

Use and cost of antidotes in 2 hospital emergency departments

RAQUEL AGUILAR SALMERÓN¹, DOLORS SOY MUNER², SANTIAGO NOGUÉ XARAU³

¹Servicio de Farmacia. Hospital Dr. Josep Trueta. Girona, Spain. ²Servicio de Farmacia. Hospital Clínic. Barcelona, Spain. ³Sección de Toxicología. Área de Urgencias. Hospital Clínic. Barcelona, Spain.

CORRESPONDENCE:

Santiago Nogué Xarau
Sección de Toxicología
Área de Urgencias
Hospital Clínic
Villarroel, 170
08036 Barcelona, Spain
E-mail: SNOGUE@clinic.ub.es

RECEIVED:

27-4-2009

ACCEPTED:

21-6-2009

CONFLICT OF INTEREST:

None

Background and objectives: Antidotes are basic resources among the options available for treating certain types of acute intoxication. The aim of this study was to describe the use of antidotes in the emergency departments of 2 hospitals and to determine the cost of using these drugs in the context of the overall treatment of patients who have been poisoned.

Material and methods: Prospective descriptive study of the use and cost of antidotes administered in the emergency departments of 2 university teaching hospitals. Data were collected from March through November 2006. Variables assessed were the use, suitability, and efficacy of each antidote, and the total expenditure on drugs (antidotes plus other medications).

Results: Antidotes were administered 228 times to 184 patients (8.7% of acute intoxications attended during the study period). Use of the antidote was considered justified in the attempt to reverse the effect of poisoning in 85.3% of the cases, corresponding to 10 of the 14 antidotes used. The expected reversal was achieved in 73.9% of the cases. Use was inappropriate in 16% of the administrations of flumazenil and 4% of the administrations of naloxone. Adverse events were recorded in 6.5% of the cases in which antidotes were used. Expenditure on antidotes accounted for 81.97% of the total amount spent on the pharmacologic treatment of poisoned patients and 1.1% of the amount spent on all drugs used in emergency department care during the study period.

Conclusions: The use of antidotes in the emergency department is largely appropriate but not free of side effects. Flumazenil and naloxone were used too often. Expenditure on antidotes is very low. [Emergencias 2009;21:276-282]

Key words: Antidote. Acute intoxication. Drug costs. Hospital emergency health services.

Introduction

Acute poisoning (AP) is treated initially in both outpatient health care settings (primary care and ambulances) and hospital settings. However, most patients with poisoning end up being attended in emergency departments (ED), sometimes because the severity of poisoning requires hospitalization or predominantly because of the need for diagnostic tests and treatments not available at non-hospital centres¹.

The basic measures for the treatment of AP can be summarized in four points: life support, which involves common measures to treat any urgent and serious pathology, reducing absorption

of the toxin, increasing its elimination and the use of specific antidotes.

The use of antidotes may reduce the use of other medical resources needed for the treatment of poisoning, shorten hospital stay and even save life². However, these drugs are not without side effects and in some cases, their economic cost is high³. It is therefore necessary to evaluate the benefit/risk involved in the administration of antidotes.

Today there are few objective data on how poisoning is treated in the ED, although there are records like "Multicatox"⁴, the Spanish Registry of Toxicovigilance⁵ or the group of Toxicology, Spanish Society of Emergency Medicine (SEMESTOX)⁶.

Recently the results of a multicenter (HISPATOX) study aimed at evaluating the current implementation of gastrointestinal decontamination techniques in emergency departments and outpatient services⁷ have been published. However, few studies have evaluated the use of antidotes and their cost-effectiveness⁸.

The hypotheses underlying this study considered two aspects. First, easy access to antidote kits in the ED may lead, in some cases, to inappropriate use and, secondly, that the cost associated with the use of antidotes is probably very low relative to the overall cost of drug treatment of intoxicated patients. The study had two objectives: to describe the use of antidotes in clinical practice and establish the cost of such treatment in the ED of two hospitals.

Method

We designed a prospective, descriptive study to determine the use and cost of pharmaceutical antidotes used in the emergency departments of two university hospitals. One is a tertiary hospital of high complexity (HC) but no pediatric service (Hospital Clinic, Barcelona) and the other is a referral hospital (R) at the provincial level (Hospital Dr. Josep Trueta de Girona). The study period covered nine months (March to November 2006).

For the collection of variables we designed a database that included four sections: (i) patient data (age, sex, origin and means of transportation to the ED), (ii) diagnosis (toxin responsible for the indication to administer antidote, accompanying toxin, route of administration, intentionality of poisoning and reason for indicating the antidote), (iii) antidote (route of administration, total dose, time between exposure to the toxin and antidote administration, out-of-hospital or hospital patient, efficacy, safety and appropriateness of indications), and (iv) concomitant medication (fluids and volume administered and/or active ingredients, commercial presentation, dosage and total dose).

We daily reviewed all discharge reports of patients seen in both EDs whose visit was related to exposure to a toxic agent, which allowed us to calculate the total number of poisonings treated during the study period. Of these cases we included as cases those whose discharge report mentioned the administration of one or more antidotes or there was reasonable suspicion thereof, which was later confirmed by review of the patient's medical history.

We also included patients who received antidotes although the initial diagnosis was not poisoning. Data on medication administered during the stay in the emergency room and not available in the discharge report were consulted in the medical history, especially in the section of nursing records.

Each antidote was recorded on the specific data sheet. The results of the use of antidotes were recorded in an Access database, and the cost of drug therapy in Excel, with access restricted to the study investigators in order to preserve confidentiality of the data.

We defined the following variables (i) Appropriateness of antidote: it was considered appropriate when the antidote was specific for the type of poisoning, the real or potential severity was high, the expected benefits outweighed the associated risk, and there were no contraindications. As a source of information we used the protocol of acute poisoning of the Hospital Clinic of Barcelona⁹ and evaluation of this variable was discussed, case by case, with a specialist in Clinical Toxicology. (ii) Effectiveness: it was considered effective when the effects achieved after administration of the antidote were expected. And (iii) pharmaceutical costs: the cost was defined as representing the total dose of antidote and, when appropriate, the concomitant medication, using the retail price (RRP) of 2006, according to data from the Drug catalog, General Council of Official Colleges of Pharmacists¹⁰.

We performed a descriptive, numerical and graphic study for each antidote. The association between qualitative variables was performed using Chi² test. For quantitative variables, we used student t-test for two independent variables. Data processing was carried out using SPSS software version 13.0 for Windows.

Results

During the study period a total of 142,648 medical emergencies were treated in the two hospitals, of which 2,107 corresponded to acute poisoning, which represents 1.4% of ED attendance. For hospitals, the incidence was 1.8% for the HC hospital and 0.8% for the R hospital at the provincial level.

Antidotes were administered to 184 patients, of which 113 (61.4%) were treated at the HC hospital and 71 (38.6%) at the R hospital representing 8.7% of all cases. However, the proportion of patients receiving antidotes in the first

hospital was significantly lower than that of the R hospital A (6.6% vs 17.9%, $p < 0.05$).

The highest frequency of poisoning in the total population studied was observed in the age group 21 to 30 years (24%), followed by that aged 31 to 40 years (22.4%), and the number of poisoned patients declined as age increased until the group older than 60 years where there was a new increase. Mean age of all cases attended was 42 years [standard deviation (SD) = 18 years] in the HC hospital and 35 years (SD = 20 years) in the R hospital which also attended 5 children aged less than 10 years. Women constituted 51.1% of the patients. Gender and age distribution was similar in the two hospitals. Until the age of 40, cases were mainly men, but as from 41 years there was a greater frequency of poisoning in women, this difference being more marked after 60 years but not significantly so. Figure 1 shows the distribution of poisoned patients stratified by age and sex, according to hospital centre.

The most commonly implicated toxins were medical drugs (43.5%) and illicit drugs (17.9%). Table 1 shows the distribution of poisoned patients who received antidotes according to the toxic agent involved, by sex, age and hospital centre.

As regards precedence, 66.3% of the patients came from home, 14.7% were found with decreased consciousness in public, 7.6% were referred from another hospital and 3.3% from a basic health area; for the rest, this information was not in the medical record. The majority (65%) were taken to hospital by ambulance and a quarter (25.5%) attended ED by their own means or with companions; on two occasions a transport helicopter was used, while firefighters transported three patients.

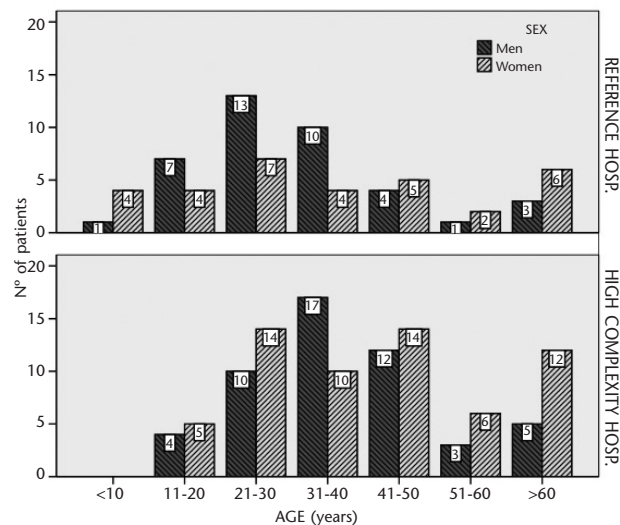


Figure 1. Distribution of poisoned patients according to age and sex.

A total of 184 patients receiving 228 antidotes were included in the study, but it is noteworthy that only 14 different drugs were used. The HC hospital attended 58.8% of the cases and the rest were treated at the R hospital. The antidotes administered were: flumazenil (46.5%), naloxone (25.4%), normobaric oxygen (7.4%), sodium bicarbonate (4.3%), N-acetylcysteine (3.5%), albumin, penicillin G sodium and silibinin (2.6% each), biperiden (1.7%), glucose (1.3%), atropine, methylene blue, ethanol and calcium folinate (0.4% each). Although in most cases only one antidote was used, 42 patients (22.8%) received two or more antidotes; the most frequent combinations were flumazenil and naloxone (32 patients) and penicillin G sodium and silibinin (6 patients).

Table 1. Distribution of poisoned patients according to age and sex, according to cause of poisoning

	Hospital Clínic				Hospital Trueta				Total		
	Men		Women		Men		Women		N°	%	Age±SD
	N°	%	N°	%	N°	%	N°	%			
Hemoglobinizing agent			1	1.6					1	0.5	26
<i>Amanita phalloides</i>	2	3.9	1	1.6	2	5.1	1	3.1	6	3.3	52 ± 29
Caustics	1	2.0	4	6.5	1	2.6			6	3.3	35 ± 21
Chlorine	2	3.9	4	6.5					6	3.3	48 ± 15
Unknown	12	23.5	8	12.9	7	17.9	6	18.8	33	17.9	36 ± 14
Drug abuse	13	25.5	7	11.3	11	28.2	2	6.3	33	17.9	33 ± 11
Insecticides (carbamates)							1	3.1	1	0.5	78
Medication	19	37.3	30	48.4	14	35.9	17	53.1	80	43.5	43 ± 20
Methanol	1	2.0							1	0.5	18
Carbon monoxide	1	2.0	7	11.3	4	10.3	5	15.6	17	9.2	33 ± 23
Total	51	100	62	100	39	100	32	100	184	100	

SD: Standard deviation.

The use of antidotes was conducted exclusively in hospitals in 74.2% of patients and in out-of-hospital settings in 16%. In the remaining 18 of the 184 patients, antidotes were administered in the ED and during transport in ambulances or on being attended at primary care centers.

In the evaluation of appropriate antidote administration to specifically reverse the effects of the poison, 89.5% were deemed appropriate. In 27 cases (14.7%) this was deemed doubtful, not indicated or with alternatives. These cases involved 4 of the 14 antidotes used, corresponding to 3 cases of caustic substance ingestion where the administration of oral albumin was delayed by more than one hour and the rest were cases of slightly decreased level of consciousness with a Glasgow Coma Scale score of ≥ 12), with a clear component of poisoning by alcohol or gamma-hydroxybutyrate without the presence of other drugs. Table 2 shows the percentages of appropriate use and effectiveness of each of the antidotes. The antidote administered achieved the desired effect in 136 cases (73.9%).

Adverse reactions were recorded in 6.5% of patients, as follows: (i) opiate withdrawal syndrome (nausea, vomiting, epigastric pain and agitation after administration of naloxone), (ii) restlessness, dystonic movements and generalized stiffness after using flumazenil, (iii) metabolic alkalosis after intravenous infusion of sodium bicarbonate (iv) hypersensitivity reaction to N-acetylcysteine, or (v) hyperglycemia after administration of intravenous hypertonic glucose. Table 2 shows the percentage and number of patients who experienced these adverse effects.

The total cost of antidote use in the 184 poisoned patients during their stay in the ED was 5,566.91 €, with an average cost per patient of 30.25 €. Taking into account the total cost of drug administration in the ED during the study period, the cost of antidotes was 1.1%. Table 3 shows the cost of pharmacological treatment with antidotes including fluid therapy, medication used for digestive tract decontamination and other medication administered. The percentage of antidote versus total medication cost 81.97%. However, this percentage varied widely depending on the antidote used; while the administration of flumazenil accounted for 80% of the total cost of treatment and 85.5% in the case of silibinin, the cost of administering naloxone accounted for 3.2% of total drug treatment. The average cost per patient of antidote treatment was as follows: flumazenil (32.30 €), naloxone (0.97 €), sodium

Table 2. Antidotes administered during the study period

	N° Cases	Suitability n (%)	Effectivity n (%)	Adverse reactions n (%)
Albumin	6	3 (50%)	3 (50%)	No
Atropine	1	1 (100%)	No valorable	No
Methylene blue	1	1 (100%)	1 (100%)	No
Sodium bicarbonate	10	9 (90%)	9 (90%)	1 (10%)
Biperiden	4	4 (100%)	4 (100%)	No
Ethanol	1	1 (100%)	1 (100%)	No
Flumazenil	106	1 (84%)	1 (80%)	3 (2.8%)
Calcium folinate	1	1 (100%)	1 (100%)	No
Glucose	3	3 (100%)	3 (100%)	2 (66.6%)
N-acetilcisteina	8	1 (100%)	1 (100%)	1 (12.5%)
Naloxone	58	1 (96%)	1 (67%)	5 (8.6%)
Normobaric oxygen	17	1 (100%)	1 (100%)	No
Penicillin G sodium	6	1 (100%)	1 (100%)	No
Silibinin	6	1 (100%)	1 (100%)	No

bicarbonate (1.50 €), N-acetylcysteine (86.48 €), albumin (14,25 €), penicillin G (9.30 €), silibinin (176.01 €), biperiden (0.62 €), glucose (15.72 €), atropine (3.41 €), methylene blue (4.97 €), ethanol (86.49 €) and calcium folinate (75.78 €).

The average length of stay in the ED was 11 h (SD = 10 h). After being attended, the majority of patients (53.8%) were discharged home and 18.5% were admitted to hospital, half of whom were admitted to intensive care unit (8.7%). Regarding mortality, two patients died: one was a case of carbamate insecticide ingestion and the other anoxic encephalopathy after an overdose of methadone.

Discussion

According to epidemiological studies, acute poisoning in Spain accounts for 1% of all cases attended in the ED¹¹. The results of the present study show a similar incidence for the R hospital and higher in the HC hospital, probably because the latter has a Clinical Toxicology Unit and acts as a reference hospital for toxicological cases for the whole región of Cataluña.

Patient epidemiological profile was similar in the two hospital centres. The lowest incidence of poisoning corresponded to the pediatric population. In recent years there has been a significant decrease in home poisoning of children¹², but the low incidence found in the present study is essentially related to the fact that one of the study centres, the HC hospital, does not attend children, which represents a limitation of the study.

The proportion of patients receiving antidotes during the study period was not high. However, the difference between the two hospitals (17.9 vs

Table 3. Cost of pharmacological treatment for the 184 patients with acute poisoning

	Hospital Clinic	Hospital Trueta	Total
Cost of treatment with antidotes (€) (including fluid therapy)	3,198.04	2,368.87	5,566.91
Mean cost per patient (€)	30.87	38.83	33.82
Cost of concomitant medication (€)	844.56	418.88	1,224.47
– Cost of fluid therapy	227.69	101.93	329.62
Mean cost per patient (€)	3.61	3.51	3.58
– Cost of medication for digestive tract decontamination	182.84	124.07	306.91
Mean cost per patient (€)	8.31	8.27	8.29
– Cost of other medication	414.71	173.23	587.94
Mean cost per patient (€)	7.40	7.87	7.54
Total cost of treatment (€)	4,023.28	2,768.10	6,791.38
Mean total cost per patient (€)	37.60	45.37	40.42
Cost of antidote/Total cost (%)	79.49	85.58	81.97

6.6%) was statistically significant despite similar patient profiles, which suggests over-use and/or under-use of one of these centres.

A noteworthy finding was that only 14 types of antidote were used to treat 184 cases of poisoning from the two hospitals. A previous study designed to determine the availability of antidotes in different healthcare settings showed that 67 different agents could be used, although not all were strictly necessary¹³. However, this apparently limited use does not affect the need to have an adequate stock of effective antidotes.

In general, the ED use of antidotes in the two hospitals was appropriate, but the present study indicated that naloxone and flumazenil were overused (and not indicated in 4% and 16% of the cases). Another noteworthy finding was that adverse reactions were associated with 5 of the 14 antidotes used; although none was severe, it must be remembered that the use of antidotes has been associated with severe reactions, including heart arrest¹⁴. One of the factors that could contribute to the appearance of antidote-induced adverse reactions is the fact that they are not so frequently used, which means that healthcare staff are less accustomed to handling these drugs. Thus for example, the reaction of hypersensitivity to N-acetylcysteine detected in the present series may well have been the result of rapid infusion - in 20 minutes instead of 60 minutes as recommended by the majority of clinical guidelines.

Another factor possibly related with the appearance of adverse reactions is prescription error. An example of this is the prescription for flumazenil which did not always include the quantity of mg to be administered; in some cases it was prescribed in terms of the number of ampoules or of mL. Considering that there are two pharmaceutical presentations of flumazenil (0.5 mg/5 mL and

1 mg/10 mL), prescribing the number of ampoules or mL could lead to overdosing or underdosing.

The present study highlights the limited use of antidotes in out-of-hospital settings, as only 25.8% of patients received antidotes in primary care centers or in ambulances. This is difficult to justify given that 10 of the 14 antidotes used (albumin, atropine, sodium bicarbonate, biperiden, ethanol, flumazenil, folinate calcium, glucose, naloxone and normobaric oxygen) are indicated for out-of-hospital and in-hospital use¹².

In contrast to other groups of pharmaceutical drugs, antidotes have received little attention in terms of cost-effectiveness studies. However, clinical guidelines increasingly consider not only contraindications and dosages but also pharmacoeconomic aspects, especially when new, more expensive drugs are compared with conventional drugs as for example the antidote fomepizol versus ethanol for the treatment of intoxication with methanol or ethylene glycol¹⁵.

Antidote cost with respect to the total pharmacological cost of treating cases of poisoning varied greatly according to the antidote used (from 3.2% for naloxone to 85.5% for silibinin); overall, this was 82%. Although this percentage is high, it still only represents 1.1% of pharmacological costs in the ED. In the case of antidotes, the greatest cost is associated with unused drugs in stock that have to be discarded on reaching their expiry dates, and some of these are expensive. This probably explains the low availability of certain antidotes (hydroxocobalamin, digital anti-antibodies or serum antivenom) observed in a previous study by our group¹³, and may also be the main reason why the Public Health Service has established protocols to coordinate stocks of antidotes for distribution to different healthcare entities, as well as guidelines on their correct use.

In conclusion, antidotes are specific drugs for a very limited number of acute poisoning events and, therefore, the use of each one is only justified in a small number of cases. The results of this study indicate excessive use of flumazenil and naloxone, as well as some errors in the prescription and/or administration of antidotes associated with adverse effects. Finally, the cost of antidote treatment was very low.

References

- 1 Riquelme A, Burillo-Putze G, Jiménez A. Epidemiología global de la intoxicación aguda en un área de salud. *Aten Primaria*. 2001;28:506-9.
- 2 Ries NL, Dart RC. New developments in antidotes. *Med Clin North Am*. 2005;89:1379-97.
- 3 Listado de Especialidades Farmacéuticas Extranjeras disponibles a través de la Agencia Española de Medicamentos y Productos Sanitarios. (Consultado el 9 de octubre de 2006). Disponible en: <http://www.sefh.es/descargas/MedicamentosExtranjeros.xls>.
- 4 Munné P. Intoxicaciones agudas. Estudio multicéntrico en hospitales de Cataluña. Tesis doctoral, Universidad de Barcelona, 1999.
- 5 Ferrer A, Nogué S, Vargas F, Castillo O. Toxicovigilancia: una herramienta útil para la salud pública. *Med Clin*. 2000;115:238.
- 6 Burillo-Putze G, Munné P, Dueñas A, Pinillos MA, Naveiro JM, Cobo J, et al. National multicentre study of acute intoxication in emergency departments of Spain. *Eur J Emerg Med*. 2003;10:101-4.
- 7 Burillo G, Munné P, Dueñas A, Trujillo M, Jiménez A, Adrián M, et al. Intoxicaciones agudas: perfil epidemiológico y clínico y análisis de las técnicas de descontaminación digestiva utilizadas en los servicios de urgencias españoles en el año 2006 –Estudio HISPATOX–. *Emergencias*. 2008;20:15-26.
- 8 Nogué S, Munné P, Soy D, Millá J. Disponibilidad, utilidad y coste de los antidotos en Cataluña. *Med Clin (Barc)*. 1998;110:609-13.
- 9 Nogué S, Munné P, Nicolás JM, Sanz P, Amigó M. Intoxicaciones Agudas. Protocolos de tratamiento. Barcelona: Morales i Torres Editores S.L., 2003.
- 10 Catálogo de Medicamentos. Colección Consejo Plus. Tomo I. Madrid: Consejo General de Colegios Oficiales de Farmacia; 2006.
- 11 Ferrer A, Nogué S, Dueñas A, Civeira E, Bajo Á, Royo R, et al. Perfil epidemiológico actual de las intoxicaciones agudas en urgencias. En: Net A, Marruecos L. Intoxicaciones Agudas Graves. Barcelona: Ars Medica; 2006. p. 1-15.
- 12 Mintegui S, Benito J, Vázquez MA, Fernández A, Gortázar P, Grau G. Intoxicaciones en urgencias: cambios epidemiológicos en los últimos 10 años. *An Esp Pediatr*. 2002;56:23-29.
- 13 Aguilar R, Soy D, Nogué S. Disponibilidad de antidotos en los ámbitos sanitarios de Cataluña. *Med Clin (Barc)*. 2006;127:770-3.
- 14 Cassidy N, Tracey JA. Cardiac arrest following therapeutic administration of N-acetylcysteine for paracetamol overdose. *Clin Toxicol*. 2008;46:921.
- 15 Guía clínica para el tratamiento de las intoxicaciones por metanol y etilenglicol. Indicaciones del fomepizol. Reunión de consenso. Barcelona, 2006. (Consultado el 19 de febrero de 2007). Disponible en: <http://wzar.unizar.es/stc/actividades/IntoxMetanolEtilenglicol.pdf>.

Utilización y coste de los antídotos en dos servicios de urgencias hospitalarios

Aguilar Salmerón R, Soy Muner D, Nogué Xarau S

Objetivo: Los antídotos constituyen una medida básica para el tratamiento de determinadas intoxicaciones agudas. El objetivo de este estudio es describir la utilización de antídotos en la práctica clínica de los servicios de urgencias (SU) de dos hospitales y precisar el coste que representa la terapéutica antidótica respecto al coste global del tratamiento farmacológico del enfermo intoxicado.

Método: Estudio prospectivo y descriptivo, diseñado para conocer la utilización y el coste farmacéutico de los antídotos administrados en los SU de dos hospitales universitarios. El periodo de recogida de datos fue de marzo a noviembre de 2006. Las variables evaluadas fueron el uso, la idoneidad y la eficacia del antídoto, así como el coste del tratamiento farmacológico (antídotos y medicación concomitante).

Resultados: Se realizaron 228 administraciones de 14 antídotos diferentes a 184 pacientes (el 8,7% de las intoxicaciones agudas atendidas durante el periodo de estudio). Se consideró que el uso del antídoto había estado justificada para intentar revertir los efectos del tóxico en el 85,3% de los casos, correspondientes a 10 de los 14 antídotos utilizados. Tras la administración, se consiguieron los efectos esperados en el 73,9% de los casos. El 16% de las administraciones de flumazenilo y el 4% de las de naloxona no estuvieron bien indicadas. Se observaron reacciones adversas en el 6,5% de las administraciones. El coste que representaron los antídotos respecto al coste global del tratamiento farmacológico de los pacientes intoxicados fue del 81,97%, cifra que supone el 1,1% del gasto farmacológico total del SU durante el periodo de estudio.

Conclusiones: La indicación de los antídotos en urgencias fue globalmente adecuada, pero no exenta de efectos secundarios. El flumazenilo y la naloxona fueron utilizados con excesiva frecuencia. El coste económico que representa el tratamiento con antídotos es muy bajo. [Emergencias 2009;21:276-282]

Palabras clave: Antídoto. Intoxicación aguda. Gasto farmacológico. Servicio de urgencias hospitalario.