches, which contain up to 7.5 mg of clonidine.[18] Absorption is rapid (median time of symptom onset 30 minutes[19]) and symptoms can persist for up to 24 hours. The classic toxicity triad is:

- skin pallor
- miosis, and
- bradycardia.[20]

Children are particularly susceptible to the systemic effects of clonidine, most commonly presenting with altered mental status.[21] It is recommended that asymptomatic children presenting after oral ingestion of clonidine be observed for 4–6 hours. If a transdermal patch or sustained release formula has been ingested, observation for 24 hours is recommended.[22]

Oral hypoglycaemics

Oral hypoglycaemics, used to control blood glucose in patients with type 2 diabetes, are among the most common medications prescribed. Ingestion in children is also common with 1500–2600 cases reported annually in the US.[3,6] Over 50% of ingestions are sulphonylureas.[23] Death is an uncommon outcome, but up to 30% of patients with sulphonylurea ingestion have symptomatic hypoglycaemia.[24] Biguanide ingestions do not cause hypoglycaemia.[3]

Sulphonylureas are absorbed rapidly from the gastrointestinal tract. They may have a prolonged duration of action, and many are formulated in extended release preparations. Clinically, the principal manifestation of sulfonylurea intoxication is hypoglycaemia. There are reported cases of hypoglycaemia after ingestion of a single tablet by children under 5 years of age[3,25] and reported cases of hypoglycaemia developing after 8 hours and up to 20 hours after ingestion. Therefore, all small children who ingest sulphonylureas should be observed in hospital and given food early.[26] Asymptomatic children ingesting normal release preparations should be monitored for at least 8 hours, and those taking extended release preparations observed for 24 hours.[3,24,25,27–29] Treatment should be instigated if blood sugar levels are below 3.3 mmol/L.[30]

Opioids

The multiple forms of opioids are commonly prescribed analgesics. Opioid exposures are common in children.[31] Opioid intoxication has only mild impact on the cardiovascular system with the exception of propoxyphene, which is a cardiac sodium channel blocker and in overdose may cause QRS widening, AV block and arrhythmias.[31] All symptomatic patients need to be observed. Treatment of severe respiratory or CNS depression is with naloxone, an opioid antagonist.

Children who ingest codeine less than 5 mg/kg are unlikely to become symptomatic.[31] Methadone exposure in children is becoming more frequent. Of the 63 cases detailed in the literature, seven (11%) died; and 45 (72%) of the reported children were symptomatic.[32] Significant toxicity occurred at doses as low as 5 mg. Symptoms lasting from 12 hours to almost 3 days have been reported.[31]

Buprenorphine, an opioid agonist/antagonist, is 25–50 times more potent than morphine. It can be used for the treatment of opioid drug dependence.[33,34] In a review of overdose in children the clinical effects included drowsiness (55%), vomiting (21%), respiratory depression (7%), agitation (5%), and coma (2%). There were no fatalities. The mean time to onset of effects was 1 hour. Duration of clinical effects was under 24 hours in almost all cases, and under 8 hours in 70%. Any child ingesting >2 mg, and any child less than 2 years of age with any history of ingestion, should be observed for a minimum of 6 hours.[33]

Diphenoxylate-atropine (Lomotil®) is a combination product used as an antidiarrhoeal that contains 2.5 mg of diphenoxylate and 0.025 mg of atropine per tablet. Diphenoxylate is structurally similar to pethidine and has the potential to cause opioid related symptoms. The combination of the opioid effects and the anticholinergic effects of atropine may lead to decreased gut motility and delayed absorption. For children who have ingested diphenoxylate-atropine, the recommendation is that they be observed for a minimum of 12 hours. Clinical effects vary between opioid and anticholinergic toxicity; drowsiness, irritability and ataxia.[35]

Antimalarials

Antimalarials – chloroquine and quinine, are highly toxic but exposure is infrequent. In 2008, only 830 potential cases were reported in the US.[2] Chloroquine is prescribed for the prevention and treatment of malaria, rheumatoid disease, and lupus erythematosus. Riou et al[36] reported that ingestion of more than 5 g of chloroquine was associated with fatal outcomes. The interval between ingestion and symptom onset is short, and death occurs within 12 hours. In severe poisoning, cardiovascular signs appear early; hypotension and myocardial depression can lead to cardiogenic shock or ventricular arrhythmia. Neurological signs include: altered conscious state, coma, and seizure. Myopathy, neuropathy and hypokalaemia can also occur.

Quinine ingestion generally has a milder cardiac and neurological course. Ocular toxicity occurs in a dose dependant manner, developing 6–12 hours after ingestion, but may be delayed by one or more days. Permanent blindness can occur. Ototoxicity is part of a symptom complex comprising tinnitus, nausea, dysphoria and deafness collectively known as 'cinchonism'. Hearing loss is almost always reversible in acute ingestion.

Alcohols

Toxic alcohols usually refer to ethylene glycol, methanol, isopropyl alcohol and acetone. However, it should be noted that death can occur

Table 1. Fatal toxic doses in a child weighing 10 kg

Drug	Minimal potential fatal dose (mg/kg)	Maximum available dose (single tablet or maximum strength) in Australian formulary[18]	Number of tablets (or amount) that can cause fatality
Tricyclic antidepressants			
Amitriptyline	15	50 mg	2–4
Imipramine	15	25 mg	6
Antipsychotics			
Chlorpromazine	15	100 mg	2–4
		10 mg/mL (mixture)	20 mL
Clozapine	10	200	1
Calcium channel antagonists			
Nifedipine	15	60 mg	2–3
Verapamil	15	240 mg	1–3
Diltiazem	15	360 mg	1
Antarrhythmics			
Beta blockers (propranolol)	Unknown	160 mg	1–2
Disopyramide	15	150 mg	1
Flecainide	25	100 mg	2–3
Clonidine	Unknown	0.3 mg tablet	1
		7.5 mg patch	1 patch
Antimalarials			
Chloroquine	20	NA	NA
Hydroxychloroquine	20	200 mg	1
Quinine	80	300 mg	2–5
Camphor	100		
Eucalyptus oil	Unknown	100% solution	7.5 mL
Methyl salicylate	350	98% solution	3.0 mL
Alcohols			
Methanol	0.5 mL/kg of 100% methanol		15 mL of 40% solution[9]
Ethylene glycol	800 mg/kg or 1.4 mL/kg	95% w/v ethylene glycol	10–14 mL[9]
Isopropyl alcohol		70% solution	140–280 mL
Ethanol	Dependant on concentration (eg. wine, essence) Note: 30–60 mL of cologne could be fatal		
Podophyllin	15–20%, 0.35–0.98 g	Ointment contains 10 g Liquid paint 6 mL (contains 1.2 g)[18]	Less than one container (ointment or paint)
Household cleaning products	Various		See text
Oral hypoglcaemics			
Glibenclamide	<1.0	5 mg	1
Glipizide	<1.0	5 mg	1
Opioids			
Codeine	7–14	30 (combination drug)	2–4
Methadone	5	20 mg	1
Methadone liquid	5	5 mg/mL	10 mL
Morphine		200 mg	1
Diphenoxylate	1–2	2.5 mg	5
Oxycodone	Unknown	80 mg	Unknown

Adapted from Bar-Oz B, Levichek Z, Koren G. Medications that can be fatal for a toddler with one tablet or teaspoonful: a 2004 update. Pediatr Drugs 2004;6:123–6 and Osterhoudt K. The toxic toddler: drugs that can kill in small doses. Contemporary Pediatrics 2000;3:73

following the ingestion of ethyl alcohol. Clinicians must be aware of the potential for hypoglycaemia in addition to CNS depression following ethyl alcohol ingestion in children. Klys et al[37] described the case of a 5 year old boy who drank 120–150 g of vodka containing 40% alcohol (50–60 g of pure ethanol). The child was found dead in his bed the next morning.

Ethylene glycol is used most widely used as a radiator coolant. Methanol is used in paint, varnish removers, antifreeze, and copier fluids as an industrial solvent. It may also be used as a fuel octane booster and as fuel for picnic stoves and soldering torches. These substances cause major toxicity only through their metabolites, so initial symptoms may be mild or absent. Treatment even in asymptomatic patients is initiated as early as possible to inhibit production of toxic metabolites.[38] The lethal dose of ethylene glycol is 1.4 mL/kg, although death has occurred with just 30 mL of the concentrate in adults.[39]

With respect to methanol, serious toxicity may occur from ingestion of 0.25 mL/kg of 100% and death following 0.5 mL/kg of 100% methanol.[40] The metabolic products of methanol and ethylene glycol are organic acids and the presence of a metabolic acidosis and an osmolar gap indicates poisoning.

Isopropanol, found in household rubbing alcohol, is rapidly absorbed within 30 minutes after ingestion; 80–90% of isopropyl alcohol is metabolised via alcohol dehydrogenase to acetone while the remainder is eliminated unchanged by the kidneys.[41] As the metabolite is a ketone, metabolic acidosis does not occur. Unlike ethylene glycol and methanol, most of the clinical effects in isopropanol intoxication are due to the parent compound. Acetone causes only mild CNS depression and clinical signs occur within hour of ingestion. When severe, CNS effects include ataxia, confusion, stupor and coma. Gastrointestinal effects include nausea, vomiting, abdominal pain and gastritis. Hypotension due to cardiac depression and vasodilatation can occur.[42]

Household products

Most poisonings in children aged less than 2 years are with household products, with the majority presenting minor or no medical concern. In general, less than 100 mL is unlikely to cause harm.[43,44]

Cleaning products

Soaps are emulsifiers of fatty acids that cause mild gastrointestinal and mucosal irritation. Detergents, more complex compounds, have low toxicity except when very alkaline products such as concentrated bleach or dishwasher detergent is ingested.[43] Toxicity is related to pH. Any product with a pH less than 3 or more than 13 is considered toxic. Significant exposures include: lavatory cleaners (containing bisulphites, pH 1.4), and drain and oven cleaners (containing sodium hydroxide, pH 13–14).[45] Granular bleaches are more toxic as they tend to be more concentrated and have prolonged mucosal contact.

Children must be observed in the hospital setting if they present with symptoms of:

- drooling or refusing to swallow, or
- complaining of pain in the mouth or chest.[44]

Hydrocarbons

Hydrocarbons constituted 1.9% of all exposures reported on the NPDS in 2008.[2] While this number is small, these exposures represented the 19th most common poisoning and the 22nd most common cause of death listed. These compounds are dangerous because of the risk of aspiration and severe chemical pneumonitis.[44]

The toxicity of hydrocarbons is directly related to their physical properties, specifically the viscosity, volatility, surface tension, and chemical activity of the side chains. The viscosity is a measure of resistance to flow. Substances with a lower viscosity (eg. turpentine, gasoline, naphtha) are associated with a higher chance of aspiration. The surface tension is a measure of the cohesive force between molecules. Like the viscosity, the surface tension is also inversely related to aspiration risk – the lower the viscosity, the higher the risk of aspiration. Volatility is the tendency for a liquid to change to a gaseous phase. The degree of volatility is directly related with the risk of aspiration (and hypoxia). The amount of hydrocarbon ingested has not consistently been linked to the degree of aspiration and hence pulmonary toxicity. The viscosity is the single most important chemical property associated with aspiration risk.[46]

All organ systems can be affected by hydrocarbon ingestion. The pulmonary system is the most commonly involved.[47] Examples of small dose exposures leading to death include cases of:

- a 14 month old boy ingested/aspirated a mouthful of lamp oil (kerosene and gasoline) and died[48]
- a 15 month old boy who ingested/aspirated one mouthful of motor oil and died 51 days after ingestion[49]
- a 2 year old girl ingested/aspirated 15–30 mL of hair-weaving remover (ie. 20% mineral oil, 30% mineral spirits) and died 2 days after ingestion.[50]

Eucalyptus oil

Toxicity of eucalyptus was first reported in 1925.[51] Tibballs[52] reviewed paediatric ingestions over 11 years. The mean age was 23.5 months. Clinical effects, observed in 59%, included depressed conscious state, vomiting and ataxia; aspiration occurred in 11% of patients. All patients recovered.

Significant depression of conscious state followed ingestion of 5 mL or more of eucalyptus oil and minor depression of consciousness may occur after the ingestion of 2–3 mL of 100% oil. Symptom onset occurs within 30 minutes.[53] The most common sources of exposure are vaporiser solutions (74%).

Camphor

Camphor is a common ingredient in a wide range of over-the-counter topical liniments, including Vick's VapoRub® and Tiger Balm® (many brands containing 9–11% camphor). Higher concentrations can be found overseas and bought online.[54,55] Camphor acts as a topical rubefacient,

inducing local hyperaemia and warmth. It is also used as an insecticide, particularly in the prevention of silverfish infestation in wardrobes. Seizures, the most severe manifestation of toxicity, occur within 90 minutes.[56] Asymptomatic patients should be observed for 6–8 hours.

Methyl salicylates

In 2003 in the US, 62% of all salicylate exposures were due to substances containing methyl salicylate,[6] a substance used as a traditional remedy for muscle and joint aches. High concentrations of methyl salicylates are found in oil of wintergreen (98% methyl salicylate). Each mL of oil of wintergreen contains 1.5 g of salicylate, one teaspoon is equivalent to approximately 7000 mg of salicylate or 21.7 adult aspirin (325 mg) tablets.[57] The potentially lethal dose is 3 mL.[8] In Australia, methyl salicylates are found as oils in products such as Austral Balm®, or in liniments and creams such as Metsal®, Dencorub® and Tiger Balm®, which contain 30–40% methyl salicylate. In liquid form they are rapidly absorbed and toxic blood levels are reached earlier than ingestion of aspirin containing tablets.[58]

Salicylate poisoning causes direct stimulation of the medulla causing:

- nausea
- vomiting
- tinnitus
- deafness
- hyperventilation, and
- respiratory alkalosis.

Metabolic effects include metabolic acidosis, hypoglycaemia and hypokalaemia. Fever and sweating are common. Later effects include gastrointestinal haemorrhage, altered mental status with coma, and seizures associated with cerebral oedema, pulmonary oedema, respiratory distress syndrome and renal failure. In adults the estimated fatal dose is 60–100 mL.[59] There are no agreed guidelines regarding the period of observation, but it is expected that symptoms occur rapidly.

Other household products

Methacrylic acid containing primers used in artificial nail cosmetic products (glue) are highly corrosive and have been associated with respiratory toxicity and cutaneous burn.[60] These glues may also cause methaemoglobinaemia.[61]

Acrylonitrile (an artificial fingernail glue remover) is metabolised by the liver to cyanide. There is a long latency period (up to 16 hours) as it is metabolised into the toxic cyanide compound. The toxic amount is 5–30 mL.[62]

Napthalene (moth balls) causes haemolysis and methaemoglobinaemia.

Conclusion

Paediatric exposures are typically nonintentional and involve substances left within reach of the exploring toddler, or administered by an adult in a manner that leads to a dosing error. Hence, primary measures aimed at risk reduction should have an impact on the number and nature of these adverse events. Childproof locks and keeping dangerous household cleaners out of reach should be effective in reducing accidental ingestion. Adult exposures are far more likely to be intentional and risk reduction methods such as blister packaging and container labelling are unlikely to reduce incidence or fatality.

Given the potential number of intoxicants, this article has explored substances that:

- are known to cause significant morbidity and mortality in low doses
- are less familiar to the general practitioner
- require prolonged observation, and
- require hospital referral.

It has not been our intention to outline management and we would recommend the reader to look up further details in any of the standard toxicology texts. The authors encourage readers to contact the Poison Information Service early whenever there is a concern of 'small dose... big poison'.

Resource

Poison Information Centre 13 11 26 (24 hours a day, 7 days a week service).

Conflict of interest: none declared.

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