Taking stock: UK national antidote availability increasing, but further improvements are required

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ABSTRACT

Background A 2010/2011 audit of the Royal College of Emergency Medicine (RCEM) National Poisons Information Service (NPIS) UK guidelines on antidote availability demonstrated variable stocking of antidotes for the management of poisoned patients; the guidelines were updated and republished in 2013.

Aim To assess if antidote stocking has improved since the 2010/2011 audit and introduction of the 2013 guidelines.

Methods Questionnaires were sent to Chief Pharmacists at all 215 acute hospitals in England, Wales and Northern Ireland in October 2014. Data were collected on the timing of availability (category A antidotes should be available immediately, category B within 1 h and category C can be held supraregionally) and stock levels.

Results 169 (78.6%) responses were received. Atropine, calcium gluconate and flumazenil (category A) were the only antidotes available in all hospitals within the recommended time and stock levels. Forty-one (24.3%) hospitals held every category A antidote; this increased to 81 (47.9%) for those holding at least one cyanide antidote and all other category A antidotes. The proportion of hospitals stocking category A/B antidotes within the recommended time increased for 20 (90.9%) category A/B antidotes. Fomepizole (category B) availability increased to 62.1% of hospitals from 11.4% in 2010/2011. Other than penicillamine (63.3% hospitals), there was poor availability (2.4%–36.1%) of category C antidotes.

Conclusions Availability of category A and B antidotes has improved since the 2010/2011 audit and 2013 guidelines. However, there remains significant variability particularly for category C antidotes. More work is required to ensure that those treating poisoned patients have timely access to antidotes focusing particularly on category C antidotes.

BACKGROUND

Antidotes are an important component of the management of poisoned patients, and early and timely administration is important for the efficacy of many antidotes and optimum management of poisoned patients presenting to the emergency department (ED). The Royal College of Emergency Medicine (RCEM) and National Poisons Information Service (NPIS) first issued national guidelines on the stocking of antidotes in 2006; these were updated in 2008 and again in 2013.¹ These guidelines provide clear recommendations for the timing of availability and minimum stock levels for antidotes in UK hospitals treating poisoned patients.

A UK 2010/2011 audit in England, Wales and Scotland demonstrated variable levels of antidote availability in hospitals across the country with significant improvement being required for compliance with the national guidelines.² In this audit, 30 (15.3%) hospitals did not stock any antidote for toxic alcohol poisoning and 9 (4.6%) hospitals stocked no cyanide antidotes.² Studies in the USA, Canada and New Zealand have also shown significant problems in the availability of antidotes despite national guidance.^{3–6}

The RCEM/NPIS antidote guidelines were developed to provide advice to hospitals to ensure appropriate and timely availability of antidotes for the optimum management of poisoned patients. The antidotes are split into three different categories based on the urgency with which they may be required and also how frequently they are used. Category A antidotes are recommended to be available immediately within the ED. Category B antidotes should be available for use within 1 h (therefore, recommended to be stocked in the hospital). Category C antidotes are recommended to be held supraregionally because they are used less commonly and immediate treatment is generally not required. Having fewer sites holding these antidotes reduces the risk of wasting unused stock. The guidelines also recommend minimum stock levels based on the amount required for the treatment of an adult poisoned patient for the first 24 h.¹ Antivenoms for non-indigenous venomous animals are held supraregionally, and are subject to separate procurement and distribution arrangements through Public Health England.

Changes introduced in the 2013 guidelines included alterations in categories for viper venom antiserum (from category B to A) and pralidoxime (from category B to C); the recommendation of a designated storage facility for antidotes within the ED; recommending fomepizole as the antidote of choice for toxic alcohol poisoning and updating minimum stock levels to allow for the provision of the first 24 h of treatment. The 2013 RCEM/NPIS guideline was also supported by a letter from the Chief Pharmaceutical Officers for England, Wales and Scotland and the National Clinical Director for Emergency Care for NHS England.¹

This study aimed to assess if antidote stocking has improved since the 2010/2011 audit and the introduction of the 2013 RCEM/NPIS Guidelines.

METHODS

Questionnaires were sent to the Chief Pharmacists of all 215 acute hospitals in England (187 hospitals), Wales (16 hospitals) and Northern Ireland (12

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hospitals). A separate audit is currently being undertaken in Scotland. Acute hospitals were defined as those with type 1 EDs (those open 24 h and consultant led, with full resuscitation facilities) and/or acute medical admissions units.

A questionnaire similar to that used in the 2010 audit² was created, which included all of the antidotes on the RCEM/NPIS guidelines with tick boxes for the timing of availability and stock levels. Unlike the 2010 audit, we included all of the antidotes included in the RCEM/NPIS guideline. In addition, as in the previous audit, intravenous lipid emulsion (ILE or 'lipid rescue') was also included, although this is not currently listed in the guidelines.

The questionnaire was sent electronically to Chief Pharmacists at the 215 identified hospitals in October 2014, requesting a response electronically or by post. A follow-up electronic reminder was sent in December 2014; non-responders then received a telephone call to either the pharmacy department or medicines information service in January 2015. Responses received by 22 March 2015 were included in the analysis.

Questionnaire responses were collated in an Excel spreadsheet and separated by country for analysis. For each antidote, the following data were collected: the number of hospitals stocking the antidote, availability within the recommended time (category A should be immediately available within the ED, category B should be available within 1 h and category C are recommended for supraregional stocking), whether recommended stock levels were held and time to availability if not stocked in the hospital.

RESULTS

A total of 169 responses were received, equating to an overall response rate of 78.6% (England: 145 responses (77.5% response rate), Wales: 13 (81.3%) and Northern Ireland: 11 (91.7%)). This was lower than the 2010–2011 audit response rate of 87.5%.

The availability, timing of availability and stock levels compared with the guidelines is shown in tables 1–3 for category A, B and C antidotes, respectively. Figures 1 and 2 compare the data with the 2010 audit² for availability of antidotes both within the recommended time and at minimum recommended stock levels.

Category A: recommended for immediate availability in the ED

Forty-one (24.3%) hospitals held every category A antidote for immediate availability and this increased to 81 (47.9%) for those holding at least one cyanide antidote and all other category A antidotes. Excluding cyanide antidotes and accounting for the recommendation for stocking either glyceryl trinitrate or isosorbide dinitrate, 9 out of 15 (60%) category A antidotes were available immediately at recommended stock levels in over 90% of hospitals.

Atropine, calcium gluconate and flumazenil were the only category A antidotes available in all hospitals with both the recommended availability and minimum stock levels. A number of other category A antidotes (acetylcysteine, activated charcoal, calcium chloride, glucagon, naloxone and procyclidine) were available in all hospitals, but not available immediately as recommended in the guidelines.

Four cyanide antidotes are included in the guidelines in category A. All hospitals stocked at least one antidote for cyanide poisoning; an improvement compared with the previous audit that found 4.6% of hospitals did not stock any cyanide antidote. There was an increase in the proportion of hospitals stocking

hydroxocobalamin (21.4% in 2010 audit to 55.6% in 2015 audit), dicobalt edetate (73.5%–82.2%) and sodium thiosulfate (66.3%–77.5%), and a small decrease in the proportion of hospitals stocking sodium nitrite (57.1%–56.2%).

The guidelines recommend stocking either glyceryl trinitrate or isosorbide dinitrate for the treatment of toxin-related hypertension and all hospitals stocked at least one of these two treatments.

Category B: recommended to be available within 1 h

As shown in table 2, all category B antidotes were available within 1 h in 30 (17.6%) hospitals, and 62 (36.7%) had all category B antidotes, excluding phentolamine and/or pyridoxine (for which there are known current supply/manufacturing problems), available within 1 h. Octreotide and protamine were the only category B antidotes available within 1 h and at recommended stock levels in over 90% of hospitals.

Fomepizole is the antidote of choice for toxic alcohol (ethylene glycol, diethylene glycol and methanol) poisoning and was available within 1 h in 124 (73.4%) hospitals, an increase from 16.8% of hospitals in the 2010 audit. Eighty-nine (52.7%) hospitals had both fomepizole and intravenous ethanol available within the recommended 1 h, 36 (21.3%) had only fomepizole and 33 (19.5%) had only intravenous ethanol available. There were only 11 (6.5%) hospitals where neither antidote was available within 1 h, compared with 17.3% of hospitals in the 2010–2011 audit.

Category C: can be held supraregionally

As shown in table 3, the category C antidotes were available, as expected, in fewer hospitals. There was significant variation from stocking of glucarpidase in only four (2.4%) hospitals to stocking of penicillamine in 107 (63.3%) hospitals. Information about the source of availability for hospitals not stocking category C antidotes is also shown in table 3.

Intravenous lipid emulsion was stocked in 166 (98.2%) hospitals and was immediately available in 121 (71.6%) hospitals. In the 2010–2011 audit, it was stocked in 87.2% of hospitals and immediately available in 62.2%.

For comparison between individual countries, there was availability of the recommended antidotes within the recommended time in at least 90% of hospitals for 10/20 (50%) category A and 8/14 (57.1%) category B antidotes in England, 12/20 (60%) category A and 7/14 (50%) category B antidotes in Wales and 13/20 (65%) category A and 9/14 (64.3%) category B antidotes in Northern Ireland.

DISCUSSION

The availability of most antidotes, particularly those in category A and category B, has improved since the 2010/2011 audit and the introduction of the latest guidelines in 2013. There have been large increases in timely availability of hydroxocobalamin, viper venom antiserum, cyproheptadine and fomepizole. The percentage of hospitals stocking antidotes available within the recommended time increased for 20 out of 22 (90.9%) category A and B antidotes included in both audits. However, despite the introduction and update of the national guidelines with the support of the Chief Pharmaceutical Officer for England and the National Clinical Director for Emergency Care for England, less than a quarter of hospitals have every category A antidote available for immediate use. A lack of availability of antidotes for use in emergency situations has significant clinical implications for the optimum management of poisoned patients. During this audit period, there was a known supply problem

Table 1 Availability of category A antidotes that should be immediately available (N=169)

Antidote	2014–2015 No. (%) of hospitals stocking the antidote	2014–2015 No. (%) of hospitals with the antidote available immediately	2010–2011 % Hospitals with the antidote available immediately*	% Change from 2010 to 2015 audit in immediate availability (±%) (95% CI)
Acetylcysteine	169 (100)	168 (99.4)	95.9	+3.5 (0.5 to 6.5)
Activated charcoal	169 (100)	167 (98.8)	95.4	+3.4 (0.1 to 6.8)
Atropine	169 (100)	169 (100)	NA	NA
Calcium chloride	169 (100)	159 (94.1)	NA	NA
Calcium gluconate	169 (100)	169 (100)	NA	NA
Calcium gluconate gel	147 (87.0)	137 (81.1)	68.4	+12.7 (3.9 to 21.5)
Dicobalt edetate	156 (92.3)	140 (82.2)	73.5	+9.3 (1.0 to 17.8)
Flumazenil	169 (100)	169 (100)	90.3	+9.7 (5.6 to 13.8)
Glucagon	169 (100)	161 (95.3)	89.3	+6.0 (0.6 to 11.4)
Glyceryl trinitrate†	155 (91.7)	150 (88.8)	NA	NA
Hydroxocobalamin	107 (63.3)	94 (55.6)	21.4	+34.2 (24.8 to 43.6)
Isosorbide dinitrate†	90 (53.3)	57 (33.7)	NA	NA
Methylthioninium chloride	163 (96.4)	145 (85.5)	74.5	+11.0 (3.3 to 19.4)
Naloxone	169 (100)	168 (99.4)	92.9	+6.5 (2.8 to 10.3)
Procyclidine	169 (100)	165 (97.6)	NA	NA
Sodium bicarbonate 8.4%	164 (97.0)	155 (91.7)	NA	NA
Sodium bicarbonate 1.26% or 1.24%	161 (95.3)	139 (82.2)	NA	NA
Sodium nitrite	104 (61.4)	95 (56.2)	57.1	−0.9 (−9.3 to 11.1)
Sodium thiosulfate	149 (88.2)	131 (77.5)	66.3	+11.2 (2.1 to 20.3)
Viper venom antiserum‡	134 (84.8)	118 (74.7)	44.9	+29.8 (20.1 to 39.5)

*Not all antidotes were included in the 2015 audit (these are marked in the table as NA).

†Either glyceryl trinitrate or isosorbide dinitrate are recommended to be stocked.

‡Viper venom antiserum does not need to be stocked in Northern Ireland (N=158). Category B in previous guidelines: to be available within 1 h.

due to the discontinuation of production of phentolamine in the UK. This was out of control of the hospitals stocking antidotes. Supply problems with sodium nitrite and acetylcysteine were also reported, although the results suggest that acetylcysteine availability was not affected. Other antidotes were unaffected by supply problems.

The availability of cyanide poisoning antidotes has improved, and all responding hospitals stocked at least one of the

recommended antidotes. Dicobalt edetate is recommended for severe cases in which there is a strong clinical certainty of cyanide poisoning, and is now available immediately in 82.2% of hospitals. Hydroxocobalamin is recommended for severe cyanide poisoning related to smoke inhalation (with severe lactic acidosis, coma or cardiovascular compromise); availability has more than doubled since the previous audit, but less than half of hospitals had the recommended stock available for immediate

Table 2 Availability of category B antidotes that should be available within 1 h

Antidote	2014–2015 No. (%) of hospitals stocking the antidote	2014–2015 No. (%) of hospitals with the antidote available within 1 h	2010–2011 % Hospitals with the antidote available within 1 h*	% Change from 2010 audit in availability within 1 h (±%) (95% CI)
Calcium folinate	156 (92.3)	148 (87.6)	77.0	+10.6 (2.8 to 18.2)
Cyproheptadine	134 (79.3)	131 (77.5)	45.9	+31.6 (22.2 to 41.0)
Dantrolene	165 (97.6)	161 (95.3)	93.4	+1.9 (−2.8 to 6.6)
Deferoxamine	166 (98.2)	163 (96.4)	91.3	+5.1 (0.3 to 10.0)
Digoxin-specific antibody fragments	157 (92.9)	157 (92.9)	82.1	+10.8 (4.1 to 17.4)
Intravenous ethanol	125 (74.0)	122 (72.2)	72.4	−0.2 (−8.9 to 9.5)
Fomepizole	128 (75.7)	124 (73.4)	16.8	+56.6 (48.1 to 68.0)
Mesna†	161 (95.3)	155 (91.7)	NA	NA
Octreotide	168 (99.4)	163 (96.4)	84.2	+12.2 (6.5 to 18.1)
Phentolamine‡	87 (51.5)	84 (49.7)	NA	NA
Phytomenadione	169 (100)	165 (97.6)	93.9	+3.7 (0.3 to 7.8)
Polyethylene glycol	161 (95.3)	156 (92.3)	84.2	+8.1 (1.6 to 14.6)
Protamine	169 (100)	169 (100.0)	NA	NA
Pyridoxine	125 (74.0)	117 (69.2)	NA	NA

*Not all antidotes were included in the 2010 audit (these are marked as NA in the table).

†Mesna is only required in hospitals commonly using cyclophosphamide.

‡Phentolamine has been discontinued. Unlicensed preparations are stocked in some hospitals.

Table 3 Availability of category C antidotes recommended for supraregional stocking and for hospitals not stocking the antidotes information provided on the source of availability

Antidote	No. (%) of hospitals stocking antidote	No. (%) of hospitals not stocking antidote	For hospitals not stocking the antidote		
			No. (%) of providing information on source of availability	No. (%) of reporting unknown source of availability	No. (%) of providing no data on potential availability
Berlin blue	11 (6.5)	158 (93.5)	58 (36.7)	10 (6.3)	90 (57.0)
Botulinum antitoxin	25 (14.8)	144 (85.2)	76 (52.8)	5 (3.5)	63 (43.8)
Dimercaprol	60 (35.5)	109 (64.5)	48 (44.0)	3 (2.8)	58 (53.2)
Glucarpidase	4 (2.4)	165 (97.6)	26 (15.8)	23 (13.9)	116 (70.3)
Penicillamine	107 (63.3)	62 (36.7)	18 (29.0)	5 (8.1)	39 (62.9)
Pralidoxime	61 (36.1)	108 (63.9)	59 (54.6)	4 (3.7)	45 (41.7)
Sodium calcium edetate	28 (16.6)	141 (83.4)	62 (44.0)	10 (7.1)	60 (48.9)
Succimer (DMSA)	13 (7.7)	156 (92.3)	56 (35.9)	15 (9.6)	85 (54.5)
Unithiol (DMPS)	9 (5.3)	160 (94.7)	58 (36.3)	14 (8.8)	88 (55.0)

treatment. Cyanide poisoning antidotes are used in the management of critically unwell patients and delays in antidote administration could result in mortality.

Despite improvements in availability of category A antidotes, the lack of immediate availability in some hospitals for antidotes, including calcium gluconate gel, dicobalt edetate, 8.4% sodium bicarbonate and viper venom antiserum, is of concern particularly in view of the urgency with which their use may be required. In view of clear guidelines and recommendations, it would be difficult to defend a clinical incident occurring due to inadequate access to these antidotes.

Fomepizole was designated the antidote of choice for ethylene glycol or methanol poisoning in the 2013 guidelines and recommended as a category B antidote to be stocked for availability within 1 h. There has been a significant increase in the availability of fomepizole within 1 h from 16.8% to 73.4% of hospitals. Therefore, many hospitals now have timely access to the preferred treatment for toxic alcohol poisoning, although there remain a small number (6.5%) with no appropriate antidote stocked for treating this important and potentially serious life-threatening poisoning.

Inadequate stocking of antidotes has been a concern across the world despite there being numerous international guidelines. Studies in Canada, the USA and New Zealand have all

demonstrated inadequate stocking of antidotes, and the cost and infrequent use of antidotes have been suggested as contributing factors.^{3–6} Canadian studies before and after the introduction of guidelines for antidote stocking have demonstrated improvements in availability of antidotes, but a persistent lack of stock for many essential antidotes in some hospitals.^{3–4} The use of a national internet accessible antidote database has been suggested as a method to share information and improve availability.⁶ Transferring antidotes from other hospitals can result in delays in administration of antidotes, partly due to the infrequent and unplanned nature of the arrangements.⁵

A recent US study has illustrated the impact of drug shortages on the supply of antidotes for the management of poisoned patients.⁷ In this study, 141 (8.1%) of US drug shortages over a 13-year period were for drugs used to treat poisoned patients, with a median shortage duration of 164 days. There have been problems with the supply of a number of antidotes in the UK in recent years. This was illustrated in our audit by the poor stocking of phentolamine, which was only available in about half of the hospitals; UK production of phentolamine was discontinued in August 2012, and since this time, guidance on alternative antidotes has been available from NPIS on TOXBASE.⁸ Pyridoxine was also relatively poorly stocked; currently, the high strength pyridoxine product is not routinely available, and

Figure 1 Percentage of hospitals holding recommended stock levels of category A antidotes for immediate availability. Comparison with 2007 and 2010–2011 audits. *Viper venom antiserum has been changed to category A (having previously been in category B) in the 2013 guidelines and is not required in Northern Ireland.

Figure 2 Percentage of hospitals holding recommended stock levels of category B antidotes for availability within 1 h. Comparison with 2007 and 2010–2011 audits.

hospitals need a minimum stock requirement of 100 vials for the treatment of isoniazid poisoning.

The high cost of some antidotes and the need to replace stock, which may expire before being used, are possible reasons for poor stocking. Examples include digoxin-specific antibody fragments and fomepizole. A Canadian study found that the shelf life, replacement of stock and frequency of use are all important in determining cost to departments along with the cost of individual drugs.⁹ The American College of Medical Toxicology and American Academy of Clinical Toxicology have suggested that the recent FDA Safety and Innovation Act could help the process of extending the shelf life for some rarely used antidotes as part of other methods to improve availability and reduce shortages.¹⁰ However, cost and supply problems alone do not account for the lack of available antidote stocks; activated charcoal and methylthionium chloride are two examples of less expensive antidotes that are currently inadequately stocked.

There was significant variation in the stocking of supraregional category C antidotes. Data on the time to availability of category C antidotes were poorly recorded, and this limited the assessment of the effectiveness of supraregional stocking systems. In many cases, the nearest source for availability of category C antidotes was recorded as 'unknown', suggesting a lack of coordination or available location information for supraregional antidotes.

Few hospitals stock category C antidotes, and for those that do not, generally less than half provided information on where they would source the antidote. It is important for hospitals not stocking category C antidotes to have plans in place to source these antidotes when required. For example, sodium calcium edetate is indicated for the treatment of lead encephalopathy, although this is a rare diagnosis, prompt treatment is required. In this audit, 16.8% of hospitals stocked the antidote, and for those that did not, only 44% were able to provide information on where it would be sourced from. Further work is urgently needed in this area to facilitate systematic supraregional availability of these less commonly used antidotes to ensure that they are available in a timely manner when required for the management of poisoned patients.

Limitations

Compared with the 2010–2011 audit, Scotland was not included, and Northern Ireland was included. The audit was delayed in Scotland until recommendations were made for the access of rarely used medicines, and a separate audit using the same questionnaire is now being undertaken. The overall

response rate was lower on this occasion (78.6% vs 87.5%). There is a risk that hospitals not responding have comparatively poor levels of stock and the lower response rate may have made some contribution to the apparent improvements demonstrated. However, there was an absolute increase in the number of hospitals stocking antidotes, including fomepizole, cyproheptadine, viper venom antiserum, dicobalt edetate and hydroxocobalamin, compared with the previous audit despite the lower response rate. There were also changes to categories, such as viper venom antiserum, being added to category A, and a larger number of antidotes were included in the audit this year. These factors affect the comparison between the two audits. There were also known manufacturing or supply problems with phentolamine, acetylcysteine and sodium nitrite during the audit period.

CONCLUSION

The availability of category A and B antidotes has improved in England, Wales and Northern Ireland since the 2010 audit and the updated 2013 RCEM/NPIS antidote stocking guidelines. However, there is still significant variability in the availability of

What this paper adds

What is already known on this subject

- ▶ A 2010/2011 audit of the UK guidelines on antidote availability demonstrated variable stocking of antidotes for the management of poisoned patients.
- ▶ The Royal College of Emergency Medicine (RCEM) and National Poisons Information Service (NPIS) updated national antidote stocking guidelines for the UK in 2013.
- ▶ These guidelines provide clear recommendations for the timing of availability and minimum stock levels for antidotes in UK hospitals treating poisoned patients.

What this study adds

- ▶ Availability of antidotes in the UK has improved since the 2010/2011 audit and introduction of 2013 guidelines.
- ▶ This includes large increases in timely availability of hydroxocobalamin, viper venom antiserum, cyproheptadine and fomepizole. However, there remains significant variability, particularly for supraregionally stocked antidotes.
- ▶ More work is required to ensure that those treating poisoned patients have timely access to antidotes.

antidotes, particularly the category C supraregional antidotes, and a national mechanism is needed to improve and ensure systematic availability of these category C antidotes.

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