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Full Length Research Paper

Medication errors associated to notification of drug allergies: Effect of computerized order entry on their prevention

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Some adverse drug reactions are due to hypersensitivity reactions. Drug allergy related errors in a handwritten treatment compared with those in an electronic prescribing system, characteristics of reported allergies and economic impact were analyzed. Prospective, observational study was carried out in two phases. 1st Phase (manual prescriptions), errors due to drug allergy were detected when pharmacists registered allergies and then warned the physician. 2nd Phase (electronic prescription) physicians registered allergies and entered treatments in a computerized physician order entry. The program warned avoiding prescription error. 3,682 patients were included. In phase 1, the incidence of prescription errors due to drug allergy was 13.7%, while in phase 2, it was 1.5% (p<0.001). The main drugs involved were antimicrobials. 52 reported allergies (29.7%) were confirmed by a positive allergy test. Alternative therapy was needed in 45 cases (22%), of which 44.1% were due to betalactamic allergy. On average, the alternative antimicrobial treatment multiplied costs per day by 4.4 fold. Computerized physician order entry is an effective tool in preventing medication errors associated with drug allergy. It is important to verify the drug allergy, because incorrectly reported allergies lead to less efficient treatments.

Key words: Computerized prescription order entry; drug allergy; prescription errors.

INTRODUCTION

Adverse drug events are one of the leading causes of morbidity and mortality in hospitalized patients and increase hospital stays and sanitary costs. The World Health Organization (WHO) defines Adverse Drug Reaction (ADR) as a response which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function (Edwards et al., 2000). Studies over the past 15 years have demonstrated that ADRs affect 10-20% of hospitalized patients (Gomes et al., 2005).

According to The World Allergy Organization, more than 10% of all ADR are unpredictable drug hypersensitivity reactions. Both, under-diagnosis due to under-reporting and over-diagnosis due to the over-use

Abreviations list

5-HT3: 5-hydroxtryptamine; ACEI: Angiotensin Converting Enzime Inhibitor; ADR: Adverse Drug Reaction
ARA-II: Angiotensin-II receptor antagonists; CDS: Clinical Decisión Support; CI: Confidence Interval
CPOE: Computerized Prescription Order Entry; NSAID: Nonsteroidal anti-inflammatory drugs; WHO: World Health Organization

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of the term “allergy”, are common and frequently reactions to a drug are rarely diagnosed and classified accurately. These events are associated with significant mortality rates and they have a high socio-economic impact on direct and indirect costs (Pawankar et al., 2011; Bousquet et al., 2009; Pirmohamed et al., 2004). Every day, hospitals admit patients who self-report allergies but only 6-10% of them actually have drug allergies (Bousquet et al., 2009; Solennsky et al., 2006). Labeling a non-allergic patient as allergic may have counter-productive effects because the patient may then be treated with alternative drugs which might be less efficient. Diagnosis is critical for drug hypersensitivity reactions management and prevention and to ensure optimal treatment (Pawankar et al., 2011; Bigby et al., 1986; Pilzer et al., 1996).

New technologies like Computerized Prescription Order Entry (CPOE), have demonstrated to be an effective system to prevent ADR associated with prescription errors. These errors are frequently originated by the prescriber´s ignorance of the patient´s allergies. Lack of communication among the staff or with the patient, or lack of knowledge about the medication is usually the underlying reason for these errors. It is estimated that lack of information about the patient is the second cause of prescription error and this includes the ignorance of a drug allergy (12%) (Lesar et al., 1995). The large number of commercialized drugs makes it difficult to remember the composition, chemical group to which they belong and chemical structure that are behind the cause of the hypersensitivity. Therefore, CPOE may be a useful tool for the prevention of hypersensitivity reactions in patients who have registered their allergies in this prescription system.

We carried out a study with the purpose of evaluating the usefulness of CPOE software in the reduction of drug-allergy errors in hospitalized patients, and also analyzing drug allergy characteristics. The primary objective was to identify, compare and evaluate drug-allergy related errors of a manual prescribing system with those in an electronic prescribing system during the prescription phase. Secondary objectives were to analyze the characteristics of the reported allergies: type of reaction, confirmation of the allergy by specific allergy studies, implicated drug and their chemical groups, time since drug allergy was first reported, necessity of an alternative treatment and its economic impact.

MATERIALS AND METHODS

We designed a prospective, observational and longitudinal study over a period of four months in hospitalized patients in a general University Hospital. It was carried out in two phases.

Phase 1

Manual prescription (one month) prior to implantation of CPOE (control group)

Manual prescriptions were handwritten by the prescriber. One copy was sent to the Pharmacy Department where pharmacists transcribed and validated the medical order into the drug management program. If the patient was allergic to some drug this allergy was noted on the handwritten order form by the physician and also entered in the FarmaTools® computerized program by the pharmacist. Afterwards, if a physician prescribed a drug to which the patient was allergic, or a drug that might have a cross allergy with another drug, an alert would appear warning the pharmacist about the incompatibility, so he would contact the physician to warn him and avoid administration if necessary.

In this first phase the main variable was the percentage of prescription errors resulting from the handwritten prescription of drugs despite a history of allergies. Moreover, those patients who had an allergy reported by the physician in the order form were interviewed and the following variables were registered: drug or therapeutic group of the reported allergy, type of reaction and symptoms, time passed from the first reaction and if they had any allergy tests available. The collected information was recorded in an anonymous data base in accordance with the Spanish Data Protection Law.

Reported allergy cases were classified in three categories: *confirmed allergy*, when the allergy reaction was confirmed by a positive skin test; *unconfirmed allergy*, when the symptoms described by the patient were unspecific and it was not possible to establish if it was a true allergy, an adverse effect or intolerance to a drug or an excessive pharmacologic response; and *non-allergic reaction* when the interview with patient confirmed that there had not been an actual drug reaction.

Phase 2

Computerized Prescription Order Entry (3 months) (experimental group)

The CPOE was established in 2009. From this time onwards, clinicians prescribed by the electronic prescription system and took charge of registering allergies into the program before drug prescription. Transcription made in phase one by the pharmacists was suppressed.

Table 1. Time since first reaction to drug (Phase 1)

Time since first reaction	Number of drugs allergies reported	% Drug allergies reported
> 20 years ago	87	49.7%
> 10 years ago	36	20.6%
5-10 years ago	11	6.3%
0-5 years ago	19	10.8%
At admittance	9	5.1%
Unknown	13	7.4%

Errors resulting from the prescription of a drug despite a history of allergies in this case using CPOE.

Furthermore, as through this computerized system investigators could identify the prescribing physicians, contact them and retrieve other new variables such as: necessity of an alternative treatment and economic impact of these alternative treatments using refence prices from the Official Spanish College of Pharmacy Catalogue (www.portalfarma.es).

In both periods patients hospitalized in medical and surgical units, aged 18 or older, who reported drug allergy at admission were included. Those hospitalized in reanimation or intensive care units and who were unable to answer the interviewer´s questions were excluded. The fact that the duration of these two phases differs is explained by the reduction in the number of hospitalized patients between the first and second periods. In order to include comparable sample sizes in both periods, phase two is three times longer than phase one.

Data were obtained from manual treatment orders, from the FarmaTools® drug management program and from the interviews with the physicians and patients.

The percentage difference in the distribution of qualitative variables was compared by determining the 95% confidence interval. Comparisons between periods for qualitative data are performed by Chi-squared test.

The conditions of normal clinical practice were maintained at all times, without any additional interventions on the patients. It was approved by Hospital´s Clinical Investigation Ethical Committee, following the standards of observational clinical studies.

RESULTS

Data were collected from 3,682 patients, 1,842 in phase 1 and 1840 in phase 2. The study showed that in phase 1 (manual prescription) the incidence of prescription errors due to drug allergy was 13.7% (24 of 175 reported allergies, eight of them related to confirmed allergies) CI (9%-19.7%) while in phase 2 (electronic prescription) the incidence was 1.5% (3 of 196 reported allergies) CI (0.3%-4.4%) ($p<0.001$).

The type of drug involved was similar in both phases; antimicrobial drugs in 42.5% and 46.9% of the incidents in phases 1 and 2 respectively (mainly betalactamics), and analgesics (23.6% and 13.6% in phases 1 and 2 respectively).

In phase one, 108 of the 1,842 patients that were admitted to the medical or surgical departments in our hospital, reported a drug allergy (5.8%). A total of 197 allergies were reported. 175 were included and 22 were discounted because they did not fulfil all inclusion criteria. Most patients were between 60 and 79 years old (58.3%), and the gender distribution was almost equal (51.8% women).

52 cases of reported allergies (29.7%) were classified as confirmed by a positive allergy test. 111 cases (63.4%) were classified as unconfirmed allergies. When the pharmacist interviewed the patients and concluded that 12 cases (6.8%) had been incorrectly reported as allergic reactions and were actually transcription errors.

According to our data, most patients had suffered the first allergic reaction more than 20 years earlier (49.7%) (table 1).

By type of reaction, 75 cases were classified as a cutaneous reaction, 51 as an anaphylactic reaction, 30 as drug intolerance and 6 as side effects (gastrointestinal bleeding due to aspirin, cough due to angiotensin converting enzyme inhibitors, fever or antimicrobial drug related diarrhoea) (table 2).

The distribution of the type of drug involved was: 42.5% antimicrobials (23% betalactamics, 7% aminoglycosides, 5.5% sulphonamides) and 23.6% analgesics (4.5% opiates, 23.6% NSAIDs).

In phase two, 1840 patients were admitted in hospital departments where the Computerized Order Entry Prescription (CPOE) system was employed. 198 drug allergies were reported in 157 patients (8.5% of admitted patients). 2 patients did not fulfill inclusion criteria, because one was discharged and the other was transferred to intensive care. Finally we included 155 patients and 196 allergies.

The groups of drugs involved were similar to phase one: 46.9% antimicrobials (31.6% betalactamics and 15.3% non-betalactamics), 13.6% analgesics (48% pyr-

Table 2. Drug Reaction Type (Phase 1)

Reaction Type	Number of drug reactions	% Drug reactions
Cutaneous	75	42.8%
Anaphylactic	51	29.1%
Intolerancie	30	17.1%
Idiosincratic	1	0.7%
Adverse effect (ACEIs cough, antimicrobial diarrea, salicylate induced hemorrhage, etc.)	6	3.4%
Others	12	6.8%

azolones and 10.7% salicylates).

In our study, an alternative was needed in 45 cases (22%), of which 44.1% were due to betalactamics, 13.9% to NSAIDs, 9.3% to aspirin and 9.3% tometoclopramide (table 3) (The drug group most frequently requiring replacement was antimicrobial agents (44%).

The economic impact of using an alternative drug prescription is shown in table 4. It has been estimated that on overage the alternative antimicrobials treatment increased treatment-costs/day by 4.4-fold. Costs of prescribing clopidogrel instead of aspirin were 25 times higher. Replacing metoclopramide with anti 5-HT3, done in four patients, had the highest economic impact, increased by 148.6- fold.

DISCUSSION

Patient safety requires improved knowledge and communication among healthcare professionals in order to create high-quality health care environments. Medication errors are often related to the prescription of drugs to which the patient had suffered some allergic reaction in the past. Frequently, patients inform clinicians about their allergies orally, without a written clinical report, and are unspecific when reporting allergic reactions.

In this context, new technologies like CPOE have a demonstrated ability to reduce prescription errors mainly because they facilitate communication and provide clinical decision support (CDS) (Villamañán et al., 2011a). Computerized warnings related to drug allergy associated to CPOE is an effective tool to help avoid the prescription of drugs to which the patient is allergic (Villamañán et al., 2011b).

Previous studies have shown that use of this technology in the ordering process helps to reduce potential hypersensitivity reactions (Millar et al., 2001). According to our results, this type of prescription error associated to drug allergy was reduced from 13.7%, when the pharmacological treatment was handwritten, to 1.5%, when this work was computerized.

Other published series agree with these observations. Bates et al. in a comparative medication error study found that errors associated with drug allergy fell from 4.1% when handwritten prescriptions were used to 0.6% when using CPOE (Bates et al., 1999). Bobb et al. reported that three out of four prescription errors could be avoided with CPOE (Bobb et al., 2004).

However, other studies have had less conclusive results. According to Delgado et al., prescription errors associated with drug allergy were reduced from 1.6% when physicians wrote out the pharmacological treatment for hospitalized patients to 1.1% when they used CPOE (Delgado et al. 2007), this small difference between the two prescribing methods could be a consequence of the complexity of CPOE software management when the physician registers an allergy.

Still other published studies have shown how an excess of warnings and recommendations can lead the physicians overriding the program. Lin et al. found a low approval of the recommendations; up to 80% were overridden for several reasons: the patient was monitorized, there was not a true allergy or the patient tolerated the drug (Lin et al., 2008). According to Hunteman et al. this percentage rose up to 97%, justified by the authors due to the high level of warnings cancelled mainly because the patient had previously tolerated the medication, the benefit outweighed the risk or the drug was therapeutically appropriate (Hunteman et al., 2009). Nevertheless, a physician is overriding a triggered warning when prescribing a drug to which the patient is allergic can have severe consequences (Hsieh et al., 2004).

Our study, like others (Gamboa, 2009), found that the drug group which most frequently produced allergies was antimicrobial agents (42.5% in phase one and 46.9% in phase two), and mostly betalactamic drugs. The second most allergenic drug type was analgesics (23.6% in phase I and 13.6% in phase II), most of the reactions were pseudo-allergic and mediated by mast cells or basophiles, without an immune mediatedpathogenic mechanism. Because of this non-

Table 3. Alternative Treatments (Phase 2)

Cancelled treatment	Alternative treatment	Number of cases(43)
Aspirin	Clopidogrel	2
Aspirin	Ticlopidine	1
Aspirin	Triflusal	1
Amoxicillin-clavulanate	Cephtriaxone	1
Amoxicillin-clavulanate	Phosphocine	2
Amoxicillin-clavulanate	Levofloxacin	8
Amoxicillin-clavulanate	Meropenem	1
Amoxicillin-clavulanate	Doxiciclin	1
Amoxicillin-clavulanate	Tobramycin+Clarithromycin	1
Amoxicillin-clavulanate	Azithromycin	1
Amoxicillin-clavulanate	Aztreonam	1
Amoxicillin-clavulanate	Vancomycin+Tigecycline	1
Amoxicillin-clavulanate	Piperacillin-Tazobactam	1
Amoxicillin-clavulanate	Vancomycin+Levofloxacin	1
Dexketoprophen	Morphine	1
Dexketoprofphen	Pyrazolone+ Acetaminophen	2
Pyrazolone	Tramadol	1
Pyrazolone	Acetaminophen	2
Metoclopramide	Ondansetron	2
Metoclopramide	Granisetron	2
Piperacillin-Tazobactam	Tigecycline+Amikacin	1
ACEI	ARA-II	1
ACEI	ACEI	1
ACEI	Doxazosin	1
NSAIDs	Acetaminophen	1
Acetaminophen	Pyrazolone	1
Enoxaparin	Fondaparinux	1
Omeprazole	Ranitidine	1
Acenocumarol	Enoxaparin	1
Sulfonamide	Atovaquone	1

ACEI: Angiotensin Converting Enzime Inhibitor, ARA-II: Angiotensin-II Receptor Antagonists

immunologic mechanism, these adverse reactions may occur the first time the host is exposed to the agent. In fact clinicians or patients often mistake a pseudo-allergic reaction related to analgesics with a true anaphylactic reaction.

According to our data, most allergic patients were aged 60 to 79 years old. As in the Hunteman et al. study (Hunteman et al., 2009). However, in other series (Alergológica, 2005; Gaig et al., 2009), the average age was lower, most probably because they included not hospitalized patients who were generally older. Hospitalized patients are frequently polymedicated which increase the probability of drug allergy. The gender distribution was almost equal between men and women in our study, while other series report a higher incidence of women (Alergológica, 2005; Gamboa, 2009). This might be explained by the fact that more men than women were hospitalized when data was collected.

Often patients inform the physicians about their allergies orally and vaguely without a pharmacological history to confirm the allergy. Actually, only 30% had confirmed cases of an allergic reaction (Lazarou et al., 1998; Pirmohamed et al., 2004; Pilzer et al., 1996). Hunteman et al., who found that 49% of drug allergies reported were not confirmed (Hunteman et al., 2009),

Table 4. Relative daily cost of alternative treatment (Phase 2)

Cancelled Treatment	Alternative Treatment	# of Cases	Relative Cost (N-Fold)
Acenocumarol	Enoxaparin	1	40.83
Amoxicillin-Clavulanate	Azithromycin	1	4.17
Amoxicillin-Clavulanate	Aztreonam	1	4.81
Amoxicillin-Clavulanate	Ceftriaxona	1	0.65
Amoxicillin-Clavulanate	Doxiciclina	1	0.43
Amoxicillin-Clavulanate	Levofloxacin	8	2.70
Amoxicillin-Clavulanate	Meropenem	1	11.86
Amoxicillin-Clavulanate	Phosphocine	2	0.17
Amoxicillin-Clavulanate	Piperacillin-Tazobactam	1	2.50
Amoxicillin-Clavulanate	Tobramycin+Clarithromycin	1	6.17
Amoxicillin-Clavulanate	Vancomycin+Levofloxacin	1	5.01
Amoxicillin-Clavulanate	Vancomycin+Tigecycline	1	13.63
Aspirin	Clopidogrel	2	25.75
Aspirin	Ticlopidine	1	7.75
Aspirin	Triflusal	1	2.50
Dexketoprophen	Morphine	1	0.70
Dexketoprophen	Pyrazolone/Acetaminophen	2	9.90
ACEI	ARA-II	1	5.57
ACEI	Doxazosin	1	1.47
ACEI	ACEI	1	1.00
Enoxaparin	Fondaparinux	1	2.82
Metoclopramide	Granisetron	2	152.29
Metoclopramide	Ondansetron	2	145.00
NSAIDs	Acetaminophen	1	1.00
Omeprazole	Ranitidine	1	1.05
Pyrazolone	Acetaminophen	1	10.00
Piperacillin-Tazobactam	Tigecycline+Amikacin	1	4.74
Pyrazolone	Acetaminophen	2	10.00
Pyrazolone	Tramadol	1	2.33
Sulfonamide	Atovaquone	1	42.00

ACEI: Angiotensin Converting Enzime Inhibitor, ARA-II: Angiotensin-II Receptor Antagonists

and in *Alergologia 2005* study only in 26.6% of drug reported allergies were confirmed (Alergológica, 2005). Our results support this hypothesis previously suggested by other authors

To label a patient wrongly as allergic to certain drugs can be harmful and lead to the use less effective and more expensive alternative drugs. Betalactamic drugs are perhaps the paradigm of this. It has been estimated that 10% of patients treated with these drugs suffer adverse reactions that their clinicians report as allergic reactions. When these patients are studied, 90% of them has been wrongly labelled and had not had a true hypersensitivity reaction (Bigby et al., 1986; Bousquet et al., 2009). This group of drugs are the treatment of choice for many infections and, according to some authors (Alergológica, 2005; Kim et al., 2008), the use of alternative treatments is associated with higher rates of morbi-mortality.

In this study the incidence of patients with confirmed allergy to betalactamics was 54% of all the reported betalactamic allergy cases. This percentage is higher than in previous reports (Silva et al., 2009; Serrano et al., 2009). There is not clear explanation for the difference, it could be due to the clinicians asking for fewer confirmatory tests or the different quality of the results. Anyway, more than half of the patients labelled as allergic to betalactamic drugs in our hospital are not actually allergic and could potentially receive these drugs drugs if they were necessary but the clinicians choose another, in many cases unnecessary, antimicrobial drug

and this might promote the development of resistant micro-organisms and costs (Khan et al., 2008; Reeder et al., 2008).

Taking into account the results of our study, most of our patients had their first allergic reaction to the drug 20 or more years earlier and were never actually tested for allergy. It is also known that immediate hypersensitivity reactions decrease when time passes. Less than 20% of the betalactamic antimicrobial allergy patients maintain IgE antibodies to these drugs when the skin test is repeated (Gruchalla et al., 2006; Lee et al, 2000). Likewise, some studies suggest that a significant number of these allergies are related to the excipient rather than the drug itself (Pifferi et al., 2003; Barbaud, 1995). Consequently patients who suffered an allergic reaction a long time ago should be tested again for antibody levels. Negative results in a new allergy test indicate that there are no more antibodies present or that the former reaction was not a consequence of an IgE-mediated reaction. In either case, these drugs can be readministered with the same risk of suffering from an immediate anaphylactic reaction as in the general population (less than 4%) (Hunteman et al., 2009).

Regarding the type of reaction the patient described our data are consistent with most authors (Gamboa, 2009; Sazo et al., 1997), in that the most common clinical manifestations were cutaneous.

One of the advantages of CPOE over manual prescription is the possibility of identifying the clinician at any time and the ease facility of communication between health professionals that provides. In the second phase of the study, thanks to the CPOE we could identify and contact all physicians responsible for the treatments to identify the patients in whom an alternative drug was necessary. 22% of the allergic patients required an alternative treatment and nearly half of these instances were due to betalactamic allergies. In this case, the most common alternative was levofloxacin (42.1%). Lee et al. found that the first alternative to betalctamic antimicrobial was vancomycin (38.5%) while levofloxacin was fourth most common alternative drug (21.7%) (Lee et al., 2000). According to Serrano et al (2009) quinolones were prescribed in this case in first place while glycopeptides in second (Serrano et al., 2009). These differences in alternative treatments used could be explained by the different illnesses to treat or by different local microbiological resistance patterns.

In our study, the prescription of an alternative treatment resulted, in most cases, in an increase in costs, especially when it came to antimicrobials. This group of drugs accounted for almost half the casesrequiring an alternative treatment (44.2%) and the need for an alternative regimen quadrupled the costs in drugs on average. In reviewing the literature, we have found unspecific references about increasing health care costs in this regard. According to the Sade et al (2003) study, the mean antibiotic costs for penicillin-allergic patients were 63% higher (Sade et al., 2003). We believe that confirming the existence of the allergy by meticulous history taking and allergy testing is essential, not only for patient safety but also for economy reasons. More studies are needed in this area.

Study limitations: Registration of patients with allergies could have been missed due to lack of communication between the patient and the physician or due to a lack of registration by the physician in the pharmacotherapeutic treatment history during patient admission. When calculating economic impact resulting from the prescription of an alternative to betalactamic antimicrobials, amoxicillin-clavulanic was considered the standard treatment because it is the most used betalactamic antimicrobial in our media.

CONCLUSIONS

Using a CPOE that includes a support alert for drug allergies is an effective tool to prevent prescription errors related to drug allergy.

Properly recording the patient's medication history in these programs is essential to prevent re-exposure to the drug. The programs also provide accessible information on existing alternatives and prices.

The main type of drugs involved in our study are antimicrobials, especially beta-lactamics. It is important to verify the drug allergy, because frequently reported allergies cause false alarms that lead to the prescription of less efficient alternative treatments.

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