A survey of the antidote preparedness in Norwegian hospitals

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ABSTRACT

Objectives Antidotes are an important part of the emergency preparedness in hospitals. In the case of a major chemical accident or a fire, large quantities of antidotes may be needed within a short period of time. For time-critical antidotes it is therefore necessary that they be immediately available. We wanted to evaluate the antidote preparedness in Norwegian hospitals as regards the national recommendations and compare this with other international guidelines.

Methods A digital survey was sent to the 50 hospitals in Norway that treat acute poisonings. Of these, four hospitals are categorised as regional hospitals, 15 as large hospitals and 31 as small hospitals. Each hospital was asked which antidotes they stockpiled from a list of 35 antidotes. The financial costs (low, moderate, high) were added to an established efficacy scale to illustrate the cost-effectiveness of the different antidotes.

Results The response rate was 100%. Eleven of fifty (22%) hospitals stockpiled all antidotes recommended for their hospital size. All four regional hospitals had all the recommended antidotes. Large hospitals which were not regional hospitals had the least availability of antidotes, and only one large hospital stockpiled all antidotes recommended for this hospital size.

Conclusions We found varying compliance with the national recommendations for antidote storage in hospitals. To strengthen antidote preparedness, we recommend standardised European guidelines to support national guidelines.

BACKGROUND

Combined with supportive care, antidotes are cornerstones in the treatment of poisonings. They are also important elements in chemical and radiological incident preparedness. Some medical conditions require immediate antidote availability, whereas for other conditions antidotes are not considered time-critical for adequate treatment. In recent years there has been an increased focus on preparedness for chemical incidents, for example, those caused by industrial accidents or terror attacks.1,2 Studies from different countries have shown insufficient stocking of antidotes.3–8 Lack of guidelines has been proposed as one possible cause.3,7 In 1997, the International Programme on Chemical Safety (IPCS) published a list of antidotes considered useful in the treatment of poisoning and classified them according to the urgency of availability.9 Consensus guidelines for stockpiling of emergency antidotes in the United States (US) followed in 2000,10 and were updated in 200911 and 2018.12 These guidelines were also classified in relation to their urgency for availability. Similar guidelines exist for the United Kingdom (UK).13 There is no European consensus on this matter, and each country has to formulate their own guidelines.

In 2000, Solheim et al conducted a survey to describe the antidote preparedness situation in Norway.14 They concluded that antidote preparedness was not satisfactory and that guidelines were lacking. They recommended a list of antidotes which should be available in hospitals based on the hospital size. In 2007, the Norwegian Poison Information Centre published national recommendations for antidote stocking in hospitals. These recommendations were divided into three groups: (1) recommendations for all hospitals, (2) recommendations for large hospitals and (3) recommendations for regional hospitals (table 1). Current recommendations are still categorised in these groups and recommended antidotes are continuously updated. There are no minimum quantities recommended, only an estimate of the amount needed to treat one patient (70kg). No follow-up study has been conducted after the publication of these recommendations.

Our aim was to describe the antidote preparedness in Norwegian hospitals according to the national recommendations and compare this model with other strategies found internationally. Since the cost of antidote preparedness may be a limiting factor, we wanted to discuss the element of cost versus effect.

METHODS

A digital survey was conducted in all hospitals that treat acute poisonings in Norway (n=50). These are all public hospitals, as the few private ones that exist only have an elective function. The survey was sent to the nurse or doctor who followed up the antidote storage. In hospitals where the hospital pharmacy had the daily responsibility for this follow-up, the survey was sent to a hospital pharmacist. Norway is a sparsely inhabited country with some areas having long distances between hospitals. The organisation of them is therefore a hierarchy of hospitals in each health region and local hospital trust instead of number of beds. There are a total of six university hospitals and four health regions. We defined a regional hospital as the largest university hospital in each of the four health regions. Each health region has several local hospital trusts, and a large hospital was defined as the hospital with the largest hospital catchment population in each local hospital trust. Other hospitals were categorised as
small. A total of 31 hospitals were categorised as small, 15 as large and four as regional. An email with a link to the survey was sent in April 2016. After two email reminders, hospitals were contacted by phone until the survey closed in June 2016. Each hospital was asked whether they had antidote storage, the availability of individual antidotes from a list of 35 antidotes (table 1), in what quantities, and when the content was last revised. If a product was not a part of the antidote storage they were asked whether it was available in another location at the hospital. The national recommendations also include drugs which are used routinely at hospitals for other indications, for example, norepinephrine and insulin. These were not included in the survey. We also asked about the availability of diethylenetriamine pentaaçetate (DTPA) for binding radioactive plutonium, americium and curium, as part of the preparedness for radiation emergencies. This was not included in our national recommendations, but is recommended to be stockpiled by the World Health Organization (WHO). Some antidotes are not relevant in all regions, for example, vipers antivenom where there are no vipers or silibinin where there are no relevant mushrooms. This was corrected for in our data processing.

To assess the cost of treating a poisoning case with antidote, the cost of one 70 kg patient was calculated. This was based on the estimated amounts in the national recommendations. We chose to divide the costs into three groups: low (<300 euros), moderate (300–1000 euros) and high (>1000 euros). The costs are calculated from the prices current in October 2018.

RESULTS

All 50 hospitals responded to the survey. Half (54%) of the hospitals had revised their antidote list after January 2015, 14% between 2012 and 2014, 6% before 2012, and 26% did not know when the list was last revised.

Some 11/50 (22%) hospitals stored all antidotes recommended for their hospital size. All four regional hospitals were fully compliant with the recommendations and 1/15 (7%) of large hospitals. For small hospitals the corresponding number was 6/31 (19%). Further, some small hospitals chose to have fomepizole instead of intravenous (IV) ethanol and some had pralidoxime instead of obidoxime, both of which were considered adequate.

Table 2 shows the availability of each antidote. Cyp rodeptadine for serotonergic syndrome was the antidote which was least available in large hospitals and sodium sulphate for barium poisoning was the least available antidote in small hospitals. Only one hospital stockpiled DTPA for internal contamination with radioactive plutonium, americium and curium.

Table 3 shows the treatment cost for one 70 kg patient. Figure 1 is an updated version of IPCS’s efficacy scale of important and commonly used antidotes, with cost added to create a cost/efficacy scale.

DISCUSSION

Antidote availability in Norwegian hospitals is still very variable, and only 22% of hospitals have stocks compliant with national recommendations. Frequently used antidotes are available in all hospitals, whereas those used more rarely are less available or in too small quantities to treat a single patient.

Lack of guidelines was suggested as a possible cause of poor antidote preparedness in Norway after the survey in 2000. Studies from Canada and the UK have suggested likewise. Our survey shows that antidote preparedness is still unsatisfactory and that hospitals are not compliant with national recommendations. There are several reasons for this poor compliance. One probable cause is the lack of a clear definition as to what characterises small and large hospitals in the recommendations. Previously, Norwegian hospitals were organised as local, central and regional hospitals. These terms are no longer in use and this classification is therefore likely outdated. Other international guidelines focus predominantly on the timely availability of antidotes. This requires a critical evaluation of the efficacies of the different antidotes and the need for prompt administration. When preparing a preparedness plan, it is essential to know whether the treatment is time-critical and where one can obtain additional supplies at short notice. As it would be in many countries, some regions of Norway have lengthy transportation times to hospitals and between hospitals, and air transport is difficult because of challenging weather conditions. Another element to be considered in the risk and vulnerability analysis is the opening hours of the hospital pharmacies with regard to obtaining antidotes if nearby hospitals do not stockpile or replenish used antidotes. In Norway, hospital pharmacies have

Table 1: Recommendations for antidote stocking in Norwegian hospitals

| Recommended in all hospitals | Additional recommendations for large and regional hospitals | Additional recommendations for regional hospitals |
|------------------------------|----------------------------------------------------------|-------------------------------------------------|
| Acetylcysteine               | Calcium folinate injection                               | DMPS                                            |
| Activated charcoal           | Cyproheptadine                                           | DMSA                                            |
| Atropine                     | Dantrolene                                               | Penicillamine                                   |
| Biperiden                    | Deferoxamine                                             | Prussian blue                                   |
| Calcium gluconate (local and IV) | Digoxin immune FAB (DigiFab)                             | Sodium calcium edetate                          |
| Ethanol IV                   | Fomepizole                                               |                                                  |
| Flumazenil                   | Methylthionium chloride                                  |                                                  |
| Glucagon                     | Obidoxime                                                |                                                  |
| Hydroxocobalamin             | Octreotide                                               |                                                  |
| Ipecac syrup                 | Pyridoxine injection                                     |                                                  |
| Lipid emulsion               | Silibinin                                                |                                                  |
| Naloxone                     | Sodium thiosulfate                                       |                                                  |
| Physostigmine                | Vipera berus antivenom (ViperaTAb)                       |                                                  |
| Phytomenadione               |                                                          |                                                  |
| Protamine sulfate            |                                                          |                                                  |
| Sodium sulfate               |                                                          |                                                  |

DMPS, dimercaptopropanesulphonate; DMSA, dimercaptosuccinic acid; IV, intravenous.
Table 2  Availability of antidotes in Norwegian hospitals

| Antidote                              | Hospitals (n=50) | Hospitals which can give full treatment to at least one 70 kg patient (n=50) | Regional hospital following recommendations (n=4) | Large hospitals following recommendations (n=15) | Small hospitals following recommendations (n=31) |
|---------------------------------------|-----------------|--------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Acetylcysteine                        | 50 (100)        | 45 (90)*                                                                  | 4 (100)                                          | 15 (100)                                      | 31 (100)                                      |
| Activated charcoal                    | 50 (100)        | 27 (54)*†                                                                 | 4 (100)                                          | 15 (100)                                      | 31 (100)                                      |
| Atropine                              | 50 (100)        | 50 (100)*†                                                                | 4 (100)                                          | 15 (100)                                      | 31 (100)                                      |
| Biperiden                             | 49 (98)         | 49 (98)*                                                                  | 4 (100)                                          | 15 (100)                                      | 30 (97)                                       |
| Calcium folinate injection            | 36 (72)         | 1 (2)*                                                                   | 4 (100)                                          | 13 (87)                                       | 195                                           |
| Calcium gluconate injection           | 47 (94)         | 47 (94)*                                                                  | 4 (100)                                          | 15 (100)                                      | 28 (90)                                       |
| Calcium gluconate local treatment     | 48 (96)         | 48 (96)*                                                                  | 4 (100)                                          | 15 (100)                                      | 295                                           |
| Cyproheptadine                        | 8 (16)          | 8 (16)*                                                                   | 4 (100)                                          | 4 (27)                                        | 0                                             |
| Dantrolene                            | 49 (98)         | 1 (2)*†                                                                   | 4 (100)                                          | 15 (100)                                      | 305                                           |
| Deferoxamine                          | 44 (88)         | 21 (42)*                                                                  | 4 (100)                                          | 14 (93)                                       | 265                                           |
| Digoxin immune FAB (DigiFab)          | 17 (34)         | 13 (26)*†                                                                  | 4 (100)                                          | 7 (47)                                        | 65                                            |
| DMPS (IV or orally)                   | 12 (24)         | 4 (8)*†                                                                   | 4 (100)                                          | 55                                           | 35                                            |
| DMSA                                  | 6 (12)          | 5 (10)*                                                                   | 4 (100)                                          | 15                                           | 15                                            |
| DTPA*                                 | 1 (2)           | 1 (2)*                                                                    | 15                                               | 0                                            | 0                                             |
| Ethanol IV                            | 45 (90)         | 28 (56)*†                                                                  | 4 (100)                                          | 14 (93)                                       | 27 (87)                                       |
| Fluamzenil                            | 50 (100)        | 34 (68)*†                                                                  | 4 (100)                                          | 15 (100)                                      | 31 (100)                                      |
| Fomepizole                            | 32 (64)         | 12 (24)*                                                                  | 4 (100)                                          | 14 (93)                                       | 146                                           |
| Glucagon                              | 43 (86)         | 29 (58)*                                                                  | 4 (100)                                          | 13 (87)                                       | 26 (84)                                       |
| Hydroxocobalamin                      | 45 (90)         | 32 (64)*                                                                  | 4 (100)                                          | 15 (100)                                      | 26 (84)                                       |
| Ipecac syrup                          | 49 (98)         | 49 (98)*                                                                  | 4 (100)                                          | 15 (100)                                      | 30 (97)                                       |
| Lipid emulsion                        | 48 (96)         | 37 (74)*                                                                  | 4 (100)                                          | 13 (87)                                       | 31 (100)                                      |
| Methyleneithion chloride              | 36 (72)         | 19 (38)*                                                                  | 4 (100)                                          | 13 (87)                                       | 195                                           |
| Naloxone                              | 50 (100)        | 50 (100)*                                                                  | 4 (100)                                          | 15 (100)                                      | 31 (100)                                      |
| Obidoxime                             | 27 (54)         | 27 (54)*                                                                  | 3 (75)                                           | 12 (80)                                       | 125                                           |
| Octreotide                            | 40 (80)         | 40 (80)*                                                                  | 4 (100)                                          | 14 (93)                                       | 225                                           |
| Penicillamine                         | 7 (14)          | 7 (14)*                                                                   | 4 (100)                                          | 35                                           | 0                                             |
| Physostigmine                         | 48 (96)         | 48 (96)*                                                                  | 4 (100)                                          | 15 (100)                                      | 29 (94)                                       |
| Phytomenadione                        | 50 (100)        | 47 (94)*                                                                  | 4 (100)                                          | 15 (100)                                      | 31 (100)                                      |
| Protamine sulfate                     | 44 (88)         | 44 (88)*                                                                  | 4 (100)                                          | 14 (93)                                       | 26 (84)                                       |
| Prussian blue                         | 5 (10)          | 4 (8)*                                                                    | 4 (100)                                          | 15                                           | 0                                             |
| Pyridoxine injection                  | 25 (50)         | 25 (50)*                                                                  | 4 (100)                                          | 13 (87)                                       | 85                                            |
| Silibinin                             | 18 (36)         | 7 (14)*†                                                                  | 4 (100)                                          | 10 (71)*†                                     | 49                                            |
| Sodium calcium edetate                | 11 (22)         | 4 (8)*†                                                                   | 4 (100)                                          | 35                                           | 45                                            |
| Sodium sulfate                        | 18 (36)         | 10 (20)*                                                                  | 4 (100)                                          | 6 (40)                                        | 8 (26)                                        |
| Sodium thiosulfate                    | 43 (86)         | 18 (36)*                                                                  | 4 (100)                                          | 15 (100)                                      | 245                                           |
| Viperab susanavan (ViperaTAb)          | 25 (50)         | 25 (50)*                                                                  | 3 (100)*†                                        | 10 (71)*†                                     | 12*                                           |

*The remaining hospitals did not specify whether they have enough for one 70 kg patient.
†The remaining hospitals specified that they do not have enough for one 70 kg patient.
‡All hospitals have verified that they have enough for one 70 kg patient.
§Not recommended for this hospital size.
¶Corrected for regions where there are no vipers or relevant mushrooms.
DMPS, dimercaptopropanesulphonate; DMSA, dimercaptosuccinic acid; DTPA, diethylenetriamine pentaacetate; IV, intravenous.

limited opening hours and most are closed during weekends and holidays. Some hospitals have a pharmacist on call when the pharmacy is closed, but this differs in the various regions.

Drug costs has been mentioned as another possible reason why hospitals do not stockpile recommended antidotes. Treatment with digoxin immune FAB is a typical example (cost approximately 2500 euros for one 40 mg vial), and this antidote is stockpiled by only half the large hospitals. In spite of the price aspect, we found that even cheap antidotes (eg, sodium sulfate and cyproheptadine) were among the least available in small and large hospitals. The cost to treat one 70 kg patient is less than 150 euros. Similar findings have been found in Australia and British Columbia. Shelf-life is another factor to consider together with cost, and whether agreements exist for replacement after the expiry date. The latter varies between countries, and for the antidotes in this survey no agreement for replacement after the expiry date exists in Norway.

There are several aspects to the cost, including the direct cost of the antidote, and the potential additional cost based on the choice of alternative antidotes. This is illustrated by the use of fomepizole versus ethanol for toxic alcohol poisoning, where the cost of the antidote does not reflect the total cost, and thus should be taken into consideration. Ethanol and fomepizole are ‘equally’ effective against toxic alcohols given optimal
are not drunk, fewer nursing staff are therefore required.21 Dialysis can be postponed or even eliminated, and as the patients have a dramatic impact on the overall cost. Further, the need for zole may also reduce the need for intensive care beds, which will 50 mL 70% alcohol is approximately 150 euros. Using fomepizole is expensive in Norway and the price for a vial of tals are supposed to stockpile both IV ethanol and fomepizole. Large and regional hospi-

tals are supposed to have IV ethanol. Sodium thiosulfate is not an emergency treatment, and sodium calcium edetate is recommended in the international guidelines. Conversely, sodium sulfate and ipecac syrup that are recommended in all Norwegian hospitals are not included in the international guidelines. These are rare antidotes used in special circumstances. Ipecac syrup is only exceptionally used in children in the prehos-
pital setting when hospital transportation time is lengthy. Sodium sulfate for barium poisoning is not an emergency treatment, and only 36% of all hospitals stockpile this antidote. The fact that so few hospitals stockpiled this antidote does affect the overall result. Compared with other recommendations, these antidotes are not recommended to be immediately available, and it should therefore be considered whether it is necessary for all hospitals to stockpile these particular antidotes.

There are a few antidotes for internal contamination with radioactive materials, but these are not mentioned in our national recommendations. Prussian blue is only recommended for thallium poisoning and not caesium-137. In 2017, national guidelines for handling CBRNE incidents involving personal injury was published and regional stockpiling of Prussian blue and DTPA were recommended.24 They should therefore also be included in the national recommendations for stockpiling of antidotes in hospitals.

Drug shortage has been a repeated problem worldwide in recent years. The delivery situation in Norway is particularly vulnerable since almost half of the antidotes are not licensed in our country. A drug shortage will be discovered late, and in the worst case scenario will have an important impact on patient care and outcome. Taking this into consideration and the fact circumstances, but ethanol has adverse effects on the central nervous system and requires frequent therapeutic drug moni-
toring.21 International treatment guidelines therefore recommend fomepizole as the antidote of choice,21 corresponding to the guidelines for antidote stocking in hospitals in the UK and US.12 13 According to our national recommendations, all hospi-
tals are supposed to have IV ethanol. Large and regional hospi-
tals are supposed to stockpile both IV ethanol and fomepizole. IV ethanol is expensive in Norway and the price for a vial of 50 mL 70% alcohol is approximately 150 euros. Using fomepizole may also reduce the need for intensive care beds, which will have a dramatic impact on the overall cost. Further, the need for dialysis can be postponed or even eliminated, and as the patients are not drunk, fewer nursing staff are therefore required.21

Some novel antidotes are not yet part of our recommendations, partly because of the cost. Antidotes against direct oral anticoagulants are among the latest antidotes on the market. Idarucizumab against dabigatran was approved in Europe in 2015, and included in our national recommendations in June 2016. Andexanet alfa, the newest antidote approved in Europe last year, is not yet marketed in Norway. These antidotes score highly on the efficiency scale, but the costs for andexanet alfa are between US$29 040 and US$58 080 (26 400 euros and 52 800 euros) per patient treated.22 This is a significantly higher cost than all the other antidotes in our recommendations. The studies also lack a control group, have surrogate endpoints, and some have questioned whether this correlates with clinical improve-
ment.22 23 These are considerations to take into account when evaluating what antidotes to stockpile.

When comparing the Norwegian guidelines with international guidelines,12 13 the main difference is that the latter are based on the timely availability of the antidote, and not hospital size. They are also clear as to what is the preferred antidote where there are several treatments options, for example, fomepizole for toxic alcohol poisoning and hydroxocobalamin for cyanide poisoning. The Norwegian guidelines, on the other hand, are not entirely clear on this matter since large and regional hospitals are recom-

mended to stockpile all treatments options. The most commonly used antidotes that all Norwegian hospitals stockpile are also recommended in the international guidelines. Conversely, the antidotes in our national recommendations are not entirely clear on this matter as antidotes are not included in the international guidelines. These are rare antidotes used in special circumstances. Ipecac syrup is only exceptionally used in children in the prehos-
pital setting when hospital transportation time is lengthy. Sodium thiosulfate, sodium calcium edetate and DTPA were recommended.24 They should therefore also be included in the national recommendations for stockpiling of antidotes in hospitals.

Drug shortage has been a repeated problem worldwide in recent years. The delivery situation in Norway is particularly vulnerable since almost half of the antidotes are not licensed in our country. A drug shortage will be discovered late, and in the worst case scenario will have an important impact on patient care and outcome. Taking this into consideration and the fact circumstances, but ethanol has adverse effects on the central nervous system and requires frequent therapeutic drug moni-
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tals are supposed to have IV ethanol. Large and regional hospi-
tals are supposed to stockpile both IV ethanol and fomepizole. IV ethanol is expensive in Norway and the price for a vial of 50 mL 70% alcohol is approximately 150 euros. Using fomepizole may also reduce the need for intensive care beds, which will have a dramatic impact on the overall cost. Further, the need for dialysis can be postponed or even eliminated, and as the patients are not drunk, fewer nursing staff are therefore required.21

Some novel antidotes are not yet part of our recommendations, partly because of the cost. Antidotes against direct oral anticoagulants are among the latest antidotes on the market. Idarucizumab against dabigatran was approved in Europe in 2015, and included in our national recommendations in June

| Table 3 | Price category for antidote treatment for one 70 kg patient based on national recommendations |
| Antidote | Cost* |
| Acetylcysteine | Low |
| Activated charcoal | Low |
| Atropine | Low |
| Biperiden | Low |
| Calcium folinate injection | High |
| Calcium gluconate IV treatment | Low |
| Calcium gluconate local treatment | Low |
| Cyproheptadine | Low |
| Dantrolene | High |
| Deferoxamine | Low |
| Digoxin immune FAB (DigiFab) | High |
| DMPS | Moderate |
| DMSA | High |
| Ethanol IV | High |
| Flumazenil | Low |
| Fomepizole | High |
| Glucagon | Moderate |
| Hydroxocobalamin | High |
| Ipecac syrup | Low |
| Lipid emulsion | Low |
| Methyleneion chloride | Moderate |
| Naloxone | Low |
| Obidoxime | Low |
| Octreotide | Low |
| Penicillamine | Low |
| Physostigmine | Low |
| Phytomenadione | Low |
| Protamine sulfate | Low |
| Prussian blue | Moderate |
| Pyridoxine injection | Low |
| Sibillin | High |
| Sodium calcium edetate | Moderate |
| Sodium sulfate | Low |
| Sodium thiosulfate | Moderate |
| Vipera berus antivenom (ViperaTab) | High |

*Cost: low: <300 euros; moderate: 300–1000 euros; high: >1000 euros. DMPS, dimercaptopropanesulphonate; DMSA, dimercaptosuccinic acid ; IV, intravenous.
CONCLUSIONS

Every country needs to rely on a certain stocking of antidotes for treatment for poisoning, incidents and disaster preparedness. We found varying compliance with the national recommendations for hospital storage of antidotes, where a sizeable proportion of small- and large-sized hospitals did not follow the recommendations. In a broader perspective one should consider whether it is time for standardised European guidelines, supplied with national recommendations based on local poisoning epidemiology.

Limitations

This study refers to self-reported data, and hospital stockpiles were not manually counted by the researchers. Three reminders were sent in respect of unreturned questionnaires, which may have led some hospitals to correct their shortcomings in the meantime. Subsequent to this survey, two amendments to the national recommendations were made for large and regional hospitals, namely levocarnitine against valproic acid and idarucizumab against dabigatran were included in the recommendations.

Correction notice

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Contributors

YEL contributed to the initial idea, study design, data collection, data analysis, data interpretation, literature search and writing the manuscript. AG contributed to the study design and writing the manuscript. BJ5 contributed to the study design and writing the manuscript. BJ contributed to the initial idea, study design and writing the manuscript. ERN contributed to the initial idea and writing the manuscript. KEH contributed to the initial idea, study design, data interpretation and writing the manuscript.

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