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ORIGINAL ARTICLE

Incidence rate of adverse drug effects in a hospital emergency unit and its associated factors

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Abstract
Introduction: Adverse drug effects (ADE) are the reason for 0.86% to 38.2% of emergency hospital admissions, and a large percentage of them are avoidable. Rational prescription and pharmacotherapy monitoring reduce the appearance of such health problems.
Method: Study performed in a tertiary hospital emergency unit with patients selected using a two-phase random sample. The information was obtained from a validated questionnaire and from the clinical history. The data were grouped according to the following cause-effect schema: 1-Potential risk factors for an ADE. 2-Effects likely to be caused by drugs. 3-Consequences of ADE. 4-Potential confounding factors. The information obtained was evaluated by four independent evaluators using the Dader method.
Results: Eight hundred forty patients were included in the study, and 33% of them came to the emergency unit due to an ADE. ADE were more frequently observed in female patients, those with higher drug consumption, older patients, those with an underlying illness and in those from underprivileged backgrounds. The factors determining risk of an ADE are the quantity of drugs consumed, sex and the health practices index.
Discussion: One third of emergency hospital admissions were due to ADE, and these were associated with the same factors found in other studies (number of drugs consumed, female sex, age and social background). In addition, we observed that ADE are predominant in patients with low values on the health practices index, and in those with underlying illnesses.

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PALABRAS CLAVE
Resultados negativos de la medicación;
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Sexo;
Clase social;
Índice de prácticas de la salud;
Comorbilidad

Incidencia de resultados negativos de medicación en un servicio de urgencias hospitalario y factores asociados

Resumen
Introducción: Los resultados negativos de la medicación (RNM) motivan entre un 0,86-38,2% de las urgencias hospitalarias y en un alto porcentaje son evitables. La prescripción racional y el seguimiento farmacoterapéutico reducen la aparición de estos problemas de salud.
Método: Estudio en el servicio de urgencias de un hospital de tercer nivel con selección de pacientes por muestreo aleatorio bietápico. La información se obtuvo de un cuestionario validado y de la historia clínica. Los datos se estructuraron dentro del siguiente esquema causa-efecto: 1) factores potenciales de riesgo de un RNM; 2) efectos provocados de manera plausible por fármacos; 3) consecuencias del RNM, y 4) potenciales factores de confusión. La información obtenida fue evaluada según la metodología Dáder por cuatro evaluadores independientes.
Resultados: Se incluyeron 840 pacientes en el estudio, de los cuales el 33% acudió a urgencias por un RNM. Los RNM se observaron con mayor frecuencia en las mujeres, con mayor consumo de fármacos, en los pacientes mayores, en aquellos con alguna enfermedad de base y en los pertenecientes a clases sociales más desfavorecidas. Los factores que determinan el riesgo de aparición de los RNM son la cantidad de medicamentos consumidos, el sexo y el índice de prácticas de la salud.
Discusión: Un tercio de las urgencias hospitalarias fueron debidas a RNM y se asociaron a los mismos factores que otros estudios (número de fármacos consumidos, sexo femenino, edad y clase social). Además, se observó un predominio de los RNM en los pacientes con valores bajos del índice de prácticas de la salud y en aquellos con enfermedades de base.

Introduction

The total cost of pharmaceutical prescriptions in Spain in 2006 was €10636.24x10^6, a 5.8% increase from 2005.[1] This consumption, which has experienced a sustained increase, is not always accompanied by the intended medical results, and can even lead to new health problems,[2,3] which, in addition to adverse reactions and side effects, can be provoked through unnecessary use, prolonged inefficiency, dosage, inadequate duration and method of administration, and even lack of necessary drug. In the USA, 100 000 people die every year due to adverse reactions to drug, and 7000 due to errors in the administration of these drugs.[4]

Adverse drug effects (ADE) have been defined and classified in different ways,[5-7] but all are, for the most part, preventable. Pharmacotherapeutic follow-up,[8-12] rational prescription of drugs, computerised drug indications in expert systems,[13,14] training of health care professionals, and a review of all drugs before giving new prescriptions[15,16] are all useful tools for reducing ADE.

Between 0.86% and 38.2%[17-28] of hospital emergency cases are caused by ADE, hospitalisation being required in as many as 24% of cases,[17,20] and between 66%-72.7%[17,19,23,24] are considered avoidable.

The objective of this study was to determine the rate of ADE incidence that causes emergencies at a tertiary hospital in the Canary Islands, Spain, and the drugs and factors associated with them.

Methods

The study was carried out in the Emergency Unit at Nuestra Señora de Candelaria University Hospital in Tenerife, Canary Islands, which is a tertiary hospital with coverage for 481 000 inhabitants, with 936 acute beds. The hospital attended to 122 465 emergencies during 2005, with 15% of cases being admitted.[29] The population studied consisted of those patients who sought treatment between 15 March and 14 June 2006, excluding those cases of voluntary drug intoxication, gynaecological emergencies that were attended in the gynaecological department, paediatric cases, and patients that did not provide the required information. We also avoided duplications from successive visits by the same patient, by only considering data obtained during the first visit. The losses due to lack of patient collaboration were compared to participants in order to assess any possible selection bias.

Patients were selected through a two-phase randomised sample, with days of the year as primary units and patients considered as secondary units. The number was set at 800 for a 50% incidence of ADE, with 95% confidence intervals and ±3% error level, which yielded a power of 98% in the application of bilateral hypothesis tests for a significance level of 5%, and allowed for using logistical regression models with up to 40 explanatory variables.

Before being included in the study, each patient gave their informed consent. The questionnaire components were then completed, based on the form produced by the Pharmaceutical Care Group of Granada to detect ADE in emergency wards, which was validated in Spain.[30,31] Interviews were performed in the emergency triage unit by 10 pharmacists. If the patient's health was so poor that he or she were unable to complete the questionnaire, the information was obtained from a family member or care provider. Missing data from the questionnaire were taken from clinical records.

Table 1 Definition of adverse drug effects according to the Third Consensus of Granada[3]

Category	Type	Definition
Necessary	Untreated health problems (ADE 1)	The patient suffers a health problem associated with the lack of a needed drug
	Unnecessary drug effects (ADE 2)	The patient suffers a health problem associated with receiving an unneeded drug
Effective	Non-quantitative ineffectiveness (ADE 3)	The patient suffers a health problem associated with non-quantitative ineffectiveness of the drug
	Quantitative ineffectiveness (ADE 4)	The patient suffers a health problem associated with quantitative ineffectiveness of the drug
Safe	Non-quantitative lack of safety (ADE 5)	The patient suffers a health problem associated with non-quantitative lack of safety
	Quantitative lack of safety (ADE 6)	The patient suffers a health problem associated with quantitative lack of safety

ADE indicates adverse drug effects.

The data were structured within a cause-effect schema as follows:

1. Potential ADE risk factors: consumption of drugs categorised by anatomical, therapeutic, and chemical classifications,[32] the drug prescriber (emergency doctor, primary care staff member, specialist, pharmacist, self-prescribed). Medical allergies were also categorised by the aforementioned classifications.
2. Effects that were possibly provoked by the drugs: ADE included in the classification table by the Third Consensus of Granada[3] (Table 1) and defined as the medical diagnosis upon patient discharge (categorised according the ICD-9[33]) associated with a 'necessary', 'effective', or 'safe' drug, according to the Dader method,[34] and 'avoidable' according to the Baena et al method.[35]
3. ADE consequences: hospitalisation and severity according to the scale by Tafreshi et al.[19]
4. Potential confounding factors: modified Charlson co-morbidity index,[36] health practices index (HPI),[37] social background according to the Spanish Epidemiology Society,[38-40] age, and sex.

Eight different pharmacists and three doctors participated in evaluating the obtained information, and each case was examined by four different, independent evaluators, one of which was always a doctor. In the case of disagreement between the evaluators, the doctor's criteria prevailed.

Data processing

The characteristics of the sample have been summarised, with categorical variables as percentages, ordinal variables (those that follow a gradient from better to worse) and non-normal scales as median values (P_{25}-P_{75}, range), and normal scales as mean (SD).

The first type of variables were compared using Pearson's chi-square test, the second type using the Kruskal-Wallis H-test and Mann-Whitney U-test, and the third group of variables were compared using Bonferroni-Scheffe post-hoc ANOVA tests and Student's *t*-tests. The comparisons between different groups with overall significance values of the differences between them will appear with the significance between the specific groups that produce these differences.

Using ADE as the dependent variable, we adjusted multivariate logistical regression models, using a backward strategy and Wald criteria. These models' predictive variables were those factors that exhibited potential risk, selected from among those that reached significant values in the simple comparisons, had the highest univariate odds ratio from among those within the same category, and provided the greatest amount of information.

Statistical calculations were performed using Sample Power 5.0 and SPSS 15.0© software by SPSS Inc., Chicago, Illinois, USA.

Results

The final sample was made up of 888 patients, 33 of whom were excluded as they did not comply with inclusion criteria, and 15 declined to participate. The 840 patients finally included in the study equally represented both sexes, and had a mean age of 42 years (range: 28-62 years). Information was obtained directly from the patients in 95% of cases.

Within the sample, 33% of patients went to the emergency unit due to ADE: 16% 'effective', 14% 'necessary', and 3% 'safe'. According to type, 40% of cases were produced by the lack of necessary pharmacological treatment, 27% by quantitative ineffectiveness of the drug, 23% by non-quantitative ineffectiveness, and 8% by safety problems unrelated to dosage.

ADE were associated with respiratory (14%; $P<.001$) and digestive (13%; $P<.001$) system diseases, injuries and poisoning (8%; $P<.001$), mental disorders (6%; $P<.001$), and infectious and parasitic diseases (3%; $P<.003$).

Table 2 Comparison of the frequencies of adverse drug effects according to pharmacological group of the implicated drug*

Group ($P<.001$)**		Musculoskeletal system	Systemic antibiotics	Respiratory system	Gastrointestinal tract and metabolism	Blood and haematopoietic organs	Cardiovascular system	Urogenital system and sex hormones
	ADE, %	19	8	12	8	4	7	1
Nervous system	35	0.006	NS	NS	<0.001	0.001	<0.001	0.003
Musculoskeletal system	19		NS	0.021	<0.001	<0.001	<0.001	<0.001
Systemic antibiotics	8			NS	<0.001	<0.001	–	<0.001
Respiratory system	12				<0.001	0.004	<0.001	0.006
Gastrointestinal tract and metabolism	8					NS	NS	–
Blood and haematopoietic organs	4						NS	–
Cardiovascular system	7							–

– Comparison was not possible due to lack of data in the cell.
ADE indicates adverse drug effects; NS, the difference was not statistically significant.
*Only those groups with a sufficiently large sample size for applying Pearson's chi-square test are presented. **Overall significant difference. Significant difference between specific groups is shown.

ADE were the cause of 33% of all hospitalisations, even though we did not observe a significant relationship between the need for hospitalisation and the presence of ADE. However, the results from the analysis of hospitalisations by category of ADE indicated that patients with 'necessary'-related ADE required a greater level of hospitalisation than those with 'effective'-related ADE. (20% vs 10%; $P=.011$).

Modifiable factors

The level of drug consumption was greater in patients with ADE (3 [1-5]) than in those without ADE (1 [0-3]) ($P<.001$). Two drugs (0-5) were consumed in the 'necessary' category, 2 drugs (2-4) in 'effective' category, and 5 drugs (4-9) in the 'safe', with a difference between each ($P<.001$). We observed differences by type ($P<.001$), with a range of consumption between 8 (3-12) drugs for type 6 and 2 (0-5) drugs for type 1. Table 2 displays the frequencies of ADE by pharmacological group, and Table 3 displays them by category.

The differences observed between drug prescribers are detailed in Table 4, and those found between categories are displayed in Table 5.

The HPI was lower in patients with ADE (3.2-4 vs 3.3-4; $P=.004$), which was maintained with respect to the category of ADE ($P=.003$).

Non-modifiable factors

Sixty-one percent of ADE occurred in women ($P<.001$), with differences observed between the groups: 'necessary' (16% vs 11%; $P=.050$), 'effective' (20% vs 13%; $P=.008$), and 'safe' (4% vs 2%; $P=.025$).

Patients with ADE tended to be older (47.32-69 years vs 40.27-59 years; $P<.001$). Patients had a mean age of 48 (33-70) years in the 'necessary' category, 42 (28-62) years in the 'effective' category, and 57 (47-75) years in the 'safe' category ($P=.006$ between the last two categories).

ADE were produced with greater frequency in patients of lower social background (80% in classes IV-V vs 20% in classes I-III; $P=.047$).

We observed a greater frequency of ADE in patients with some type of underlying disease (51% vs 49%; $P=.006$). Of which, 16% of cases were 'necessary', 17% 'effective', and 5% 'safe' ($P=.005$ for safety). The Charlson co-morbidity index was greater in patients with ADE (4 vs 2; $P=.001$), and was 1 (0-4) for 'necessary', 0 (0–3) for 'effective', and 2 (0–5) for 'safe' ($P=.016$ between the last two categories).

Risk factors

Table 6 shows the results of the final adjustment to the multivariate logistical regression model with the Charlson

Table 3 Frequency of adverse drug effects by category according to the therapeutic group of the associated drug

Treatment group	Necessary, %	Effective, %	Safe, %
Nervous system	50	35	24
Musculoskeletal system	13	20	14
Systemic antibiotics	0	9	5
Respiratory system	25	12	8
Gastrointestinal tract and metabolism	6	10	3
Blood and haematopoietic organs	0	1	22
Antineoplastic and immunomodulatory agents	0	0	19
Cardiovascular system	6	8	3
Systemic hormone preparations	0	2	0
Dermatological condition	0	2	0
Urogenital system and sex hormones	0	1	0
Sensory organs	0	1	3

Table 4 Frequency of the adverse drug effects according to the origin of the drug prescription

Origin of the prescription (P<.001)*		Emergency unit	Primary care	Specialist	Pharmacist	P**
	%	11	42	30	3	
Emergency unit	11					<.001
Primary care	42	<.001				.014
Specialist	30	<.001	<.001			<.001
Pharmacist	3	–	–	–		–
Self-prescribed	15	NS	<.001	<.001	–	<.001

– Comparison was not performed due to the lack of sample size necessary for performing the test.
NS indicates the difference was not statistically significant.
*Overall significant different between the different prescription origins. Significant difference is shown within the box for each of the corresponding origins.
**Significant difference between each prescription origin and all others. We used Pearson's chi-square tests for these comparisons.

Table 5 Frequencies of the adverse drug effects by category and according to the origin of the prescribed drug

Origin of the prescription	Necessary, %	Effective, %	Safe, %	*P**
Emergency unit	6	13	3	NS
Primary care	56	47	11	<.001
Specialist	31	21	78	<.001
Pharmacist	0	2	6	NS
Self-prescribed	6	18	3	NS

NS indicates the difference was not statistically significant.
*Comparison between each origin and the others using Pearson's chi-square test.

Table 6 Results of the multivariate logistical regression analysis of the adverse drug effects*

Factor	OR (95% CI)	*P*
Each most taken drug	1.16 (1.10-1.23)	<.001
Female	1.63 (1.20-2.21)	.002
Each point less on the HPI	1.17 (1.04-1.33)	.011

CI indicates confidence interval; HPI: health practices index; OR: odds ratio.
*Factors whose regression coefficients reached a significance of P<.05. These include: Charlson co-morbidity index, number of drugs consumed, sex, age, social background, and health practices index.

co-morbidity index, the number of drugs consumed, sex, age, social background, and the HPI as potential risk factors for the appearance of ADE. The model only retained the quantity of drugs consumed, sex, and HPI as factors possibly associated to ADE, rejecting the rest.

Discussion

One third of all hospital emergencies during the study period were due to ADE. In previous studies on drug-related hospital emergencies,[17-24,26] a wide range of values have been produced for this type of situation (0.86%-38.2%), which could be due to the variability in study design and the definition of drug-related emergencies.

Prospective studies, as opposed retrospective studies, can bring to light much more information regarding the reasons for seeking emergency treatment and the pharmacological treatment given, which lead to a greater prevalence of ADE detected.[22] The number of hospital emergencies due to ADE at Nuestra Señora de Candelaria University Hospital was similar to the results from other prospective studies focusing on ADE.[18,19,21,24]

In this study, the distribution of ADE was similar to that observed by Baena,[18] with 'effective'-related ADE being the most common. However, other authors have detected such emergencies mostly due to safety-related ADE,[19,21] and this difference could be due to the fact that in our study, we excluded those cases of attempted suicide.

Otero et al[17] observed that 2.5% of emergency visits were related to adverse effects from drugs, excluding cases of voluntary and accidental intoxications, as well as those due to failure to comply with the treatment and treatment failure, focusing on safety issues. The prevalence described here was similar to that found in the 'safe' category of our study.

Problems due to untreated indications (ADE 1) were the most common in our study, constituting 40% of all ADE-related visits, which is a result similar to those from other studies.[21,24] However, Tafreshi et al[19] observed that only 14% of drug-related emergency cases were due to untreated indications.

In our study, problems due to pharmacological ineffectiveness constituted 50% of ADE-related hospital emergencies, this being a lower value than those described by the Baena study,[18] but much higher than the results from Tuneu et al.[21]

Safety ADE reached a similar prevalence to that observed in the Baena et al[18] and Otero et al[17] studies, but were much lower than those described by other authors.[19,21,22] These differences could be explained given that we excluded patients with voluntary drug intoxications. Another possible cause of this discrepancy could be the disparity between studies regarding patient age, since greater longevity is associated with toxicity issues. 21% of our study patients were over 65 years of age, whereas in the Tuneu et al study,[21] over half of all patients surpassed this age.

We observed a relationship between the diagnosis of patients that sought treatment in the emergency unit and the appearance of ADE. Poorly defined health states, symptoms, and signs, musculoskeletal system and connective tissue diseases, respiratory diseases, and gastrointestinal diseases were the most common diagnoses in patients that sought emergency treatment for ADE. In the study by Baena, musculoskeletal diseases constituted the most common diagnosis in ADE patients.

Twelve percent of ADE patients required hospitalisation, which fell within the range of values for this variable in the medical literature.[22,24]

Patients with untreated indications that required hospitalisation mainly suffered from respiratory system and circulatory system diseases that were not being treated. This result differs from the Baena study,[18] in which hospital admissions for this type of ADE were primarily due to abandoned treatment.

With regard to the analysis of potentially modifiable factors, the appearance of ADE was correlated with the number of drugs consumed, in a similar way to other studies.[18,21,27] Interactions between drugs were more

probable when increasing the number of different drugs consumed, which therefore made it more likely for ADE to appear. However, other authors[19,28] found no correlation between the number of drugs and ADE appearance.

Primary care medical staff prescribed over 40% of the drugs associated with ADE. This could be due to the elevated number of repeat prescriptions given,[16] in which contact between the doctor and patient is minimal, hindering adequate pharmacotherapeutic follow-up.

Baena[18] analysed the relationship between the appearance of ADE and the number of prescribers, observing that it was confounded by the number of different drugs consumed. In our study, we were unable to perform this analysis, since our system of gathering information only discerned the type of prescriber, but not how many of them were different.

Patients that sought attention at the emergency unit for reasons unrelated to drugs had better HPI than those patients that sought attention for ADE. Patients with 'effective'-related ADE, among which were those with quantitative ineffectiveness problems secondary to non-compliance with treatment, had low HPI values.

With regard to the factors that affected ADE, patients that sought emergency treatment for ADE were older, on average, than those that suffered other health problems. The association between age and ADE has been described in several different studies.[17,18,21] As tissues age, the pharmacokinetics in drugs could be modified by reduced drug metabolisation.

ADE were much more prominent in patients from lower social backgrounds, as was also described by Martín et al.[28]

Underlying diseases and ADE analysis indicated that ADE occurred more frequently in patients with some type of disease, as well as in patients with a higher modified Charlson co-mobordity index. Co-morbidity was associated with increased drug consumption, which in turn increased the risk of suffering ADE.

With respect to ADE risk factors, the only significant relationships that we observed were with sex, the number of drugs consumed, and HPI.

Sex turned out to be a predictive factor, indicating that women were 1.63 times more likely to suffer from ADE than men. The same correlation has been observed in previous studies,[17,18] but not in others.[21,26,27] In our study, we observed an increased rate of drug consumption in women. A greater exposure to drugs increases the possibility of suffering ADE secondary to interactions between them. Furthermore, the body's response to these drugs could be influenced by differences in weight and the proportion of fatty tissue in women as opposed to men.

Conclusions

ADE frequently cause hospital emergencies and occasionally require hospitalisation, constituting an important health problem. The factors associated with ADE are: the number of drugs consumed, the prescribing doctor, HPI, sex, social background, and the presence of underlying disease. Informing and educating patients could be useful for reducing ADE, and this practice should be especially emphasised in those most susceptible to suffer ADE, such as patients with multiple conditions and drugs. Coordination between doctors and pharmacists also facilitates pharmacotherapeutic patient follow-up, allowing ADE to be prevented, detected, and resolved.

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Conflict of interest

The authors affirm that they have no conflicts of interest.

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