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# Integrating pharmacovigilance into the routine of pharmacy department: experience of nine years

## Integración de la farmacovigilancia en la rutina del servicio de farmacia: nueve años de experiencia

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## Abstract

**Objective:** To describe our pharmacovigilance program and to analyze the reported adverse drug reactions.

**Method:** Observational longitudinal study conducted from 2008 to 2016. The Pharmacy Department leads the pharmacovigilance program and performs prospective, retrospective, intensive, and spontaneous reporting of inpatients and outpatients (emergencies, day hospital, external consultations, and nursing homes). Each adverse drug reaction is incorporated in the electronic health record of the patient along with an alert.

**Results:** A total of 2,631 adverse drug reactions were reported in 2,436 patients. Of these patients, 52% were men with a mean age of 63.3 [0-98] years. A total of 92.8% drug events were reported by the pharmacists and 7.2% by doctors, nurses, and technicians. A total of 63.7% were reported in inpatients, 19.2% in emergencies, 10.6% in external consultations, 6.2% in the day hospital, and 0.3% in diagnostic radiology. There was an increase in adverse drug reactions detected by prospective and intensive pharmacovigilance. Principal therapeutic groups involved in adverse drug events were antineoplastic agents (21.3%), antibacterials (12.3%), antithrombotics (7.7%), analgesics (6.7%), corticosteroids (5.2%), psycholeptics (5.2%), diuretics (4.9%),

**KEYWORDS**
Pharmacovigilance; Adverse drug reactions; Drug monitoring; Hospital pharmacy services; Adverse drug event; Drug reaction reporting systems.

## Resumen

**Objetivo:** Describir un programa de farmacovigilancia llevado a cabo por un servicio de farmacia y analizar las sospechas de reacciones adversas a medicamentos recogidas.

**Método:** Estudio observacional, longitudinal, de nueve años de duración (2008-2016). El programa de farmacovigilancia está liderado por el servicio de farmacia, que realiza farmacovigilancia prospectiva, retrospectiva, intensiva y voluntaria en el paciente hospitalizado y ambulatorio (urgencias, hospital de día, consultas externas y centros sociosanitarios). Las reacciones adversas se incorporan en la historia clínica electrónica del paciente y se añade una alerta que indica su presencia.

**Resultados:** Se recogieron 2.631 reacciones adversas a medicamentos en 2.436 pacientes (52% varones) con una media [rango] de edad de 63,3 [0-98] años. El 92,8% de las reacciones fueron notificadas por el farmacéutico y el 7,2% por médicos, enfermería y técnicos. El 63,7% se notificaron en hospitalización, el 19,2% en urgencias, el 10,6% en consultas externas, el 6,2% en hospital de día y el 0,3% en radiología. Se observó un incremento de notificación por farmacovigilancia prospectiva e intensiva. Los grupos terapéuticos mayoritariamente implicados fueron: antineoplásicos (21,3%), antibacterianos (12,3%), antitrombóticos (7,7%), analgésicos (6,7%), corticosteroides (5,2%), psicolépticos (5,2%), diuréti-

**PALABRAS CLAVE**
Farmacovigilancia; Reacción adversa al medicamento; Monitorización de fármacos; Farmacia hospitalaria; Efecto adverso por medicamentos; Sistemas de detección de efectos adversos.

antivirals (4.9%), antiinflammatories and antirheumatics (4.2%), and immunosupressants (3.3%). Adverse drug reactions mainly affected the skin and appendages (19.7%) and gastrointestinal tract (19.1%). Adverse drug reactions were mild (38.7%), severe (30.8%), and moderate (30.5%). In total, 60.9% of patients recovered from drug events and 31.7% were in recovery. The most frequent response was treatment interruption in 65% of cases and the patients received additional specific treatment in 56% of cases.

**Conclusions:** The incorporation of the pharmacovigilance program within the daily routine of the hospital pharmacist provides added value to the safety and pharmacotherapy of the patient.

cos (4,9%), antivirales (4,9%), antiinflamatorios y antirreumáticos (4,2%) e inmunosupresores (3,3%). Las reacciones adversas detectadas afectaron mayoritariamente a la piel y anejos (19,7%) y al tracto gastrointestinal (19,1%). Respecto a su gravedad, el 38,7% fueron leves, el 30,8% graves y el 30,5% moderadas. El 60,9% de los pacientes se recuperaron de las reacciones adversas y el 31,7% se encontraban en proceso de recuperación. Se interrumpió el tratamiento en el 65% de los casos y el 56% de los pacientes recibieron tratamiento específico.

**Conclusiones:** La incorporación del programa de farmacovigilancia en la rutina diaria del farmacéutico de hospital aporta un valor añadido a la seguridad de la farmacoterapia del paciente.

## Introduction

Medicines must be efficacious, safe, and of sufficient quality such that they can be marketed and used by patients. Studies conducted during the research and development of a drug provide reliable information on its efficacy; however, information on its safety may be less reliable. Such detailed information can only be acquired via its use in the general population under conditions of standard practice. The practice of pharmacovigilance[1] is dedicated to this aspect, and is a public health activity whose purpose is to identify, quantify, assess, and prevent adverse drug reactions (ADR) or any other drug-associated problem once a drug has been marketed[2,3] in order to ensure a favourable risk/benefit ratio[1].

The objective of pharmacovigilance is to detect early ADRs and previously unknown interactions, detect increases in the frequency of an already known ADR, identify risk factors, report drug risks and benefits, and disseminate this information to the scientific community and the general population with the ultimate aim making the use of medicines safer[4].

An ADR is any harmful and unintended response to a drug, which occurs at a dose normally used in humans for prophylaxis, diagnosis, or therapy, or to modify a physiological function[5]. ADRs are the cause of many complications that can lead to emergency care, hospitalization, and even death. It is estimated that 5% of all hospital admissions are due to ADRs. They are the fifth most common cause of hospital death in the European Union, with approximately 197,000 deaths and entailing a total cost to society of €79 billion. Therefore, their avoidance should be a priority objective in care protocols[6].

Currently, the Principality of Andorra is part of the International Pharmaceutical Surveillance Program of the World Health Organization (WHO)[7]. In addition, since 2004, the Nostra Senyora Meritxell Hospital (HNSM) has implemented a pharmacovigilance program that makes it easier to detect, record and report in-hospital ADRs.

The objective of this article was to describe the HNSM pharmacovigilance program, which is integrated in the daily routine of the hospital pharmacist, and to analyze the suspected ADRs collected over the 9 years that were used to establish specific safety programs.

## Methods

The HNSM is an acute care hospital and the only hospital in the Principality of Andorra. According to 2016 data, it responsible for 78,264 inhabitants[8]. Each year it has an average of 6,800 hospital admissions, 37,700 visits to the emergency room, 1,600 intravenous chemotherapy sessions, and 3,400 drug dispensations to outpatients.

The pharmacy service leads the pharmacovigilance program, which comprises voluntary, prospective, retrospective, and intensive pharmacovigilance, as another part of its daily activity[7,9,10].

Voluntary pharmacovigilance is the spontaneous reporting of ADRs by health personnel. Prospective pharmacovigilance is the detection of ADRs using the electronic medical record (EMR) and computer-assisted prescription (CAP) in hospitalized patients (intensive care unit, pediatrics, gynaecology, general and trauma surgery, internal medicine, and psychiatry) and the nursing home attached to the hospital. Retrospective pharmacovigilance is the identification of ADRs by reviewing the EMRs at discharge using the minimum basic data set (MBDS). Intensive pharmacovigilance is the proactive detection of ADRs in emergency departments, outpatient clinics, and day hospitals, including the oncology hospital day. In addition, specific programs have been established, such as the detection of ADRs during the administration of intravenous immunoglobulins and contrast media in the radiodiagnosis department.

Prospective, retrospective, and intensive methods can be used to detect suspected ADRs using a list of warning signs (Annex 1) associated with possible drug damage, which includes diagnoses, the prescription of certain medications/antidotes, or clinical situations, such as the sudden interruption of an active medication. A yellow card specific to the pharmacy service is used to record ADR reports. Subsequently, the reported ADR is entered as a document in the patient's EMR in PDF format, making it available for consultation each time the patient is admitted. Each ADR is incorporated in the patient's EMR along with an alert[7]. The ADRs are recorded in a purpose-built database. Finally, annual general pharmacological safety and pharmacovigilance refresher sessions are held on the concepts of ADR. All reports are sent to the Andorran National Pharmacovigilance System.

This study was an observational longitudinal study that was approved by the HNSM ethics committee. The study analyzed suspected ADRs reported by the HNSM pharmacovigilance program during the period 2008 to 2016.

The data collected were obtained from the yellow card: date reported, reporting system, reporting staff (pharmacist, doctor, nurse, technicians), the patient's biodemographic data, clinical service at admission and responsible physician, date of the ADR, suspected medication/s and therapeutic group/s, clinical manifestation and affected organs, action taken concerning the ADR, need or otherwise for pharmacological treatment, severity, causality, and outcome. The card includes a field for additional observations related to analytical data, known allergies, risk factors, or previous exposure to the drug.

The detection method was classified as voluntary, intensive, prospective, and retrospective. The suspect drugs and the therapeutic groups to which they belong were classified using the Anatomical Therapeutic Chemical (ATC) classification system[11], and the clinical manifestations and organs affected were classified using the system/organ classes of the WHO-adverse reaction terminology system[12]. Adverse drug reactions were classified as mild, moderate, or severe, where severe was defined using the WHO criteria[13]. The Karch-Lasagna algorithm[14] was used to establish causality, grouping ADRs into probable (defined and probable), doubtful, and unlikely. The outcome of the ADR was classified as recovered patient, in recovery, recovered with sequelae, and death.

### Statistical data analysis

We conducted a descriptive statistical analysis of all the variables collected. Continuous quantitative variables are expressed as means and interquartile range. Qualitative variables are expresed as absolute and relative frequencies. All data were analysed using the G-Stat 2.0 statistical software package.

## Results

We analyzed 2,631 ADRs in 2,436 patients (52% men) with a mean age of 63.3 [0-98] years. More than one ADR was detected in 7.4% of the patients.

The ADRs were reported by the pharmacist in 92.8% of cases and spontaneously reported by medical, nursing, and technical staff in 7.2% of cases. More than one active ingredient was considered to be involved in 25.9%

of the ADRs. In total, 63.7% of ADRs were detected in hospitalized patients, 19.2% in the emergency department, 10.6% in outpatient clinics, 6.2% in the day hospital, and 0.3% in the radiodiagnosis department.

Between 2008 and 2016, there was a change in the ADR detection method. From the fifth year onward, there was a decrease in ADRs identified using the MBDS and an increase in those detected by prospective (CAP) or intensive pharmacovigilance (Figure 1).

The majority of ADRs were detected in patients admitted to internal medicine (50%), oncology (10%), pneumology (9%), emergencies (4.4%), and rheumatology (2.8%).

The pharmacological group most frequently involved was antineoplastics (responsible for 21.3% of ADRs) of which 17.4% were oral antineoplastics. Specific active principles stood out as responsible for the ADRs in their therapeutic group (Figure 2), although in some groups great variability was observed in the active principles involved.

The majority of the ADRs reported affected the skin and appendages and the gastrointestinal tract, whereas the least reported were ADRs leading to infections and musculoskeletal disorders (Figure 3).

Of the ADRs, 92.8% were considered probable, 6.7% doubtful, and 0.5% unlikely. Regarding severity, 38.7% of ADRs were mild, 30.5% were moderate, and 30.8% were severe. Within the therapeutic groups (Table 1), antineoplastics and antithrombotics mainly caused clinical blood abnormalities and caused a high percentage of the severe adverse reactions. On the other hand, antibacterials and analgesics more frequently affected the skin and appendages and caused more mild adverse reactions. In both cases, the ADRs led to treatment interruption.

The most frequent response was treatment interruption (65%), followed by no change (25.2%), and dose modification (9.8%). The patients received additional specific treatment in 56% of cases.

Most of the patients recovered from the ADR (60.9%) or were in recovery at the time of reporting (31.7%). Only 1.8% experienced sequelae. The result was unknown in 3.7% of cases. The ADR was considered to be the cause of death in 1.9% of cases. The mean age of patients with fatal ADRs was 70 [49-97] years. Antineoplastics (40%) were the main therapeutic group involved in mortal ADRs.

The different detection methods identified severe ADRs in similar percentages (retrospective MBDS: 34%; prospective CAP: 29%; intensive: 28%; voluntary reporting 23%). The profiles of the detected ADRs were different under each method. The ADRs detected by MBDS and voluntary reporting were mainly caused by antineoplastic agents (17% and 32%, respectively) and antibacterial agents (12% and 16%, respectively). The ADRs detected by intensive pharmacovigilance were mainly caused by antineoplastics (48%) and antivirals (18%), whereas those detected by prospective pharmacovigilance using CAP were mainly caused by antibacterials (17%) and antithrombotics (12%).

## Discussion

This study presents the results of the pharmacovigilance program established in our hospital and led by the pharmacy service. Consequently, the pharmacist detected the great majority of the ADRs (around 93%), whereas the other clinical staff contributed less to their detection. However, awareness within medical community of the relevance of reporting ADRs contributes to the inclusion of suspected ADRs in the EMR and discharge reports in natural language, in the knowledge that that they will be collected, recorded, and reported by the hospital pharmacist[7].

The incidence of ADRs is subject to great variability, and one of the main factors to be considered is the detection method. Spontaneous reporting is considered to be the most efficient method to identify previously unknown ADRs, although it is associated with a high level of under-reporting and only 6% to 10% of ADRs are detected in this way. Retrospective pharmacovigilance involves the systematic review of the EHR, but is affected by the quality of the data introduced, filters, and computer systems used. On the other hand, prospective pharmacovigilance detects ADRs when they occur and may include interviews with the patient or health staff, thereby increasing the probability of detection and contextualization, although this method is demanding in terms of time and trained staff. The advantages and disadvantages of prospective pharmacovigilance are shared by intensive pharmacovigilance, but this method is even more demanding than the former method and involves a specific search for ADRs[15].

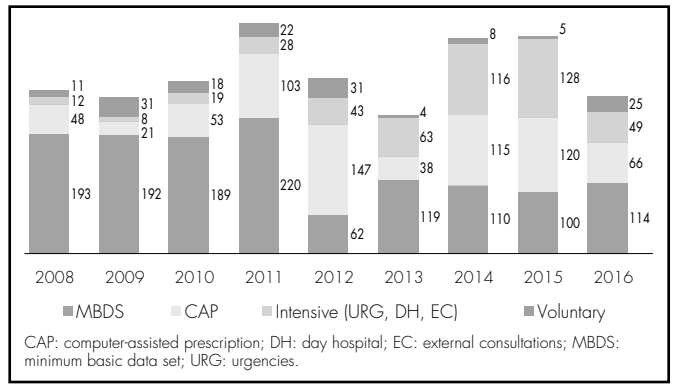


**Figure 1.** *Evolution of the number of adverse drug reactions by detection method: 2008 to 2016.*

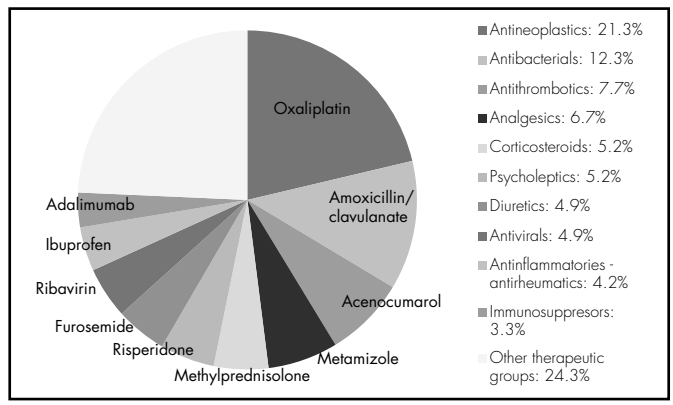


**Figure 2.** *Therapeutic groups involved in adverse reactions due to drugs and main active ingredients. The most frequent active ingredient is indicated for each therapeutic group.*

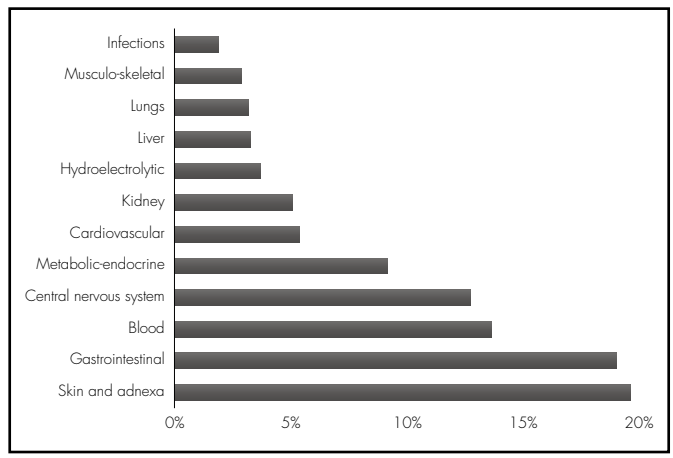


**Figure 3.** *Distribution of clinical manifestations caused by adverse drug reactions.*

In our hospital, we use a combination of methods to maximise the detection of ADRs, which is the same approach as that applied in 55.2% of the studies dedicated to this issue[16]. In their metaanalysis, Martins *et al.*[15] suggested that prospective pharmacovigilance was the most useful method, detecting 4.7% to 57.3% of ADRs in the different studies, followed by retrospective pharmacovigilance (1.7-5.6%) and intensive pharmacovigilance (1.6-4.4%)[15]. In this study, half of the ADRs were detected by retrospective pharmacovigilance although, as of 2012, this method became less

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**Table 1.** Clinical manifestations, severity, and action followed according to therapeutic group most frequently involved in adverse reactions detected

| Therapeutic group | Main clinical manifestations | | | Severity | | | | | | Action | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Type | *n* | % | Severe | | Moderate | | Mild | | Interruption | | Without Change | | Change dose | |
| | | | | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| **Antineoplastics *n* = 737** | Blood | 123 | 25.0 | 272 | 36.9 | 252 | 34.2 | 213 | 28.9 | 320 | 43.4 | 323 | 43.9 | 94 | 12.7 |
| | GI | 114 | 23.2 | | | | | | | | | | | | |
| | Skin | 99 | 20.1 | | | | | | | | | | | | |
| | CNS | 39 | 7.9 | | | | | | | | | | | | |
| **Antibacterials *n* = 410** | Skin | 145 | 41.4 | 94 | 22.9 | 116 | 28.3 | 200 | 48.8 | 323 | 78.8 | 79 | 19.3 | 8 | 1.9 |
| | GI | 99 | 28.3 | | | | | | | | | | | | |
| | Blood | 31 | 8.9 | | | | | | | | | | | | |
| | CNS | 22 | 6.3 | | | | | | | | | | | | |
| **Antithrombotics *n* = 261** | Blood | 149 | 65.4 | 122 | 46.5 | 74 | 28.5 | 65 | 24.9 | 217 | 83.1 | 21 | 8.1 | 23 | 8.8 |
| | GI | 45 | 19.7 | | | | | | | | | | | | |
| | Skin | 16 | 7.0 | | | | | | | | | | | | |
| | Liver | 5 | 2.2 | | | | | | | | | | | | |
| **Analgesics *n* = 224** | Skin | 66 | 32.7 | 51 | 22.8 | 58 | 25.9 | 115 | 51.3 | 172 | 76.8 | 29 | 12.9 | 23 | 10.3 |
| | CNS | 55 | 27.2 | | | | | | | | | | | | |
| | GI | 47 | 23.3 | | | | | | | | | | | | |
| | Lungs | 12 | 5.9 | | | | | | | | | | | | |

GI, gastrointestinal tract; CNS, central nervous system.

common in parallel with the increased use of prospective and intensive pharmacovigilance. This change could have been due to the increased involvement, awareness, and experience of pharmacists in the detection of ADR, who were able to incorporate this activity into their daily routine, as recommended by the WHO[17].

Unlike the vast majority of pharmacovigilance studies[15,16], we included data from all hospital areas as well as data obtained during hospital admission, before hospitalization, during outpatient consultations, and in the day hospital, given that the present study addresses a global hospital program framed within the policy of patient safety. In specific areas, such as outpatient clinics and the day hospital, ADRs were associated with biological drugs, antiretroviral drugs, oral and intravenous antineoplastics, antivirals and immunoglobulins, drugs with the capacity to produce severe ADRs, and very often, novel drugs, which particularly require pharmacovigilance[17]. Furthermore, intensive pharmacovigilance by the hospital pharmacist in the emergency room offers an opportunity to detect community ADRs that require hospital care.

In this study, 50% of the ADRs were associated with patients referred to internal medicine. Miguel *et al.*[18] analyzed ADRs in the internal medicine, surgery, ICU, paediatric, and obstetric departments and observed significant differences between medical services in the detection of ADRs[18]. In addition, risk factors for ADRs include age, the number and type of drugs prescribed, comorbidities, the severity of the disease, and the length of hospital stay. Thus, for each additional drug, the risk of an ADR is multiplied by 1.1 (confidence interval 95%: 1.06-1.14) due to drug-drug interactions and additive effects[19]. These findings would explain our results, because elderly patients are admitted more frequently to medical units and, presumably, have more comorbidities and polymedication. In addition, the average stay is usually longer than that in surgical units.

The main therapeutic groups responsible for ADRs were, in order of frequency, antineoplastics, antiinfectives, antithrombotic agents, analgesics, systemic corticosteroids, and psycholeptics. Although there is high variability between studies, it has been estimated that antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, and non-steroidal anti-inflammatory drugs are responsible for 60% to 70% of ADRs[20,21]. Some studies that have included antineoplastic agents have shown that these are among the three or five drug groups that cause ADRs[16]. This disparity could be attributed to the area in which the study was conducted, the detection methods used, each hospital's medication policy, and staff experience. It was also observed that not all drugs equally contribute to ADRs in their respective therapeutic groups. For example, within their groups, acenocoumarol, metamizole, and methylprednisolone were responsible for more than 40% of the ADRs. These data help to identify which drugs need special surveillance in our health care setting.

The areas most affected by ADRs were the skin and appendages, gastrointestinal tract, blood, and central nervous system (CNS). The literature reports different findings and suggests that the gastrointestinal tract, CNS, and skin are more frequently affected by ADRs. Patients and health staff can easily and quickly detect cutaneous ADRs because of their manifestations, as well as those that affect the gastrointestinal tract[22]. In general, the detection of ADRs depends on staff experience because ADRs can manifest in an insidious manner and can be easily confused with the clinical manifestations of the disease itself[16].

It is relevant to highlight the high percentage of reported severe ADRs. A previous study conducted between 2004 and 2007 in the same hospital found that 50% of ADRs were mild, 28% were severe, and 24% were moderate[10]. In the longer period 2008 to 2016, similar proportions of ADRs were observed: 38.7% were mild, 30.8% were severe, and 30.5% were moderate. These figures suggest that severe ADRs should entail special attention and priority in their reporting. In addition, more than half of the ADRs received additional specific treatment, which could be related to the increased detection of severe ADRs.

A different pattern was observed in ADRs associated with the four major therapeutic groups. Antineoplastics and antithrombotics, which are considered to be high-risk drugs, are the cause of predominantly severe ADRs related to their mechanism of action. For this reason, the immediate therapeutic measure is to interrupt treatment. On the other hand, antibacterials and analgesics caused a higher percentage of unexpected, moderate, and mild ADRs that affected the skin and appendages. However, the response to these ADRs was also to interrupt treatment, possibly because of the availability of a larger alternative therapeutic arsenal or because they involved allergies. Finally, of the 1.9% deaths caused by ADRs, 40% were due to antineoplastics. In these cases, a relevant issue is the complexity of determining to what degree the drug is directly involved versus the underlying disease. One of the limitations of the present study is that it did not analyze factors related to the development and duration of ADRs, such as the number and type of concomitant medications, the number of patient comorbidities, and the length of hospital stay.

Neither did the study determine potential associations between risk factors and the ADRs detected. On the other hand, it is difficult to assess the global incidence of ADRs, given that the results from different areas were analyzed in combination. However, little-known factors were analysed, such as the response to ADRs, the percentage of ADRs treated, the involvement of more than one active ingredient, and the results per the-

rapeutic group. In summary, the analysis of the detected ADRs provides us with a more detailed understanding of drug safety in our health care setting.

The nine years of the study period have demonstrated that the incorporation of the pharmacovigilance program within the daily routine of the hospital pharmacist provides added value to the safety and pharmacotherapy of the patient.

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## Conflicts of interests

No conflict of interests.

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## Presentation at Congresses

"Integration of pharmacovigilance in a pharmacy service: 9 years' experience": 62nd Congreso de la Sociedad Española de Farmacia Hospitalaria, Madrid, Spain, October 18-21, 2017.

## Contribution to the scientific literature

There are a few active pharmacovigilance programs in Spanish hospital pharmacy services. The majority of relevant studies specifically estimate adverse reactions in different settings and over relatively short periods. The pharmacovigilance program in our hospital provides added value to patient safety because it is integrated within the daily routine of the hospital pharmacists in an ongoing and comprehensive way in all areas of activity. Furthermore, adverse reactions can be analysed globally or analysed according to the selected variables of interest. Identifying the drugs most commonly involved in adverse reactions allows specific safety programs to be established in hospitals and the general population.

Given the magnitude and diversity of the data collected by the hospital pharmacist, this pharmacovigilance program represents an innovation in the field of hospital pharmacy.

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**Annex I.** Warning signs used to detect adverse drug reactions

| **Alerting interruptions** | |
|---|---|
| Unexpected suspension of active treatment | |
| **Alerting prescriptions** | |
| Antidotes. | Corticosteroids. |
| Antiemetics. | Electrolytic supplement. |
| Antihistamines. | Loperamide. |
| Biperidene. | Oral vancomycin |
| Continuous intravenous perfusion of omeprazol (80 mg/12h). | Potassium exchange resins |
| **Alerting diagnostics** | |
| ***Gastrointestinal disorders*** | |
| Abdominal discomfort | Nausea |
| Constipation | Pancreatitis |
| Diarrhea | Rectorragia |
| Epigastralgia | Stomatitis |
| Gastritis | Vomiting |
| Gastrointestinal bleeding | |
| ***Blood disorders*** | |
| Anemia | Neutropenia |
| Hemorrhages or bruises | Pancytopenia |
| Hyperdecoagulation | Thrombocytopenia |
| Leucopenia | |
| ***Nervous system disorders*** | |
| Asthenia | Headache |
| Ataxia | Hypoacusia |
| Blurred vision | Light-headedness |
| Bradypsychia | Metal flavour |
| Confusional syndrome | Mydriasis |
| Corticosteroid-induced psychosis | Neuroleptic malignant syndrome |
| Decreased level of consciousness | Paresthesia |
| Disorientation | Serotonin syndrome |
| Dizziness | Tinnitus |
| Drowsiness | Trembling |
| Dysarthria | Unstable walk |
| Extrapyramidal abnormalities | Vasovagal syncope |
| Falls | Vision loss |
| Hallucinations | |
| ***Skin and appendages disorders*** | |
| Acne | Lipodystrophy |
| Allergy | Palmo-plantar erythrodysesthesia |
| Anaphylaxis | Pruritus |
| Angioedema | Rash |
| Asthenia | Reactions at injection site |
| Erythema | Stevens-Johnson syndrome |
| Exanthema | Toxicodermitis |
| Facial blush | Urticaria |
| Irritation | |

| **Alerting diagnostics *(cont.)*** | |
|---|---|
| ***Cardiovascular disorders*** | |
| Bradycardia | Prolonged QT interval |
| Hypotension | Tachycardia |
| ***Respiratory disorders*** | |
| ACEI-associated cough | Pneumonitis |
| Antineoplastic-associated tachypnea | Pulmonary embolism in young women |
| ***Kidney disorders*** | |
| Kidney failure | Vasculitis |
| Nephritis | |
| ***Metabolic-endocrine disorders*** | |
| Elevated prolactin | Hypoglycemia |
| Gynecomastia | Metabolic acidosis |
| Hyperglycemia | |
| ***Musculoskeletal disorders*** | |
| Dystonia | Myopathy |
| Muscle pain | Rhabdomyolysis |
| ***Infections*** | |
| Antineoplastic- or vaccine-associated fever | Oral candidiasis |
| Clostridium difficile infection/ pseudomembranous colitis | |
| ***Liver disorders*** | |
| Cholestasis | Increased transaminase |
| Cytolysis | Jaundice |
| Hepatitis | Liver function abnormality |
| Increased bilirubin | |
| ***Hydro-electrolyte disorders*** | |
| Hyperkalemia | Hyponatremia |
| Hypocalcemia | Hypophosphatemia |
| Hypomagnesemia | |

ACEI: angiotensin-converting enzyme inhibitors.