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ORIGINAL ARTICLE

Detecting adverse drug events during the hospital stay

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KEYWORDS
Adverse drug event;
Medication error;
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Abstract
Introduction: The principal objective was to determine the incidence rate of adverse drug events (ADEs) in hospitalised patients and evaluate the event prevention percentage.
Methods: Multi-centre, prospective observational study lasting 4 months, performed in 5 hospitals providing different levels of care. We included all adult patients who were admitted to one of the selected centres for longer than 48 hours and who required pharmacological treatment. ADEs were identified by direct observation and the use of previously defined alarm signals. The Karch-Lasagna scale was used to determine the causality relationship, and the Schumock and Thornton questionnaire adapted by Otero was used to evaluate ADE preventability. Preventable drug-induced adverse events were classified according to the taxonomy that the Ruiz-Jarabo 2000 group defined, and coordinated by ISMP-Spain.
Results: We included 1550 patients, 159 of whom experienced at least one ADE (10.3%). The preventability percentage was 51.6%, which represented 5.3% of the total sample. The endocrine system (34.8%) and the cardiovascular system (20.7%) were the most affected by preventable ADEs. Antibiotics were responsible for 16.5% of all ADEs. Nine point three percent of all preventable ADEs were triggered by use of opiates. The vast majority of preventable ADEs (36.3%) resulted from omitting a necessary medication. Only 4.4% of preventable ADEs are considered to be serious.

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Conclusions: There is a high incidence rate of ADEs during patients' hospital stay (10.3%), and half of them (51.6%) could have been prevented. Implementation of an automatic alarm system and certain best practices for problem spots along the care circuit will help detect and avoid preventable ADEs.

PALABRAS CLAVE
Acontecimiento adverso producido por medicamento;
Errores de medicación;
Seguridad del paciente hospitalizado;
Señales de alerta;
Prevención de errores de medicación

Detección de acontecimientos adversos producidos por medicamentos durante la estancia hospitalaria

Resumen
Introducción: El objetivo principal ha sido determinar la incidencia de acontecimientos adversos producidos por medicamentos (AAM) en pacientes hospitalizados y evaluar su porcentaje de prevención.
Métodos: Estudio multicéntrico, prospectivo y observacional de 4 meses de duración, realizado en cinco hospitales de distinto nivel asistencial. Se incluyó a todos los pacientes adultos que ingresaron por más de 48 h en alguna de las unidades seleccionadas y requirieron tratamiento farmacológico. La identificación de los AAM se realizó mediante la observación directa y la utilización de unas señales de alerta, previamente definidas. Se utilizó el algoritmo de Karch-Lasagna, para determinar la relación de causalidad, y el cuestionario de Schumock y Thornton adaptado por Otero et al para evaluar la evitabilidad del AAM. Los AAM prevenibles se clasificaron siguiendo la taxonomía definida por el Grupo Ruiz-Jarabo 2000, coordinado por el ISMP-España.
Resultados: Se incluyó a 1.550 pacientes, de los que 159 presentaron, al menos, un AAM (10,3 %). La tasa de evitabilidad fue del 51,6 %, lo que representa un 5,3 % de la muestra total. El sistema endocrino (34,8 %) y el cardiovascular (20,7 %) fueron los más afectados por los AAM prevenibles. Los antibióticos representaron el 16,5 % de todos los AAM. En cuanto a los AAM prevenibles, el 9,3 % de ellos se desencadenaron por la utilización de opiáceos. La gran mayoría de los AAM evitables fue consecuencia de la omisión de un medicamento necesario (36,3 %). Sólo un 4,4 % de los AAM evitables se consideró graves.
Conclusiones: La incidencia de pacientes con AAM durante la estancia hospitalaria es alta (10,3 %), y la mitad de ellos (51,6 %) se podría haber prevenido. La implantación de un sistema automático de alertas y ciertas prácticas de mejoras en los puntos conflictivos del circuito sanitario ayudarían a la detección y la prevención de los AAM evitables.

Introduction

Adverse drug events (ADEs) constitute an important issue directly affecting the quality of health care and the patient's safety. Bates et al[1] define an ADE as any mild or severe condition caused by therapeutic use, or omission, of a medication. ADEs may be classified as preventable and non-preventable. Preventable events are the result of a medication error, and therefore involve damage and error. Non-preventable events are those that appear despite proper use of the drug (presence of damage but not error), and they are known as adverse drug reactions (ADRs).[2]

The importance of ADEs in health care systems increased following the publication of 2 reports written by the Institute of Medicine in the United States: *To Err is Human: Building a Safer Health System*[3] and *Crossing the Quality Chasm: a New Health System for the 21st Century.*[4] These reports point to the lack of safety in health care and expose the impact of adverse effects caused by clinical errors; medication errors are among those mentioned. Publication of these reports led to new studies presenting the different situations found in different countries and hospitals with regard to the patient's clinical safety. The incidence rate these studies calculate for preventable ADEs ranges between 1.4% and 10%.[5-7] Based on this data, we may state that there is a high rate of morbidity attributed to using medications in hospitalised patients, and that this is preventable in a large percentage of cases. It is therefore necessary to adopt preventative measures that allow us to improve patient safety when it comes to medication use.

The present study aims to determine the incidence rate for ADEs in 5 hospitals providing different levels of care. Using this information, we intend to raise hospitals' awareness about the current repercussions of ADEs in our country, and introduce improvements in the health care system designed to prevent such events. Based on the literature review,[5-7]

we assume that if we know the most common ADEs and evaluate the causes that can precipitate them, it will then be possible to act in critical areas by applying improvement strategies that prevent repeating that error in subsequent situations.

As a result, the main goal of the study is to identify those ADEs that appear in hospitalised patients, classify them according to their preventability and focus on those cases that could have been prevented.

Methods

Design

This prospective, observational multi-centre study lasting four months (from July 1, to October 31, 2007) was carried out in medical units (internal and digestive medicine, cardiology) and surgical units (digestive, urological, and traumatology) in 5 hospitals providing different levels of care. Hospital Clínic in Barcelona (tertiary hospital, 819 beds), Hospital of Sant Bernabé de Berga (secondary hospital, 120 beds), Hospital Parc Taulí in Sabadell (care level 2b, 820 beds), Hospital General of Vic (secondary hospital, 250 beds) and Hospital of Igualada (secondary hospital, 300 beds).

Sample

We intend to calculate for a sample size that will permit us to estimate the results we obtain for the general population with maximum precision. Considering the 1.4% rate of preventable ADEs anticipated by the literature, we calculated that a sample of 1550 patients would provide ±0.6% precision with a 95% confidence interval. For that sample size, the precision for detecting an ADE was ±1.3%, and it also enabled us to analyse more prevalent secondary objectives with a precision of at least ±2.5% (estimation done in the point of maximum variability, for proportions of 50%).[8]

Inclusion criteria: patients over 18 years of age receiving pharmacological treatment and admitted to one of the units included in the study during a period >48 hours.

The study focused on detecting and analysing ADEs that occurred during the patient's hospital stay. We did not include any ADEs that the patient may have presented prior to arriving at the hospital and which may have caused or contributed to the hospital admission. We excluded phlebitis as an ADE, since it may distort general results of the study due to how difficult it is to attribute it to drugs and evaluate its degree of preventability.

Detecting ADEs

ADEs were detected by reviewing clinical and nursing reports belonging to patients in the unit or department being monitored, with the help of some previously selected warning signs that were taken from the literature review. The warning signs were classified as suspicious diagnosis[9]; abnormalities in certain analytic tests and the presence of some trigger drugs. Furthermore, a member of the research team interviewed the doctors and nurses at the hospital department or unit daily to gather more information about the patients or to be notified in the event an ADE had been identified. Upon detecting or suspecting an ADE, we reviewed the clinical history once more in order to confirm it as either an ADE or an event in the progression of the disease.

Determining the cause

The modified Karch and Lasagna algorithm[10] was applied to determine a causal relationship between the suspicious drug and the detected ADE. This enabled us to objectively establish the relationship between the drug and the ADE by attributing a probability category to it based on the drug's imputability according to the algorithm. The resulting total score allows us to determine the ADE's probability category out of a set of five different categories ranging from "unlikely" to "definite" (and including "conditional," "possible," and "probable"). In the study, we excluded the ADEs which received a score <4 after applying the Karch and Lasagna algorithm, and they were then classified as "improbable" or "conditional." When the ADE resulted from omitted treatment or underdose of the drug in question, the algorithm was not applied as we did not study this type of ADE. In such cases, we used an algorithm modified by Hallas et al.[11] All of the cases were approved by consensus with a doctor on the care team and evaluated by a third party when doubts and disagreements arose.

Determining preventability

We used the Schumock and Thornton[12] questionnaire adapted by Otero et al[6] to evaluate the preventability of an ADE by the drug in question. If one of the questions has a positive answer, the ADE is considered to be preventable. The questions are not exclusive, so an ADE may have more than two positive answers; however, this does not mean that it is more preventable than an ADE with only one positive answer.

Taxonomy

Once a preventable ADE was detected, it was classified according to the taxonomy[13] defined in 2000 by the Ruiz-Jarabo 2000 group coordinated by ISMP-Spain and financed by the Spanish Society of Hospital Pharmacy (SEFH in Spanish). This classification is by type, origin, cause, and severity of the drug error. This taxonomy standardises ADE detection, analysis, classification and record-keeping, which makes comparing different studies easier and allows us to understand the true state of the problem.

Statistical analysis

Analysis was performed with SPSS software, version 14.0. We carried out a descriptive analysis with central tendency and dispersion measurements for quantitative variables and relative frequencies for categorical variables. We also studied ADE-related variables using the χ^2 test, Student *t*-test or non-parametric tests depending on variable type and conditions of application. *P*-values <.05 were considered to be statistically significant.

Ethical considerations

The study was carried out according to the principles set forth in the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments established by world medical assemblies and the Good Clinical Practice (GCP) standards of the International Conference on Harmonisation (ICH). The study was approved by the clinical research ethics committee at each of the centres. The Spanish law protecting personal data was applicable, and data was handled separately from personal information in order to respect the identities of the patient, hospital or centre.

Results

Patients

The sample included 1550 patients, with 894 men (57.7%) and 656 women (42.3%). The mean (standard deviation) for age was 66.3 (17.9) years; the most representative interval (42.5%) included patients aged 60 to 80 years. The average number of drugs prescribed per patient was 11.1 (5.9) and the mean hospital stay was 8.5 (7.2) days. In the breakdown by hospital unit, we observe that the average number of drugs prescribed was similar for medical and surgical units (11.3 [5.7] and 11.1 [6.2] respectively), but the hospital stay was longer for patients admitted to medical units (9.4 [8.1] days vs 7.6 [6.1] days for surgical units).

Patients with and without ADEs were compared in order to reveal the factors favouring the appearance of ADEs (Table 1). Age, number of drugs prescribed, and length of hospital stay seem to be risk factors for triggering an ADE. Patients with ADEs were older than those with no ADEs by a mean of 3.2 years (95% confidence interval [CI], 0.2-6.1); their hospital stay was longer than the other group's by a mean of 6.42 days (95% CI, 4.77-8.07), and they had an average of 4.47 more prescribed medications (95% CI, 3.45-5.46) than the other group did.

These differences increased when patients were compared by ADE preventability. Patients with preventable ADEs were a mean of 5.4 years older (95% CI, 0.1-10.7), stayed in the hospital a mean of 3.7 days longer (95% CI, 0.6-6.8) and were prescribed a mean of 2.6 more drugs (95% CI, 0.5-4.6) than patients with unpreventable ADEs (Table 2).

The patient type (medical or surgical) and sex (male, female) were not determining factors for triggering ADE (Tables 1 and 2).

Adverse drug events

We identified 194 ADEs in 159 patients (10.3% of the study population; 95% CI, 8.8-11.8); 1.8% of the patients (28/1550) presented more than one ADE. By category of probability of a causal relationship, 50.5% (98/194) of the ADEs are classified as likely; 28.5% (55/194) as possible, and only 1% (2/194) as definite ADEs. We were unable to classify 20% of the ADEs (39/194), as they resulted from treatment omission or underdose.

By applying preventability criteria, it was determined that 46.7% of the ADEs (91/194), which affected 51.6% of the patients (82/159), could have been avoided. This indicates that 5.3% (95% CI, 4.2-6.4) of the patients included in the study suffered a condition during the hospital stay which could have been prevented (Appendix 1).

Detecting ADEs

Prior section of warning signs (certain diagnoses, analytic tests, or the use of certain drugs) and a daily interview between a member of the research team and the pertinent medical team enabled us to detect and identify ADEs. Based on these warning signs, we selected those that were truly useful in our situation and which could be a tool for avoiding ADEs considered to be preventable. The most common suspicious diagnoses (n=186) were as follows: cutaneous eruptions (11.3%; 21/186), all of which were considered to be unpreventable ADEs, and hyperglycaemias (11.3%; 21/186), half of which (11/21) may have been preventable. We detected numerous gastrointestinal abnormalities (25.3%; 47/186), most of which were considered non-preventable (78.7%; 37/47). Most noteworthy among the cardiovascular

Table 1 Influence of risk factors in the development of adverse drug events (ADEs)

	Patients. total(n=1550)	Patients without ADE (n=1391)	Patients with ADEs (n=159)	Statistics[a]
Medications per patient, mean (SD)	11.1 (5.9)	10.7 (5.7)	15.2 (6.7)	$P<.001$; $t=9.208$
Hospital stay, mean (SD), d	8.5 (7.2)	7.8 (6.5)	14.1 (9.8)	$P<.001$; $t=10.996$
Age, mean (SD), y	66.3 (17.9)	66 (17.9)	69.2 (16.9)	$P=.035$; $t=-2.123$
Sex				$P=.595$; $\chi^2=0.283$
Men	57.7% (894/1.550)	90.2% (806/894)	9.8% (88/894)	
Women	42.3% (656/1.550)	89.2% (585/656)	10.8% (71/656)	
Unit				$P=.0787$; $\chi^2=3.09$
Medical	50% (775/1.550)	88.4% (685/775)	11.6% (90/775)	
Surgical	50% (775/1.550)	91.1% (706/775)	8.9% (69/775)	

SD indicates standard deviation.
[a] $P=.05$ is considered statistically significant.

Table 2 Influence of risk factors on preventability of adverse drug events (ADEs)

	Total patients with ADEs (n=159)	Patients with preventable ADEs[a] (n=82)	Patients with non-preventable ADEs (n=77)	Statistics[b]
Medications per patient, mean (SD)	15.2 (6.7)	16.5 (6.7)	13.9 (6.4)	P=.015; t=—2.454
Hospital stay, mean (SD), d	14.1 (9.8)	16.1 (9.7)	12.4 (9.9)	P=.018; t=—2.399
Age, mean (SD), y	69.2 (16.9)	71.8 (15.9)	66.4 (17.8)	P=.045; t=—2.018
Sex				P=.249; χ^2=1.328
Men	9.8% (88/894)	47.7% (42/88)	52.3% (46/88)	
Women	10.8% (71/656)	56.3% (40/71)	43.7% (31/71)	
Unit				P=.654; χ^2=0.2
Medical	11.6% (90/775)	50% (45/90)	50% (45/90)	
Surgical	8.9% (69/775)	53.6% (37/69)	46.4% (32/69)	

SD indicates standard deviation.
[a]Some patients presented more than one ADE; these cases could be a combination of preventable and non-preventable. When a patient developed a preventable ADE, he/she was included in the "preventable" patient group.
[b]Differences are statistically significant for P=.05.

abnormalities (11.3%; 21/186) was prolonged hypertension (7%; 13/186) due to lack of proper blood pressure control or omission of a necessary drug (Table 3).

Analytical tests (n=60) were very useful tools that enabled us to find 60 ADEs (some confirmed a suspicious diagnosis). We observed abnormalities in potassium levels (25%; 15/60) and INR values (10%; 6/60) which could have been avoided in both cases. Other abnormal parameters included an increase in creatinine concentrations (11.7%; 7/60) and elevated blood transaminase (13.3%; 8/60) (Table 4).

Trigger drugs (n=7) that aided in the detection an ADE were dexchlorpheniramine (n=4), polystyrene sulphonate sodium (n=2), and flumazenil (n=1).

Implicated medications

The 194 ADEs resulted from the use of 70 different drugs. Antibiotics were the treatment group that precipitated the most ADEs (16.3%; 32/197) throughout the study, although we consider most of them to be non-preventable (29/32). Opiates caused 9.1% (18/197) of the ADEs, and half of the cases (9/18) could have been avoided with proper use. Corticoids caused 5.6% (11/197) of the total, and all were considered non-preventable ADEs. Analgesics, and metamizol in particular, accounted for 5.1% of the ADEs (10/197), but the vast majority (9/10) were considered non-preventable. Diuretics, particularly furosemide, accounted for 4.1% (8/197), and 5/8 were preventable. To a lesser extent we saw that the local anaesthetic and insulin groups each made up 2.5% of the total ADEs (5/197). Other drugs involved are described in Table 5.

A considerable number of ADEs (16.8%; 33/197) resulted from omitting a necessary medication, or compatibility errors with the patient's normal medications. These ADEs were detected through a review of the patient's pharmacotherapeutic history. Drug interactions caused 2.5% (n=5) of the ADE, and all were considered to be preventable.

Classifying preventable ADEs

The ADEs are classified by the associated type of medication error, by the Spanish taxonomy criteria established by the Ruiz-Jarabo 2000 Group,[13] and broken down by type and severity of the error.

Type of error: thirty-six point three percent (33/91) of the preventable ADEs were triggered by skipping a necessary medication or dose, 28.6% (26/91) resulted from administering an incorrect dose, whether an overdose (11/26; 42.3%) or an underdose (15/26; 57.7%) and the use of an incorrect medication resulted in 16.5% (15/91) of the ADEs (Table 6).

Severity of the error: eighty-four point six percent (77/91) of the ADEs fell into category E (the error contributed to or caused temporary damage to the patient, requiring intervention); 10.9% (10/91) fell into category F (the patient required hospitalisation, or the hospital stay was extended due to the error). Only 4.4% (4/91) were considered severe, and fell into category H (the error placed the patient's life at risk, and a life-saving intervention was necessary) (Table 7).

Discussion

The incidence rate of ADEs detected in hospitalised patients was 10.3% (95% CI, 8.8-11.8), and half of the cases (51.6%) could have been avoided.

The results obtained are comparable with those from two previous studies: one meta-analysis by Lazarou et al,[14] which identifies and incidence rate of 10.9%, and one review of 10 studies by Kanjanarant et al,[7] which found a mean range of 1%-10% of preventable ADEs in hospitalised patients. Only 4 of the studies in the review consider omission of a necessary drug as a cause of ADE.

However, the reviewed literature includes studies[5,6,15] that show much lower incidence rates than the ones observed

Table 3 Affected systems and organs and signs of adverse drug events (ADEs) detected in the study

System/ organ and signs	Total ADEs[a] (n=194), No. (%)	Preventable ADEs[a] (n=91), No. (%)	Non-preventable ADEs[a] (n=103), No. (%)
Digestive	47 (25.3)	10 (10.9)	37 (39.4)
Nausea and vomiting	15 (8.1)	1 (1.1)	14 (14.9)
Diarrhoea	14 (7.5)	3 (3.3)	11 (11.7)
Constipation	8 (4.3)	5 (5.4)	3 (3.2)
Abdominal pain	1 (0.5)	1 (1.1)	
Epigastralgia	1 (0.5)		1 (1.1)
Hepatitis, elevated transaminases	8 (4.3)		8 (8.5)
Endocrine	42 (22.6)	32 (34.8)	10 (10.6)
Hyperglycaemia	21 (11.3)	11 (12)	10 (10.6)
Hypoglycaemia	1 (0.5)	1 (1.1)	
Hyperkalaemia	7 (3.8)	7 (7.6)	
Hypokalaemia	8 (4.3)	8 (8.7)	
Hyperuricaemia	2 (1.1)	2 (2.2)	
Acidosis, alkalosis	2 (1.1)		2 (2.1)
Oedemas	1 (0.5)	1 (1.1)	
Skin and appendages	23 (12.4)	0	23 (24.5)
Skin eruptions	21 (11.3)		21 (22.3)
Erythema multiforme	1 (0.5)		1 (1.1)
Glossitis	1 (0.5)		1 (1.1)
Cardiovascular	21 (11.3)	19 (20.7)	2 (2.1)
Tachycardia	4 (2.2)	3 (3.3)	1 (1.1)
Bradycardia	2 (1.1)	2 (2.2)	
Arterial hypotension	2 (1.1)	1 (1.1)	1 (1.1)
Arterial hypertension	13 (7)	13 (14.10)	
Central nervous system and senses	18 (9.7)	9 (9.8)	9 (9.6)
Ataxia	1 (0.5)	1 (0.5)	
Convulsions	3 (1.6)	3 (1.6)	
Extrapyramidal disorder	1 (0.5)		1 (1.1)
Loss of consciousness	3 (1.6)	3 (1.6)	
Confusion	1 (0.5)		1 (1.1)
Headache	3 (1.6)	1 (0.5)	2 (2.1)
Dizziness	1 (0.5)		1 (1.1)
Drowsiness	4 (2.2)		4 (4.3)
Paraesthesia	1 (0.5)	1 (0.5)	
Haematic-coagulation	10 (5.4)	7 (7.6)	3 (3.2)
Anaemia	1 (0.5)	1 (0.5)	
Leukocytopenia (with neutrocytopenia)	1 (0.5)		1 (1.1)
Pancytopenia	1 (0.5)		1 (1.1)
Thrombocytopenia	1 (0.5)		1 (1.1)
Coagulation disorders	6 (3.2)	6 (3.1)	
General	8 (4.3)	8 (8.7)	0
Fever	4 (2.2)	4 (2.1)	
Pain	4 (2.2)	4 (2.1)	
Nephrourological	7 (3.8)	1 (1.1)	6 (6.4)
Urine retention	2 (1.1)		2 (2.1)
Haematuriaa	2 (1.1)	1 (1.1)	1 (1.1)
Candidiasis	3 (1.6)		3 (3.2)
Psychiatric effects	6 (3.2)	5 (5.4)	1 (1.1)
Nervousness, agitation, delirium, insomnia	6 (3.2)	5 (5.4)	1 (1.1)
Respiratory	2 (1.1)	1 (1.1)	1 (1.1)
Dyspnoea	2 (1.1)	1 (1.1)	1 (1.1)
Osteomuscular collagen	2 (1.1)	0	2 (2.1)
Vasculitis	1 (0.5)		1 (1.1)
Myalgia	1 (0.5)		1 (1.1)
Total	186	92	94

ADEs not listed were detected using an analytical test or trigger drug.
[a]Percentages were calculated from the total for each column. An ADE may affect more than one organ or system.

Table 4 Adverse drug events (ADEs) detected through use of analytical testss

Analytical tests	Total ADEs,[a] No. (%)	Preventable ADEs,[a] No. (%)	Non-preventable ADEs,[a] No. (%)
Glycaemia	21 (35)	11 (29.7)	10 (43.5)
Potassium concentrations	15 (25)	15 (40.5)	
Transaminases	8 (13.3)	0	8 (34.8)
Creatinine	7 (11.7)	4 (10.8)	3 (13)
INR	6 (10)	6 (16.2)	
Alkaline phosphatase	1 (1.7)		1 (4.3)
Clostridium difficile +	1 (1.7)		1 (4.3)
Haemoglobin	1 (1.7)	1 (2.7)	
Total	60	37	23

[a]Percentages were calculated from the total for each column. Some ADEs were detected using analytical tests or trigger drugs.

in our study. This situation could result from the fact that many of these studies do not contemplate ADEs caused by the omission of a necessary drug. Bates et al[5] estimate that 6.1% of hospitalised patients suffer from ADE, and 28% of these cases are preventable (overall incidence rate of 1.7%). On the other hand, Senst et al [15] detected 74 ADEs, which means that 2.3% of hospitalised patients had an ADE during their stay. An extrapolation factor was applied in this study (5% was added to the results obtained, corresponding to patients who were discharged before developing an ADE) and overall incidence rate was estimated at 4.2% (135 ADEs). The preventability rate was 15% (n=11), but after the extrapolation, 20 ADES were considered as avoidable. In our area, Otero et al[6] described an ADE rate of 7.2% in hospitalised patients, out of which 20% could have been prevented (overall incidence rate of 1.4%).

As a result, the incidence rate of patients with an ADE during hospitalisation ranged between 1% and 10.9%, but when we limited the analysis to those studies including treatment omission as a cause of ADE, the incidence rate fell into a range between 7.2% and 10.9%. The results we obtained in our study fit within these ranges, and we therefore consider the study population to be comparable with that used in previous studies.

In this project, we estimate that ADEs could have been prevented in 51.6% of the patients.

This percentage is higher than percentages in the literature we reviewed, in which the numbers range from 15% to 42%.[5,6,15] This is probably due to the large number of omissions and reconciliation errors we detected in participating hospitals. These results make having a computerised system as an aid to avoiding detected preventable ADEs more interesting.

ADEs were caused by various different drugs. The treatments that caused the most ADEs were antibiotics, but this was not preventable in 90% of the cases, and accounts for 28% of all cases of non-preventable ADEs. These data coincide with the results gathered from the literature we reviewed in which antibiotics made up 30%-35% of the non-preventable ADEs.[1,6,15]

Opiates caused 10% of the preventable ADEs (9/91); our result is similar to that found by Bates et al,[1] which attributed 20% of preventable ADEs to this drug group. In other studies we reviewed, the principal drugs involved in preventable ADEs were antibiotics (22.9% vs our 3%) and cardiovascular treatments (17.9%[7] vs 6.6%).

The symptoms that were triggered as part of an ADE were classified according to the affected organ or system. The digestive tract (39.4%; 37/103) and the skin and its appendages (24.4%; 19/103) were the systems that presented the most non-preventable ADEs. These results coincide with the information provided by Otero et al,[6] in which 19.1% of the non-preventable ADEs alter the digestive system, followed by the endocrine system (19.8%).

With regard to preventable ADEs, we observed that damage appeared mostly in the endocrine (34.8%; 32/91) and cardiovascular systems (20.7%; 19/91). This is also described by Otero et al[6] in the study stating that endocrine abnormalities made up 28.3% of the preventable ADEs, followed by the digestive system (22.6%) and cardiovascular system (18,9%). However, Senst et al[15] pointed to the central nervous system (36%) and cardiovascular system (36%) as being the most affected by preventable ADEs.

We performed an analysis in order to learn the origin, type and severity of the errors that caused preventable ADEs with a view to acting upon them and avoiding similar future situations. Prescription errors made up a high percentage of the total detected errors, which is similar to results in the literature we reviewed.[5-7] The main error types we detected were as follows: omission of a necessary medication, including reconciliation error with habitual medication (36.3%; 33/91), incorrect dosages (28.6%; 26/91), and incorrect drug choice (16.5%; 15/91). The same situation was also observed in studies considering omission to be a cause of ADE (with a rate of 15% for the article by Otero et al[6] and 12% for the review by Kanjanarant et al[7]). The identified percentage of preventable ADEs caused by improper dosage is comparable with the percentage determined by Kanjanarant et al[7] in their review (22.4%). Improper drug choice was described in most of the studies we reviewed (from 15% to 38%).[6,8] For Bates et al,[1] the most common errors were in dosage, choice of drug and incorrect frequency of administration. These three errors occurred at the time the drug was prescribed.

Tabla 5 Medications implicated in adverse drug events (ADEs) in this study

Drug group or cause of ADE	Total ADEs[a] (n=194)	Preventable ADEs[a] (n=91; 46.9%)	Non-preventable ADEs[a] (n=103; 53.1%)
Antibiotics	32 (16.3%)	3 (3.2%)	29 (28%)
Amoxicillin/clavulanic acid	12 (6.1%)		12 (11.5%)
Piperacillina/tazobactam	3 (1.5%)		3 (2.9%)
Levofloxacin	2 (1%)		2 (2%)
Ceftriaxone	2 (1%)		(2%)
Vancomycin	2 (1%)	2 (2.2%)	
Imipenem	2 (1%)		2 (2%)
Ciprofloxacin	1 (0.5%)		1 (1%)
Co-trimoxazole	1 (0.5%)		1 (1%)
Gentamicin	1 (0.5%)	1 (1.1%)	
Erythromycin/neomycin	1 (0.5%)		1 (1%)
Metronidazole	1 (0.5%)		1 (1%)
Amikacin	1 (0.5%)		1 (1%)
Pure opiate agonists	18 (9.1%)	9 (9.7%)	9 (8.7%)
Corticoids	11 (5.6%)		11 (10.6%)
Analgesics	10 (5.1%)	1 (1.1%)	9 (8.7%)
Diuretics	8 (4.1%)	5 (5.4%)	3 (2.9%)
Local anaesthetics	5 (2.5%)		5 (4.8%)
Insulins	5 (2.5%)	5 (5.4%)	
Colchicine	4 (2%)		4 (3.8%)
Parenteral nutrition	4 (2%)	4 (4.3%)	
NSAIDs	4 (2%)	2 (2.2%)	2 (2%)
Nitrates	4 (2%)	2 (2.2%)	2 (2%)
Laxatives	4 (2%)	3 (3.2%)	1 (1%)
Oral anticoagulants	3 (1.5%)	3 (3.2%)	
Calcium polystyrene sulphonate	3 (1.5%)	1 (1.1%)	2 (2%)
Heparin	3 (1.5%)	1 (1.1%)	2 (2%)
Antiepileptics	3 (1.5%)	3 (3.2%)	
Beta-blockers	3 (1.5%)	1 (1.1%)	2 (2%)
ACE inhibitors	3 (1.5%)	3 (3.2%)	
Antimycotics	2 (1%)		2 (2%)
General anaesthetics	2 (1%)		2 (2%)
Anti-anxiety drugs, sedatives	2 (1%)	1 (1.1%)	1 (1%)
Antituberculosis drugs	2 (1%)		2 (2%)
Antiemetics	2 (1%)		2 (2%)
Antihistamines	2 (1%)		2 (2%)
Psycholeptics	2 (1%)		2 (2%)
Potassium chloride (KCl)	2 (1%)	1 (1.1%)	1 (1%)
Allopurinol	2 (1%)	1 (1.1%)	1 (1%)
Others	13 (6.6%)	5 (5.4%)	8 (7.7%)
Interactions	5 (2.5%)	5 (5.3%)	
Acenocoumarol + metamizol	1 (0.5%)	1 (1%)	
Acenocoumarol + omeprazol	1 (0.5%)	1 (1%)	
Acenocoumarol + co-trimoxazole	1 (0.5%)	1 (1%)	
ACEI + diuretics	1 (0.5%)	1 (1%)	
ACEI + potassium chloride	1 (0.5%)	1 (1%)	
Omission of a necessary drug	18 (9.1%)	18 (19.4%)	
Antihypertensive drug	9 (4.6%)	9 (9.7%)	
Potassium chloride	3 (1.5%)	3 (3.2%)	
Calcium polystyrene sulphonate	2 (1%)	2 (2.2%)	
Laxatives	2 (1%)	2 (2.2%)	
Analgesics	1 (0.5%)	1 (1%)	
Hyperuricaemia correctors	1 (0.5%)	1 (1%)	
Compatibility problems	15 (7.6%)	15 (16.1%)	
Oral antidiabetics	6 (3%)	6 (6.5%)	
Antipsychotics	3 (1.5%)	3 (3.2%)	
Calcium polystyrene sulphonate	2 (1%)	2 (2.2%)	
Alzheimer medication	1 (0.5%)	1 (1%)	
Hormone replacement therapy	1 (0.5%)	1 (1%)	
Beta-blockers 1 (0.5%)	1 (1%)		
Antiarrhythmic drugs	1 (0.5%)	1 (1%)	
Totals	197	93	104

ACE inhibitors indicates angiotensin-converting enzyme inhibitors; NSAID, non-steroidal anti-inflammatory drugs..

[a]Percentages were calculated from the total for each column. There are more drugs than ADEs, since an ADE can be caused by more than one drug.

Table 6 Type of error detected in adverse drug reactions (ADEs)

Type of error (n=91)	No. (%)
Omission of a necessary dose or medication	33 (36.3)
Lack of prescription	29 (87.9)
Administration of an incorrect dose	26 (28.6)
Overdose	11 (42.3)
Underdose	15 (57.7)
Incorrect drug	15 (16.5)
Inappropriate drug choice	13 (14.3)
Insufficient treatment monitoring	6 (6.6)
Errors in medication preparation, manipulation or conditioning	5 (5.5)
Inappropriate duration for the patient	3 (3.3)
Use of an unnecessary medication	2 (2.2)
Incorrect administration technique	1 (1.1)

The incidence rate for ADEs considered to be severe (4.4%; 4/91) was lower than what we saw in the literature; some studies detected a rate of severe ADEs as high as 42%.[15]

The study has some limitations, mainly owing to the method used and the study setting. The analysis was carried out in specific hospital units, and results cannot therefore be extrapolated for other hospital units due to their ample variability and varying degrees of specialisation. However, previous studies[6] coincide with our data, and while we cannot make generalisations about the results, we could say that the main problems we observed can also be found in other health districts. Secondly, we must consider the difficulty involved in using an observational method to identify all ADEs that might arise during the patient's hospital stay. Observation was not covert, which may have affected the results due to the Hawthorne effect,[16] which leads to improved activity on the part of the worker being observed. Another topic for discussion was the lack of precision in our understanding of what caused ADEs. Many of the preventable ADEs we identified were the result of human error, although there is no clear idea of what precipitated this error.

To conclude, we can state that a high percentage of patients (10.3%) presented ADEs during the hospital stay, and half of those ADEs (51.6%) could have been avoided. This fact justifies the need to create a system to improve the quality of the care process during a patient's hospital stay. Therefore, we propose implementing a system of alerts at troublesome points along the circuit, primarily for prescription, pharmaceutical validation and pharmacotherapy follow-up, as an aid to detecting preventable ADEs. We propose four lines of action to handle the problem: daily checks of certain specific analytical parameters (glycaemia, INR, potassium, and creatinine); increasing precautions for certain drugs considered to have a high potential risk of preventable ADEs; improving pharmacotherapeutic follow-up on patients with a higher probability of developing an ADE and ensuring good treatment compatibility once the patient has been admitted to hospital, whether by using a more extensive personal interview or by having the ability to access reliable data about his/her normal medications.

We estimate that preventable risks could be reduced by 71.4% by applying the preventative measures we propose, resulting in increased patient safety and care quality during the hospital stay.

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Table 7 Severity of error detected in adverse drug reactions

Category	Definition	Total errors (n=91), No. (%)
E	The error contributed to or caused temporary damage to the patient and required an intervention	77 (84.6)
F	The patient was hospitalised or the hospital stay extended due to error	10 (10.9)
H	The error placed the patient's life at risk and a life-saving intervention was necessary	4 (4.4)

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Appendix 1 List of preventable adverse events caused by use of medications (ADEs)

Drug group	Drug	ADE	ADE description	Cases, No.
Analgesic	Paracetamol	Pain	Extravasion from catheter used to administer analgesic. There was no follow-up, and the patient did not receive drug for 8 hours	1
Anti-anxiety	Zolpidem	Loss of consciousness	Poisoning due to administration of an unnecessarily high dose. Required administration of flumazenil as an antidote to the poisoning	1
Calcium antagonist	Amlodipine	Oedemas	Higher dose than patient's normal dose led to retaining water and oedema forming in legs	1
Antiarrhythmics	Amiodarone	Sustained tachycardia	Doses and frequencies were lower than the patient needed	1
Antibiotic	Gentamicin	Renal failure	Renal failure after administering antibiotic due to not adjusting dosage according to renal function.	1
	Vancomycin		Creatinine increased by 1.7 for gentamicin and by 2.14 and 1.5 for vancomycin (along with toxic plasma levels of the drug)	2
Anticoagulant	Acenocoumarol	Thrombosis	Thrombosis after skipping a dose of anticoagulant due to an electronic verification error	1
			Thrombosis due to changing from enoxaparin to acenocoumarol too quickly without checking INR	1
		Coagulation disorders	Coagulation disorder (INR below the normal range) due to lack of analytical tests	1
Antiepileptic	Carbamazepine	Convulsions with respiratory failure	IUnderdose of carbamazepine (dose was lower than patient's normal dose)	2
			Skipping a dose of antiepileptic that was needed in order to carry out a test	1
NSAID	Diclofenac	Hypertension, oedemas	Sodium and water retention with corresponding increase in arterial pressure that remained high in a hypertensive patient. The drug was not discontinued at any time	1
	Indomethacin, ASA, metamizol, and dexketoprofen	Stomach-ache	NSAID overdose caused epigastralgia	1
Beta-blockers	Carvedilol	Tachycardia and dyspnoea	Administering a beta-blocker to a patient with acute heart failure	1
PCA pump	Ropivacaine+ fentanyl	Paraesthesia	Erroneous placement of catheter for administering analgesic, causing paraesthesia of the leg	1
Hyperuricaemia correctors	Allopurinol	Renal failure	Dose was not adjusted for the patient (initial creatinine level: 1.35 mg/dL). Pharmacy issued alert but dose was not changed (300 mg/day). Nephrotoxicity appeared within 3 days (creatinine levels of 2.17 mg/dL)	1
Diuretic	Furosemide	Hypokalaemia	Electrolytic imbalances due to lack of analytical tests and potassium sources	3
	Torasemide	Hypokalaemia		1
	Furosemide + hydrochloro-thiazide	Hyperuricaemia with an acute attack of gout	Electrolytic imbalances made worse by diuretics due to lack of analytic tests, which caused an acute attack of gout	1
Anti-peptic ulcer drug	Ranitidine	Agitation, nervousness	Patient received higher dose than necessary due to dose not being adjusted for renal failure	1
Drug used for poisonings	Calcium polystyrene sulphonate	Hypokalaemia	Administering an unnecessary medication. Lack of analytic test; hypokalaemia was observed, but drug was not discontinued	1
Heparin	Enoxaparin	Haematuria	Patient received higher dose than necessary due to dose not being adjusted for renal failure	1

(Continue)

Appendix 1 List of preventable adverse events caused by use of medications (ADEs) *(Continuation)*

Drug group	Drug	ADE	ADE description	Cases, No.
ACEI	Captopril	Hypertension	Sustained hypertension due to ACEI underdoseA	2
	Enalapril	Hyperkalaemia	Sustained hyperkalaemia as an adverse reaction to ACEIs with no testing for the electrolytic imbalances this could create	1
Insulin		Glycaemic abnormalities (diabetes)	Glycaemic abnormalities due to insulin underdose. Doses were lower than the patient normally received	5
Laxative		Diarrhoea	Excessive laxative use (3 or 4 laxatives used at once without waiting for them to take effect)	
Nitrate	Nitroglycerine	Loss of consciousness, ataxia	Erroneous drug choice due to not running analytic test, resulting in worsening of patient's clinical state (ataxia, arrhythmias and finally, lack of consciousness)	2
Parenteral nutrition		Fever	Incorrect handling of the catheter for parenteral nutrition resulting in *Staphylococcus epidermidis* infection and fever of 39ºC	4
Pure opiate agonisto	Fentanyl	Dyspnoea	Of the cases in which the patient was in pain,	1
		Pain	one was caused by drug underdose, 2 were	1
		Nausea, vomiting, disorientation	caused by failure to administer the prescribed dose, and once due to failure to transcribe.	1
		Constipation	In the other cases, the dosage was higher than necessary due to lack of a proper titre, which	1
	Morphine	Pain	caused adverse reactions from opium receptor	2
		Agitation, insomnia, anxiety	stimulation (respiratory failure, euphoria, myosis, hallucinations etc)	1
	Pethidine hydrochloride	Constipation	Lack of prophylactic laxatives to avoid constipation, a known side effect of opiates	1
	Tramadol	Constipation		1
Potassium chloride		Hyperkalaemia	Administration of potassium chloride to a patient who did not require that supplement, leading to sustained hyperkalaemia (without drug being discontinued)	1
Total ADEs				53

Appendix 2 List of the preventable adverse drug events caused by interactions, omissions or medical reconciliation errors

Cause of ADE	Drug	ADE	ADE description	Cases, No.
Interaction	Metamizol +acenocoumarol	Coagulation disorders	Interaction of these drugs increased the effect of acenocoumarol (INR=9.21)	1
	Acenocoumarol + omeprazol	Coagulation disorders	Interaction of these drugs increased acenocoumarol's anticoagulant effect (INR=7)	1
	Acenocoumarol + co-trimoxazolel	Coagulation disorders	Documented drug interaction between co-trimoxazole (which was dosed too high) and acenocoumarol, which increases its blood levels and risk of haemorrhage (INR=7.64)	1
	ACEI + diuretics	Hypotension	Excess of drugs with a hypotensive effect (enalapril + spironolactone + furosemide)	1
	Potassium chloride + ACEI	Hyperkalaemia	ACEIs increase plasma potassium levels as a matter of course. Administering additional potassium chloride was unnecessary	1
Reconciliation error			Patient's habitual drug was discontinued during the hospital stay	15
Omission of a necessary drugo				18
ADE totals				38