



ORIGINALES

Comparison of the traditional pharmaceutical validation method *versus* an assisted pharmaceutical validation in hospitalized patients

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Abstract

Objective: To analyze pharmaceutical interventions that have been carried out with the support of an automated system for validation of treatments vs. the traditional method without computer support.

Method: The automated program, ALTOMEDICAMENTOS® version 0, has 925 052 data with information regarding approximately 20 000 medicines, analyzing doses, administration routes, number of days with such a treatment, dosing in renal and liver failure, interactions control, similar drugs, and enteral medicines. During eight days, in four different hospitals (high complexity with over 1 000 beds, 400-bed intermediate, geriatric and monographic), the same patients and treatments were analyzed using both systems.

Results: 3,490 patients were analyzed, with 42 155 different treatments. 238 interventions were performed using the traditional system (interventions 0.56% / possible interventions) vs. 580 (1.38%) with the automated one. Very significant pharmaceutical interventions were 0.14% vs. 0.46%; significant was 0.38% vs. 0.90%; non-significant was 0.05% vs. 0.01%, respectively. If both systems are simultaneously used, interventions are performed in 1.85% vs. 0.56% with just the traditional system. Using only the traditional model, 30.5% of the possible interventions are detected, whereas without manual review and only the automated one, 84% of the possible interventions are detected.

Comparación entre el método de validación farmacéutica tradicional *versus* validación farmacéutica asistida en pacientes hospitalizados

Resumen

Objetivo: Analizar las intervenciones farmacéuticas realizadas con el apoyo de un sistema automático de validación de tratamientos vs. el método tradicional sin apoyo informático.

Metodos: El programa automatizado, ALTOMEDICAMENTOS® version 0, cuenta con 925.052 celdas con información de aproximadamente 20.000 medicamentos, analizando dosis, vías de administración, días de tratamiento, dosificación en insuficiencia renal y hepática, control de interacciones, de medicamentos semejantes y de medicamentos por vía enteral. Durante ocho días distribuidos en cuatro hospitales diferentes (alta complejidad con más de 1.000 camas, intermedio de 400 camas, geriátrico y monográfico), los mismos pacientes y tratamientos se analizaron mediante los dos sistemas.

Resultados: Se han analizado 3.490 pacientes diferentes con 42.155 tratamientos. Por el sistema tradicional se han realizado 238 intervenciones (0,56% intervenciones/posibles intervenciones) vs. 580 (1,38%) con el automatizado. Las intervenciones farmacéuticas muy significativas fueron 0,14 vs. 0,46%, las significativas 0,38 vs. 0,90%, las no significativas 0,05 vs. 0,01%. Las intervenciones fueron del 1,85% al utilizar los dos sistemas vs. 0.56% usando solo el sistema tradicional. El sistema tradicional detectó el 30,5% de las posibles intervenciones, sin embargo con el sistema automático se detectaron el 84% de dichas intervenciones.

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Recibido el 28 de septiembre de 2015; aceptado el 19 de febrero de 2016.

DOI: 10.7399/fh.2016.40.3.9960



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Conclusions: The automated system increases pharmaceutical interventions between 2.43 to 3.64 times. According to the results of this study the traditional validation system needs to be revised relying on automated systems. The automated program works correctly in different hospitals.

KEYWORDS

Automation; Medication review; Decision support; Drug prescriptions; Medications errors; Clinical alarms

Farm Hosp. 2016;40(3):165-171

Introduction

During the late 20th century, validation of the medical prescription in hospitalized patients was performed by a pharmacist who analyzed the prescribed treatments for a patient using professional criteria and, in a few cases, using computerized help systems in order to improve the use of medicines. Nowadays, this is changing, towards a greater pharmaceutical integration in the medical team using computerized physician order entry¹.

In the UK, medical errors constitute approximately 20% of medical malpractice claims, and associated costs could be higher than 750 million pounds a year. It is advisable to check the dose, frequency, drug administration route, as well as drug interactions, especially in children. This also indicates that patients require monitoring and regular medication review².

In the EMOPEM Study (Multicenter Study for the Prevention of Medication Errors), medication errors were analyzed in 26 Spanish hospitals over a four year period: the error rate was higher for non-automated prescriptions than for automated prescriptions. The risk of medication errors by non-automated prescriptions in the four year study was 2.4; 3.38; 6.01 and 14.97 times greater than when the prescription was automated³.

In the report "To Err is Human", healthcare costs (direct medical costs) of adverse events comprise about 4% of total health expenditures in the United States⁴. However, in Utah's case the report indicates it is 5%. In both cases, about half of the healthcare costs were due to preventable medical errors⁵. In a study by the FDA evaluating fatal medication errors from 1993-1998, the most common errors, in 41% of cases were caused by the administration of an inadequate dose or the wrong drug⁶.

In Spain, according to an ENEAS study, the percentage of medication errors in specialized care was 3%⁷, while in primary care, according to the APEAS study⁸, 5.38% of errors were caused by the misuse of drugs.

Medication errors are unfortunately very high, so it is necessary to implement automated systems to decrease errors, such as computer-assisted prescription systems, which may help on prescriptions based on patient's clinical data, or automated systems to assist pharmaceutical validation.

Conclusiones: La automatización multiplica entre 2,43 a 3,64 veces las intervenciones farmacéuticas. En base a los resultados de este estudio el sistema tradicional de validación debería ser modificado, apoyándose en sistemas automatizados. El programa automático funciona en diferentes hospitales.

PALABRAS CLAVE

Automatización; Revisión de la medicación; Soporte de decisión; Prescripción de medicamentos; Errores de medicación; Alarmas clínicas

Farm Hosp. 2016;40(3):165-171

Currently, there are no available databases that review the individual profile of the 20,000 drugs marketed in Spain, although there are specific experiences of drugs included in hospitals formulary⁹ and pharmaceutical databases of drugs primarily marketed in the USA that analyze patients with renal failure or adverse events^{10,11}.

The ALTOMEDICAMENTOS[®] program is a database of relevant information about medications that can help the pharmacist in error detection and improve pharmaceutical treatments.

The aim of this study was to analyze the traditional pharmaceutical interventions validation system *versus* pharmaceutical interventions using the support of an automated system (ALTOMEDICAMENTOS[®] program) to control: 1) Dosage, as a medicine as well as active ingredient; by administration route and age (children, adults, elderly); 2) Alert days; 3) Administration routes for active ingredient and for medicines for human use; 4) Renal failure (creatinine value or not solely based on age); 5) Liver failure; 6) Interactions; 7) Therapeutic duplicity; 8) Enteral Drug administration and 9) Minimum required dose. Our hypothesis is that assisted is superior to traditional validation system in the number of interventions.

Methods

The project was carried out in several different types of hospitals so that the results would cover different types of treatments and subsequently be extrapolated to other hospitals: High complexity with over 1,000 beds, 400-bed General Hospital, Geriatric Hospital and Monographic Hospital. All participating hospitals used Farma-tools[®] software.

The design has been a cross over prospective study. All patients, whose treatment was computerized in unit dose, were analyzed, either by electronic prescription from the doctor or by transcription at the Pharmacy Department. The same patients, using the same treatments, were analyzed using both methods: traditional observational detection without automatic support *versus* decision-making support system ALTOMEDICAMENTOS[®]. The calculated sample size was 250 patients ($p < 0.05$ with an estimate of double effect between one branch and another), though, for an appropriate extrapolation

for different levels of care, patients of 8 non-continuous days were included, ie, separated in time, from the four different hospitals.

The primary variable consisted of the pharmaceutical interventions carried out with and without the support of an automated database and the statistical analysis was undertaken with a McNemar test.

ALTOMEDICAMENTOS® database, software version 0 contains:

- 549,521 data with information on 26,133 drugs regarding high dosage for adults and children (from infants to 12 years old)
- 105,063 data with the administration route dosage of each of the active ingredients marketed in Spain, with the doses in different units of measurement according to prescriptions for such active ingredients.
- 4,279 data with information regarding dosage in renal failure for 1,069 active ingredients.
- 7,300 data with information regarding a prolonged prescription depending on the active ingredient and route administration prescribed
- 198,029 data with information about marketed drugs and their active ingredients.
- 21,505 data with information from drug interactions.
- 953 data with information from 237 active ingredients in liver failure dosage.
- 38,402 data with information on 5,847 drugs that cannot be administered via enteral tubes or that are to be administered with caution, given the characteristics of the drug (pharmaceutical specialty).

The ALTOMEDICAMENTOS® program has been created by a hospital pharmacist, who is responsible for continuous updating. It is a complex program that contains high amounts of data to assist in identifying problems and errors in patient treatment prescription, the information of this database has been obtained from different primary, secondary, and tertiary sources:

I) High or maximum dose control

The program consists of a database with high or maximum authorized dosage for adults based on the technical data approved by the AEMPS (Spanish Agency for Medicines and Health Products) or by the EMA (European Medicines Agency); although for old drugs, for which this information does not exist, the medicine is analyzed in terms of the approved prospectus. If daily care needs indicate that values expressed above are not up to date, then values in clinical practice are used.

Elevated pediatric doses were determined based on pediatric literature, since the data sheets do not always contain this information or are not up to date for this group of patients. The following information sources were used: British National Formulary for Children¹², Pediatric Dosage Handbook¹³, and the technical specifications of the AEMPS and EMA.

In addition to Kg per patient weight dosage, the dose for the 80th percentile of weight for each age group from neonates to the age of 12 was calculated. Therefore if there is no registered child weight (currently there is no Spanish healthcare system that requires a child's weight to be indicated when prescribing a medication) the program will detect the error by having the possibility to calculate the high dose for the 80th percentile of children of that age. The 80th percentile was chosen to avoid excessive alerts that would occur with a lower percentile.

Dosage control is performed both by medicines for human use, as well as by active ingredient depending on their administration route.

II) Alert Days control

Alert Days control will detect a treatment prescribed during a long period of time (iv antibiotics, methotrexate, vaccines ...), and therefore allows for the detection of errors as well as follow-up therapy.

III) Administration route control

Administration routes of active ingredients as well as medicines for human use are analyzed for the recommended routes, with a warning if an undescribed administration route is used.

IV) Renal Failure control

Renal Failure control examines the dosage of approximately 1,000 active ingredients according to the degree of patient renal function.

It also calculates the real or estimated rate of glomerular filtration (in case of unavailability of creatinine) of all patients. The estimate is made by choosing between different kinds of mathematical formulas, although CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)¹⁴, Cockcroft-Gault and MDRD4 (Dialysis Renal Disease Modification 4)¹⁵ are usually the most standard used.

V) Liver failure control

Over 200 active ingredients, that might be modified in liver failure, are analyzed cross-checking them with bilirubin values; the Child-Pugh¹⁶ score of the patients could also be used.

VI) Interaction control

Clinically relevant interactions of patients are analyzed, using information from relevant interactions from Stocley 2013¹⁷, top 100 interactions 2012¹⁸ and data sheets or recommendations of regulatory agencies (Competent Authority, EMA). The results are classified as significant and very significant.

VII) Therapeutic duplicity control

Therapeutic drug duplicity is analyzed by active ingredient, detecting whether a patient has similar active ingredients within the fourth level of the ATC classification (Anatomical Therapeutic Chemical Classification System)¹⁹.

VIII) Enteral medicines control

This control analyses medicines that must not be administered via an enteral tube: around 5,800 pharmaceutical products should not be administered through an enteral tube or, if administration is necessary, with special precautions

IX) Minimum dose control

When a low dose is prescribed, either in adults or pediatrics, a warning will appear.

The procedure undergone was to analyze the same patients and treatments using both systems: first, a manual treatment review is performed and then, late in the morning, the automatic control one. This is done so to avoid knowing beforehand which interventions are alerted by the ALTOMEDICAMENTOS® program. All interventions were carried out by the same pharmacist residents, and staff pharmacists who usually review medical prescriptions. One limitation to bear in mind is that during the analysis of interventions, the automated system might obtain worse results, since there might be errors that would have been previously modified with the manual system and have been detected and corrected before that of automated system. As such, prior manual interventions that led to changes in treatment and subsequently would have appeared in automatic control, were analyzed independently. To correct this error, the information was expressed as it was, and moreover as if prior to the automated control, the treatment would not have been modified.

Interventions were classified according to the significance code:

- “very significant”: Intervention to increase the effectiveness and / or toxicity and provide an important increase in the quality of care;
- “Significant”: Intervention to improve patient care and provide an increase in the quality of care;
- “Indifferent or negligible”: Intervention that does not produce changes in patient care²⁰.

Results

3,490 patients with 42,155 different pharmaceutical treatments were analyzed in a non-continuous 8-day period. The same treatments of patients were reviewed using both methods: 238 pharmaceutical interventions (0.56%=interventions / possible interventions) were performed with the traditional observation system; 160 (0.38%) significant, 58 (0.14%) very significant and 20 (0.05%) did not produce clinical significance in the patient although some may be efficient (therapeutic exchange, for example).

With the support of the automated system, there were 580 pharmaceutical interventions (1.38%): 378 (0.90%) significant, 196 (0.46%) very significant and 6 (0.01%) not clinically significant. Some possible interventions of the ALTOMEDICAMENTOS® program were initially lost because the pharmacist had previously changed the treatment, but this was corrected by calculating the total interventions.

Total interventions with the ALTOMEDICAMENTOS® program were calculated taking into account those that were identified and modified by the pharmacist prior to the automated review. In total there were 655 interventions (1.55%); 420 (1%) significant, 229 (0.54%) very significant and 6 (0.01%) were not clinically significant.

Given the 780 interventions performed, 38 alerts matched in both the automated and manual review. If both the traditional and automated systems are used, the interventions undertaken by the pharmacist are multiplied by 3.27; increasing from 238 interventions through traditional observation to 780 in combination. If we

Table 1. Percentage of interventions per possible interventions

42155 possible interventions	Traditional System		Automated System		McNemar Tests	Difference (IC)
	interventions	%	interventions	%		
Total interventions	238	0,56	580	1,38	p = 0.0000	0,81 (0,68-0,94)
Very significant interventions	58	0,14	196	0,46	p = 0.0000	0,33 (0,25-0,41)
Significant interventions	160	0,38	378	0,90	p = 0.0000	0,52 (0,4-0,63)
Non-significant interventions	20	0,05	6	0,01	p = 0.006	0,03 (0,01-0,06)

Bhapkar Test p = 0.0000, McNemar Test for directional change p = 0.0000

compare only the type of interventions that the program makes, eliminating the therapeutic exchanges or those due to manual prescription, allergies..., the interventions increase from 180 to 655. In our case interventions multiplied by 3.64.

Different interventions regarding the possible situations that were analyzed are presented in tables 1-4.

To summarize, on the basis of very significant or significant interventions, the differences between manual

and automated procedures of ALTOMEDICAMENTOS® program were statistically significant in favor of the automated system. Only the non-clinically significant interventions were somewhat greater on some occasions with the traditional method, mainly because the ALTOMEDICAMENTOS® program does not perform therapeutic exchanges.

The automation with the ALTOMEDICAMENTOS® program multiplies pharmaceutical interventions between

Table 2. Percentage of interventions per possible interventions adding those that would have been automatically detected

42155 possible interventions	Traditional System		Automated System		McNemar Tests	Difference (IC)
	interventions	%	interventions	%		
Total interventions	238	0,56	655	1,55	p = 0.0000	0,99 (0,87-1,11)
Very significant interventions	58	0,14	229	0,54	p = 0.0000	0,41 (0,33-0,48)
Significant interventions	160	0,38	420	1,00	p = 0.0000	0,62 (0,51-0,72)
Non-significant interventions	20	0,05	6	0,01	p = 0.006	0,03 (0,01-0,06)

Bhapkar Test p = 0.0000, McNemar Test for directional change p = 0.0000

Table 3. Percentage of interventions per possible interventions, comparing only those interventions analyzed by the program: no manual prescriptions, exchange therapy or allergies

42155 possible interventions	Traditional System		Automated System		McNemar Tests	Difference (IC)
	interventions	%	interventions	%		
Total interventions	180	0,43	655	1,55	p = 0.0000	1,13 (1,02-1,25)
Very significant interventions	54	0,13	229	0,54	p = 0.0000	0,42 (0,34-0,49)
Significant interventions	122	0,29	420	1,00	p = 0.0000	0,71 (0,6-0,81)
Non-significant interventions	1	0,00	6	0,01	p=0.1250	0,01 (0-0,03)

Bhapkar Test p = 0.0000, McNemar Test for directional change p = 0.0000

Table 4. Percentage of interventions per possible interventions if the traditional system and automated system is used together verses use of just the traditional system

42155 possible interventions	Traditional System		Automated System		McNemar Tests	Difference (IC)
	interventions	%	interventions	%		
Total interventions	238	0,56	780	1,85	p = 0.0000	1,29 (1,18-1,4)
Very significant interventions	58	0,14	246	0,58	p = 0.0000	0,45 (0,37-0,52)
Significant interventions	160	0,38	508	1,21	p = 0.0000	0,83 (0,73-0,92)
Non-significant interventions	20	0,05	26	0,06	p=0.0313	0,01 (0-0,03)

Bhapkar Test p = 0.0000, McNemar Test for directional change p = 0.0000

2.43 and 3.64 times, thus reducing medication errors and improving treatment safety and quality of care.

Using the traditional method, 30.5% of the possible interventions were detected. Using the automated review alone, with no manual review, 84% of the possible interventions were detected.

Discussion

The Preamble of the WHO Collaborating Centre for Patient Safety Solutions²¹ defines Patient Safety Solutions as: "Every system design or intervention that has demonstrated the ability to prevent or mitigate harm to the patient, from health care processes". This paper considers the implementation of automated systems to reduce the potential for medical errors, wherever feasible. In the pharmaceutical field, computer software programs have been designed to either help prescribers or to support clinical decisions regarding laboratory values or other clinical situations⁹⁻¹¹.

According to the report "Evolution Implementation of Safe Practices Regarding Drug Use in Spanish Hospitals" (2007-2011)²², certain key practices are being implemented in order to minimize medication errors, such as the incorporation of new technologies in information and communication, electronic prescription systems, decision support for clinical decisions, and electronic record management. In this report changes in electronic prescribing percentages (31.7% in 2007 to 60.3% in 2011) are shown; the availability of updates and support systems to electronic prescription or, if hospitals do not have it, the use of preprinted prescriptions (25.8% to 45.5%). They also indicate a wider incorporation in hospitals of these new technologies, which have proven to be very effective in reducing medication errors. The change in alerts for health professionals regarding overdosing and under-dosing of all high-risk medications increased from 31.4% to 40.5%, although this section refers only to high-risk medications, not all prescribed medications, so it is necessary to advance in controlling all the medication prescribed to the patient. These data imply that given the computerization of treatments, it is feasible to work in a high percentage of hospitals with automatic validation support systems for medical treatments.

The traditional review system by treatment observation must be modified to improve efficiency. In our case, the differences between the traditional system and the result of an automated pharmaceutical validation support system shows particularly notable differences, multiplying pharmaceutical interventions between 2.43 to 3.64 times, and thus preventing adverse events related to medications. These important differences may be due to the service overload inherent in the traditional model of reviewing hundreds or thousands of treatments in a short amount of time. In addition, the time spent by the pharmacist on prescription control is less than that spent

by the traditional method, though this time has not yet been measured in the traditional method. The automated system spent 6 min and 44 sec to undergo such control on 3,584 treatment from 320 patients.

Traditional treatment control made by a pharmacist based only on their knowledge to validate it, may be greatly improved with technological resources, and is not in line with the times, in which automated systems can provide improvements in patient treatment. This does not imply that pharmacists are no longer an added value, since they are able to detect errors or undertake improvements that are not automatically detected, as well as eliminate the non-significant alerts that at any time could cause fatigue alert in the prescriber.

Therefore, Version 1 of the ALTOMEDICAMENTOS® program has been designed to classify alerts between particularly important and less important. Such a feature may help to increase the efficiency of the pharmacist. This is a simple tool which can detect a large number of alarms and also generates documented recommendations, as in the case of dosage for renal failure patients.

The ALTOMEDICAMENTOS® system can also analyze the treatment of thousands of patients in health care residences, specific types of patients across the health area via the prescription process: elderly, children, patients with kidney or liver failure, and even expand up to the entire general population of our area. This opens up new ways of working that may develop a new professional approach to hospital pharmacy in the future through automated validation systems and follow-up with patients in their homes through the prescription of their medicines.

Pharmacy Services must be prepared for the fourth industrial revolution which is expected to take place shortly, with the development of work integration systems between machines and humans. It seems reasonable to start adapting to changes before they occur, by incorporating tools that clearly improve our efficiency.

Authors such as Bindoff et al have developed an automated system to improve the identification of drug-related problems. The program designed also found significantly more potential problems associated to prescriptions than pharmacists did. They conclude that automatic systems should help pharmacists in providing medication reviews to improve their clinical skills and time management, and improving their ability to contribute to the quality in the use of medicines²³.

Kuperman et al. discuss the complex process of prescribing and how errors in medication might lead to many injuries otherwise preventable: The paper differentiates between supporting basic clinical decision that would include checking for allergies to medicines, the basic orientation of the dosage, decisions regarding medications to be included in the prescription form, checking the therapeutic duplication, and medicine interactions; and assistance for advanced decisions including kidney

failure and geriatric patients dosage support, laboratory tests related to medication, the use of medicines in pregnancy, and drug contraindications. Assistance to the clinical decision in medication management is recommended to improve patient safety and decrease associated costs²⁴.

In our case, if we focus on the capability of detection using only the traditional model, 30.5% of possible interventions were detected whereas 69.5% (an excessively high percentage) went unnoticed; however without manual review and with the automated review alone, 84% of the possible interventions were detected and only 16% went unnoticed. The results suggest the urgent need to implement automated systems in treatment validation processes. Furthermore, this would also prevent discrepancies on pharmacists' performances when medical validation is done²⁵.

We may conclude with a comparison of both systems: the traditional pharmaceutical validation method is insufficient to ensure safety in patient therapy; therefore it is necessary to support the current system with automated systems based upon hospital pharmacist skills. It should be noted that although the automatic system detects many more treatment failures or improvements, there are still errors that a pharmacist would detect which the automated system does not, and as such it is necessary to combine and integrate both systems. In our experience the ALTOMEDICAMENTOS® program has worked well in different hospitals with different working methods, although it would be necessary to eliminate the less efficient alerts currently showing up in the system to further improve program performance.

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