

Prompt and adequate treatment of poisoning may be facilitated by a collaborative approach to antidote storage

New unified national guidance on antidotes availability in the UK was released in May 2008 from the British Association for Emergency Medicine, Guy's and St. Thomas' Poisons Unit and the National Poisons Information Service. This guidance addresses key concerns about the stocking of antidotes in UK emergency departments and provides departments with a template for making appropriate arrangements for the timely treatment of a range of poison cases as explained by James Allen.

Introduction

In the year 2000 poisoning was the ninth most common cause of death globally in young adults aged 15–29 years.¹ In this year an estimated 250,000 people worldwide died as a result of intentional ingestion of chemicals,¹ ensuring that poison prevention and management were on the agenda for the World Health Organisation (WHO).

Admissions relating to poisoning are common throughout the UK. In 2006 poisoning accounted for around 13% of hospital admissions.² The ability and capacity to treat these admissions highlights a number of practical pharmaceutical issues coupled with governance issues surrounding the timely availability of antidotes and the quantities available. This article will cover the practical aspects of the newly launched guidance on antidote availability throughout UK emergency departments. References and further reading provide an opportunity to discover more about this area of emergency medicine.

Background

After reaching a peak in 1999, deaths relating to poisonings have been steadily decreasing in the UK.³ In 2006 approximately 2570 deaths were attributed to poisonings, the lowest recorded number since 1995.² In 2005 The British Association for Emergency

Medicine (BAEM) and Guys & St Thomas' Poisons Unit surveyed emergency departments throughout England. They found that there were significant inconsistencies regarding stocking and availability of antidotes. As a result of this, the BAEM and Guys & St Thomas' Poisons Unit collaborative⁴ launched the 2006 guideline on antidote availability for A&E departments; this was shortly followed by separate guidance issued by the National Poisons Information Service (NPIS).⁵

Re-evaluation and comparison of

these guidelines highlighted significant overlap and some key differences in the recommendations published by BAEM and the NPIS. When a second survey was undertaken in 2008 significant progress had been made regarding the inadequacies in antidote availability.⁶ However, inconsistencies between BAEM and NPIS guidelines still existed (see Table 1) and it was clear unified guidance was necessary to ensure further progress.

In May 2008 the BAEM, Guys & St Thomas' Poisons Unit and the NPIS

Table 1. Key differences between the superseded BAEM and the NPIS guidelines.

British Association for Emergency Medicine (BAEM) and Guys & St Thomas' Poisons Unit	National Poisons Information Service (NPIS)
Time-scales for access to antidotes - Immediately - Within 1 hour - Within 4 hours - Supra regional	Location of antidote denoted the suggested time-scale for access. The locations suggested were as follows: A – Within the hospital B – Local arrangement for supply C – Not essential to stock
Suggested stocking quantities based on quantities sufficient to treat 1 patient for 24 hours	Stock required to treat 2 patients for 48 hours for all medicines within category A.
Provided dosing information	Retained dosing information within Toxbase website
Contained Cyanokit within the immediately available group	Suggested Cyanokit was not necessary

Further information regarding specific antidotes can be found in the main body of the article

collaborative published new unified guidance on the stocking of antidotes throughout UK emergency departments.⁷ Areas of duplication and confusion between earlier guidelines were addressed, time-scales rationalised and the role of newer antidotes formalised.

Timely access to antidotes

A number of international and national surveys have highlighted problems surrounding the timely access to antidotes.^{8–10} In an attempt to address this the International Programme on Chemical Safety (IPCS) published recommendations on the availability of antidotes in the early 1990s.¹¹ Within this guidance initial time-scales were suggested but no specific reference to individual antidotes was provided.¹¹

The timescale for antidote availability remains central to the UK published guidance.^{4–6} Nevertheless, it is necessary to be mindful of the balancing act surrounding governance to the patient and economy for the organisation. Undoubtedly, sourcing initial stocks from supra-regional centres — and even local hospitals — provides an inherent risk of treatment delay to the poisoned patient. However, the relatively low incidence of some poisonings can make it uneconomical and impractical to stock large quantities of all the potentially necessary antidotes.

Specific antidotes are listed within the guidance based on the urgency of access and administration after poisoning has been diagnosed. These time-dependency levels are categorised as antidote availability requirements as follows:⁷

- Immediately — held within the emergency department
- Within 1 hour — held within the hospital
- Regionally or held as supra-regional stock — obtainable from local hospitals, regional centres and poisons centres.

Often the time to diagnosis and development of a treatment plan can delay the administration of the antidote. Once a

diagnosis is confirmed further treatment delays should ideally be limited and it is for this reason that the original 4-hour time-scale was removed from the new guidance. The majority of medicines within this group have been shared throughout the two more acute time-scales. The regionally held group of antidotes do not have a specific time window for access. Urgency will be patient specific, but is expected to be a number of hours.

Points for local reflection

Local hospitals will need to give special consideration to the suggestion of stocking fomepizole (Antizol[®]) and formalising the inclusion of Digibind[®] (digoxin-specific antibody fragments), Cyanokit[®] and European Viper venom antiserum to the 'within the hospital' time-scale category.



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Fomepizole (Antizol[®]) is a competitive inhibitor of alcohol dehydrogenase.¹² It is used to treat ethylene glycol (a major constituent of antifreeze) and methanol poisoning.¹² By inhibiting alcohol dehydrogenase the hepatotoxic metabolites are avoided and clearance of the parent compounds can be undertaken unchanged by the kidneys. It is currently unlicensed in the UK and on an acquisition basis relatively expensive compared with the traditional treatment option of ethanol as an alternative competitive inhibitor. These factors have hitherto ensured it is rarely stocked in the UK,⁶ but when taking into account the ease of administration and the predictable kinetics (which negate the need for blood assays) fomepizole can be considered an economic option.¹³ Because it is suggested as a first-line option alongside ethanol, hospitals rarely dealing with these poisoning cases may choose not to stock this antidote. Although this is a governance

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issue in its own right the required decision about whether to stock fomepizole must be explained clearly to clinicians dealing with these poisonings. Studies from the US, where fomepizole is licensed and more readily available, suggested that when the option of either ethanol or fomepizole was provided by poisons advice services the delay to treatment was longer than when ethanol was suggested as the sole choice of therapy.¹⁴ This may have resulted from clinicians' unfamiliarity with fomepizole or because of time spent sourcing fomepizole in centres where it is not held. Both highlight an educational need of the clinicians involved in treating these patients and represent a potential educational need in the UK.

Digibind[®] consists of antigen-binding fragments (Fab) derived from specific anti-digoxin antibodies.¹⁵ When administered intravenously the affinity of Fab for digoxin is greater than that of digoxin for its receptor and digoxin is attracted away from its receptor on cardiac tissue.¹⁵ The inactive Fab-digoxin complex is eliminated renally with a proportion of the Fab proteins catabolised in the kidney by the proximal renal tubular cells.¹⁵ It is the only specific antidote for significant digoxin toxicity where patients are in circulatory collapse secondary to significant bradycardia. Its high cost and specific storage requirements (below 8°C) have meant traditionally it has been kept within pharmacy departments or even supra-regionally for smaller hospitals where expiry is a significant possibility. The need for rapid access within the emergency department has ensured this antidote was formalised to a 'within hospital' time scale.

Cyanokit[®] (Hydroxocobalamin) was originally thought unnecessary in the NPIS guidelines.⁴ There is recent evidence,

Emergency medicines

however, for its use in the specific scenario of comatose smoke inhalation victims where cyanide poisoning is a significant possibility.^{16,17} In this scenario hydroxocobalamin molecules bind cyanide molecules on a one-to-one basis to create cyanocobalamin, which is subsequently renally eliminated.¹⁸ It is now suggested as the only preparation suitable to treat smoke inhalation victims who have a severe lactic acidosis, are comatose, in cardiac arrest or have clear signs of cardiovascular extremis.⁷

The European adder (*Vipera berus*) is the only venomous snake native to the UK.¹⁹ Each year in the UK adders bite around 100 people with around 50% of these bites being on the hand secondary to attempting to pick up the adder.^{19,20} Not all individuals bitten will seek medical attention — a fact that complicates the collation of robust incidence data.¹⁹

There is significant seasonality in terms of the adder population and this obviously has a consequence on monthly prevalence of adder bites in the UK. The majority of bites occur within the months of June to August with July being the peak month.^{19,20} This is because adders spend much of the winter months hibernating. However, in some southern parts of the UK adders may emerge as early as January and continue activity throughout the year until November.¹⁹ Adders are not distributed evenly throughout the UK¹⁹ and this is reflected in the distribution of bites with the mean yearly number of bites ranging

from one in some UK regions to eight for the whole of Scotland.¹⁹ Much of the data are collated from small geographical areas attached to one hospital and extrapolated to national scale and so are not accurate.¹⁹

The relative low potency and small amounts of venom delivered when bitten mean that deaths from adder bites are very rare in adults. Only around 14 deaths have been observed in the UK over a period of nearly 100 years.²¹ Severe systemic symptoms can be observed and include persistent hypotension, syncope and anaphylactoid reactions. It has been noticed that constituents within the venom can have significant cardiac effects including heart block and T wave inversion.¹⁹ However, for the most part, adder bites in adults cause pain, local tissue swelling and bruising because of the cytotoxic nature of the venom.¹⁹ The viper venom antiserum, is indicated in cases displaying one or more of the following:^{20,21}

- Persistent hypotension (with or without systemic shock),
- Signs consistent with systemic envenoming i.e. Leucocytosis, ECG abnormalities or metabolic acidosis
- Extensive or rapidly progressing swelling
- Any case involving swelling of the forearm.

The removal of the 4-hour timescale has led to the suggestion of that viper venom antiserum should be available for areas of high prevalence within the more acute (1 hour) timescale.⁷ Since robust UK prevalence data are not known (and is likely to be dynamic with climate changes) smaller departments may still want to make individual decisions based on local numbers of adder bites presenting to their departments. It is worth noting that for the north

of England and Scotland detailed lists of holding centres are contained within Toxbase.²²

The relative high cost of these antidotes and the relative rarity of their use meant that when surveyed in 2008 responses suggested these antidotes were rarely stocked. A potential solution to the initial burden of purchasing these antidotes would be to collaborate with neighbouring hospitals and



poisons centres. This would entail individual departments ensuring there were sufficient stocks to initiate therapy on the pretence that further stocks could be collated from neighbouring hospitals and used if deemed necessary. This collaborative approach is supported in the unified BAEM and NPIS guidance and the original 1998 guidance by IPCS, both of which encourage national networks to be set up for sharing resources so as to provide consistency regarding access to antidotes.¹¹ To an extent this system already exists within the South East and London regions who have a 'rarely used medicine (RUM) list'²³ and provide stock lists for poisons centres within Toxbase.²² These alleviate the burden on some trusts and provide shared access to resources.

The collaborative approach is being taken one step further in the US where data mining of the hospital pharmacy computer system provides an up-to-date database of antidote availability. This database is then used to direct the attending ambulance technicians (where a source of poisoning is confirmed) to an emergency department equipped to manage the patient.²⁴ Obviously this later option doesn't cover patients in which the poison is unknown and where some of the aforementioned issues remain.

Table 2. Recommended unlicensed medicines and their therapeutic uses*

Unlicensed medicine	Therapeutic use
Calcium gluconate gel	Hydrogen fluoride exposure
Cyanokit (Hydroxycobalamin)	Cyanide poisoning – Specifically comatose smoke inhalation victims
Sodium thiosulphate and Sodium nitrite	Severe cyanide poisoning
Fomepizole	Ethylene glycol and Methanol poisonings
Pyridoxine (High dose) injection	Isoniazid poisoning
Methylene blue	Methaemoglobinaemia
European Adder antivenom	Adder bites

*excluding supra-regionally stored antidotes

Self-sufficiency

Throughout the UK there is significant heterogeneity in the operational aspects of emergency departments. Larger emergency departments may have the capacity to manage poisoned patients for 24–48 hours in clinical decision units whereas other departments may move patients much earlier to admissions wards to complete antidote therapy. Historically guidelines did not purvey this approach to implementer organisations, but left very specific guidelines regarding suggested stocking levels.^{4,5}

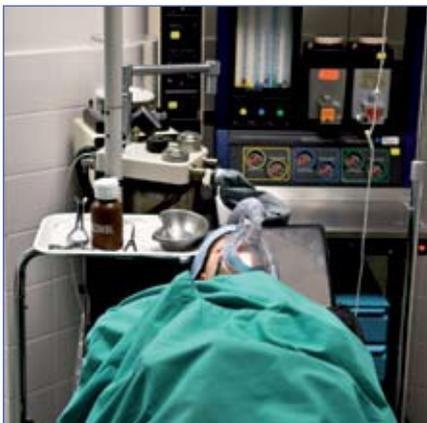
The initial BAEM antidote guideline suggested the quantities required to treat an average adult patient for 24 hours.⁵ This approach was intended to allow discretion by the implementer trust to take into account environmental factors and the incidence of local poison patterns. The NPIS guidelines contained more formal guidance suggesting that medicines within its most urgent category were stocked in sufficient quantities to treat 2 patients for 48 hours.⁴ This approach was relatively restrictive because the majority of departments did not treat patients for 48 hours and in some cases this would involve stocking significant quantities of antidotes. Acute antidotes such as glucagon, which are used in high doses for the treatment of beta-blocker overdose, would necessitate stocking in excess of 40 vials for a single patient. The specific storage requirements, relatively low incidence of this type of poisoning and quantities involved made holding entire stocks of antidotes such as glucagon impractical.

In reality the majority of hospitals hold sufficient stocks in their emergency departments to start therapy and then continue treatment by sourcing further supplies from within the organisation (glucagon is a good example). The suggestion that it is required directly in the department excluded this approach and alienated many of the implementer trusts.

The new guideline suggests a pragmatic approach and prefers that individual emergency departments use discretion to stock quantities appropriate for their

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needs. Departments in areas where there are local factories using hydrogen fluoride may require a larger stock of calcium gluconate gel whereas this may be less crucial in more rural departments where pesticide poisonings are statistically higher. Where trusts choose to maintain lower than recommended stock levels in the department it will be crucial to have sufficient stocks to begin therapy with sufficient time to engage robust mechanisms of obtaining further supplies.



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Duplication

The original BAEM guideline sparked debate throughout implementer trusts because of the inclusion of what appeared to be antidotes with duplicate therapeutic purposes.⁵ The predominant areas of contention were the antidotes to treat dystonic reactions, cyanide and heavy metal poisoning. In each case a number of antidotes were recommended with little clarity provided as to their individual necessity. When surveyed in 2008 some of the inconsistencies were related to individual trusts making decisions regarding which of the 'duplicate' antidotes to stock.

The duplicate inclusion of both benztropine and procyclidine for dystonic

reactions has been rectified in the new unified guidance. Difficulties in obtaining benztropine formalised procyclidine as the drug of choice within this therapeutic area and a reference stating benztropine as unnecessary has been included in the updated guidance.⁷

The heavy metal chelating agents listed in the guidance still remain within the supra-regional time frame. The lack of clarity relating to these medicines was to some degree intentional because it was felt this would ensure advice was sought from the specialist poisons centres. This would then allow the opportunity for intervention to obviate potentially inappropriate use of these toxic antidotes. It was highlighted in the survey results that a number of trusts had chosen to stock penicillamine as an alternative to succimer (2,3-dimercaptosuccinic acid). Penicillamine can be used as a chelating agent for poisonings related to copper and it can be used to aid the urinary elimination of lead.²⁵ Penicillamine is, however, limited in its effectiveness in treating poisonings of heavy metals such as lead and arsenic. It should not be considered a complete alternative to succimer (2,3-dimercaptosuccinic acid).⁷

Originally for cyanide poisoning there were a range of antidotes listed with no suggestion of their relatively separate requirements. Cyanokit[®] (as mentioned previously) is required in the most acute timescale because it can be used in the acutely unwell presenting patient. No other preparation of hydroxocobalamin is suitable and as such the availability of Cyanokit[®] is a necessity.⁷ The other agents listed are dicobalt edetate (which is also contained in the DOH pods for major incidents) and the combination of sodium nitrite and sodium thiosulphate.⁷ It should be noted that

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sodium thiosulphate and sodium nitrite are required in combination for severe cyanide poisonings and holding them individually is not considered sufficient.⁷ Within the new guidance dicobalt edetate has been suggested as the agent of choice for severe cyanide poisonings with the combination of sodium nitrite and sodium thiosulphate a second line alternative.⁷

Unlicensed antidotes in the emergency department

One significant governance issue for pharmacists is organising the timely access to unlicensed antidotes within the emergency department. A number of antidotes remain unlicensed in the UK and to meet the recommended timescales it is a necessity to hold these medicines as stock. Recognition of the practical concerns surrounding advanced supply of unlicensed medicines is contained within the new guidance. This provides national support for an issue that may concern trust governance groups throughout the UK. It is necessary to be mindful of the consequences of significant delays to treatment. Contained in Table 2 are the unlicensed antidotes recommended within the new BAEM guidelines. It is clear from the therapeutic uses that delay in sourcing the majority of these antidotes would have significant impact on the morbidity or mortality of the poisoned patient.

Residency and robust on-call arrangements provide some scope for these medicines to be retained within the pharmacy department. However, antidotes such as Cyanokit[®] are needed within such a short time frame that even this approach is unlikely to meet the needs of the patient. Retrospective collection of patient data for some of the unlicensed medicines is a further option to ensure legislative requirements are met and is used by a number of trusts throughout the UK.

Conclusion

Medicines management extends further than the 'on the floor' clinical aspects of the poisoned patient. The unified guidance provides individual emergency departments with a template to encourage a robust approach to ensuring sufficient quantities and timely access to antidotes.

This article provides background to the key questions asked of previous guidance relating to antidotes. It is hoped that pharmacists with a responsibility to antidote availability may use the information provided in conjunction with the unified guidance to

inform choices relating to their individual departments and encourage a collaborative approach to antidote availability throughout the UK. ❀

Declarations of interest

The author has no interests to declare.

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Further Reading

UK Resources:

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2. Toxbase. The primary clinical toxicology database of the National Poisons Information Service. Registration is required Available via www.toxbase.org.
3. Department of Health. *Treatment of poisoning by selected chemical compounds — the Blain Report — an expert group on the management of chemical casualties caused by terrorist activity* available via www.dh.gov.uk.
4. Department of Health. *Accessing nerve agent antidote service (NAAS) pods* important change from midnight 31st March 2002 available via www.dh.gov.uk.
5. NPIS guide to observations and investigations for the toxicology patient. Accessible via Toxbase (Login required) www.toxbase.org.

International Resources:

1. International Programme on Chemical Safety available via www.who.int/ipcs/en/.
2. Toxseek. The American searchable database of poisons which includes journal searching functionality available via http://toxseek.nlm.nih.gov/toxseek/ui8/searchfr.jsp?select_edcategory=Allcat.
3. American Association of Poison Control Centres. Contains out of hospital patient management guidelines for the US available via www.aapcc.org/dnn/PatientManagementGuidelines/tabid/158/Default.aspx.
4. EUROTOX. The Federation of national societies of toxicology in Europe available via <http://www.eurotox.com/>.
5. The International Program on Chemical Safety (IPCS) — Intox Chemical Database available at <http://www.intox.org/>.