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ORIGINAL ARTICLE

Antidote use in a paediatric emergency department[☆],[☆☆]

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L. Martínez Sánchez[a],[*], A.F. Almario Hernández[a], L. Escuredo Argullós[a], P. Maçao[b], V. Trenchs Sainz de la Maza[a], C. Luaces Cubells[a]

[a] *Servicio de Urgencias de Pediatría, Hospital Sant Joan de Deu, Esplugues de Llobregat, Barcelona, Spain*
[b] *Servicio de Pediatría, Hospital Pediátrico de Coimbra, Coimbra, Portugal*

Abstract
Introduction: Poisoning is an infrequent cause of consultation in a paediatric emergency department (PED), but it can be potentially serious. Paediatricians should know how to use the available antidotes properly.
Objectives: To analyse the use of antidotes in a PED and to assess the suitability of their indications.
Materials and methods: A retrospective review of antidote use in a PED between January 2008 and June 2012. Inclusion criteria were age younger than 18 years and consultation for suspicious poisoning by a substance that could be treated with an antidote. The adequacy of antidote indication was based on the recommendations of the Spanish Society of Paediatric Emergencies (SSPE).
Results: A total of 1728 consultations for suspicious poisoning (0.4% of the total visits in the PED) were recorded. In 353 cases (20.4%) the involved poison could be treated with an antidote. Sixty-seven patients received an antidote (3.9% of consultations for suspicious poisoning), and a total of 69 administrations of an antidote were made: 100% oxygen (46), N-acetylcysteine (10), flumazenil (4), naloxone (3), deferoxamine (2), vitamin K (2), bicarbonate (1), and carnitine (1). In three cases there was no indication for administration: flumazenil without respiratory depression, and vitamin K following coumarin exposure. As side effects, agitation was noted after the use of flumazenil, and a decrease in the prothrombin time during infusion of N-acetylcysteine.

Conclusions: The administration of antidotes in this PED is uncommon and, mainly, in accordance with the SSPE recommendations, and without serious side effects. The use of flumazenil needs to be limited to the cases with a clear indication and without any contraindication.

Uso de antídotos en un servicio de urgencias pediátricas

Resumen
Introducción: La intoxicación es un motivo de consulta poco frecuente en un servicio de urgencias pediátricas (SUP) pero potencialmente grave. Conviene que el pediatra conozca el uso adecuado de los antídotos disponibles.
Objetivos: Analizar el uso de antídotos en un SUP y evaluar la idoneidad de su indicación.
Materiales y métodos: Estudio retrospectivo de los pacientes que consultaron, entre enero del 2008 y junio del 2012, por sospecha de intoxicación por una sustancia para la cual existe antídoto. La evaluación de la idoneidad de la indicación del antídoto se basó en las recomendaciones de la Sociedad Española de Urgencias de Pediatría.
Resultados: Se recogieron 1.728 consultas por sospecha de intoxicación (0,4% de las visitas). En 353 (20,4%) el tóxico implicado podía ser tratado con un antídoto. Recibieron antídoto 67 pacientes (3,9% de las consultas por sospecha de intoxicación) y se realizaron en total 69 administraciones de antídoto: oxígeno 100% (46), N-acetilcisteína (10), flumazenilo (4), naloxona (3), desferroxamina (2), vitamina K (2), bicarbonato (1) y carnitina (1). En 3 casos no existía indicación del antídoto: flumazenilo sin depresión respiratoria (2) y vitamina K tras exposición a cumarínico (1). Como efecto secundario se objetivó agitación psicomotriz tras uso de flumazenilo y disminución del tiempo de protrombina durante la infusión de N-acetilcisteína.
Conclusiones: La administración de antídotos en este SUP es infrecuente, mayoritariamente acorde a las recomendaciones y sin efectos secundarios importantes. Debe insistirse en la necesidad de limitar el uso de flumazenilo a los casos claramente indicados, y comprobando siempre la ausencia de contraindicaciones.

Introduction

Suspected poisoning is an infrequent reason for seeking paediatric emergency services in Spain (0.3%),[1] but is a potentially serious situation that calls for rapid clinical decision-making. Thus, it is crucial that paediatricians know how to manage suspected poisonings and the treatments available for them.

In 1961, Clemmensen et al. demonstrated that the use of stabilisation and supportive measures, at the opposite end of the spectrum of toxin-specific treatment, was the most successful approach to reducing mortality in severely poisoned patients.[2] This is still the case today, and the action algorithms for any type of poisoning start with assessment and treatment with the Airway-Breathing-Circulation approach.

Still, administration of an antidote can be the key in the management of certain types of severe poisoning. Some examples are the use of N-acetylcysteine (NAC) to treat paracetamol-induced hepatotoxicity, or more recently developed treatments like hyperinsulinaemia-euglycaemia therapy for calcium-channel blocker poisoning, fomepizole for toxic alcohol poisoning, or lipid emulsion therapy for severe cardiotoxicity induced by lipophilic toxins. At any rate, the risks and benefits of an antidote must be weighted up before its administration, taking into account the patient's clinical status, the predicted action of the toxic substance, and the possible adverse effects associated with the antidote.

The aim of this study is to analyse the use of antidotes in paediatric patients with suspected poisoning and assess the appropriateness of their administration.

Materials and methods

We conducted a retrospective, descriptive, and observational study in the emergency department of an urban tertiary care maternity and children's hospital that serves a referral population of 1,300,000 and has about 100,000 paediatric visits a year.

We included all patients aged 0–18 years consulted for suspected poisoning with a substance that could be treated with an antidote. The study was conducted from January 2008 to June 2012.

Electronic medical records were reviewed to gather the data. We collected data on epidemiological and clinical variables, including antidote use, appropriateness of antidote administration, and any adverse effects.

Table 1 Toxic substances that could be treated with an antidote ($n = 353$).

	Number of cases	%
Paracetamol	120	34%
Benzodiazepines	118	33.4%
CO	46	13.3%
Coumarins	13	3.6%
Valproate	7	2%
Iron	5	1.4%
Methemoglobinizing drugs	4	1.1%
Oral hypoglycaemics	3	0.8%
Opioids		
Dextromethorphan	17	4.8%
Codeine	3	0.8%
Methadone	1	0.2%
Morphine	1	0.2%
Beta-blockers	3	0.8%
Calcium-channel blockers	2	0.5%
Organophosphates	2	0.5%
Methanol	2	0.5%
Propylene glycol	1	0.2%
Cholinergics	1	0.2%
Unknown (suspected poisoning + neurological depression)	4	1.1%

The appropriateness of antidote administration was determined in terms of adherence to the recommendations for the use of antidotes in paediatric poisonings by the Asociación Española de Pediatría (Spanish Association of Paediatrics) and the Sociedad Española de Urgencias de Pediatría (Spanish Society of Paediatric Emergency Medicine, [SEUP]), specified in the third edition of the *Manual de intoxicaciones en Pediatría*.[3] For each case, we considered the clinical state of the patient recorded in the emergency room record, the results of complementary tests, and the risk-benefit assessment (expected antidote effect, coingestion of other toxins, disease history, allergies, etc.).

We analysed the data with the SPSS software version 20. The majority of the variables were nominal and dichotomous, and have been expressed as percentages, absolute frequencies, and means.

Results

In the period under study there were 1728 cases of suspected poisoning, accounting for 0.4% of emergency room visits. Of all cases of suspected poisoning, 353 (20.4%) corresponded to exposure to toxins for which an antidote exists. The toxins involved in these cases are listed in Table 1. The toxins observed most frequently were paracetamol, benzodiazepines, and carbon monoxide (CO).

Sixty-seven patients (3.9% of patients with suspected poisoning) were given at least one antidote. Antidotes were administered in 19.0% of the 353 cases of exposure to a substance for which an antidote was available.

The patients who received an antidote had a median age of 9.5 years (interquartile range: 3–14.6 years), and the

majority were male (50–74.6%). Exposure was accidental in most cases (56–83.6%), although there was suicidal intent in 8 cases (11.9%), and recreational use in 3 (4.5%). The most frequent route of exposure was inhalation (46–68.6%), followed by ingestion (19–28.35%).

Eight different antidotes were used. The one used most frequently was 100% oxygen, which was given to 46 patients with suspected CO poisoning; followed by NAC, administered intravenously to 10 patients with acetaminophen intoxication; and then flumazenil, given to four patients with various levels of decreased consciousness. Of these four patients, one was a male adolescent presenting with agitation and symptoms of alcohol poisoning who had received a supratherapeutic dose of intravenous midazolam before arriving to the hospital. Upon arrival to the hospital, he had a Glasgow Coma Scale score of 6 and respiratory depression. He was given flumazenil after which the coma reversed and the agitation symptoms resumed. Another patient was a 17-month-old child with suspected poisoning in the context of abuse who presented with ataxia and progressive decrease in the level of consciousness. Since opioids and benzodiazepines were detected in his urine by means of semiquantitative immunofluorescence testing, his level of consciousness worsened, and he developed hypoventilation, he was given naloxone followed by flumazenil, and responded to the latter. The remaining patients who received flumazenil were two adolescents with a significant decrease in the level of consciousness and no respiratory abnormalities in the context of suspected benzodiazepine poisoning.

Naloxone was given to three patients with decreased level of consciousness and suspected poisoning. Two of them had respiratory compromise, and the third received naloxone as a therapeutic test in the context of a mild decrease in the level of consciousness of unknown source. Two of these patients were given two antidotes: one received naloxone and flumazenil (child with progressive coma, hypoventilation, and semiquantitative detection of benzodiazepine and opioid substances in urine), and the other naloxone and bicarbonate (patient with suspected ingestion of multiple substances, access to opioids and tricyclic antidepressants, and electrocardiographic abnormalities).

Desferrioxamine was given in two cases of iron poisoning with metabolic acidosis and high serum iron levels. Vitamin K was used in two patients; one received it intravenously after ingesting a rodenticide, and another through the oral route following ingestion of an oral anticoagulant. Lastly, a patient with toxic levels of valproate and neurological signs was given carnitine. Since 2 antidotes were given in two cases, there were a total of 69 antidote administrations.

Based on the current recommendations for antidote administration in children, antidotes were used correctly in 66 of the 69 administrations (95.6%). Administration was not indicated in a patient with rodenticide exposure (Klerat Bloc®: 4-hydroxycoumarin) and no clinical or laboratory abnormalities that received intravenous vitamin K, and in two patients who received flumazenil in the context of decreased level of consciousness without respiratory or circulatory depression.

We observed the following side effects after antidote administration: agitation in 1 patient following flumazenil administration, and decreased prothrombin index

Table 2 Administered antidotes, appropriateness of administration, and observed side effects.

Administered antidote			Appropriateness of administration			Side effects	
	$N = 69$	% of patients	$N = 69$	% of each antidote's administrations			% of each antidote's administrations
Oxygen	46	66.6%	46	100%		0	0%
NAC	10	14.5%	10	100%		1	10%
Flumazenil	4	5.8%	2	50%		1	25%
Naloxone	3	4.3%	3	100%		0	0%
Desferrioxamine	2	2.9%	2	100%		0	0%
Vitamin K	2	2.9%	1	50%		0	0%
Carnitine	1	1.4%	1	100%		0	0%
Bicarbonate	1	1.4%	1	100%		0	0%

(prothrombin index = 59.5%) in a patient given intravenous NAC. The incidence of adverse events for all instances of antidote administration was 2.9%: 10% corresponded to the use of NAC and 25% to the use of flumazenil. Table 2 summarises the characteristics of the 69 antidote administrations in the PED for the 67 patients.

Before arrival to the hospital, seven patients received an antidote other than oxygen either out-of-hospital or in a referring facility. The most frequently used antidote was flumazenil (five cases, in one of them in combination with naloxone). The two remaining patients were given hydroxycobalamin and NAC, respectively. Since we had no clinical data on the previous state of these patients, we could not assess whether the administration of these antidotes was appropriate.

In the subset of patients exposed to a toxin that could be treated with an antidote, there was no case in which the antidote indicated was not administered.

Patient outcomes were generally favourable. Of all patients given an antidote, 40.3% (27) required admission to the hospital. A 3-year-old child who had inhaled smoke in a fire died after receiving and not responding to advanced cardiopulmonary resuscitation, 100% oxygen, and hydroxycobalamin.

Discussion

Antidote administration in paediatric poisonings is infrequent and, from what we observed in our sample, adheres to the recommendations.

The literature on the use of antidotes in the paediatric population is scarce, and we believe that this study is the first that analyses the appropriateness of antidote administration in a Spanish PED.

According to the data of the Grupo de trabajo de Intoxicaciones (Intoxication working group) of the SEUP, in a total of 349 cases of suspected intoxication seen in 51 PEDs between 2008 and 2011, an antidote was given in 18 cases (5.1%).[3] The rate of antidote administration in our sample was slightly lower (3.8%), and closer to the rate reported by the American Association of Poison Control Centres (AAPCC). The 2011 annual report of the AAPCC noted that an antidote was given in 1.5% of the cases of suspected intoxication in patients younger than 20 years.[4]

The three studies show a similar distribution in the most frequently used antidotes: oxygen, NAC, and naloxone in the study of the Grupo de Trabajo de Intoxicaciones (Poisoning working group) of the SEUP; oxygen, NAC, and flumazenil (followed by naloxone) in our study; and NAC, naloxone, and flumazenil in the AAPCC report. It is important to consider that the AAPCC study did not include oxygen among the antidotes, a fact that may account for the lower rate of antidote administration it reported.

We could not analyse the possible differences in antidote administration in the adult and the paediatric populations, as our study was conducted in a maternity and children's hospital. However, Aguilar et al., who analysed the use of antidotes in two hospitals in Catalonia in 2006, allow us to make this comparison. Their study included an urban tertiary hospital for adults with a referral region similar to ours, and where 6.6% of the patients seeking services for exposure to a toxin were given an antidote. The most frequently used antidotes were flumazenil, naloxone, and oxygen.[5]

The lower rate of antidote administration in the paediatric population could be due to the fact that in most children seen for suspected poisoning, exposure is unintentional and does not reach toxic levels. Also, as observed in our study, exposure in most children involves substances for which there is no specific antidote (79.6% of cases in our sample).

Regarding the appropriateness of antidote administration, the results showed that in most cases antidote administration adhered to current recommendations. Their use was not clearly indicated in only three cases, and no contraindications for the administered antidote were found in the clinical histories of any of the patients. Flumazenil was used to treat benzodiazepine-induced coma without respiratory depression in two of the three cases of non-indicated administration.

Flumazenil is one of the most controversial antidotes used. On one hand, the prognosis for benzodiazepine intoxication is generally good, and on the other, lowering the seizure threshold can trigger convulsions, especially in the most susceptible patients (previous history of convulsions, or coingestion of other epileptogenic substances). For this reason, it is recommended exclusively in cases of pure benzodiazepine poisoning in which supportive measures are not enough.[6,7] To avoid iatrogenic complications due to this antidote, there are quality indicators for the

management of poisoning cases in adults and children specifically meant to monitor the correct administration of flumazenil.[8,9]

A few recent studies show that the incidence of convulsions associated to flumazenil administration is very low, particularly in children. In the study by Kreshak et al, none of the 83 paediatric patients given flumazenil had convulsions that could be attributed to the antidote.[10] This study, which included 13 patients exposed to epileptogenic substances, suggests that the safety profile of flumazenil is better in children than in adults. However, the sample was too small to justify a change in the recommendations. On the other hand, Veriaiah et al.[11] reported that a single convulsive episode occurred in 1 of the 80 patients with poisoning treated with flumazenil. In this case, the patient had ingested a mix of benzodiazepines and neuroleptics. Other patients who received flumazenil despite having ingested multiple toxic substances (not proconvulsant) or a previous (but not recent) history of convulsions did not experience any adverse effects. Therefore, the authors considered that patients with multiple poisoning without involvement of proconvulsant substances and a non-recent history of convulsions may be included in the low-risk group for treatment with flumazenil.

In our study, none of the patients given flumazenil were at the risk of developing convulsions, nor had any, but one patient developed psychomotor agitation that could be attributed to the administration of the antidote. Thus, this was the antidote whose use was not indicated most frequently, as well as the antidote with the highest rate of side effects. Consequently, it must be used with caution, and should not be administered if it is not clearly indicated or if there are any contraindications.

We also identified the intravenous administration of vitamin K for prophylaxis in a child aged 1 year and 11 months that may have ingested coumarin who had no bleeding and had normal serial laboratory tests. International recommendations indicate administration of vitamin K for treating the unintentional ingestion of small amounts of anticoagulant just in the cases with bleeding or abnormal International Normalised Ratio values. Also, since intravenous administration of vitamin K may cause anaphylactoid reactions,[12–14] administration by the oral route is recommended if the patient is stable.[15–17]

The work of Aguilar et al. also analyses the appropriateness of antidote administration in emergency departments. Their study found that in 89.5% of administrations, the used antidote was specifically indicated to reverse the effects of the toxic substance. Albumin and flumazenil were the antidotes administered most frequently without a clear indication.[5]

The side effects observed in this study included agitation secondary to flumazenil, and a decrease in prothrombin index in association with NAC administration. This decrease in prothrombin index has been reported before, although its mechanism is not well understood.[18] This effect is transient, and is a possibility that must be considered in the interpretation of isolated clotting disturbances in patients with paracetamol poisoning when there are no other signs of hepatotoxicity. Parenteral use of NAC has also been associated to anaphylactoid reactions with an incidence that ranges from 3.7% to 23% in different studies.[18,19]

A recent study analysed the development of side effects in 660 adult patients with paracetamol poisoning that received parenteral NAC.[20] Adverse reactions developed in 12.4% of patients. The most frequent reaction was vomiting (3.5% of all patients who received NAC), followed by allergic reactions that ranged from urticaria (2.4%) to bronchospasm (0.9%) and hypotension (0.15%). More than 60% of adverse reactions in this study occurred during infusion of the loading dose.

There is strong evidence that the risk of allergic reactions is associated with the infusion rate of NAC, so it is recommended that the initial dose be given over 1 h. There are also descriptions of cases of seizures due to dilutional hyponatraemia in young children due to the high dilution volume established for standard dosage.[19] Thus, dilution volume should be adjusted to the weight of the patient.

When it comes to the rest of the antidotes used in our sample, considerable side effects have been reported for naloxone and desferrioxamine. Naloxone can cause a variety of cardiorespiratory alterations in children that range from tachypnoea, tachycardia, and hypertension to pulmonary oedema,[21] and even cardiac arrest in extremely preterm neonates.[22] One of the adverse effects associated to desferrioxamine is development of acute respiratory distress syndrome in patients in whom desferrioxamine infusion continues beyond 24 h.[23–25]

This study has limitations. Since it is a retrospective study, we have to assume that there are missing data that were not recorded at the time of service. We considered that antidote administration had no side effects if none were recorded in the medical history or detected by the complementary tests performed. Thus, it is possible that there were mild effects that were not documented. Likewise, retrospective data collection poses challenges in the identification of cases treated with oxygen before arrival to the hospital, as it is common that this intervention is not properly documented in clinical histories, and it doesn't allow us to assess the appropriateness of prehospital antidote administration. To perform such an assessment, it would be necessary to conduct a prospective study that gathered data on the patients' transfer to the hospital.

Also, this is a single-centre study and its results cannot be generalised. A multi-centre study would allow a broader assessment of antidote use in paediatric emergencies, although we also believe that each centre needs to be analysed individually to identify poor practices in care and to implement the measures needed for improvement.

In conclusion, although antidotes are rarely administered in this PED, in most cases their use adheres to current recommendations and does not cause significant adverse effects. Still, we must emphasise that flumazenil should only be used in cases of pure benzodiazepine poisoning with respiratory depression refractory to supportive care, as in all other cases the risk of potential side effects may outweigh the potential benefits of its administration.

Conflicts of interest

The authors have no conflicts of interest to declare.

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