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Research Article

RESOURCE-SPARING COMPUTERIZED TOOL FOR DETECTION OF ADVERSE DRUG REACTIONS

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Abstract

Aims: To develop and validate a computerized methodology of adverse drug reactions (ADRs) detection that could assist manual chart review (CR), with low costs of implementation and maintenance.

Methods: A computerized clinical decision support tool (CT) was built, as well as drug databases and algorithms that allowed to identifying ADRs from few input data obtained through chart review. A retrospective study of 118 random patients was performed for validation.

Results: CT detected 65 ADRs in 29 patients (versus 12 ADRs in 12 patients in CR) with low resources needed (29.5 versus 69 person-hours), allowing to identify a prevalence of 24.8% ADRs (versus 10.2%). CT suggested ADRs and also described frequent ADRs for each drug (allowing inexperienced reviewers to identify previously unsuspected ADR signs).

Conclusions: CT is a promising Pharmacovigilance methodology, particularly at a time of world economic crisis, since it allows continuous surveillance with five times greater detection and half the resources needed by CR. It may be of use in hospitals without electronic records.

Keywords: adverse drug reactions, pharmacovigilance, chart review, computers.

Introduction:

Adverse drug reactions (ADRs) are frequent, costly, often preventable and are responsible for many deaths in hospitalized patients. ADRs are among the most frequent causes of death in developed countries[1]. It is estimated that they occur in a mean of 16.88% of patients during hospitalization (CI95%:13.56-20.21)[2] and that they are associated with an overall median of 5.3% of hospital admissions (interquartile range 2.7-9.0%)[3]. The costs of

drug-related problems (which include ADRs) may be higher than the total cost of cardiovascular or diabetes care[4]; while the mean additional cost attributable to an ADR is estimated to be US$3332[5].

Consequently, the identification and ultimately the prevention of ADRs is one of the few ways to simultaneously increase quality in Health Care and decrease its costs. There are several methods of ADR identification[6]. Manual chart review has good detection rates and is considered by some as the "gold standard" to identify adverse drug reactions in health care organizations[7], but it is time and personnel costly: some studies estimated a cost of 55 person-hours per week[8]. This makes it impossible to use as a methodology of continuous detection of ADRs in all hospitalized patients.

On the other hand, computerized surveillance is increasingly appealing[9,10]. Many different strategies of computerized Pharmacovigilance were assessed in a recent systematic review[11], with different levels of complexity in implementation and integration, and consequently with a variety of costs in acquisition and maintenance. However, this type of surveillance requires that all patient information is computerized, which is not possible in many hospitals, such as ours.

Therefore, our purpose was to design and validate a computerized tool for ADR detection that would assist chart review, simultaneously increasing detection and decreasing associated costs for the detection of ADRs. Since we live in an era of social and economic crisis, we wanted to build a program that would have low costs of implementation and maintenance, and that did not require health system integration.

Materials and methods

Study setting

A retrospective study was performed at Central University Hospital of Coimbra, Portugal. From all hospitalized patients in 2010, we selected a random sample of 118 patients to perform manual chart review and computerized assessment, independently, to validate our methodology and to compare: number and types of ADRs identified, risk factors for ADRs, and time spent in each methodology. The study was approved by hospital's institutional review board.

Definition of ADR

World Health Organization's definition of an ADR was applied: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy"[12]. Previous works utilized

computerized systems to identify adverse drug events ("an injury resulting from medical intervention related to a drug")[13-16], but we aimed to assess specifically ADRs.

Outcome assessment

The primary outcome was frequency of ADRs (including ADRs that led to admission, ADR_{Ad}, and ADRs that occurred during hospitalization, ADR_{In}). We assessed: number of ADRs, number of patients that suffered from an ADR, number of patients exposed to drugs, length of hospital stay. We registered number of ADRs computer-detected and number of ADRs computer-undetected. Secondary outcomes included: particular diagnosis, ward, age, gender, length of hospital stay, number and name of drugs administered to each patient, and other clinical data as detailed below.

Manual chart review

From each patient, chart was reviewed, including: discharge note, diaries, all drugs administered, laboratory and coding data, as well as every aspect that could constitute a symptom or sign of an ADR, even if not detected previously by responsible medical team. For complete validation, all cases were reviewed (not just the cases with a positive computer alert).

All ADRs were registered, described and classified according to WHO's causality assessment[17], preventability (Schumock criteria[18]) and severity (Hartwig[19]). ADRs classified as conditional or unlikely were excluded from the analysis (but registered). Associated drugs (and all administered) were registered. Reviewer also registered if ADR was previously undetected, as well as age, gender, ward, hospitalization time, and other relevant clinical information.

Computerized system - Chart Helper

Considering the need of a costless computerized system, we built a program that did not require Health system integration. The main difficulty was to build manually databases with drug information in portuguese, since there were none available in our country that linked adverse drug reactions, their symptoms and signs to each drug. We used the Hospital Formulary[20], and the official list of portuguese ambulatory drugs, available in the site of INFARMED[21], the Portuguese Regulatory Authority of Drugs, to build a database with all drugs available in Portugal. We then built an ADR database with the 10 more frequent ADRs, all ADRs that were potentially fatal for each drug, and other clinically relevant ADRs for each drug according to INFARMED[21] and Meyler's side

effects of Drugs book[22]. We also added to that database: the symptoms of each ADR, signs, laboratorial alterations, diagnosis and compatible coding information (for that, we used also International Classification of Diseases 9th Revision, Clinical Modification: ICD-9-CM[23]).

We built a program, Chart Helper, with Visual Studio 2010, aiming for a simple and user-friendly interface with the reviewer. For each patient, the user of Chart Helper (the chart reviewer) registered age, gender, chart number, hospitalization and discharge dates (duration of hospital stay was automatically calculated), and diagnosis and procedures codes (from ICD-9-CM[23]). Some data must be input manually because in most of portuguese hospitals, not all patient data is computerized (most data is stored in paper records).

All drugs administered during hospitalization were also selected from a list by the reviewer, as well as relevant symptoms, signs and laboratorial alterations. The user could input symptoms and signs not previously present in the database, but detected in the chart review, therefore increasing overall detection of ADRs.

We intended to take advantage of two types of input data: first, already existing coding and administrative data with useful clinical information, and second, manual chart review to identify symptoms or other alterations missing in coding data but detected by the user. The program tool used all of these input data, our ADR databases and some algorithms to generate two types of results:

1. Suggested ADR(s) for that patient. The program detected if a symptom, sign, diagnostic code or laboratorial alteration that the patient had, was compatible with an ADR of any of the drugs administered to him. Respective drug, ADR and alert were specified by program as a decision support tool, and then the reviewer would decide if the suggested ADR really occurred and would classify it according to WHO's causality assessment[17] (available in the program): certain, probable/likely, possible, conditional/unclassified, inaccessible /unclassifiable.
2. Frequent ADRs for each drug. For each drug administered to that patient, a list of frequent (and of fatal) ADRs was available for consultation by the user. Therefore, this memory support tool would allow less experienced users to pay more attention to certain signs and symptoms throughout the chart that could indicate an undiagnosed ADR of a drug administered to that patient.

All data (input and result data) were automatically stored in a database by Chart Helper for further analysis. Conditional and unlikely ADRs were excluded from our analysis (but also automatically registered in the

database).

Data analysis

We calculated sample size (to identify ADR prevalence of 10%) using an online calculator (100 patients were necessary)[24]. Statistical analyses were done with the Chi-square test for categorical variables (or Fisher's exact test whenever possible), Student's t-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis when dealing with variables without normal distribution, using SPSS v20. The *a priori* level of significance for all comparisons was $p<0.05$.

Results

Characterization of sample

From the random sample of 118 patients hospitalized in 2010, mean participant age was 60 years. 40.7% were female.

Table-1: Describes socio-demographic participants' characteristics.

Characteristics	***Number***	***Relative frequency (%)***
Female gender	48	40.7 %
Age *(sd: standard deviation)*	Mean: 60 years	sd: 20
Mean number of days hospitalized *(sd)*	10.1	sd: 20.0
Mean number of drugs administered per patient	5.2	sd: 3.8
Wards more frequently occupied		
Surgery	18	15.25 %
Urology	14	11.86 %
Medicine	10	8.48 %

Demographic characteristics of participants

Chart review

Chart review allowed the identification of 12 ADRs in 12 patients, one of them fatal (due to infection after the use of chemotherapy). 117 patients were exposed to drugs, thus ADR prevalence was 10.2% (12/117).

The most frequent ADRs were hyperkalemia (16.7% of all ADRs) and warfarin leading to International Normalized Ratio levels that led to surgery delay (16.7%).

Systems more frequently affected were hematologic (33.3%), renal (25%) and cardiovascular (16.7%). Drugs more frequently involved were non steroidal anti-inflammatory drugs (NSAIDs, 25%), antibiotics (16.7%), anticoagulants (16.7%) and diuretics (16.7%).

Five ADRs were preventable (according to Schumok's classification). There were 3 severe ADRs, 5 moderate and 4 mild (Hartwig classification). Twenty-four adverse events were identified.

Patients with ADRs were exposed to a higher number of drugs than patients without ADRs (Mann-Whitney test, p=0.001); there was no statistically significant difference in age, hospitalization time, number of days in intensive care units, or gender (Fisher's exact test).

Computerized clinical decision tool

1. Program

Chart helper, the program built, requires that some data are entered as the chart review is performed, as detailed in the Methods section and illustrated in *figure 1a*. Afterwards, according to each patient, two types of results are generated: list of frequent ADRs for drugs administered and list of suggested ADRs (*figure 1b and 1c*).

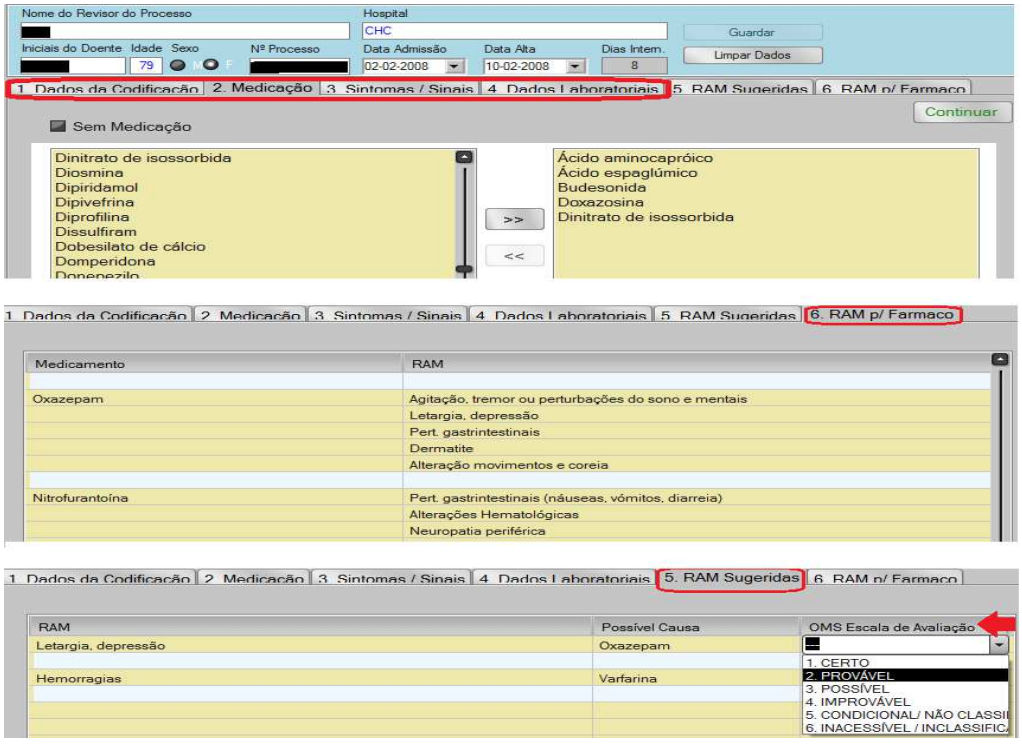

Figure-1: Some examples of Chart Helper interface.

1a. Data input (above)

Some of the data that must be entered by reviewer (red square): coding data (if available), drug names administered to that patient, symptoms and signs and laboratorial data. **1b. List of ADRs (middle)** List of frequent and fatal ADRs for the drugs administered to that patient, working as a "memory enhancer". This allows less experienced reviewers to pay more attention to certain symptoms (or other alterations) that may represent an ADR in that patient. **1c Suggested ADRs (below)** If the patient had symptoms, signs, codes or any laboratorial alteration that is compatible of an ADR to a drug administered to that patient, the program suggests an ADR and respective drug (an ADR alert). In the example above, there are 2 ADRs suggested for that patient (hemorrhage by warfarin and lethargy or depression by oxazepam). These must be classified according to WHO's causality of ADRs (red arrow) by the reviewer.

2. ADR detection

Sixty-five ADRs (unlikely ADRs were excluded) were identified by computerized system in 29 patients, leading to a prevalence of ADRs of 24.8% (29/117) and including 17 ADRs certain or probable (prevalence of 14.5%). Two ADRs were undetected by computer (both with warfarin leading to INR levels that caused surgery delay). On the other hand, 53 ADRs were only detected by computerized system (manual chart review did not detect them), all of which were validated by further manual chart review to identify if they were true ADRs. From 81 alerts, 65 were true ADRs (positive predictive value of 80%).

Most frequent ADRs detected by computer were laboratorial alterations (24.29% of ADRs), agitation (14.63%) and diarrhea or constipation (13.82%). Systems more frequently affected were: hematologic (31.71%), gastrointestinal (26.02%) and renal (16.23%).

The drugs more frequently involved were: NSAIDs (15.45%), antihypertensives (14.63%) and antidepressants or antianxiety agents (14.63%).

Discussion

Our work allowed us to develop and validate a computerized methodology easy and fast to apply, and nearly costless to our National Health System. This effective computerized methodology detected five times more ADRs (65 versus 12 ADRs) than manual chart review with approximately half the resources (69 versus 29.5 person-hours).

Our approach is new, because we started from chart review with integrated data (instead of separate laboratorial data or other indicators from health systems), and developed databases and algorithms to create automation, while leaving the ultimate decision of ADR causality assessment to the health professional reviewer (the user of the system), with a simple user-friendly interface.

Methodology comparison

Table-2: Presents the comparison between manual chart review and computerized methodology.

	Manual chart review	**Computerized method**
Total number of ADRs (excluding "unlikely")	12	65
Patients with ADR	12	29
ADR prevalence	10.2%	24.8%
Total number of person-hours spent	69	29.5
Fatal ADRs	1	1
ADRs previously diagnosed in clinical history	3	3
ADRs previously coded (E code)	1	1
Number of adverse events (including ADR)	24	77
Number of ADR associated with admission *versus* ADR that occurred during hospitalization	2 *vs* 10	2 *vs* 63
WHO's causality assessment		
Certain	4	7
Probable / likely	5	15
Possible	3	43
Unlikely or conditional/unclassified or inaccessible /unclassifiable	0	31

Comparison of ADR detection by each methodology.

Strengths of this study

We believe our work has several strengths. The greatest strength of this study lies in its results, showing a clear superiority over manual chart review, with a prevalence of ADRs identified of 24.8%.

Second, the low resources required, much lower than manual chart review, allows the application of this method as a continuous method of Pharmacovigilance, which was not previously possible for chart review. Even in small hospitals where it isn't feasible to implement complex computerized systems, ADR monitoring can be improved through this resource sparing system. In fact, we believe that this solution might be interesting for those hospitals in which patient information is not computerized.

Third, this program elaborates a list of frequent and fatal ADRs per drugs administered to each patient, allowing even inexperienced reviewers to detect symptoms (or signs, laboratorial data or codes) that may constitute an ADR, working as a supporting memory tool.

Fourth, it does not need *a posteriori* validation, since it integrates validation and causality assessment performed by a reviewer during each assessment.

Last, unlike the previously published studies that reviewed only charts of ADR alerts, we intended to identify also ADRs undetected by this computerized methodology and to perform a true validation, therefore we performed chart review to all patients.

Limitations of this work and suggestions for future work

This work has also several limitations. Further testing and validation should be performed, namely in other hospitals, other countries, and with a higher number of patients. This validation study had a retrospective design, but it would be interesting to test this computerized approach prospectively, to enhance ADRs detection and treatment. It is a resource-sparing tool because it has a low level of automation, however, it would be interesting to integrate it in the health system and to add further automation: although the costs would rise exponentially, we believe that interesting results would be provided. This program also allows us to compare different reviewers, therefore a study in which we compare ADR detection with this computerized system among different reviewers could reveal subjectivity factors unknown so far.

Finally, although one of the biggest difficulties was building it in portuguese language, translation into English (and the adaptation of all databases of drugs and ADRs) for validation in other countries is relatively easy and could also show interesting results.

Conclusions

This computerized clinical decision support tool for ADR detection might be an useful Pharmacovigilance

methodology in the future, particularly at a time of world economic crisis, since it allows continuous surveillance with a higher ADR detection (five times greater) and half the resources needed by manual chart review. It is a promising method that requires further studies.

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