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REVIEW-THEMED ISSUE

Who gets antidotes? choosing the chosen few

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An understanding of mechanisms, potential benefits and risks of antidotes is essential for clinicians who manage poisoned patients. Of the dozens of antidotes currently available, only a few are regularly used. These include activated charcoal, acetylcysteine, naloxone, sodium bicarbonate, atropine, flumazenil, therapeutic antibodies and various vitamins. Even then, most are used in a minority of poisonings. There is little randomized trial evidence to support the use of most antidotes. Consequently, decisions about when to use them are often based on a mechanistic understanding of the poisoning and the expected influence of the antidote on the patient's clinical course. For some antidotes, such as atropine and insulin, the doses employed can be orders of magnitude higher than standard dosing. Importantly, most poisoned patients who reach hospital can recover with supportive care alone. In low risk patients, the routine use of even low risk antidotes such as activated charcoal is unwarranted. In more serious poisonings, decisions regarding antidote use are generally guided by a risk/benefit assessment based on low quality evidence.

Keywords adverse reaction, antidote, benefits, evidence, overdose, toxicity

Introduction

'Don't just do something, stand there' – Anon

This themed issue of the journal contains a series of articles covering the contemporary approach to a range of antidotes. Derived from the Greek antididonai ('*given against*'), antidotes appear from the earliest medical history. The concept is an appealing one: for every poison there really should exist an antidote. 'What's the antidote?' is a common response to a diagnosis of poisoning. However, most patients do not require antidotes, which are only indicated in a small group of patients. The reasons that most patients do not get antidotes or antidotes are failed to be administered where indicated, go beyond standard factors (cost, availability, prescriber knowledge, disease severity) that determine whether treatment is used for other indications. Indications for appropriate use continue to evolve and may contribute to clinical uncertainty in individual cases.

Over the centuries, many more antidotes have been adopted and discarded than are in current use. Many examples exist of well-intentioned use of highly toxic antidotes, for example, nicotine and chloroform [1]. There is still a wide range of antidotes proposed for serious poisonings. Many are stocked but rarely used. An understanding of the mechanisms, potential benefits and risks of each antidote underpins the practice of clinical toxicology.

The most intuitive antidotes are those that operate through a well-defined mechanism, such as competitive receptor antagonists (e.g. naloxone and flumazenil) [2], vitamins (K, B6, folinic acid) to overcome enzyme inhibition [3], replenishing antioxidant defences (acetylcysteine) [4] or those that reduce the effective concentration of toxin (e.g. activated charcoal [5], therapeutic antibodies that bind toxin) (Table1). For these antidotes, both dose and duration of treatment are often titrated.

Some antidotes have established roles in other diseases, but their use as 'antidotes' requires much higher doses in light of the grossly disturbed physiology of the poisoning. Examples include β-adrenoceptor agonists (e.g. isoproterenol and epinephrine) for β-adrenoceptor blocker poisoning [6] and atropine for anticholinesterase pesticide poisoning [7]. Other agents such as insulin and glucagon sometimes are used at extraordinary doses as inotropic antidotes in order to address downstream or secondary toxicities through other mechanisms [6].

The use of high doses of antidotes has implications for drug supply and staff training. For example, although inotropes are

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Table 1

The ABC or (3Rs) of antidote mechanisms/actions.

	A	B	C
Action	Absorption/Abate (Reduce dose)	Block/Bypass (Restore function)	Control/Cope with consequences (Rescue and support)
Timing	Early	Variable (depends on agent time course)	Variable (depends on recovery time course)
Maximal efficacy	Moderate (very time dependent)	High	Low to moderate
Dosing adjustment	Fixed (or varies with exposure /concentration)	Titrated against direct toxic effect	Titrated against physiological disturbance
Example toxin 1 Methotrexate	Carboxypeptidase	Folinic acid	Colony stimulating factor
Example toxin 2 Warfarin	Activated charcoal	Vitamin K_1	Clotting factor replacement
Example toxin 3 Benztropine	Activated charcoal	Physostigmine	Benzodiazepines

commonly available for cardiac supportive care, they are not generally included in recommended antidote stocking lists (Table 2) [8, 9], whereas agents such as atropine that can have very high dose requirements (up to 200 mg day^{-1}) are. Moreover, other drugs that counteract the effects of certain poisonings are not generally regarded as 'antidotes', for example, prazosin in scorpion envenoming [10], vasopressin in calcium antagonist overdose [6], antihistamines in scombroid poisoning and benzodiazepines for toxin-induced seizures [11].

Benefit from antidotes is generally time-dependent and uncertain

Evidence for most antidotes is based on animal studies and uncontrolled human series. In a few cases, the results are so striking that they meet 'all or none' criteria for high quality evidence. This concept, proposed by the Oxford Centre for evidence based medicine, considers strong evidence for effectiveness is 'met when all patients died before the treatment became available, but some now survive on it or when some patients died before the treatment became available, but none now die on it' [12]. Perhaps the best example of this is acetylcysteine, which consistently prevents fulminant hepatic failure (the mechanism of paracetamol-mediated death) when given in the first 6 to 8 h following acute overdose. Prior to its introduction, death occurred in 3 to 5% of patients with paracetamol overdose [4]. As such, a placebo-controlled randomized trial of acetylcysteine in this setting is both redundant and unethical.

For other antidotes, a clinical effect is pharmacologically expected, obvious and rapid (e.g. reversal of coma with flumazenil or naloxone, or resolution of delirium with physostigmine). However, this does not necessarily translate into improved clinical outcomes over supportive care [2].

Many diagnoses result almost automatically in a series of treatments. For example, myocardial infarction may trigger up to six or seven new evidence-based prescriptions. However, such a reflexive approach is not recommended for any antidote or poisoning. The explanation for this lies, in part, in the time course of most poisonings and the often narrow window in which an antidote might be useful (Tables 1, 2). Most orally ingested toxins are rapidly absorbed and reach maximal toxic effect within a few hours. For most lethal agents, the majority of deaths occur in the prehospital setting [13]. Patients who reach hospital typically arrive 2 to 4 h after ingestion [14]. Thereafter, drug concentrations are more likely to be falling than rising (once distribution and elimination outweigh absorption). For some drugs, patients rapidly acquire tolerance for receptor-mediated effects [15]. Thus it is largely the agents with both serious AND delayed toxicity that present a challenge for management and that warrant antidotes. This includes many controlled release drugs, poisons targeting mitochondria and other intracellular processes, such as paraquat, and poisons that generate more toxic metabolites, such as most organophosphates, some alcohols and paracetamol.

However, for many poisoned patients, clinical improvement is expected with nothing more than supportive care. Indeed, most clearly preventable deaths from poisoning are due to a lack of timely supportive care rather than failure to administer an antidote [13]. Even low risk gastrointestinal decontamination methods such as activated charcoal have been shown to not warrant routine use in randomized controlled trials in both developed and developing world settings [5, 16, 17].

It is difficult to provide evidence for the effect of an antidote on anything other than surrogate outcomes, and then only for common poisonings. The key to optimal antidote use involves identifying situations in which their use might result in meaningful improvements in morbidity or mortality. In light of the limited evidence, this determination is often more art than science. For example, antidotes may be indicated relatively early in the course of poisoning when there are established predictors of a poor outcome (e.g. high serum methanol concentrations, marked QRS or QT prolongation). The determination may be based simply on a global impression when patients appear to be rapidly deteriorating while receiving maximal supportive care.

Poison-induced cardiac arrest and refractory shock are leading causes of in-hospital death from poisoning that might be responsive to antidotes. They represent situations in which the risk : benefit ratio is more likely to be favourable despite the

Table 2

Antidotes in current use

Antidote (Action*)	Most common/important poisoning indication	Other indications	Widely stocked†	Maximum daily dose‡
Acetylcysteine (B/C)	Paracetamol	Amanita, paraquat	UK, US, Ca, Au	30 g
Activated charcoal (A)	Large overdoses of toxic substances (carbamazepine, colchicine, paracetamol, CCB)	Sustained release drug overdose	UK, US, Ca, Au	240 g
Andexanet (A)	Rivaroxaban, apixaban	Other Factor Xa inhibitors		
Atropine (B)	Organophosphorus pesticide	Carbamates, cardiac glycoside, CCB and β-adrenoceptor blockers	UK, US, Ca, Au	200 mg
Benzodiazepines (C)	Amphetamines	Other stimulants, drug induced delirium	Я	
Calcium salts (B)	CCB	Hydrofluoric acid	UK, US, Ca, Au	30 g
Calcium trisodium pentetate (A)	Plutonium	Curium, Americium		
Carboxypeptidase (A)	Methotrexate			
Carnitine (B)	Valproate			
Cyanide kit OR dicobalt edetate OR hydroxocobalamin (A)	Cyanide		UK, US, Au	1 kit 10 g
Cyproheptadine (B) (or chlorpromazine)	Serotonin syndrome		UK,	
Dantrolene (C)	Neuroleptic malignant syndrome	Malignant hyperthermia	UK,	
Deferrioxamine (A)	Iron		UK, US, Ca, Au	36 g
Digoxin specific Fab fragments (A)	Digoxin toxicity	Other cardiac glycosides: plants (e.g. oleander), toads (bufotoxins).	UK, US, Ca, Au	800 mg
Dimercaprol (A)	Arsenic	Mercury, lead	US, Ca	1.5 g
Ethanol (B)	Methanol	Ethylene glycol	UK, US, Ca, Au	500 g
Flumazenil (B)	Benzodiazepine	Zopiclone/zolpidem	UK, US, Ca, Au	20 mg
Folinic acid (B)	Methotrexate		UK, US, Ca, Au	
Fomepizole (B)	Methanol, ethylene glycol	Diethylene glycol Disulfiram reaction	UK, US, Ca	4.5 g
Glucagon (C)	β-adrenoceptor blocker	CCB	UK, US, Ca, Au	250 mg
Insulin (B/C)	CCB	β-adrenoceptor blocker, potassium	Я	10 000 IU
Intralipid (A)	Bupivicaine	Lignocaine, drug-induced cardiac arrest	UK, Я	500 ml
Methylthioninium chloride (methylene blue) (B)	Methemoglobinemia	Refractory shock	UK, US, Ca, Au	1000 mg
Naloxone (B)	Opioid		UK, US, Ca, Au	20 mg
Octreotide (B)	Sulfonylurea	Insulin (if endogenous contribution suspected)	UK, US, Ca, Au	1500 μg
Phenobarbitone (C)	Theophylline/caffeine	Strychnine	Я	
Physostigmine (B)	Anticholinergic drugs	Plants (*Datura*, etc...)	US	4 mg
Phytomenadione (B) (vitamin K)	Warfarin	Long acting rodenticides i.e. superwarfarins such as brodifacoum	UK, Ca, Я	100 mg

(continues)

Table 2

(Continued)

Antidote (Action*)	Most common/important poisoning indication	Other indications	Widely stocked†	Maximum daily dose‡
Polyethylene glycol (A)	Modified-release drug overdose	Iron, lithium	Я	
Potassium iodide (A)	Radiation			
Pralidoxime (B)	Organophosphate		UK, US, Ca, Au	12 g
Protamine (A)	Heparin			
Prussian blue (A)	Thallium	Cesium		
Pyridoxine (B)	Isoniazid		US	24 g
Silibinin (A)	*Amanita phalloides*	Other cyclopeptide mushrooms		5 g
Sodium bicarbonate (A)	Sodium channel blocking drugs	Salicylate, CCBs, phenobarbital, chlorphenoxy herbicides	Я	500 mEq
Succimer (A)	Lead	Arsenic, mercury		3000 mg
Antivenom/antitoxin-mono or polyvalent (A)	Snakes	Scorpions, spiders, stonefish, jellyfish, botulism	UK, US, Ca, Au	

*Actions - A pharmacokinetic to reduce dose, B block/bypass toxic effect to restore normal function, C control/cope with consequences to rescue patient. Я likely to be stocked anyway for other indications; CCB calcium channel blocker. †Routinely recommended as stocked in Emergency Departments in the United Kingdom (UK), United States (US), Canada (Ca) or Australia (Au) [8, 9, 32, 33]. Chelating agents for chronic heavy metal exposures do not require urgent administration, but the absence of other agents from emergency departments reflects an unfavourable assessment of the cost-effectiveness of stocking based on the frequency of the indication and the cost. ‡Likely to be sufficient to treat most patients for at least 24 h, note that for some agents much more prolonged treatment may be required and these requirements are not listed.

low level of evidence associated with most antidotes. In other words, in the sickest patients, the spectre of antidote-related harms becomes less of a consideration. In this setting there is often no evidence other than case reports and animal studies (which are often of questionable relevance to overdose [18]). Frequently, the involved toxin is unclear at the time of presentation, and yet, in contrast to non-toxic causes of cardiac arrest, prolonged resuscitation can be followed by an excellent outcome [19]. A wide range of antidotes are worth consideration in suspected toxin-induced cardiac arrest (Table 3).

Risks associated with antidotes often govern the threshold for use.

Given the uncertain benefits, enthusiasm for use of particular antidotes is often determined by the risks of the treatment, which are generally much better quantified. Many commonly used antidotes are generally extremely safe (e.g. activated charcoal, vitamin K, folinic acid). Some parenteral agents commonly cause immediate hypersensitivity reactions (e.g. acetylcysteine (numbers needed to harm [NNH] 2–4 depending on rate) [4], antivenoms/antibodies (NNH <2 to >20) [20–22]). Adverse reactions to antivenoms are a major problem, particularly in resource poor nations, with severe reactions occurring in 30 to 80%. This has resulted in premedication being used prior to antivenom administration [22]. However, only epinephrine (adrenaline) appears to be beneficial based on randomized controlled trials [23].

Excessive antidote dosing is a surprisingly common problem. Due to the complex and rapidly changing poison concentrations and extreme variability among patients, any 'fixed dose' strategy can easily result in both under and over-treatment. Effects from excessive doses are fairly predictable. For example, excessive acetylcholinesterase inhibition (as seen following physostigmine for antimuscarinic toxicity) commonly results in cholinergic excess [24], excessive dextrose administration (for sulfonylurea toxicity) frequently leads to rebound hyperinsulinaemia and hypoglycaemia [25], and excessive doses of naloxone or flumazenil can precipitate withdrawal symptoms, agitated delirium and occasionally seizures, depending on the patient and toxin [2, 26]. The use of antidotes in mixed overdoses (which represent the majority of cases presenting to hospital) greatly increases the risks of adverse consequences. For example, naloxone might precipitate withdrawal and flumazenil precipitate seizures without reversing coma in patients with a concomitant antipsychotic overdose. Similarly, acetylcysteine might worsen hypotension in a patient presenting with a mixed overdose involving paracetamol and a cardiotoxic or sympatholytic drug.

Serious adverse effects of antidotes can result from dosing errors (particularly common with infrequently used antidotes), those requiring reconstitution and dilution, and those generally employed at lower doses for non-toxic conditions (such as insulin). For example, more errors are made with ethanol than fomepizole for methanol and ethylene glycol poisoning [27]. Ten-fold dosing errors have led to lethal anaphylaxis with acetylcysteine [28] and excessively high doses for pralidoxime likely explain excess deaths associated with its use in a recent randomized clinical trial [7].

A final problem is the interference with therapeutic effects of the target or other drugs. In particular, charcoal can

Table 3

Antidotes that may be used in cardiac arrest (The A to P of treatment tips for toxic tickers)

Agent	Indication
A (Airway) atropine, epinephrine (adrenaline), activated charcoal	Abolishing vagal effects and vasoconstriction are favourable for most drugs. Give charcoal to prevent ongoing absorption.
B (Breathing) bicarbonate	pH correction mitigates toxicity of many drugs
C- (Circulation) calcium	CCBs and hydrofluoric acid
D diazepam; dextrose, do not stop early	Amphetamines and other stimulants, hypoglycaemia.
E ECMO	Worth considering early if available
F Fab	Envenoming, digoxin (or colchicine)
G glucagon	Hypoglycaemia, β-adrenoceptor blockers
H hydroxocobalamin	Cyanide
I insulin	CCBs/β-adrenoceptor blockers/ hyperkalaemia
J joules	Pacing or shock as per resuscitation protocols
K correct K^+	Antimalarial overdose, salicylate, QT prolongation
L lipid	Local anaesthetics
M methylene blue, magnesium	MetHB, refractory shock, QT prolongation/torsade de pointes
NO	NO response????
P phone the Poison centre!	

enhance total body clearance of many other drugs such as anticonvulsants and oral contraceptives, while 'lipid rescue' can potentially interfere with lipid soluble medications and many biochemical assays [29]. For many antidotes, the risks can be managed safely when initiated in a closely monitored setting such as a critical care area or emergency department, where adverse effects are more easily identified and treated.

Highly individualized dosing of antidotes optimizes the risk : benefit ratio

Many antidotes have a wide dosing range, short half-lives and require repeated doses. The dose/concentration of the poison is often unknown, and the poison may have a much longer elimination rate. Such problems can often be overcome by titrating antidote doses to the required effect. For example, naloxone has a half-life of less than 1 h and initial doses required to reverse opioid induced coma can vary from 0.04 to 15 mg, depending on opioid and amount. It is common to start low and employ rapidly escalating doses to titrate to effect, and then (if prolonged antidote requirement is anticipated) start an infusion to maintain an effective antidotal response. For naloxone, this is typically half to two-thirds of the initial dose per hour [30]. The required duration of therapy will be determined by the amount of opioid ingested and its elimination rate, and the degree of individual tolerance to opioids [2].

Titration to the desired effect is also generally used for atropine (titrated to cholinergic signs in cholinesterase inhibitor poisoning) [7], flumazenil (coma) [2], vitamin K (prothrombin time) [3], protamine (activated partial thromboplastin time), octreotide (blood glucose) [25], methylene blue (methaemoglobinaemia), calcium (blood pressure) [6], insulin (blood pressure), physostigmine (coma or delirium) [24], sodium bicarbonate (blood or urine pH), ethanol (ethanol concentration) and digoxin-Fab (rate and rhythm) [31]. The dose of an antidote can be far higher than the doses required when these drugs are used for other indications (Table 2). For example atropine, pyridoxine and vitamin K may be given at doses 100-fold greater than traditional therapeutic doses.

There are exceptions to this general rule. Interventions altering drug absorption (charcoal, polyethylene glycol) are generally used in fixed supra-maximal doses in most cases. Some antidotes altering distribution or elimination also have fixed doses which aim to completely block an enzyme (e.g. fomepizole for toxic alcohol poisoning) or transporter (silibinin for *Amanita* poisoning). This is also true of those with no widely accepted method to titrate dosing (acetylcysteine).

Conclusion

There are dozens of antidotes used for hundreds of potential toxins, but only a few are used regularly. The most commonly used include activated charcoal, acetylcysteine, naloxone, sodium bicarbonate, atropine, flumazenil, therapeutic antibodies and various vitamins. Most antidotes are of low toxicity, but serious adverse effects can result from excessive use, as well as from inadequate doses. In all cases, specialist toxicological advice should be sought when treating rare poisonings or when deploying uncommonly used antidotes (in the United Kingdom through the National Poison Information Service).

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work.

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