

BRIEF REPORT

Detection of adverse drug reactions using hospital databases—a nationwide study in Portugal

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ABSTRACT

Purpose This study aimed to detect and characterize adverse drug reactions (ADRs) that occurred during hospitalization (ADR_{in}) and ADRs associated with admission (ADR_{Ad}) in Portugal from 2000 to 2009. We also intended to compare the results of this methodology with spontaneous reporting.

Methods We conducted a nationwide study using a hospital administrative database that included all acute care public hospitalizations in Portugal, from 2000 to 2009. We used International Classification of Diseases—9th Revision—Clinical Modification coding data for the detection of ADRs. Codes searched included “E” codes (E930 to E949.9, codes that exclude poisonings and errors) and five groups of diagnoses codes associated with high prevalence of ADR as found in a previous study: hypoglycemia, drug-induced neutropenia, hepatitis unspecified, anaphylactic shock due to drugs, and shock due to anesthesia.

Results From 9 271 122 hospitalizations within that period, 116 720 ADRs were detected through the database methodology, representing 1.26% from all hospitalizations. Of the ADRs, 97.3% occurred during hospitalization (ADR_{in}), whereas 2.7% were associated with admission. Age, female sex, and comorbidities such as pneumonia, heart failure, diabetes, and malignancies were associated with ADRs (all with differences statistically significant). There were 13 562 spontaneous reports from 2000 to 2009.

Conclusions Several methods have been used for the detection of ADRs, but they are difficult to apply at a national level. Spontaneous reporting is widely used but grossly underestimates the frequency of ADRs. The database methodology can be very useful to estimate ADRs frequency and to perform a simple characterization of ADRs nationwide. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—adverse drug reactions; prevalence; databases; pharmacovigilance; hospital administrative databases; pharmacoepidemiology

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INTRODUCTION

Adverse drug reactions (ADRs) are a major health care and patient safety problem, being responsible for significant morbidity, mortality, and costs in health care systems.^{1–3} It is estimated that they occur in a mean of 16.88% of patients during hospitalization (95%CI: 13.56–20.21)⁴ and that they are associated with an overall median of 5.3% of hospital admissions (interquartile range 2.7–9.0%).⁵ The cost of drug-related problems, which include ADRs, may be

higher than the total cost of cardiovascular or diabetes care.⁶ Therefore, the identification and prevention of ADRs is increasingly important.

Pharmacovigilance is the science and activities related to the detection, assessment, understanding, and prevention of all ADRs and of any other drug-related problem.⁷ Several methods can contribute to pharmacovigilance, from spontaneous reporting to intensive monitoring, but all have methodological issues:

Spontaneous reporting (reports of a health care member whenever there is a suspicion of an ADR) is a cheap method, good at the identification of new ADRs, and is the basis of the International Monitoring Program.⁷ The limitations of spontaneous reporting include underreporting,⁸ heterogeneous report quality,⁹ and risk of bias.¹⁰

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The utilization of *administrative databases* and hospital episodes statistics has been performed by a few authors to identify ADRs.^{11–14} Although not widely used, it may have advantages if developed and validated as a methodology, such as follows: information of several hospitals, years and countries already available, clinical coding data from which signals of ADRs might be extracted, low resources needed, and a detection rate higher than spontaneous reporting.¹⁵

Computerized methodologies are interesting and have good detection rates,¹⁶ but need to be performed in hospitals where patient data is computerized, which is not possible in many countries. Other difficulty is related to the low specificity of some algorithms, causing an override of alerts and making them less effective and more costly.¹⁷

Manual chart review for ADR detection consists of retrospectively or prospectively reviewing patient charts to identify ADRs, generally by experts in ADRs.^{18,19} However, it is time and personnel costly: some studies estimated a cost of 55 person-hours per week.¹⁹

*Prospective and intensive monitoring*²⁰ refer to studies performed prospectively in hospitalized patients, with patient interview or examination and health team members interview, performed by experts, to detect ADRs before discharge. They usually have the highest detection rate (intensive monitoring is considered the gold standard) but the highest cost,²¹ not allowing a nationwide study.

These methods were developed for different purposes and thus not all are eligible for a nationwide measurement of the frequency of a disease as an epidemiological tool. In fact, spontaneous reporting is used frequently to estimate frequency of ADRs, but inappropriately (one would need the number of patients receiving drugs, details of administration, and other data).

Our purpose was to identify and characterize ADRs in a nationwide study, using hospital databases with clinical information. Secondarily, we aimed to assess trends in hospitalization and in the frequency of ADRs throughout the years of 2000 to 2009.

METHODS

Study design

A retrospective study was performed for ADR identification using hospital administrative databases with information from all episodes in acute care public hospitals in Portugal, from 2000 to 2009, obtained from Administração Central do Sistema de Saúde (ACSS), the Ministry of Health's Central Authority for Health Services. This national database is built by ACSS, which aggregates data from each hospital. The hospital

database is first built and maintained at each hospital (using a standardized national approach), and then centrally by ACSS.²² To enable this, every hospital uses the same software to store patient information. Coders input data after reading the discharge note and all clinical data, and then attribute a clinical code according to International Classification of Diseases 9th Revision—Clinical Modification (ICD-9-CM). Unlike other countries, all coders in Portugal are physicians, who perform a standardized national course and examination, to assure repeatability (so that the same information recorded by different coders in different hospitals is coded similarly). There are also auditors (internal within the hospital and external at the national level of the ACSS) that perform routine verification to detect and correct errors and to assure quality; currently, they all use the same program for that purpose, "Auditor". If ACSS has any doubt when aggregating the hospital databases into one national database, they contact each hospital, which will review the processes to standardize the information and clarify that issue.

Therefore, the national database (that we obtained from ACSS) contains information on anonymized patient identification, episode, and process number, and also information on age, sex, admission date, discharge date, ward(s), hospital attended (tertiary, university), district, outcome (death, discharge, transfer), payment data (Diagnosis Related Groups), and ICD-9-CM codes for the following: diagnoses (principal diagnosis and secondary diagnoses up to 19), procedures (up to 20), and external causes (up to 20). Patient population included all patients hospitalized in all acute care public hospitals in Portugal, with discharges between 2000 and 2009 (we excluded outpatient episodes). At the time of execution of this work, hospital administrative data from the second semester of 2009 was not available.

ADR definition and identification

We followed WHO's definition of ADR: "any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy."²¹ We were not interested in adverse effects nor medication errors, considering that they are excluded by this definition.

The database of public hospitals in Portugal included information of diagnoses in the form of codes of ICD-9-CM. Codes searched for ADR identification included "E" codes and diagnostic codes. "E" codes belong to a chapter in ICD-9-CM that aims to classify external causes of injury; "E" codes from E930 to E949.9 are already designed to represent ADRs and

exclude wrong doses, errors, and poisonings. The five diagnostic codes searched in this study were selected after a validation study previously performed.¹⁵

In that study, “E” codes and 114 diagnostic codes were tested in a hospital database. Those 115 groups of codes included every code in the ICD-9-CM that contained the expressions: “Due to drugs”, “drug-related”, “*medicamentosa*”, “iatrogenic”, and “drug-induced”; others considered useful as “bleeding”, “diarrhea”, “dysrhythmias”; and others reported in the literature.^{11–14} A list of all tested codes can be requested from the corresponding author. From those 115 tested codes (which generated thousands of signals), the 40 codes with the highest numbers of signals were selected for chart review (we selected the signals that *added* information to the E codes and were not already detected in the E codes). However, considering that the 40 code groups generated more than 10 000 ADR signals, 10–20 random patient charts for each code were selected (more than 350 patient processes were reviewed) for validation. Chart review was considered the gold standard for the assessment of the positive predictive value for each code. Finally, the six groups of codes with higher PPV (positive predictive value) were selected to build a simple database methodology, with a global PPV value of 87.6%, and included the following:

- (1) “E” codes (ICD-9-CM codes of E930 to E949.9; PPV of 95%).
- (2) Other disorders of pancreatic internal secretion including hypoglycemia (ICD-9-CM codes: 251.0–2251.9; PPV of 83%).
- (3) Drug-induced or unspecified neutropenia (ICD-9-CM codes 288.00, 288.03, 288.09; PPV of 60%).
- (4) Hepatitis unspecified (ICD-9-CM 573.3; PPV of 60%).
- (5) Other anaphylactic shock including drugs (ICD-9-CM codes 995.0 to 995.3; PPV of 100%).
- (6) Shock due to anesthesia (ICD-9-CM code 995.4; PPV of 100%).

In this study, we applied those six previously validated codes for ADR detection as a simple and fast methodology,¹⁵ in a nationwide study using administrative databases, through a simple query to detect ADR episodes. We excluded repeated cases on the basis of episode number, hospital, birthday date, sex, year, ward, and hospitalization date and time.

Our main outcome was ADR detection. Secondary outcomes were the following: ADR related to admission (ADR_{Ad}) versus ADR during hospitalization period (ADR_{In}), age, sex, admission diagnosis, other diagnoses, hospital length of stay, and year (we aimed to assess trends in ADRs from 2000 to 2009).

Spontaneous reporting

The number of spontaneous reporting of ADRs in hospitalized patients from 2000 to 2009 was not available in the database and was obtained from Portuguese National Authority of Medicines and Health Products (INFARMED).

Statistical analysis

Statistical analyses regarding frequency of ADRs were carried out with the Chi-square test for categorical variables (or exact Fisher’s test whenever possible), Student’s *t*-test for normally distributed continuous variables and Mann–Whitney or Kruskal–Wallis for variables without normal distribution, using SPSS v20 (IBM Corp., Armonk, NY, USA). The *a priori* level of significance was $p < 0.05$. For the identification of a trend throughout the years, we performed a simple linear regression, using the ADR frequency as the dependent variable and the year as the independent variable.

RESULTS

Study population

The baseline characteristics of the study population ($n = 9\,271\,122$) are shown in Table 1, in comparison with the demographic characteristics of the subgroup of patients that suffered an ADR. The mean age of all hospitalized patients was 46 years, and 56% of the patients were female.

From 2000 to 2008, there was a slight increase in the number of hospitalizations in Portugal (in 2009 data refer only to first semester). There were 116 720 ADRs detected from 2000 to 2009, with a mean prevalence of 1.26%. There was an increase trend in the incidence of ADRs, statistically significant ($p < 0.001$) in linear regression analysis; in 2000, there were 8301 signals, whereas in 2008, there were 14 352 signals. Of the ADRs, 2.7% were associated with admissions, and 97.3% occurred during hospitalization.

Each alert of ADR identified through the database is characterized in Table 2.

The number of national spontaneous notifications of ADRs from 2000 to 2009 was 13 562, corresponding to a mean prevalence of 0.1%. In Table 3, we illustrate trends of hospitalization, spontaneous notifications, and ADRs identified in databases throughout time.

Risk factors of ADRs

In comparison with patients that did not suffer from an ADR, patients with ADRs were older ($p < 0.001$, Mann–Whitney test), had higher mean length of stay ($p < 0.001$, Mann–Whitney test), were more frequently

Table 1. Socio-demographic characteristics of study population compared with subgroup of patients that suffered from ADRs

Characteristic	General population		Subgroup of ADRs		<i>p</i> -value
	Value	% or SD	Value	% or SD	
Total number	9 271 122	NA	116 720	NA	NA
Mean age	46	28.04 SD	60	23.4 SD	<0.001
Female sex	5 152 684	56 %	63 186	54.1%	<0.0002
Death	410 253	4.4%	10 650	8.8%	<0.001
Mean hospital length of stay (days)	7.1	3.21 SD	13.7	22 SD	<0.001

Abbreviations: SD, standard deviation; NA, not applicable.

Table 2. Characterization of adverse drug reactions identified through the hospital database

ADR alerts	Total number	Type of ADRs		Mean age	Number of female gender (%)	Mean hospital length of stay	Number of deaths (%)
		ADR at admission	ADR during hospitalization				
E codes	90 260	252	90 008	62	49 628 (55.0%)	14	6906
Hypoglycemia	6684	1273	5411	55	3611 (54.0%)	10	1187
Neutropenia	17 035	1515	15 521	47	8140 (47.8%)	14	1968
Hepatitis	606	60	546	48	605 (99.8%)	6	4
Anaphylactic shock	2133	356	1777	47	1201 (56.3%)	12	0
Shock due to anesthesia	1	0	1	0	1(100%)	88	0

Table 3. Trends in hospitalizations, spontaneous reports and ADRs identified in databases

Year	Number of hospitalizations	Spontaneous reporting	ADRs identified by the database (%)	ADRs database—type of alert					
				E codes	Hypoglycemia	Neutropenia	Hepatitis	Anaphylactic shock	Shock due to anesthesia
2000	949 427	641	8301 (0.82%)	5750	829	1338	49	335	0
2001	959 895	1342	8769 (0.91%)	6184	699	1576	62	248	0
2002	973 328	1251	10 602 (1.1%)	8073	709	1573	92	155	0
2003	991 804	1097	12 371 (1.25%)	9853	731	1574	52	161	0
2004	982 627	1623	12 918 (1.31%)	10 423	727	1545	85	138	0
2005	1 013 770	1259	13 444 (1.33%)	9987	698	2443	86	230	0
2006	973 887	1284	13 778 (1.41%)	10 855	656	2002	69	195	1
2007	965 576	1424	14 744 (1.53%)	11 686	689	2042	48	279	0
2008	965 463	1603	14 325 (1.49%)	11 452	601	2000	44	255	0
2009*	495 345	2038	7440 (1.50%)	5997	345	942	19	137	0
Total	9 271 122	13 562	116 720 (1.26%)	90 260	6684	17 035	606	2133	1

Types of alerts identified in the databases are also identified.

*For the year of 2009, only the first semester data was available.

of the female sex ($p < 0.0002$, Fisher's exact test), and had a higher risk of death ($p < 0.001$, Fisher's exact test).

Additionally, we verified that several comorbidities (identified also through the use of diagnostic codes) were associated with a higher risk of developing an ADR: heart failure ($p < 0.0001$, Fisher's exact test), septicemia ($p < 0.0001$, Fisher's exact test), dysrhythmias ($p < 0.0001$, Fisher's exact test), hypotension ($p < 0.0001$, Fisher's exact test), cerebrovascular disease ($p < 0.0001$, Fisher's exact test), stroke ($p = 0.0000045$, Fisher's exact test), diabetes ($p < 0.0001$, Fisher's exact

test), ischemic heart disease ($p < 0.0001$, Fisher's exact test), malignancies ($p < 0.0001$, Fisher's exact test), and pneumonia ($p = 0.0000026$, Fisher's exact test).

DISCUSSION

To our knowledge, this was the first estimate of the frequency of ADRs in a nationwide level in Portugal. We identified 166 720 ADRs of 9 271 122 inpatients stays (prevalence of 1.26%); if we applied respective

PPV values (PPV values were estimated in the validation study¹⁵), this would detect 104 015 true ADRs.

We identified an increase in the number of hospitalizations from 2000 to 2009 (as expected along the evolution of the National Health Care) and in the number and percentage of ADRs. The reported increase in the frequency of ADRs is also expected, considering the higher number of drugs available, the tendency of prescribing multiple drugs per patient, improved register of clinical conditions in databases, improvement of clinical coding, and even population ageing. Each prescribing physician should consider the risk of ADRs carefully before prescribing an additional drug to a patient.

Our results were consistent with those presented in other studies that identified risk factors of ADRs, such as comorbidities,¹⁴ diabetes,²³ renal failure,²³ female sex,²⁴ and age.^{1,24} They were also consistent with the frequency of ADRs identified by previous studies that used administrative databases for a nationwide estimate: 0.89% in Spain,¹¹ 0.9% in England,²⁵ 1.83% in the Netherlands,¹² and 0.8% in Australia.²⁶ The Spanish study¹¹ identified a smaller frequency of ADRs, 0.89%, perhaps because the authors utilized solely E codes, in opposition to our work, in which we used E codes and other validated diagnostic codes. Whitstock and colleagues²⁶ utilized a methodology beyond databases, linking clinical trial data with administrative health data, but tested it solely for newly released drugs and older population in Australia, consequently identifying a smaller frequency of ADRs, 0.8%. Wu and colleagues²⁵ searched several codes using the ICD-10 coding system, but estimated only the frequency of ADRs associated with hospital admission, which might explain the slightly inferior estimate in comparison with us, 0.9%. However, a higher frequency of ADRs was found by Hooft *et al.*¹² (1.83%) although they were only referring to ADRs associated with hospital admission (including ADRs that directly caused admissions and ADRs that did not cause but were present at admission) and although they only searched E codes. This higher estimate might be related to the fact that in the Netherlands (unlike Portugal and many other countries), the coding is independent of reimbursement;¹² therefore, there is no tendency to omit a “negative” code (which could lead to bias, usually known as “coding creep”²⁷).

The strengths of our study include our comprehensive database, which contains data from all hospitalizations in every acute care public hospital in Portugal within almost a decade. Another strength comes from the validation study previously performed,¹⁵ which has enabled us to add measures of error to our estimate, identify diagnostic codes that may represent signals for ADRs other than “E” codes, and identify the error

associated with “E” codes (the PPV for “E” codes was just 95% because several drug-related errors were erroneously coded as ADRs). The database methodology has a far greater detection rate than spontaneous reporting (detecting only 12% of the ADRs identified by the database), which is perhaps the greatest advantage of this methodology considering the purpose for which it was built: to obtain a good detection rate with reasonable costs (affordable for continuous pharmacovigilance). Therefore, spontaneous reporting can be used for the identification of new ADRs, and the database methodology can be used for a fast and large-scale estimate of incidence of ADRs.

Limitations of our work are inherent to the use of administrative databases, which often contain incomplete or wrong information because of its purpose. If on one hand, reimbursement databases assure comprehensive data, on the other, they might lead to coding bias (“code creep”, in which coders select a different code to increase reimbursement to their hospital²⁷). It is not possible to estimate the error caused by these biases. Another limitation is related to the fact that we applied the PPV value of a small one-centered validation study to a large national database; for that, we had to assume that the population was the same. We could be inducing bias if the population is different. If we use the methodology of previous database studies (in which they assume that all “E” codes represent an ADR and simply search “E” codes), we would have 90 260 ADRs (“E” codes), with a prevalence of 0.97%, which is a prevalence somewhat similar to the one that we obtained. Nonetheless, we believe that this methodology is more comprehensive and enables us to identify codes that add information to “E” codes and therefore to identify ADRs previously undetected. Additionally, we suggest multi-centered validation studies in different countries to select specific diagnostic codes associated with ADRs within each country and to build an estimate of error associated with each methodology.

Although the database methodology allows us to obtain a higher frequency of ADRs than spontaneous reporting, it is low in comparison with prospective monitoring and intensive monitoring (the main methodologies used in the included studies of the systematic review that estimated a mean of 16.88% of ADRs in hospitalized patients⁴). Nevertheless, these methodologies have the highest costs, making them impossible to use in a large-scale study such as our own.

Additionally, several studies report that different methods tend to identify different types of ADRs,^{15,16} and many authors suggest the simultaneous use of several methodologies to enhance ADR detection.^{28,29}

Therefore, future studies should include a complete estimate and characterization of ADRs, nationwide, prospectively to allow the use of different methods complementarily, with causality assessment of each ADR and ideally with cost analysis.

CONCLUSION

In conclusion, this is the first nationwide estimate of ADRs in Portugal throughout almost a decade: a mean prevalence of 1.26% of ADRs (2.7% of which were associated with admission) was detected. The database methodology has flaws and underestimates the real number of ADRs, but it should be used continuously as a methodology that can complement (but not replace) other pharmacovigilance methodologies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Spontaneous reporting is the only pharmacovigilance method continuously used in Portugal. This method grossly underestimates the number of adverse drug reactions (ADRs). Chart review, computerized methods, and intensive monitoring are too resource-consuming to be utilized in a nationwide level in Portugal.
- Using hospital administrative databases, we have built a nationwide estimate of ADRs in Portuguese hospitals, from 2000 to 2009. We detected 116 720 ADRs (97.3% of which occurred during hospitalization and 2.7% were the cause of admission), with a prevalence of 1.26% of all hospitalizations. Throughout this time, there were only 13 562 spontaneous reports of ADRs in Portugal (prevalence of 0.1%).
- Databases are not widely used as a pharmacovigilance methodology, but have many potential advantages, such as a moderate ADR detection rate and relatively low resources needed.

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