A system-wide solution to antidote stocking in emergency departments: the Nova Scotia antidote program

Nancy G. Murphy, MD*†; D. Ruth Bona, RN, CSPI*; Theresa A. Hurley, BSc(Pharm), ACPR‡

ABSTRACT

Objective: Inadequate stocking of essential antidotes in hospitals is an internationally documented problem. A concrete and sustainable system-wide solution for easy access to antidotes in emergency departments (EDs) was developed and implemented in Nova Scotia, Canada.

Methods: Antidote stocking guidelines and a systemwide antidote management strategy were established. A standardized collection of antidotes housed in highly visible containers in provincial EDs was implemented for timely access. Antidote-specific online administration guidelines were developed. Using the poison centre for surveillance, the antidote program maintained a database of antidote utilization patterns; 11 years of data were available for analysis.

Results: 2/2 (100%) tertiary care, 9/9 (100%) regional EDs, and 21/25 (84%) community EDs in Nova Scotia stock antidote kits, for an overall compliance rate of 32/36 (89%). A total of 678 antidotes (excluding N-acetylcysteine) were used for 520 patients. The distribution of antidote use by hospital type was 99/678 (14.6%) at community hospitals, 379/678 (55.9%) at regional hospitals, and 200/678 (29.5%) at tertiary care hospitals. The five most commonly used antidotes were: naloxone 143/678 (21.1%), fomepizole 111/678 (16.4%), glucagon 94/678 (13.9%), calcium 70/678 (10.3%), and sodium bicarbonate 67/678 (9.9%). Of the 520 patients in whom antidotes were used, death occurred in 3% (15/520), major outcomes in 35% (183/520), and moderate outcomes in 39% (205/520).

Conclusion: The Nova Scotia Antidote Program demonstrates that a solution to inadequate antidote stocking is achievable and requires a system-wide approach with ongoing maintenance and surveillance. The frequency and distribution of antidote usage documented in this program supports the need for enhancement of emergency preparedness. The poison centre and hospital pharmacies are crucial to surveillance and maintenance of this program.

RÉSUMÉ

Introduction: L'approvisionnement insuffisant en antidotes essentiels dans les hôpitaux est un problème mondialement reconnu. Une solution concrète, durable et applicable à l'échelle du réseau pour faciliter l'accès aux antidotes dans les services des urgences (SU) a été élaborée et mise en œuvre en Nouvelle-Écosse, au Canada.

Méthode: Une équipe a conçu des lignes directrices sur l'approvisionnement en antidotes ainsi qu'une stratégie de gestion des antidotes à l'échelle du réseau. Un assortiment uniforme d'antidotes conservés dans des contenants très visibles a été mis en réserve dans divers SU à la grandeur de la province en vue d'un accès rapide. Ont été élaborées des lignes directrices sur la gestion en ligne de différents antidotes. Les gestionnaires du programme d'antidotes, aidés du centre antipoison pour la surveillance, ont entretenu une base de données sur les habitudes d'utilisation des antidotes; les chercheurs disposaient de données cumulées sur une période de 11 ans pour en faire l'analyse.

Résultats: Les trousses d'antidotes sont entreposées dans 2 hôpitaux de soins tertiaires sur 2 (100 %), dans 9 SU régionaux sur 9 (100 %) et dans 21 SU communautaires sur 25 (84 %) en Nouvelle-Écosse, et le taux général de conformité aux recommandations est de 32/36 (89 %). En tout, 678 antidotes (à l'exception de la N-acétylcystéine) ont été administrés à 520 patients. L'utilisation des antidotes selon les types d'hôpitaux était répartie comme suit : 14,6 % (99/678) dans les hôpitaux communautaires; 55,9 % (379/678) dans les hôpitaux régionaux et 29,5 % (200/678) dans les hôpitaux de soins tertiaires. Les cinq antidotes utilisés le plus souvent étaient la naloxone : 143/678 (21,1 %), le fomépizole : 111/678 (16,4 %), le glucagon : 94/678 (13,9 %), le calcium : 70/678 (10,3 %) et le bicarbonate de sodium : 67/678 (9,9 %). Sur les 520 patients qui ont reçu des antidotes, 15 (3 %) sont morts, 183 (35 %) ont connu des effets graves et 205 (39 %), des effets modérés.

Conclusions: Le programme de gestion des antidotes en Nouvelle-Écosse est la preuve qu'il est possible de trouver une solution au problème d'approvisionnement en antidotes, solution fondée sur l'ensemble du réseau, qui nécessite une surveillance et un entretien continus. La fréquence d'utilisation des antidotes et la répartition dans le réseau, documentées dans le programme, étayent la nécessité

From the *Izaak Walton Killam Regional Poison Centre, Halifax, NS; †Department of Emergency Medicine, Dalhousie University, Halifax, NS; and the ‡Pharmacy Department, Nova Scotia Health Authority, Halifax, NS.

Correspondence to: Dr. Nancy G. Murphy, IWK Regional Poison Centre, 5850 University Avenue, Halifax, NS B3K 6R8; Email: nancy.murphy@iwk.nshealth.ca

© Canadian Association of Emergency Physicians
CJEM 2019;21(1):37–46 DOI 10.1017/cem.2017.400

d'améliorer le degré de préparation aux situations d'urgence. Le centre antipoison et les pharmacies hospitalières jouent un rôle crucial dans la surveillance et l'entretien du programme.

Keywords: antidote, poison centre, emergency preparedness

INTRODUCTION

Antidotes can be an essential part of the emergency management of poisoned patients. Inadequate antidote stocking in hospitals is a well-documented occurrence on an international level. Several survey studies in different countries have documented inadequate stores of and accessibility to time-sensitive antidotes.[1-14] Canadian studies have also highlighted the scope of this problem in British Columbia (BC), Ontario, and Quebec.[1-6] The BC group published consensus guidelines for antidote stocking as a response to this issue and provided strategies for appropriate population- and hospital-based distribution. A follow-up survey demonstrated improved yet suboptimal compliance with recommendations.[5,6]

Potential reasons for these deficiencies included cost, a lack of awareness of the importance of antidotes, the absence of national standards, hospital size, and antidote availability.[2-4] Certain antidotes are not readily available in Canada and require procurement through the Special Access Program (Health Canada) that may present a challenge for some hospitals. These barriers are more significant for smaller hospitals that have limited resources.[1-3]

A solution to inadequate antidote stocking and accessibility was presented in one publication in which a toxicology cart with all necessary antidotes within an emergency department (ED) was implemented.[16] The Nova Scotia (NS) program has a similar premise but was extrapolated to an entire province. A 2004 local antidote stocking survey[7] based on consensus guidelines was conducted in EDs in the district that contain both adult and pediatric tertiary care centres. It revealed deficiencies similar to those in the literature, indicating an overall compliance of 62.5% for 14 of the currently recommended antidotes (Appendix A). This provided the impetus for a comprehensive district-wide pilot program, which resulted in 100% compliance with the antidote stocking guidelines at all eight sites. The pilot program then evolved into a province-wide program in 2009. Guidelines for antidote stocking were developed for the province, but the main features of the program that differed from other approaches in the literature are as follows:

- Placement of a highly visible room temperature antidote kit (Figure 1) and refrigerated antidote kit within each ED.
- Surveillance and maintenance of the kits in each district by a designated pharmacy.
- Antidote-specific administration instructions available online.
- Support from provincial hospital administration.
- Antidote-specific data collection obtained through real-time surveillance through poison centre consultations.

Figure 1. (a) The antidote kit. (b) Three tiers of standardized antidotes.

- Biannual interdisciplinary antidote committee meetings.
- Ongoing communication with ED chiefs, pharmacy directors, and ED nurse educators.

This paper outlines the complex process of planning and implementing such a program and describes antidote utilization patterns over an 11-year period in NS.

METHODS

This section outlines the methodology for antidote program development and implementation, followed by the methodology for data extraction and analysis. This study was approved by the research ethics board at the IWK Health Centre, in Halifax, NS.

Methods part one: Antidote program development and implementation

A multidisciplinary committee including a medical toxicologist, an emergency physician, pharmacists, pharmacy technicians, and a poison centre specialist was established. Five objectives were identified and are described below.

1. Approval and funding

Approval was obtained from the provincial hospital administration, and hospitals were encouraged to commit to the program; however, no dedicated provincial funding for this program was secured. Costs were absorbed by the pharmacy and EDs in each district. The costs included procurement and maintenance of antidotes and a room temperature and refrigerated storage box to house antidotes in EDs, as well as sharing the salary cost of a provincial antidote coordinator. The procurement cost[4] for recommended antidotes in 2005 was approximately $9,600 and is currently estimated to be $11,760.

2. Antidote stocking guidelines

The committee used the current literature and advice from expert consultants to determine recommended antidotes. Recommended quantities were based on the estimated 24-hour treatment supply for a 70-kg patient, accessibility to other sites for rarely required or expensive antidotes, the likelihood of use, expert opinion, and cost. Geographic distribution of provincial EDs allowed sharing of antidotes. Antidotes that were designated ward stock antidotes were generally stocked in larger quantities as they could be used for indications other than toxicity.

Two types of antidote kits were developed: a "full" kit containing original antidote quantities and a "modified" kit for smaller EDs with quantities that provided four hours of treatment. Current recommendations for antidotes and quantities in NS are listed in Table 1.

The designated central pharmacy for the program was located at the adult tertiary care centre. This pharmacy stocks two rarely used antidotes, sodium thiosulfate and black widow spider antivenin. The program recommends three antidotes available through the Special Access Program (SAP; black widow spider antivenin, Dimaval®, and pralidoxime). The central pharmacy is benefitted by an SAP pharmacy technician who procures SAP antidotes for that district and assists other districts as required.

3. Access to antidotes

A three-tiered yellow plastic box containing most of the antidotes (Figure 1) enhanced the visibility and accessibility of antidotes within EDs. Four antidotes were designated as ED ward stock and not included in the kits (Table 1). Antidotes requiring refrigeration were placed in a small labelled red box and located in a designated ED refrigerator.

4. Antidote administration guidelines

Evidence-informed antidote-specific monographs were developed in a standard format with information including toxicologic indications, dosing specific to antidote use, detailed preparation and administration guidelines, adverse effects, intravenous (IV) compatibility, and stability. These monographs were developed and maintained by the poison centre and are located on their website.

5. Maintenance and surveillance of the program

Stocking and replenishment. For the purposes of the program, NS was divided into nine geographical districts. Stocking and replenishment were the responsibility of the pharmacy director at each district site and was typically carried out by a trained pharmacy technician. Although specific pharmacy procedures may differ, kits are assembled at one designated district hospital and dispensed to EDs as a sealed entity with an expiry date. Each district has a policy and procedure for restocking kits in instances in which an additional

Table 1. Antidote stocking recommendations in NS

Antidote	Toxin/indication	Stock required for full kit	Stock required for modified kit	Stock location
Acetylcysteine (6 g/30 mL vial)	Acetaminophen, other hepatotoxins	72 g (12 vials)	72 g (12 vials)	ED ward stock
Atropine (0.6 mg/mL ampoule)	Cholinesterase inhibitor insecticides, nerve agents, and drug-induced bradycardia	96 mg (160 ampoules)*	96 mg (160 ampoules)*	Antidote kit
Black widow spider antivenin (Antivenin *Latrodectus mactans*) (1 vial)	Black widow spider envenomation	none	none	1 vial in central pharmacy SAP antidote
Calcium chloride (1 g/10 mL syringe)	Calcium channel blocker, toxin-induced hypocalcemia	8 g (8 syringes)	8 g (8 syringes)	Antidote kit
Calcium gluconate (2.5% gel) (1 g/10 mL ampoule)	Hydrofluoric acid exposure	2 tubes (30 g) and 25 g (25 ampoules)	1 tube (30 g) and 25 g (25 ampoules)	Antidote kit
Deferoxamine (desferrioxamine) (2 g vial)	Iron toxicity	6 g (3 vials)	4 g (2 vials)*	Antidote kit
Digoxin immune Fab (40 mg vial)	Digoxin and other cardioactive steroids	240 mg (6 vials)	240 mg (6 vials)	Antidote fridge kit
Dimaval® 250 mg/5 mL ampoule	Arsenic, lead, and mercury	2 ampoules*	1 ampoule*	Antidote kit SAP antidote
Flumazenil (0.5 mg/5 mL vial)	Benzodiazepine toxicity	2.5 mg (5 vials)*	2.5 mg (5 vials)*	ED ward stock
Fomepizole (1.5 g/1.5 mL vial)	Ethylene glycol, methanol, and glycol ethers	3 g (2 vials)*	1.5 g (1 vial)*	Antidote kit
Glucagon (1 mg kit)	Beta blocker, calcium channel blocker toxicity	40 mg*	40 mg*	Antidote kit
Hydroxocobalamin (Cyanokit) 1 × 5 g vials	Cyanide toxicity	5 g	5 g	Antidote kit
Insulin Regular 100 units/mL)	Beta blocker, calcium channel blocker toxicity	20 mL (2 × 10 mL)	20 mL (2 × 10 mL)	Ward stock, refrigerator
Lipid emulsion 20% (Intralipid)	Local anesthetic toxicity, drug-induced hemodynamic instability, or cardiac arrest	1000 mL (2 × 500 mL)	1000 mL (2 × 500 mL)	Antidote kit
Methylene blue (50 mg/5 mL vial)	Methemoglobinemia	500 mg (10 vials)	150 mg (3 vials)*	Antidote kit
Naloxone (0.4 mg/mL ampoule)	Opioids	16 mg (40 vials)*	10 mg (25 vials)*	Antidote kit
Octreotide (100 mcg/mL ampoule)	Sulfonylurea-induced hypoglycemia	400 mcg (4 ampoules)	100 mcg (1 ampoule)*	Antidote fridge kit
Pralidoxime (2-PAM) (1 g vial)	Cholinesterase inhibitor insecticides, nerve agents	2 g (2 vials)*	2 g (2 vials)*	Antidote kit SAP antidote
Pyridoxine (vitamin B_6; 3 g/30 mL vial)	Isoniazid, Gyromitra mushroom, hydrazine, undifferentiated status epilepticus, and adjunctive therapy for ethylene glycol toxicity	21 g (7 vials)	12 g (4 vials)*	Antidote kit
Sodium bicarbonate 8.4% (50 mEq/50 mL syringe)	Cyclic antidepressants, other sodium channel blocker toxicity, drug-induced metabolic acidosis, and urine alkalinisation	1000 mEq (20 syringes)	1000 mEq (20 syringes)	ED ward stock
Sodium thiosulfate 25% 250 mg/mL (100 mL vial)	Cyanide toxicity	none	none	25 g (1 vial) central pharmacy

*In the event of an overdose, additional stock will be required to treat a patient for 24 hours

supply of an antidote or antidotes are required immediately, after a kit is used, and when the stock is required on an urgent basis.

To facilitate cost containment, central tracking of expiry dates is performed in each district, and antidotes are recycled prior to expiry if possible (e.g., naloxone to operating rooms). If recycling is not successful, expired products are returned to the manufacturers for credit as permitted. For antidotes designated as ED ward stock (Table 1), a quality assurance survey is conducted annually.

Education. Education was provided by the provincial antidote coordinator to ED staff across the province. The program was publicized through multiple continuing medical education (CME) activities in the region and in written communications with ED chiefs, pharmacy directors, and ED nurse educators.

Management and data collection. The provincial antidote committee was responsible for management of the program and met biannually. The committee reviewed utilization data, advised on issues of drug

procurement and shortages, and incorporated new evidence into recommendations. The provincial antidote coordinator disseminated quarterly communications about the program to provincial stakeholders.

Antidote surveillance was recorded in a database with data collected from calls to the poison centre and direct communications with hospital pharmacists. Information collected included patient identifiers, site, date, indication, antidote(s) used, and adverse events, as well as an assessment of the final medical outcome (no effect, minor effect, moderate effect, major effect, or death, as per the American Association of Poison Control Centers [AAPCC]).[15]

Methods part two: quantitative analysis of compliance with stocking recommendations and antidote usage

Study design

This is a retrospective, non-comparative, and descriptive study.

Data sources and collection

The IWK Regional Poison Centre in Halifax, NS, serves a population of approximately 1.2 million people and receives approximately 9,000 calls annually. Health care in NS is delivered by 2 tertiary care hospitals, 9 regional hospitals, and 25 community hospitals providing emergency care. The tertiary care hospitals have 912 (adult) and 90 (pediatric) acute care beds; regional hospitals have a median of 103 acute care beds (range 73-436); and all community hospitals have less than 50 acute care beds.

Antidote utilization data for this study were extracted from the database maintained by the provincial antidote coordinator. Compliance with the antidote program was determined by direct communications with pharmacy directors at least annually in each district from May 2005 to May 2016.

The following three fields were extracted from the database for each case in which an antidote was administered: antidote used, the size of the hospital (tertiary, regional, or community), and the medical outcome as per the AAPCC.[15]

Outcome measures

1. Hospital compliance with antidote stocking recommendations.
2. Antidote utilization from May 2005 to May 2016, including type and frequency of antidote use and distribution of antidote use across hospital types.
3. Patient outcomes, as defined by the AAPCC.

Data analysis

Descriptive statistics were used to summarize the data using Microsoft® Excel.

RESULTS

Compliance with the program

From 2005 to 2009, the pilot project in the largest health district, which included the only adult and pediatric tertiary care EDs, a regional ED, and five community EDs, showed 100% compliance. After provincial expansion in 2009, 7 of the 9 regional EDs and 8 of the 25 community EDs were compliant. By 2011, all nine (100%) regional EDs were compliant; by 2013, 21 of the 25 (84%) community EDs were compliant (Appendix B).

The overall compliance with the program is 89% (32/36) of the provincial EDs that was achieved during a four year period. No EDs have withdrawn from the program.

Antidote utilization and distribution

A complete description of usage patterns is presented in Table 2. It should be noted that use of N-acetylcysteine (NAC) was not officially tracked by the program because it has been consistently well stocked. To establish context, there were 1,257 reported cases in which NAC was used during the study period.

From May 2005 to May 2016, a total of 678 antidotes were used for 520 patients. Of the 19 recommended antidotes (excluding NAC and grouping calcium formats), 17 were used during the study period. The five most commonly used antidotes were: naloxone (143/678, 21.1%), fomepizole (111/678, 16.4%), glucagon (94/678, 13.9%), calcium chloride or gluconate (70/678, 10.3%), and sodium bicarbonate (67/678, 9.9%). Antidotes considered to be rarely indicated were also used, including dimercaprol, pralidoxime, and hydroxocobalamin. Antidote utilization by hospital type was as follows: 99/678 (14.6%) at community hospitals, 379/678 (55.9%) at regional hospitals, and 200/678 (29.5%) at tertiary care hospitals (Table 3).

Table 2. Antidote utilization, 2005-2016

Antidote	Total usage		Distribution of usage		
	No. of uses	Total antidotes used (%)	Tertiary	Regional	Community
Naloxone	143	21.1%	22 (15.4%)	85 (59.4%)	36 (25.2%)
Fomepizole	111	16.4%	35 (31.5%)	66 (59.5%)	10 (9.0%)
Glucagon	94	13.9%	32 (34.0%)	53 (56.4%)	9 (9.6%)
Calcium chloride/gluconate	70	10.3%	17 (24.3%)	42 (60.0%)	11 (15.7%)
Sodium bicarbonate	67	9.9%	21 (31.3%)	35 (52.2%)	11 (16.4%)
Insulin	61	9.0%	21 (34.4%)	31 (50.8%)	9 (14.8%)
Digoxin Fab fragment	41	6.0%	19 (46.3%)	20 (48.8%)	2 (4.9%)
Intralipids	19	2.8%	9 (47.4%)	10 (52.6%)	0
Octreotide	17	2.5%	10 (58.8%)	5 (29.4%)	2 (11.8%)
Atropine	15	2.2%	2 (13.3%)	10 (66.7%)	3 (20.0%)
Pyridoxine	13	1.9%	3 (23.1%)	10 (76.9%)	0
Flumazenil	11	1.6%	1 (9.1%)	6 (54.5%)	4 (36.4%)
Deferoxamine	3	0.4%	1 (33.3%)	2 (66.7%)	0
Ethanol*	3	0.4%	1 (33.3%)	1 (33.3%)	1 (33.3%)
Cyanide antidote/hydroxocobalamin	3	0.4%	1 (33.3%)	1 (33.3%)	1 (33.3%)
Methylene blue	3	0.4%	3 (100%)	0	0
Pralidoxime	2	0.3%	0	2 (100%)	0
Dimercaprol	1	0.1%	1 (100%)	0	0
Cyanide antidote/Lilly kit†	1	0.1%	1 (100%)	0	0
Sodium thiosulfate	0	0	0	0	0
Grand total	678		200	379	99

*Antidote previously recommended by the NS antidote program
†Lilly kit was initially recommended; hydroxocobalamin is the current recommendation

Table 3. Antidote use by hospital type

Type of hospital	Number of antidotes used (N = 678)
Community	99 (14.6%)
Regional	379 (55.9%)
Tertiary	200 (29.5%)

Table 4. Medical outcomes of antidote cases

Medical outcome	Number of cases (N = 520)
Death	15 (2.9%)
Major	183 (35.2%)
Moderate	205 (39.4%)
Minor	45 (8.7%)
Confirmed non-exposure	1 (0.2%)
No effect	17 (3.3%)
Unknown	54 (10.4%)

Patient outcomes

Outcome definitions were based on standard criteria established by the AAPCC.[15] Of the 520 patients for whom antidotes were used, death occurred in 15 of the 520 (2.9%), major outcomes (e.g., life-threatening effects such as hemodynamic instability) occurred in 183 of the 520 (35.2%), moderate outcomes (e.g., not life-threatening but requiring treatment, such as isolated seizure) occurred in 205 in the 520 (39.4%), minor outcomes (e.g., transient, mild symptoms) occurred in 45 in the 520 (8.7%), and no effect occurred in 17 in the 520 (3.3%). The outcome was unknown in 54 of the 520 patients (10.4%), and one case was confirmed as a non-exposure case (Table 4).

DISCUSSION

The NS antidote program represents a tangible solution to the problem of inadequate antidote stocking and is, to our knowledge, the first of its kind. This program demonstrates that concrete and sustainable antidote stocking is achievable but requires a system-wide approach to ongoing maintenance and surveillance by a multidisciplinary group. Despite the lack of dedicated funding, overall compliance of 89% was achieved during a four year period and has been sustained since 2013, and no ED has dropped out of the program once involved.

The goal of this program is to ensure that all EDs have immediate access to time-sensitive antidotes, regardless of hospital size and geographic location. The cost for each individual hospital to be compliant with currently published stocking guidelines may represent a significant financial burden. Our program mitigates the cost of maintaining antidote stocks while considering patient safety by establishing a network of antidotes over large geographic areas. Mechanisms for the sharing of antidotes are crucial to this model and should be developed by hospital pharmacies and EDs in the event that larger doses of antidotes are required for a specific case.

The procurement cost of antidotes is a barrier to stocking, but this must be weighed against other, possibly more significant costs arising from poisonings that are not rapidly reversed with an antidote. Such costs may include those associated with the treatment of toxin-induced renal failure or another organ injury, prolonged hospital stays, patient transport, or extracorporeal methods of toxin removal. In our experience, cost has been a concern for hospital pharmacies and EDs. Efforts to contain costs were made by recommending a "modified kit" (Table 1) for smaller EDs, recycling antidotes to other areas of the hospital prior to expiry, and returning antidotes to manufacturers for credit if possible. In addition, antidote utilization patterns have informed alterations to antidote stocking recommendations. For example, pralidoxime was stocked in all antidote kits; based on our data showing rare usage, as well as the fact that atropine is the initial treatment in cholinergic toxidrome, we will be recommending that it be stocked only at regional hospitals while maintaining an overall provincial stock that could still treat a patient for a few days. Additional cost reductions have been achieved by reducing the glucagon stock. Glucagon is expensive: if the maximum dose of 10 mg/hour is administered, it costs approximately $8,000 per 24 hours. New evidence-based consensus guidelines do not include glucagon as an antidote for calcium channel blocker (CCB) toxicity,[21] and it is typically used as only adjunctive therapy, if at all, in beta-blocker (BB) toxicity.[22] Insulin is supported in the literature as an antidote for both CCB and BB toxicity and is inexpensive (approximately $50 per 24 hours). Maintaining an appropriate supply of insulin while reducing glucagon is a cost-effective approach that is supported by the evidence available. Digoxin immune Fab fragments were rarely used by community EDs during the study period. This antidote is still required for immediate treatment of digoxin toxicity, but the stocking recommendations for community hospitals will be reduced in our program as a result. This is supported by recent studies, which have called into question the current empiric dosing of digoxin immune Fab fragments as being overestimated and have documented that calculated doses are low.[17-20] This antidote costs approximately $850 per vial, which has doubled since 2005 and is no longer returnable if unused. The current stocking recommendations of six vials per site for our program already reduces this cost to some extent by providing each ED the ability to initiate treatment. Further stock can be obtained as needed. In summary, by monitoring the utilization data and regularly evaluating the evidence, costs can be reduced while preserving patient safety.

The program did increase workload within hospital pharmacies, and compliance with the antidote stocking guidelines placed a financial burden on ED and pharmacy budgets for drug procurement. At some point, this may not be sustainable without dedicated funding, and we recommend that this issue be addressed during the planning stages of any similar program.

A small hospital size has been described as a barrier to sufficient antidote stocking because of limited resources, a lack of specialist physicians, and the perception that treating poisoned patients is rare. In NS, 70.5% of antidote usage during the study period was by regional and community EDs. This contradicts the assumption that smaller hospitals do not need to stock "expensive" antidotes. The frequency of antidote use was higher than expected, every six days (excluding NAC), on average, which supports the necessity of stocking antidotes for emergency preparedness.

Most patients who required antidotes had a final recorded outcome demonstrating important morbidity and mortality information. These patients presented to the community and regional EDs in significant numbers. Our data support that having ready access to time-sensitive antidotes in these hospitals is an essential aspect of hospital emergency preparedness.

The need for consistent preparation, administration, and dosing guidelines was evident at the inception of the antidote program. Most hospital IV manuals contained information about only the non-antidotal use of medications such as insulin or glucagon. In addition, there is a multitude of resources with varying recommendations, with no step-by-step preparation instructions. In our

opinion, dedicated antidote administration guidelines are essential while implementing an antidote program for consistency, clarity, and timely administration.

Poison centre involvement proved essential to the NS antidote program. Poison centre staff promote awareness of the antidote program and administration guidelines while managing cases in real time with on-call physician backup. Poison centres are the only health care service to provide continuity of care for the poisoned patient from the time a call comes from the home to prehospital, ED, and intensive care; thus, poison centres are vital for optimizing care for this patient population.

NS was an ideal province for such a pilot program, given its relatively small geographic area and population densities, as well as its infrastructure including a poison centre, an advanced prehospital system, and two tertiary care centres serving adult and pediatric populations. The basic principles of this program could be extrapolated to larger provinces or countries to achieve success in antidote stocking.

LIMITATIONS

Antidote and patient tracking in our program relied on voluntary reporting through the poison centre, hospital pharmacies, and/or hospital pharmacy inventory systems. In addition, NAC use was not included, and it was more difficult to track antidotes not contained in the kit. Antidotes with which clinicians have a high level of comfort (e.g., naloxone) may not prompt a call to the poison centre. Therefore, actual antidote usage is undoubtedly much larger than what was reported. This study was not designed to evaluate whether antidote use was appropriate, any potential relationship between antidote stocking and patient outcome, or cost-effectiveness. Future research will examine these issues.

Another limitation was that compliance with the antidote program is not mandatory. Each district used its discretion regarding antidote kit stocking; as a result, implementation took years to achieve. Nonetheless, overall compliance is currently excellent.

CONCLUSIONS

Front-line healthcare providers need timely access to necessary antidotes, regardless of geographic location, and standardized, up-to-date guidelines for antidote administration. The NS antidote program is, to our knowledge, the first large scale program to demonstrate that a concrete and sustainable solution to ED antidote stocking is achievable with a system-wide approach and ongoing maintenance and surveillance. The frequency and distribution of antidote use in this program support the need for adequate antidote stocking in all EDs regardless of hospital size. Poison centres provide consultations to large geographic areas through telecommunication and are uniquely poised to support surveillance and improvement of an antidote program.

Acknowledgements: The authors would like to acknowledge the following people who have made contributions to this project: Mark Fletcher, Michael Howlett, Gisia Pisegna, L. Nicky Corkum, Catherine Doherty, Ardeth Reardon, Vanessa Sherwood, Laurel Ross, Patty Timms-Cluett, Peter MacMillan, Kathy Hart, David Juurlink, Wenda MacDonald, Peter Zed, and Jill Duncan.

Competing interests: None declared.

REFERENCES

1. Juurlink DN, McGuigan MA, Paton TW, Redelmeier DA. Availability of antidotes at acute care hospitals in Ontario. *CMAJ* 2001;165(1):27-30.
2. Gorman SK, Zed PJ, Purssell RA, Brubacher J, Willis GA. Antidote stocking in British Columbia hospitals. *CJEM* 2003;5(1):12-7.
3. Bailey B, Bussières JF. Antidote availability in Quebec hospital pharmacies: impact of N-acetylcysteine and naloxone consumption. *Can J Clin Pharmacol* 2000;7(4): 198-204.
4. Sivilotti MLA, Eisen JS, Lee JS, Peterson RG. Can emergency departments not afford to carry essential antidotes? *CJEM* 2002;4(1):23-33.
5. Wiens MO, Zed PJ, Lepik KJ, et al. Adequacy of antidote stocking in British Colombia hospitals: the 2005 Antidote Stocking Study. *CJEM* 2006;8(6):409-16.
6. Bailey B, Bussières JF, Dumont M. Availability of antidotes in Quebec hospitals before and after dissemination of guidelines. *Am J Health Syst Pharm* 2003 Nov 15;60(22):2345-9.
7. Dart RC, Borron SW, Caravati EM, et al.; Antidote Summit Authorship Group. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. *Ann Emerg Med* 2009;54(3):386-94.e1.
8. Wium CA, Hoffman BA. Antidotes and their availability in South Africa. *Clin Toxicol (Phila)* 47(1):77-80.
9. Thanacoody RH, Aldridge G, Laing W, et al. National audit of antidote stocking in acute hospitals in the UK. *Emerg Med J* 2013;30(5):393-96.
10. Nissen LM, Wong KH, Jones A, Roberts DM. Availability of antidotes for the treatment of acute poisoning in Queensland public hospitals. *Aust J Rural Health* 2010;18(2):78-84.

11. Gasco L, Rosbolt MB, Bebarta VS. Insufficient stocking of cyanide antidotes in US hospitals that provide emergency care. *J Pharmacol Pharmacother* 2013;4(2):95-102.
12. Al-Sohaim SI, Awang R, Zyoud SH, Rashid SM, Hashim S. Evaluate the impact of hospital types on the availability of antidotes for the management of acute toxic exposures and poisonings in Malaysia. *Hum Exp Toxicol* 2012;31(3):274-81.
13. Sohn CH, Ryoo SM, Lim KS, et al. Kind and estimated stocking amount of antidotes for initial treatment for acute poisoning at emergency medical centers in Korea. *J Korean Med Sci* 2014;29(11):1562-71.
14. Mitchell LJ, Higginson I, Smith JE, et al. 'Do you know where your cyanide kit is?': a study of perceived and actual antidote availability to emergency departments in South West of England. *Emerg Med J* 2013;30(1):43-8.
15. Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report. *Clin Toxicol (Phila)* 2015;53(10):962-1147.
16. Pettit HE, McKinney PE, Achusim LE, Lindsey DC. Toxicology cart for stocking sufficient supplies of poisoning antidotes. *Am J Health Syst Pharm* 1999;56(24):2537-9.
17. Chhabra N, Valento M, Bryant SM, Aks SE. Digoxin-specific antibody fragment dosing: A case series. *Am J Ther* 2016;23(6):e1597-601.
18. Chan BS, Isbister GK, O'Leary M, Chiew A, Buckley NA. Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1). *Clin Toxicol (Phila)* 2016;54(6):488-94.
19. Nordt SP, Clark RF, Machado C, Cantrell FL. Assessment of Digoxin-Specific Fab Fragment Dosages in Digoxin Poisoning. *Am J Ther* 2016;23(1):e63-7.
20. Chan BS, Buckley NA. Digoxin-specific antibody fragments in the treatment of digoxin toxicity. *Clin Toxicol (Phila)* 2014;52(8):824-36.
21. St-Onge M, Anseeuw K, Cantrell FL, et al. Experts consensus recommendations for the management of calcium channel blocker poisoning in adults. *Crit Care Med* 2017;45:e306-15.
22. Graudins A, Lee HM, Druda D. Calcium channel antagonist and beta-blocker overdose: antidotes and adjunct therapies. *Br J Clin Pharmacol* 2016;81(3):453-61.

APPENDIX A. LOCAL ANTIDOTE STOCKING SURVEY BEFORE IMPLEMENTATION OF THE ANTIDOTE PROGRAM (2004)

Antidote	T 1	T 2	R 1	C 1	C2	C3	C4	C5
Acetylcysteine	Y	Y	Y	Y	Y	Y	N	Y
Atropine	Y	Y	Y	Y	Y	Y	Y	Y
Calcium chloride	Y	Y	Y	Y	Y	Y	Y	Y
Calcium gluconate	Y	Y	N	N	N	Y	Y	Y
Cyanide antidote kit	Y	Y	Y	Y	N	N	N	N
Deferoxamine	Y	Y	Y	N	N	N	N	N
Digoxin immune Fab	Y	Y	Y	Y	N	N	N	N
Dimercaprol	N	N	N	N	N	N	N	N
Ethanol	Y	Y	Y	N	Y	Y	N	N
Fomepizole	Y	Y	N	N	N	N	N	N
Glucagon	Y	Y	Y	Y	Y	Y	Y	Y
Methylene blue	Y	Y	Y	Y	Y	N	N	N
Naloxone	Y	Y	Y	Y	Y	Y	Y	Y
Physostigmine	N	Y	Y	N	N	N	N	N
Pralidoxime	N	Y	N	N	N	N	N	N
Sodium bicarbonate	Y	Y	Y	Y	Y	Y	Y	Y

Note: Quantities of antidotes were not documented, only whether they were stocked in the hospital. After implementation in 2005, all sites were 100% compliant with the recommended antidotes. Ethanol and physostigmine were not included in the final recommendations.

APPENDIX B. COMPLIANCE OF EDS WITH THE NS ANTIDOTE PROGRAM BY YEAR, HOSPITAL TYPE, AND ANTIDOTE KIT TYPE

Year		2009	2010	2011	2012	2013	2014	2015 2016
Health zone 1	Regional 1	FK	FK	FK	FK	FK	FK	FK
	Regional 2	FK	FK	FK	FK	FK	FK	FK
	Regional 3	None	None	FK	FK	FK	FK	FK
	Community 1	PK	PK	PK	PK	PK	PK	PK
	Community 2	PK	PK	PK	PK	PK	PK	PK
	Community 3	FK	FK	FK	FK	FK	FK	MK
	Community 4	FK	FK	FK	FK	FK	FK	MK
	Community 5	None	None	None	FK	FK	FK	FK
	Community 6	None	None	None	FK	FK	FK	FK
Health zone 2	Regional 4	FK	FK	FK	FK	FK	FK	FK
	Regional 5	FK	FK	FK	FK	FK	FK	FK
	Regional 6	None	FK	FK	FK	FK	FK	FK
	Community 7	MK	MK	MK	MK	MK	MK	MK
	Community 8	None	None	None	None	None	None	None
	Community 9	None	None	None	None	None	None	None
Health zone 3	Regional 7	None	None	FK	FK	FK	FK	FK
	Regional 8	None	FK	FK	FK	FK	FK	FK
	Community 10	None	None	None	FK	FK	FK	FK
	Community 11	None	None	None	FK	FK	FK	MK
	Community 12	None	None	None	FK	FK	FK	FK
	Community 13	None	None	None	FK	FK	FK	MK
	Community 14	None	None	None	None	FK	FK	FK
	Community 15	None	None	None	None	FK	FK	FK
	Community 16	None	None	None	None	FK	FK	FK
	Community 17	None	None	None	None	FK	FK	FK
	Community 18	None	None	None	None	FK	FK	FK
	Community 19	None	None	None	None	FK	FK	FK
	Community 20	None	None	None	None	FK	FK	FK
Health zone 4	Tertiary 1	FK	FK	FK	FK	FK	FK	FK
	Tertiary 2	FK	FK	FK	FK	FK	FK	FK
	Regional 9	FK	FK	FK	FK	FK	FK	FK
	Community 21	FK	FK	FK	FK	FK	FK	FK
	Community 22	FK	FK	FK	FK	FK	FK	FK
	Community 23	FK	FK	FK	FK	FK	MK	MK
	Community 24	FK	FK	FK	FK	FK	MK	MK
	Community 25	FK	FK	FK	FK	FK	FK	FK
Regional compliance		7/11 (64%)	9/11 (82%)	11/11 (100%)	11/11 (100%)	11/11 (100%)	11/11 (100%)	11/11 (100%)
Community compliance	Modified or full kit	8/25 (32%)	8/25 (32%)	8/25 (32%)	14/25 (56%)	21/25 (84%)	21/25 (84%)	21/25 (84%)
	Partial kit (not fully compliant with recommendations)	2	2	2	2	2	2	2
	No kit	15	15	15	9	2	2	2
Overall		15/36 42%	17/36 47%	19/36 53%	25/36 69%	32/36 89%	32/36 89%	32/36 89%

FK = full kit; MK = modified kit; None = ED does not stock an antidote kit; PK = partial kit (not fully compliant with program stocking recommendations).