

Insufficient Stocking of Antidotes in Hospital Pharmacies: Problem, Causes, and Solution

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ABSTRACT

Over the past several years, various surveys have shown that hospital pharmacies do not have adequate stocks of antidotes to treat cases of poisoning. This article reviews these surveys to further define the problem and suggest a solution. Some hospitals rely on obtaining antidotes from other hospitals when needed. This practice is not always acceptable, because most antidotes must be readily available so that they can be given rapidly, to avoid unnecessary morbidity or mortality. Hospital stocks of antidotes may be inadequate for several reasons, including a lack of official guidelines. The authors make recommendations about the minimum quantity of antidotes that should be kept in each hospital. These suggestions are based on the levels of care provided by different types of hospitals and on the principle of ensuring treatment of a moderately to severely poisoned 70-kg adult for the first 12 h after poisoning in primary and secondary care hospitals and for the first 24 h in tertiary care centres. The economic impact of these recommendations is presented for one province. It is hoped that these suggestions will help to resolve the problem of insufficient stocking of antidotes in hospital pharmacies.

Key words: antidotes, stocking, cost analysis, guidelines

RÉSUMÉ

Au cours des dernières années, diverses enquêtes ont montré que les pharmacies d'hôpitaux n'avaient pas les quantités adéquates d'antidotes pour traiter les cas d'intoxication. Cet article passe en revue ces enquêtes pour mieux circonscrire le problème et recommander une solution. Certains hôpitaux dépendent d'autres hôpitaux pour obtenir les antidotes, au besoin. Toutefois, cette pratique n'est pas toujours acceptable, parce que la plupart des antidotes doivent être mis à disposition à temps, de sorte qu'ils puissent être administrés rapidement, et ainsi éviter des cas de morbidité ou de mortalité. De nombreuses raisons expliquent ce manque d'antidotes dans les hôpitaux, y compris l'absence de lignes directrices officielles. Les auteurs ont émis des recommandations quant aux quantités minimum d'antidotes que chaque hôpital devrait conserver. Leurs recommandations sont fondées sur le niveau de soins prodigués selon le type d'hôpital et sur le principe selon lequel il faut être en mesure de traiter un adulte de 70 kg modérément ou gravement intoxiqué, durant les premières 12 heures pour les hôpitaux de soins primaires et secondaires, et durant les premières 24 heures pour les hôpitaux de soins tertiaires. L'impact économique de ces recommandations est présenté pour une province. On espère que ces recommandations contribueront à résoudre les problèmes d'antidotes insuffisants dans les pharmacies d'hôpitaux.

Mots clés : antidotes, stocks, analyse de coût, lignes directrices

Can J Hosp Pharm 2000;53:325-37

INTRODUCTION

The optimal treatment of poisoning lies in seeking medical attention rapidly, identification of the ingested substance, access to scientific information about treating the poisoning, and availability of antidotes and substances used for decontamination, as well as supportive treatment. The pharmacy department of each hospital is responsible for the provision of antidotes and their replacement after expiration. Each department should also participate in developing protocols for the treatment of poisonings. However, because more and more antidotes are becoming available, this role may not be fulfilled adequately.

Recent studies have shown that hospital pharmacies do not have adequate amounts of selected antidotes.¹⁻¹¹ Several reasons have been suggested to explain this situation.^{3,5,12} One is the absence of any official recommendation or consensus concerning the minimal antidote stock needed, despite the wide distribution of 2 toxicological references^{12,13} that each suggest minimal amounts of antidote to be stocked. Although cost has been dismissed as a reason,⁵ evidence indicates otherwise.^{6,11} Thus, the suggested stock should be evaluated to determine if the recommended quantities of specific antidotes are realistic, given the frequency of certain poisonings and the limited budget available in some hospitals. The purpose of this article is to review the problem of inadequate stocking of antidotes in hospitals and its possible causes and to propose a partial solution by recommending minimal amounts of certain antidotes, according to the level of care of the particular hospital. The potential economic impact of these suggestions are also evaluated for one province.

THE PROBLEM

Hospital Pharmacies in the United States

In 1981, Spoerke reviewed several antidotes and other supportive medications used in the treatment of poisonings.¹ The author identified 3 types of hospitals (primary, secondary, and tertiary care) and specified which medications should be found in each hospital type, without indicating the quota per medication. Pharmaceutical considerations such as anticipated frequency of use and area of storage were presented, as well as special circumstances that might warrant stocking an unusual quantity of a drug.¹ Most of the antidotes reviewed in that article are still in use today. However, new antidotes have become available since then, including digoxin immune Fab, dimercaptosuccinic acid,

flumazenil, fomepizole, hydroxocobalamin, and polyvalent Crotalidae antivenin.

In 1986, Howland and colleagues¹⁴ reported the absence of niacinamide in hospitals within a 50-mile (80-km) radius of New York City. Niacinamide had been suggested by the poison control centre as a treatment for poisoning with Vacor (*N*-3-pyridylmethyl-*N*-*p*-nitrophenylurea, a rodenticide [now removed from the market] that causes irreversible insulin-dependent diabetes and injury to the autonomic nervous system, possibly by antagonizing the actions of nicotinamide); no niacinamide could be found, and the patient died 5 days later, despite all other appropriate therapy. The authors concluded that each hospital must designate someone to be responsible for reviewing antidote stock, so that these medications are available if they are ever needed.¹⁴ This report was probably the first clue that there was indeed a problem with the availability of antidotes, but it was not until the beginning of the 1990s that the extent of the problem became known.

A study (presented only as an abstract) carried out in the hospitals of Arizona in 1990 evaluated the availability of sufficient quantities of 6 antidotes to begin treating a 70-kg adult.⁸ The proportion of hospitals having sufficient quantities of antidotes ranged from 2% (for digoxin immune Fab) to 78% (for the antidote used in the treatment of cyanide poisoning). There were no differences in the distribution of antidotes according to the types, sizes, or populations of the hospitals. The authors suggested that guidelines be implemented to improve the situation.

Similar results were obtained in a study of polyvalent Crotalidae antivenin in 69 Arizona hospitals in the late 1980s.⁹ The study was initiated after the authors had been consulted for a patient who had received antivenin after a delay of several hours. They found that 21 (30%) of the hospitals had a stock of fewer than 8 vials of antivenin, and 31 (45%) had fewer than 13 vials, the quantities needed to treat moderate and severe poisoning, respectively. Moreover, the recent use of the antivenin favoured its presence in a hospital.⁹ In fact, in the 38 hospitals that had used at least 1 vial of antivenin in the previous year, only 5 (13%) and 11 (29%) did not have 8 and 13 vials of antivenin, respectively, whereas of the 28 hospitals that had not used any antivenin in the past year, 15 (54%) ($p = 0.001$) and 19 (68%) ($p = 0.004$) did not have these quantities of antivenin. The authors noted that it was impractical to rely on other hospitals in the region, because it usually took at least 1 to 2 h to obtain the antivenin from these sources, a delay that is unacceptable in cases of snakebite. These authors also



mentioned the necessity of guidelines concerning the quantity of antivenin and antidotes needed in a hospital.⁹

Another study, carried out in hospitals in the San Francisco region in 1991, evaluated the availability of 8 antidotes.⁷ The antidotes were present in sufficient quantities to treat a patient for 24 h in up to 67% of the hospitals, depending on the antidote.⁷ Only half of the hospitals had sufficient quantities of more than 2 of the 8 selected antidotes. The hospitals with more antidotes in sufficient quantities were teaching institutions with more than 250 beds. The acquisition cost for sufficient stocks of these 8 antidotes was US\$7859 (1991 dollars).

Chyka and Conner² surveyed 170 pharmacy directors from hospitals in Tennessee to verify the availability of 10 antidotes (*N*-acetylcysteine, cyanide antidote kit, digoxin immune Fab, dimercaprol, ethanol, flumazenil, methylene blue, naloxone, polyvalent *Crotalidae* antivenin, and pralidoxime).² The response rate was 73% (124/170). Stocking was considered adequate if there was a minimum of 2 adult doses. The antidotes that were usually available in adequate quantities were *N*-acetylcysteine, flumazenil, methylene blue, and naloxone; those that were usually not available in sufficient quantities were the cyanide antidote kit, dimercaprol, ethanol, and pralidoxime. Stocks were better in hospitals that had a pharmacist on duty 24 h/day and in those with a poison control centre. Only 7 (6%) of the 124 respondents had adequate stocks of the 10 antidotes. The authors observed that the maintenance of stocks often depended on the history of previous use, which is not necessarily the best indicator of future needs. The cost of stocking these 10 antidotes was evaluated at US\$8650 (1993 dollars).

Dart and colleagues³ conducted a similar survey of 137 hospitals in Colorado, Montana, and Nevada. The response rate was 79% (108/137). Only 1 (1%) of the respondents maintained an adequate stock of 8 antidotes (cyanide antidote kit, deferoxamine, digoxin immune Fab, ethanol, naloxone, polyvalent *Crotalidae* antivenin, pralidoxime, and pyridoxine). The authors excluded from the analysis products for which there is an alternative (such as flumazenil, for which intubation can be substituted) or for which a reasonable delay is acceptable (such as *N*-acetylcysteine). The rate of adequate stocking ranged from 2% to 98% for the various antidotes. The median number of antidotes stocked in insufficient quantities was 4. For 14 (13%) of respondents, only naloxone was stocked in adequate quantities. Multiple regression analysis demonstrated that small hospital size and lack of formal review of antidote stocks constituted 2 predictors of inadequate stock. The authors indicated that transfer of antidotes

among hospitals is of little use in many cases, given that this takes at least 1 h. An adequate stock was defined as enough to treat a 70-kg patient, and the average cost of the inventory was calculated to be US\$9751 (1996 dollars). The authors suggested that poison control centres should play a larger role in determining minimal stock of antidotes because inadequate stock is usually observed in rural and nonteaching institutions and is probably related to the absence of clear published recommendations and insufficient resources. The authors repeated the survey 15 months after the first exercise,⁴ but without any direct intervention. Despite the important media coverage that the initial study had generated, the situation remained unchanged.

Woolf and Christanthus⁵ surveyed 93 institutions in Massachusetts in 1993 and 1994; their response rate was 87% (81/93). The authors observed wide variability of inadequate stock for 16 antidotes (*N*-acetylcysteine, activated charcoal, calcium ethylenediaminetetra-acetic acid [EDTA], cyanide antidote kit, deferoxamine, digoxin immune Fab, dimercaprol, dimercaptosuccinic acid, ethanol, flumazenil, methylene blue, naloxone, physostigmine, polyvalent *Crotalidae* antivenin, pralidoxime, and pyridoxine). Only 8 (10%) of the respondents carried all 14 antidotes (excluding dimercaptosuccinic acid and polyvalent *Crotalidae* antivenin, not widely used or available in the study region); a smaller percentage carried the antidotes in adequate quantities (enough to treat a 70-kg patient). The value of the required inventory was estimated at US\$9751 (1996 dollars). These authors also concluded that clear recommendations about antidote stocks were needed.⁵

A recent report on the availability of pyridoxine for the treatment of isoniazid overdose in 130 hospitals with pediatric emergency medicine fellowships or residency positions in emergency medicine showed that between one-third and one-half of respondents would not have sufficient amounts of the vitamin to treat acute isoniazid neurotoxicity (5 g).¹⁰ The response rate for this survey was 80% (104/130).¹⁰

A survey of 76 hospitals in Oregon and Nevada examined the availability of 10 selected antidotes (*N*-acetylcysteine, cyanide antidote kit, deferoxamine, digoxin immune Fab, ethanol, fomepizole, naloxone, polyvalent *Crotalidae* antivenin, pralidoxime, and pyridoxine) and showed that only 38 (50%) of the hospitals had the recommended 24-h quantities of antidotes, and only 46 (61%) had the recommended 6-h quantities.¹¹ Interestingly, antidote stocking varied directly with frequency of use reported by the American



Association of Poison Control Centers ($r = 0.65$) and hospital size ($r = 0.41$) and varied inversely with antidote cost ($r = -0.84$).¹¹

Hospital Pharmacies in Canada

In 1994, Ontario hospitals were surveyed by telephone about the availability of pyridoxine.¹⁵ Only 16% of the hospitals had at least 5 g of pyridoxine, an amount judged to be enough to treat a typical adult overdose (5 g of isoniazid).^{12,13} Two-thirds of the hospitals did not even carry the antidote, and 18% had an insufficient amount. The authors compared the distribution of tuberculosis with hospital supplies of pyridoxine.¹⁵ The presence of tuberculosis in the public health units explained only 22% of the availability of pyridoxine. The Ontario Regional Poison Centre was consulted 3 times during that year for isoniazid poisoning, including one instance of isoniazid-related seizures; none of the 3 hospitals involved carried pyridoxine.

Also in 1994, the Poison and Drug Information Service of Alberta surveyed urban hospitals in Edmonton and Calgary as well as regional hospitals in Alberta to determine the availability of antidotes.¹⁶ The organization did not present results for all antidotes surveyed, but it did report that most hospitals did not stock sufficient glucagon for immediate treatment.¹⁶

A survey of 112 Quebec hospitals with acute care beds achieved a response rate of 86% (96/112).⁶ The antidotes surveyed were *N*-acetylcysteine, cyanide antidote kit, deferoxamine, digoxin immune Fab, dimercaprol, ethanol, flumazenil, glucagon, methylene blue, naloxone, physostigmine, pralidoxime, and pyridoxine. Stocks were adequate for at most 9 (median 3) of the 13 antidotes studied. Multiple regression analysis showed that adequate stocking was significantly correlated with the quantity of *N*-acetylcysteine and naloxone consumed annually ($r_s = 0.58$ and 0.53 , $p < 0.001$), as well as with other variables related to the size of the hospital. The quantity of *N*-acetylcysteine consumed, the number of hours that the pharmacy was open (on the weekends), and the number of annual visits to the emergency department allowed independent prediction of adequate stocks.⁶ These results indicate that the frequency of poisonings treated in a hospital influences the quantity of antidotes; this relationship was previously observed for polyvalent Crotalidae antivenin.⁹ Interestingly, the cost of acquiring adequate amounts of each antidote was inversely correlated with the number of hospitals carrying it ($r_s = -0.60$, $p = 0.03$).

A similar study was recently conducted in Ontario.* Only 1 of 179 acute care hospitals that responded to the survey carried adequate stocks of antidotes (response rate 97% [179/185]). Adequate stocks were most frequent for flumazenil (92%) and least frequent for digoxin immune Fab (9%). In a univariate analysis, teaching hospital status, annual patient volume in the emergency department, and designation as a regional trauma centre were associated with better stocking, whereas small hospital size and greater distance from the nearest neighbouring hospital were associated with poorer stocking. However, only annual emergency department volume, small hospital size, and designation as a regional trauma centre independently predicted antidote stocking in the multivariate analysis. Although the authors used the criteria of Dart and colleagues³ for the amounts of antidote needed in the first 1 to 2 h (see Table 1), it was concluded that many Ontario hospitals stock insufficient amounts of several antidotes.

Other Countries

A recent survey of the availability of 20 antidotes in Taiwan found similar problems in that country.¹⁷ The availability of antidotes ranged from 0% to 89%. The median number of antidotes stocked was 6 (range 0 to 16). The results of that survey must be tempered by the low response rate (responses were received from only 165 [20%] of the 834 hospitals surveyed).¹⁷

A study in 43 hospitals in Wales and southwest England (response rate 77%) found that hospitals in the United Kingdom also lacked adequate stocks of antidotes.¹⁸ No hospital carried all of the 34 antidotes surveyed. The hospitals carried a mean of 13 antidotes (range 7 to 33).

Medicolegal Implications

The medicolegal impact of a hospital having insufficient stocks of antidotes has been discussed recently.¹⁹ It is clear that the situation places the hospital at risk of litigation. Waiting for a shipment from another hospital and transferring the patient to another hospital are not considered acceptable alternatives.¹⁹

Guidelines

To the authors' knowledge, only 2 guidelines on the stocking of antidotes have been published with the potential for wide distribution^{12,13} (see also note

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Table 1. Antidotes and Their Administration, Including Proposed Minimal Stock, as Proposed in the Literature

Antidote	Poison Ingested or Clinical Situation	Dosage ²⁵	Delay of Action ²²	Proposed Minimal Stock						
				California ¹²	Illinois ¹³	Chyka and Conner ²	Dart et al. ³	Woolf and Christanthus ⁵	PADIS ²¹ Rural	PADIS ²¹ Other
N-Acetylcysteine 200 mg/mL, 30-mL vial	Acetaminophen	<i>IV(adult)</i> : 300–910 mg/kg	<120 min	42 g	120 g	15 g			24–30 g	30 g
Atropine 0.4 mg/mL, 1-mL vial	Carbamates, organophosphates	<i>IV(ped)</i> : 0.02–0.05 mg/kg (max. unknown) <i>IV(adult)</i> : 1–4 mg (max. unknown)	<30 min	1000 mg	60 mg				25– 50 mg	1000– 1500 mg
Calcium chloride 100 mg/mL, 10-mL vial	Calcium blockers	<i>IV(ped)</i> : 10–30 mg/kg, repeatable 3 or 4 times* <i>IV(adult)</i> : 1000 mg, repeatable 3 or 4 times*	<30 min	10 g	5 g					1–2 g
Calcium EDTA 200 mg/mL, 5-mL vial	Lead	<i>IV or IM (ped)</i> : 1–1.5 g/m ² (q8–12h) <i>IV or IM (adult)</i> : 1–1.5 g/m ² (q8–12h) or 1–2 g per 24 h (q8–12h)	<360 min	18 g	2 g					18 g†
Calcium gluconate 100 mg/mL, 10-mL vial	Hydrofluoric acid	<i>Topical gel</i> : q 4h <i>Intra-arterial (adult)</i> : 10–20 mL over 4 h	<30 min							3 g
Cyanide antidote package (Taylor): amyl nitrite (AN), 3% sodium nitrite (SN), 25% sodium thiosulfate (ST)	Cyanide, acetonitrile, cyanhydric acid, nitroprusside	<i>AN, inhaled</i> : q1–2min <i>SN, IV(adult)</i> : 300 mg <i>SN, IV(ped)</i> : 0.15–0.3 mL/kg‡ <i>ST, IV(adult)</i> : 12.5 g <i>ST, IV(ped)</i> : 1.6 mL/kg	<120 min	2 kits	3 kits	2 kits	1 kit	1 kit	1 or 2 kits	1 or 2 kits
Deferoxamine, 500-mg vial	Iron	<i>IV(adult)</i> : 10–15 mg/kg hourly up to 50 mg/kg hourly	<30 min	6 g	6 g		1 g		5 g	6 g
Digoxin immune Fab, 40-mg vial	Digoxin	<i>IV(adult)</i> : Digoxinemia (nmol/L) x 0.0073 x weight (kg) = no. of vials required (or 2–20 vials)	<30 min	20 vials	20 vials	20 vials	20 vials	10 vials	NA	6 vials
Dimercaprol BAL 100 mg/mL, 3-mL vial	Lead	<i>IM(ped)</i> : 75 mg/m ² q4h <i>IM(adult)</i> : 3–4 mg/kg q4h	<120 min	1200 mg	3 g	600 mg				12 g†
Dimercaptosuccinic acid, 100-mg capsules	Lead	<i>PO(ped)</i> : 10 mg/kg (350 mg/m ²) q8h x 5 days, then same dose q12h x 14 days		10 g	10 g					2 g†

BAL = British Anti-Lewisite, EDTA = ethylenediaminetetra-acetic acid, IV = intravenous, IM = intramuscular, NA = not available at time list was prepared, PADIS = Poison and Drug Information Service of Alberta, ped = in children, PO = by mouth, SC = subcutaneous, blank cell = information not provided.

*Infusion of 20–50 mg/kg per hour may be used instead of boluses.

†Only for tertiary-care hospitals.

‡Based on hemoglobin concentration.

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Table 1. (continued)

Antidote	Poison Ingested or Clinical Situation	Dosage ²⁵	Delay of Action ²²	Proposed Minimal Stock						
				California ¹²	Illinois ¹³	Chyka and Conner ²	Dart et al. ³	Woolf and Christanthus ⁵	PADIS ²¹ Rural	PADIS ²¹ Other
Ethanol 1 g/mL, 10-mL vial	Ethylene glycol, methanol	<i>IV(adult):</i> 10 mL/kg + 2 mL/kg per hour with a 10% solution, up to 4 mL/kg per hour	<30 min	300 g	800 g	100 g	70 g	50 g	180 g	180 g
Flumazenil 0.1 mg/mL, 5-mL vial	Benzodiazepines	<i>IV(ped):</i> 10 µg/kg up to 1 mg <i>IV(adult):</i> 0.2–0.3 mg up to 2 mg or 0.1–0.4 mg/h	<120 min	10 mg	10 mg	3 mg				5 mg
Fomepizole 1 g/mL, 1.5-mL vial (1 kit = 4 vials, 1.5 mL/vial)	Ethylene glycol, methanol	<i>IV(adult):</i> 15 mg/kg, followed by 10 mg/kg q12h x 4 doses, then 15 mg/kg q12h		1 kit						NA
Glucagon 1 mg, kit or vial	β-Blockers, calcium blockers	<i>IV(ped):</i> 50–150 µg/kg + 70 µg/kg per hour <i>IV(adult):</i> 3–10 mg + 1–5 mg/h	<30 min	100 mg	50 mg				40 mg	40 mg
Hydroxocobalamin, 2.5-g vial (1 kit = 2 vials)	Cyanide, acetonitrile, cyanhydric acid, nitroprusside	<i>IV(ped):</i> 70 mg/kg up to 2.5 g <i>IV(adult):</i> 5 g	<30 min	0						
Methylene blue 10 mg/mL, 1-mL vial	Methemo- globinemia	<i>IV(adult):</i> 1–2 mg/kg up to 7 mg/kg	<30 min	500 mg	100 mg	200 mg		100 mg	150– 200 mg	200 mg
Naloxone 0.4 mg/mL, 1-mL vial	Narcotics	<i>IV(ped):</i> 0.1 mg/kg up to 2 mg <i>IV(adult):</i> 2–10 mg <i>Perfusion:</i> 2/3 of bolus needed to reverse coma per hour	<30 min	30 mg	20 mg	20 mg	2 mg		0.8– 10 mg	10 mg
Penicillamine, 250-mg tablets	Heavy metals	<i>PO(adult):</i> 20–40 mg/kg per 24 h	<360 min	1.5 g	12.5 g	2 g				1.5 g†
Physostigmine 0.4 mg/mL, 5-mL vial	Anticholinergics	<i>IV(ped):</i> 0.02 mg/kg up to 2 mg <i>IV(adult):</i> 1–2 mg up to 4 mg	<30 min	20 mg	20 mg				1–2 mg	
Polyvalent Crotalidae antivenin (vial)	Snake venom	<i>IV(adult):</i> 5–10 vials/h		20 vials	10 vials	20 vials	5 vials	10 vials		20 vial†
Pralidoxime, 1-g vial	Organophosphates	<i>IV(ped):</i> 25–50 mg/kg (max. unknown) <i>IV(adult):</i> 1–2 g up to 12 g	<30 min	12 g	3 g		2 g	1 g	3–4 g	15 g
Pyridoxine 100 mg/mL, 1-mL vial	Isoniazid	<i>IV(adult):</i> 0.5 mg/min up to 5 g	<30 min	20 g	25 g		5 g	6 g	5–7.5 g	5 g
Vitamin K, 10 mg/mL, 1-mL vial	Warfarin	<i>IV or SC (ped):</i> 1–5 mg <i>IV or SC (adult):</i> 2.5–10 mg	<360 min	100 mg	102 mg					50 mg

BAL = British Anti-Lewisite, EDTA = ethylenediaminetetra-acetic acid, IV = intravenous, IM = intramuscular, NA = not available at time list was prepared, PADIS = Poison and Drug Information Service of Alberta, ped = in children, PO = by mouth, SC = subcutaneous, blank cell = information not provided.

*Infusion of 20–50 mg/kg per hour may be used instead of boluses.

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added in proof). However, the suggestions have not been widely promoted because they appeared in toxicology reference books. The medical teams from the California Poison Control System¹² (formerly the San Francisco Bay Area Regional Poison Control Center) and the Illinois Poison Center¹³ each published a list of antidotes and the suggestion of a minimal stock for each hospital. One of these guidelines¹² was recently used to present the concept of a toxicology cart.²⁰

The Poison and Drug Information Service of Alberta has also published an antidote list for rural hospitals²¹ (see Table 1). This list, made available on request to large and small hospitals in Alberta, was intended for use in the first few hours in cases of severe overdose, pending air or ground transport within 2 to 3 h.

At present many hospitals rely on verbal understandings with nearby institutions to obtain certain antidotes. This is a problematic situation, as noted by Dart and colleagues⁹ and Freeman,¹⁹ because certain antidotes must be administered less than 30 min after the poisoning and consequently must be available in the emergency department or in a readily accessible location, as suggested by the International Programme on Chemical Safety.²² The antidotes that must be administered in less than 30 min are atropine, β -blockers, calcium gluconate, cyanide antidote kit, dantrolene, diazepam, digoxin immune Fab, ethanol, glucagon, glucose, isoproterenol, 4-methylpyrazole (fomepizole), methylene blue, naloxone, oxygen, phentolamine, physostigmine, protamine, pyridoxine, and sodium nitroprusside.²² *N*-Acetylcysteine, deferoxamine, dimercaprol, flumazenil, neostigmine, and pralidoxime must be administered within 2 h of the poisoning.²² Polyvalent Crotalidae antivenin was not included in the list.²²

Table 1 presents the general indications and pediatric and adult dosages for 23 antidotes, as well as maximal delay (i.e., the maximal delay acceptable before starting treatment²²) and the minimal stock of the antidote, as presented in previous publications.^{2,3,5,12,13,21}

THE CAUSES

The causes for the insufficient quantities of antidotes in hospitals are multiple and must be known before the situation can be rectified. These causes depend on the antidote itself, the location of the hospital, the hospital's internal decision process, lack of awareness of the problem, and the absence of guidelines.

An antidote may be difficult to obtain, particularly if there is a change in the distributor or if the company lacks a good network for distributing its products.^{5,14} This

factor may limit antidote availability for certain hospitals and may be hard to correct, because distribution depends mainly on the financial interests of the pharmaceutical company. The cost of the antidote might be another factor explaining low availability.^{5,6,11} This factor can be exacerbated if the costly antidote has a short expiration date. However, the argument of prohibitive cost is difficult to accept if the possible impact of inadequate stocks — in terms of morbidity, mortality, and medicolegal implications — are taken into account.

Infrequency of use of an antidote or the rarity of poisonings could also lead to lack of availability.^{2,6,9,11} The size of the hospital might explain the situation, particularly for those that are not teaching hospitals or that do not have a pharmacist on staff 24 h/day.^{2,6,7,9,11} However, it is not clear if the availability of antidotes is directly related to the small size of a hospital or if there are other factors associated with small hospital size, such as low budget, a low incidence of poisonings, absence of internal review of stocks, and infrequent use of antidotes. One study has suggested that the number of poisonings seen and the size of the hospital explain more than 50% of the variability in amounts of antidotes kept in hospitals.⁶

Other factors also explain the current situation. An understanding among hospitals to share their stock or the existence of therapeutic alternatives might motivate a pharmacy to maintain insufficient stock.⁵ Given the rapidity with which most antidotes must be administered,²² such understandings are inadequate, except for antidotes that can be given more than 2 h after the poisoning. Even for those agents, difficulty in transferring the patient or in obtaining the antidote (for example, if the hospital is isolated and the weather is poor) or recent use of existing stocks by the other hospital can limit the usefulness of understandings between hospitals. For a variety of reasons, the presence of a poison control centre in the hospital favours the stocking of antidotes in sufficient quantities: there may be higher demand for the products or a better mechanism for internal review, and the hospital is likely to be larger.²

The absence of guidelines is a key element often cited to explain lack of stock.^{3,5,8} This factor can be easily corrected. Lack of knowledge of the necessary quantity of an antidote to treat a significant poisoning is another factor easily corrected by guidelines.⁵

Despite the fact that solutions to the problem exist, Bogdan and colleagues have shown that, without direct intervention, especially in the absence of official guidelines, the situation is unlikely to be rectified.⁴ The results

of educational efforts have been recently published.^{23,24} In one study, performed in Connecticut over several years, antidote stocking improved significantly with educational efforts,²³ whereas this approach appeared ineffective in another study, performed in Colorado, Montana, Idaho, and Nevada.²⁴ The hospital pharmacists from Connecticut mentioned that adequate antidote stocking was determined by utilization and cost.²³ Thus, guidelines are not the only answer.

A SOLUTION

On the basis of scientific documentation concerning the stocking of antidotes and the guidelines for treatment of poisonings in Quebec,²⁵ recommendations were made concerning the minimal stock of antidotes needed to treat a 70-kg patient with moderate to severe poisoning for roughly 12 h in a primary or secondary care hospital and for 24 h in a tertiary care hospital,²⁶ except for antidotes for frequent poisonings, such as those with acetaminophen or toxic alcohol, or rare poisonings, such as those with heavy metals. For the antidotes needed for more frequent poisonings (*N*-acetylcysteine and ethanol), the equivalent of 2 days' supply was recommended for all hospitals. For antidotes used to treat heavy metal poisonings, such as dimercaprol, calcium EDTA, and penicillamine, it was recommended that only tertiary care hospitals carry the necessary antidotes. These recommendations were validated by 5 board-certified medical toxicologists of the Centre anti-poison du Québec.

The guidelines proposed were based on the following factors: the reference dose used (Table 1), the duration of hospital autonomy before an external source of antidote is sought, and the role of the hospital (primary, secondary, or tertiary care).¹ No recommendations were made for the newly available antidote fomepizole, because of the recently stated position of the Centre anti-poison du Québec,²⁷ which stated that if fomepizole is preferred over ethanol in the treatment of poisoning with ethylene glycol or methanol, one kit (4 vials) should be kept on hand. Hospitals that see toxic alcohol poisoning frequently may want to keep 2 kits (8 vials) on hand. No guidelines were provided for dimercaptosuccinic acid because it is not available in Canada. Where it is available, one bottle of 100 capsules should be kept, possibly only in tertiary care hospitals. For cyanide poisoning, hydroxocobalamin, if available, should be preferred over the Taylor cyanide antidote package, which contains amyl nitrite, sodium nitrite, and sodium thio-

sulfate; the Taylor package is contraindicated for patients in whom carbon monoxide poisoning has not been ruled out, which limits its use. Physostigmine was included, despite concern about its potential toxicity; it is a valuable antidote in some situations, if used appropriately.²⁸

Recommendations Concerning Minimal Inventory

Recommendations concerning the minimal stock for 18 antidotes are presented in Table 2. The recommendations do not take account of the quantities needed in case of disaster, notably a terrorist attack. Besides the antidotes presented in Table 2, each hospital must keep an adequate quantity of medication for supportive treatment and for gastrointestinal decontamination, notably activated charcoal with or without sorbitol, β -blockers (propranolol or esmolol), dantrolene, dextrose, diazepam, dobutamine, dopamine, epinephrine, haloperidol, ipecac syrup, isoproterenol, leucovorin, neuromuscular blockers, oxygen, phentolamine, protamine, nitroprusside, sodium bicarbonate, solutions for intestinal irrigation, and thiamine. These medications should be readily available 24 h/day. Isolated primary or secondary care hospitals should probably keep stock as if they were tertiary care hospitals. Because of particular local needs, such as those discussed by Spoerke,¹ hospital pharmacies may want to keep either more of a specific antidote or another antidote not discussed.

ECONOMIC ANALYSIS

Methods

After a survey assessing the presence and past consumption of 13 selected antidotes (*N*-acetylcysteine, cyanide kit, deferoxamine, digoxin immune Fab, dimercaprol, ethanol, flumazenil, glucagon, methylene blue, naloxone, physostigmine, pralidoxime, and pyridoxine) in 112 hospital pharmacies in Quebec (henceforth called the total cohort),⁶ an economic analysis of the recommendations was performed. A total of 96 hospital pharmacy directors responded to the survey (called the respondent cohort); however, only 71 completed all consumption data (called the complete cohort). Some additional data about the number of beds, stretchers, and visits to the emergency department for 1996/97 were gathered for 12 of the 16 hospitals that did not respond to the survey. There was no difference among the hospitals that responded and those that did



Table 2. Recommended Minimal Stock of Antidotes for a Hospital

Antidote	Unit price,* (\$)	Primary Care Hospital		Secondary Care Hospital		Tertiary Care Hospital	
		Minimal Stock (No.)	Cost of Minimal Stock (\$)	Minimal Stock (No.)	Cost of Minimal Stock (\$)	Minimal Stock (No.)	Cost of Minimal Stock (\$)
N-Acetylcysteine 200 mg/mL, 30-mL vial	14.42	20	288.30	20	288.30	20	288.30
Atropine 0.4 mg/mL, 1-mL vial	0.17	500†	86.50	500†	86.50	2500†	432.50
Calcium EDTA 200 mg/mL, 5-mL vial	22.71	0	NA	0	NA	2	45.43
Calcium gluconate 100 mg/mL, 10 mL vial	0.63	10	6.34	10	6.34	20	12.68
Cyanide antidote package (Taylor): amyl nitrite, sodium nitrite, sodium thiosulfate	300.00	1†‡	300.00	2†	600.00	2†	600.00
Deferoxamine, 500-mg vial	13.33	20	266.60	20	266.60	50	666.50
Digoxin immune Fab, 40-mg vial	408.76	4§	1635.04	10¶	4087.60	20	8175.20
Dimercaprol BAL 100 mg/mL, 3-mL vial**	110.00	0	NA	0	NA	3	330.00
Ethanol 1 g/mL, 10-mL vial	8.36	60	501.60	60	501.60	60	501.60
Flumazenil 0.1 mg/mL, 5-mL vial	29.81	10	298.10	10	298.10	20	596.20
Glucagon 1 mg, kit or vial	32.85	25	821.25	25	821.25	50	1642.50
Methylene blue 10 mg/mL, 1-mL vial	3.60	25	90.10	25	90.10	50	180.20
Naloxone 0.4 mg/mL, 1-mL vial	2.96	50	147.90	50	147.90	100	295.80
Penicillamine, 250-mg tablets	0.25	0	NA	0	NA	30	7.50
Physostigmine 0.4 mg/mL, 5-mL vial	11.75	3	35.25	3	35.25	5	58.75
Pralidoxime, 1-g vial	25.51	5†	127.55	5†	127.55	10†	255.10
Pyridoxine 100 mg/mL, 1-mL vial	1.82	50	90.75	50	90.75	100	181.50
Vitamin K ₁ 10 mg/mL, 1-mL vial	0.64	2	1.27	2	1.27	5	3.18
Total cost	NA	NA	4696.55	NA	7449.11	NA	14272.94

BAL = British Anti-Lewisite, EDTA = ethylenediaminetetra-acetic acid, NA = not applicable.

*Acquisition price (in 1999 Canadian dollars), according to the Montréal-Estrie Group, a purchasing group that contracts for all hospitals in the Montreal and Estrie regions (representing more than 100 hospitals and organizations and \$80 million in drug purchases each year).

†Does not take into account disaster plans.

‡Ideally 2 kits if the hospital is isolated (i.e., closest hospital is more than 30 min away).

§Ideally 10 vials if the hospital is isolated (i.e., closest hospital is more than 30 min away).

¶Ideally 20 vials if the hospital is isolated (i.e., closest hospital is more than 30 min away).

**The price of dimercaprol increased significantly, to about \$260/vial, in the past year.

not in terms of number of beds, stretchers, and visits to the emergency department for 1996/97. The impact of the recommended minimal amounts of antidotes (Table 2) on the cost of inventory per hospital were simulated for a cohort of 108 hospitals (called the extrapolated cohort, which represented the total cohort minus the 4 hospitals for which no additional information could be gathered).

Costs of Antidote Consumption in 1996/97 per Volume of Activity in Complete Cohort: Seventy-one respondents (the complete cohort) provided detailed information on the consumption of each antidote during the 1996/97 fiscal year.⁶ This permitted calculation of a simple arithmetic average of the cost of antidote consumption per hospital according to 3 measures of activity: per bed, per stretcher, or per annual visit to the emergency department. All 3 cost ratios were analyzed, and the one with the smallest standard deviation was selected for cost extrapolation among respondents with missing information about consumption of antidotes, to

obtain the value for the extrapolated cohort.

Estimated Annual Cost of Antidotes in 1996/97 in Complete Cohort: The total annual cost of antidotes for 1996/97 for the complete cohort was calculated on the basis of quantities consumed, as provided by the hospitals. Quantities potentially used by the other hospitals were extrapolated from these data to obtain the values for the extrapolated cohort of 108 hospitals, according to the total numbers of annual visits to the emergency department.

Actual Inventory in Respondent Cohort: Total inventory in the respondent cohort was extrapolated to the 108 hospitals in the extrapolated cohort, on the basis of total numbers of annual visits to the emergency department, to determine total inventory in the extrapolated cohort.

Sensitivity Analysis: For the sensitivity analysis, the number of primary, secondary, and tertiary care hospitals were varied according to a "maximal scenario" (i.e.,

Table 3. Simulation of the Economic Impact of Antidote Stocking Recommendations on the Value of Antidote Inventory in the Province of Quebec

Scenario*	Actual No. of Hospital†			Total Cost, All Hospital‡
	Primary Care	Secondary Care	Tertiary Care	
Maximal	62	22	23	\$787 626 (mean \$7293/site)
Conservative	75	16	16	\$704 098 (mean \$6519/site)

*Under the maximal scenario, the number of tertiary care hospitals (those receiving transfers from other hospitals) was maximized, and under the conservative scenario, the numbers of secondary care hospitals (regional centres that may receive transfers from other local hospitals) and tertiary care hospitals were minimized. Isolated hospitals were defined as secondary (in the maximal scenario) or tertiary (in the conservative scenario). Hospitals performing hemodialysis were considered secondary or tertiary care hospitals.

†Because of restructuring of the health care system in the province of Quebec, only 107 hospitals had acute care beds at the time of the simulation, as opposed to the 112 with acute care beds at the time of the initial survey.

‡Total cost is based on extrapolation to 108 hospitals.

maximizing the number of tertiary care institutions) and a “conservative scenario” (i.e., minimizing the number of secondary and tertiary care institutions) to quantify the impact of the stocking suggestions. A primary care hospital was defined as one that usually does not receive any patient transfers from other hospitals. A secondary care hospital was defined as a regional hospital that may receive certain transfers from other hospitals in the same geographic area. A tertiary care hospital was defined as one that receives patient transfers from other hospitals, including the most serious cases. Each of the 18 administrative regions in the province of Quebec had a secondary care hospital. Isolated hospitals were defined as secondary or tertiary, depending on the scenario used (maximal or conservative, respectively). Hospitals performing hemodialysis were considered secondary or tertiary care hospitals.

Turnover of Inventory: According to the estimated annual cost of antidotes in 1996/97 in the complete cohort and the recommended inventory, the turnover of inventory was estimated for each antidote. Turnover of the antidote inventory was compared with turnover of all inventories.

Expiration: For informational purposes only, the complete stock at one hospital was validated to determine the average difference between purchase date and expiration date.

Cost Annualization: All costs are expressed in 1999 Canadian dollars, except for consumption results, which are expressed in 1996/97 Canadian dollars. No cost annualization was performed because prices were stable, as a result of a long-term group purchasing contract.

Results

Costs of Antidote Consumption in 1996/97 per Volume of Activity in Complete Cohort: In the complete cohort (71 hospitals), the average cost \pm standard deviation of antidote consumption was $\$51.85 \pm 100.19$

(median $\$22.53$) per bed, $\$627.41 \pm 658.21$ (median $\$400.22$) per stretcher, and $\$0.32 \pm 0.55$ (median $\$0.16$) per visit to the emergency department.

Estimated Annual Cost of Antidotes in 1996/97 in Complete Cohort: The annual cost of antidotes consumed by the complete cohort (71 hospitals) was $\$804\,941$, with 62 729 doses or vials of antidotes used. The annual cost of antidotes consumed in the extrapolated cohort (108 hospitals) was $\$1\,048\,404$, with 81 478 doses or vials of antidotes used in 1996/97.

Actual Inventory in Respondent Cohort: The total inventory of antidotes was $\$609\,409$ in the respondent cohort (96 hospitals with a total of 2 997 475 visits to the emergency department). The total inventory in the extrapolated cohort was $\$664\,749$ (108 hospitals with a total of 3 269 682 visits to the emergency department).

Sensitivity Analysis: Table 3 illustrates the distribution of hospitals and the cost in inventory for the sensitivity analysis. The total inventory of the 18 antidotes proposed by these recommendations ranged from $\$704\,098$ to $\$787\,626$. Therefore, the recommendations would cause an increase in the actual antidote inventory of 6% to 18%. The value of the antidotes stocked would be $\$4697$, $\$7449$, and $\$14\,933$ for primary, secondary, and tertiary care hospitals, respectively. The contribution of antidotes to the cost of the inventory, in decreasing order, was digoxin immune Fab (48% of the total cost), glucagon (14%), ethanol (7%), and the cyanide antidote kit (6%). The cyanide kit would represent a higher proportion for hospitals using the hydroxocobalamin kit.

Turnover of Inventory: The turnover of the individual antidote inventory ranged between 0.27 and 7.41 times per year for the complete cohort. A survey of Canadian hospital pharmacies²⁹ indicated that the average turnover of inventory is 8.9 times per year.

Expiration: For one hospital where the turnover of the inventory was greater than 13 times per year, the range between the purchase date and the expiration



date of antidotes was 6 to 32 months (average 17 months).

DISCUSSION

Despite the fact that it has been known for years that hospital pharmacies do not carry adequate amounts of antidotes and that formal guidelines would be helpful to correct the situation,^{2,3,5,7-9} antidote availability requires attention. There are 3 published recommendations on the minimal amount of antidotes that should be kept in hospitals^{12,13,21} (see also note added in proof), including one that was distributed only in Alberta.²¹ Because the situation has not improved,⁴ it appears that these recommendations are not widely known or followed. One reason may be the absence of recommendations according to the level of care of hospitals, as suggested by Spoerke.¹ Basing recommendations for all hospitals on the amount of various antidotes needed to treat a 70-kg patient for 24 h might be too costly and unrealistic for hospitals with small pharmacy budgets, especially if the antidotes are used infrequently. The antidote list compiled by the Poison and Drug Information Service of Alberta was intended for rural hospitals for treatment in the first few hours, pending transfer to a larger hospital.²¹ The effect of that list on antidote stocking is unknown, but its recommendations were probably not enough to completely correct the situation, as a survey performed in 1994 showed deficiency in antidote stocking.¹⁶

There was a correlation between consumption of *N*-acetylcysteine and naloxone (used as a surrogate for the number of poisonings treated at a hospital) and the number of antidotes stocked in appropriate amounts.⁶ This correlation gives credibility to the idea that frequency of poisonings and previous use of antidotes are important determinants and should be considered in recommendations for the minimal amount of antidotes to be stocked. Furthermore, turnover of the individual antidote inventory was slow (0.27 to 7.41 times per year) compared to the average of 8.9 times.²⁹ Furthermore, another study found a correlation between prior use and adequate amount of polyvalent *Crotalidae* antivenin,⁹ and a more recent one found a correlation between the availability of antidotes and annual reporting to the American Association of Poison Control Centers.¹¹

Even though cost should not be an issue, it probably is a factor. A correlation between the cost of antidotes and their presence in sufficient quantity in hospital pharmacies has been demonstrated: costly

antidotes are less frequently kept in sufficient amounts to treat a 70-kg patient for 24 h.⁶ Another study found a similar negative correlation.¹¹

In one hospital, the expiration date of the antidotes was much shorter (typically less than 3 years [average 17 months]) than the 5 years suggested previously by Dart and colleagues.³ This could increase the financial burden of keeping an adequate amount of antidotes in stock. Therefore, the economic impact of these recommendations cannot be underestimated. At the moment, the impact of the recommendations of the California Poison Control Center System¹² and the Illinois Poison Control Center¹³ are unknown. It was suggested that these recommendations would cost between \$8296 and \$24 900 in 1999.^{12,13} The higher estimate is attributed to the amount of polyvalent *Crotalidae* antivenin, digoxin immune Fab, and glucagon needed. The suggestions presented here would cause an increase in antidote inventory costs of 6% to 18%. It is felt that this increase can be supported, even by smaller hospitals, because the inventory will vary between \$4700 and \$15 000, depending on the level of care of the hospital. The recommendations can certainly help hospitals with smaller budgets to maintain an acceptable level of antidotes and ensure an optimal distribution of stock. A hospital that is more likely to treat severely poisoned patients will have more antidotes in stock than hospitals that are less likely to treat such patients.

Even though antidote sharing between hospitals is not suggested, collaboration between hospitals to facilitate the purchase of antidotes and the return of expired antidotes in unopened containers (a manufacturer can refuse to accept a returned product if it has been used or opened) can contribute to limiting additional costs and thus increase the likelihood of recommendations being followed.

The economic study reported here had certain limitations. The quantities reported by the survey respondents were quantities bought or consumed; it had to be assumed that the purchase of stock, when applicable, was similar to its consumption. Moreover, use of an antidote is not always related to poisonings, since these agents can be used in other clinical situations (for example, naloxone is used in the operating room after surgery and glucagon is used to treat hypoglycemia). Therefore, the values reported for the consumption of antidotes are probably overestimated in the proportion of the costs attributed to antidotes. This overestimation has a limited impact on the cost profile, since the most expensive antidotes (mainly digoxin immune Fab) are used only to treat poisonings. Because



some hospitals did not respond to the survey and some respondents did not complete the survey, the annual cost of antidotes and inventory had to be estimated. Extrapolation from the available data was based on visits to the emergency department, a method that may or may not be accurate. If data had been gathered from all hospitals, the results might have been different.

This paper suggests the minimal amount of antidotes to be kept in stock. These suggestions are based on whether hospitals are primary, secondary, or tertiary care hospitals. The economic impact of these suggestions on health-care costs appears to be acceptable, since the increase in the average inventory, which offers adequate stock in case of emergency, was between 6% and 18%. These suggestions were based not only on the theoretical needs of a hospital but also on the adequate evaluation of the actual situation to ensure that the proposed recommendations are applicable in the present context. These suggestions favour better antidote stocking without drastically increasing the cost of medications in a hospital. Such an intervention must be verified prospectively to evaluate its real impact. However, as suggested earlier, other measures must be taken to prevent problems in antidote supply,¹⁶ including reviewing current stocks of antidotes, evaluating the need for each antidote, including antidotes specific to a particular region, planning in case of excessive needs, assisting other hospitals in need, and planning and cooperating in case of increased need.¹⁶

In summary, the problem of inadequate stocking of antidotes appears common in North American pharmacies. Several reasons can explain the situation, including the lack of official guidelines. This report has proposed recommendations to standardize the minimal stock of antidotes kept in hospitals according to hospital type (primary, secondary, or tertiary care). Published recommendations could favour improvements in stocking, with only a marginal increase in the cost of medications. Such an intervention should be verified to ensure optimal impact.

Note Added in Proof

After final submission of this manuscript, a consensus guideline for stocking of emergency antidotes in the United States was published.³⁰ Twelve medical care providers from various disciplines developed the guidelines using a modified Delphi method. Of the 20 antidotes evaluated, 16 were recommended for stocking (*N*-acetylcysteine, atropine, calcium gluconate with calcium chloride, cyanide kit, deferoxamine, digoxin

immune Fab, dimercaprol, ethanol, fomepizole, glucagon, methylene blue, naloxone, polyvalent Crotalidae antivenin, pralidoxime, pyridoxine, and sodium bicarbonate), 2 were not recommended (antivenin for *Lactrodectus mactans* and calcium EDTA), and consensus could not be reached for 2 antidotes (flumazenil and physostigmine). The amount recommended corresponds to the amount needed to treat one or two 70-kg patients (depending on the antidote) for the first 4 h only. No distinction was made between hospitals with different levels of care, although examples of special needs were presented in the Discussion. The total cost of stocking the 16 recommended antidotes was US\$19 808.60 (year 2000 dollars).

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