EXPERIENCES OF PHARMACOVIGILANCE IN TERRITORIAL PHARMACY: ANALYSIS OF ADR IN ASL SA/2 COMPARED WITH NATIONAL AND REGIONAL DATA (2005-2008).

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Summary

Pharmacovigilance is the whole of activities that guarantee an appropriate use of drugs.
The monitoring of adverse reactions is an important instrument for the definition of drug's tolerability in its real conditions of use and in a sufficiently high number of patients.
This article analyses the reporting of adverse drug reactions through the National network of Pharmacovigilance.
The activity of reporting is under the gold standard of WHO.
There is an increase of signalling of drug adverse reactions for the ASL Sa/2 in these years, thanks to many projects completed by ASL Sa/2.
Is really important to support the activity of Pharmacovigilance through reporting of ADR to collect all the informations about drug's security in post-marketing phase.

Key words: Pharmacovigilance, adverse drug reaction (ADR), risk-benefit ratio, appropriate use of drug, National network of Pharmacovigilance, ASL (local health centers).

Pharmacovigilance: definitions and phases

Pharmacovigilance encompasses all activities and methods to identify, assess and prevent adverse drug reactions (ADR), during development and after marketing.
The term was proposed in the 70s, by a group of french toxicologists and pharmacologists to define their activities: "the risk of side effects potentially associated with drug treatment".
Pharmacovigilance has 4 main goals (1):

1) recognize, as quickly as possible, new reports of suspected adverse reactions,
2) improve and broaden the information on ADR suspected or already known,
3) assess the benefits of a drug on others or on other types of therapy,
4) communicate the information to improve the therapeutic practice.
Pharmacovigilance, recognizing as early as possible new ADR, provides an early warning signal or alarm (2). This triggers a series of events characterized by generation of a hypothesis, and by preliminary assessment of available data, the testing, evaluation and explanation of the signal itself (3).
At the time of registration of a medicine, the knowledge on its safety profile is incomplete. The randomized clinical trials submitted to regulatory authorities are often short-term also for medications used in chronic conditions or in prophylaxis and the studied population is often poorly numerous and highly selected (exclusion of particular ethnic groups, selection by age, sex, presence of concomitant diseases, etc ...). The clinical data show the most common adverse events related to the drug occurred during the studies, but informations on the risks in conditions of clinical practice are very limited.
The definition of the World Health Organization (WHO) of adverse drug reaction, in use for about 30 years, is: "a response to a drug that is harmful and not intentional, that occurs at doses normally used in humans for prophylaxis, diagnosis or treatment, or for modification of physiological function".
When a drug is discovered, synthesized or modified before marketing, it goes through a series of studies, called pre-clinical studies and clinical trials.
The pre-clinical studies are divided into two phases. The purpose of the first phase is to determine in detail the pharmacodynamic characteristics of the molecules (basic pharmacological effect and its duration, side effects), changes in vital signs (pressure changes, heart rate and breathing, body temperature), the determination of the Lethal Dose 50 (the dose capable of producing death in 50% of treated animals).
It also made the search for theratogen activity through studies of fetal toxicity by administration of the molecule during pregnancy in two species of animals (mouse and rabbit), considering the number of born dead fetuses, their weight and possible anomalies, and also tests of mutagenesis in vitro on micro-organisms (Salmonella typhi) and the search for cancerogenic activity. Other studies are conducted on the chemical stability of the molecule to develop the best formulation and determination for experiment in humans.

Animal studies have many limitations in their ability to predict human toxicity (4).
A good example is what happened with the practolol, a beta1-blocker, for some years extensively used in therapy (5). The drug caused in humans a syndrome characterized by dermatitis and sclerosing peritonitis, which led in 1976 to its withdrawal (6). This syndrome had never been seen in pre-clinical studies: successive surveys conducted on small animals (those that metabolize the practolol in a manner similar to humans, and those who metabolize in a much more extended) have shown that we can observe this reaction (7).
Pre-clinical studies are realized into two or three years and at the end of them less than 50% of the molecules tested in the trial goes on, thanks to their potential therapeutic and acceptable toxicity. After pre-clinical phase, administration has to obtain authorization from the health authorities, including the important role of ethics committees.
The clinical phase in humans is divided into three main phases, numbered I to III, to value the efficacy and tolerability of the drug, and the existence of a risk-benefit ratio.
Phase I is usually conducted in healthy volunteers and used to monitor the safety of the molecule. The number of healthy subjects or patients is usually between 20 and 80. Initial fractions of the doses used in animals, are increased up to determine the maximum tolerable dose in humans, and the bioavailability of the molecule is also studied. Phase I lasts for about 1-2 years and at least 50% of the molecules do not exceed. After the authorization of the Ministry of Health, the testing moves from *pilot* to *enlarged*.
In phase II the molecule is administered for the first time on patients.
At this stage patients are involved in a number of about 100-200, with the aim to delineate the pharmacodynamic profile (dose-effect). The testing is performed in highly specialized centers, in close contact with scientists from the pharmaceutical industry. At the end of the trial phase II, only 2-3 molecules remain as "a candidate". There are also analyzed technical-economic parameters, such as market potential and manufacturability. Phase II lasts for about 2 years.
In phase III data emerged in phase II are verified, especially the efficacy and tolerability of a drug. It is the most extensive and rigorous stage of all the process in which the molecule is put in comparison to placebo or other drugs to demonstrate the therapeutic benefit. In this phase are also tested the dosage regimens for the marketing and possible interactions with other drugs.
The searches are conducted in university or hospital.

To prevent influences by patient's expectations are used tests compared with placebo (substance with no pharmacological effects such as lactose or saline solution).
The tests are distributed randomly (random) and used in blind testing (the patient or the investigator are not aware of the drug administered), or double blind (both are not aware).
These measures are used to purify the clinical data from possible - even unconscious - contamination of data due to the investigator on the effectiveness of a drug. The duration of phase III is 3-4 years. After this stage the drug has authorization for commerce.
New trials may be requested, and at the end of the process the drug can get the final approval with specific indications for a defined disease.
In phase IV, the drug is already commercially available but vigilance can continue in parallel with the use to test for possible side effects.
At this stage we can see Pharmacovigilance as reporting of unexpected and adverse reactions.
Pharmacovigilance is concerned with assessing safety profile of drugs after marketing, their greater diffusion, during their use in everyday medical practice. In this perspective, the reporting of suspected adverse reaction represents continuous inspection of safety data relating to drugs and promotion of their rational use.

Adverse Drug Reaction (ADR)

Doctors and other health professionals are required to report all serious or unexpected suspected adverse reactions they are aware.
Adverse drug reactions concern noxious and unintended responses to a medicinal product.
The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
The reaction is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown, it meets the definition of an adverse drug reaction (8).

Serious and unexpected ADR

A serious adverse reaction is a medical occurrence that at any dose:
• results in death;
• is life-threatening (the term refers to an event in which the patient was at risk of death at the time of the reaction);

• requires in patient hospitalisation or results in prolongation of existing hospitalisation;
• results in persistent or significant disability/incapacity;
• is a congenital anomaly/birth defect;
• is a medically important event or reaction.

An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the Product Information should be considered unexpected.

The National Network of Pharmacovigilance

The activity of Pharmacovigilance includes a series of activities aimed to the continuous assessment of all information relating to the safety of medicines and to ensure, for all drugs on marketing, a risk-benefit ratio favourable for the population. The data on the safety of the medicines are derived from different sources: spontaneous reports of suspected adverse reactions, studies, scientific literature, reports submitted by pharmaceutical companies.

In Italy, according to Lgs. D. 44/97, in 2001 was established the National Network of Pharmacovigilance that collects the spontaneous reporting of adverse drug reactions. This system has created a network between the Italian Agency of the Drug (AIFA), the 21 regions, 204 local health centers, 112 hospitals, 38 research institutes and 561 pharmaceutical companies.

The National Network of Pharmacovigilance also creates a conjunction with the European EudraVigilance Network, which gathers in a European database the data provided at the national level.

The spontaneous reporting of suspected adverse reactions is an important source of information for Pharmacovigilance to detect potential signs of alarm regarding the use of all medicines available on the national territory. Activation of the National Network of Pharmacovigilance allows a coordination between central and regional authorities and an organization of the flow of informations from and for the different users involved in Pharmacovigilance nationally and internationally.

The current process requires that the records collected by specific reporting forms with only serious and unexpected ADR, should be sent to the responsible of Pharmacovigilance (for each Hospital and ASL) which send them to AIFA on the website of the Ministry of Health.

Are, however, reported all suspected adverse reactions (serious and not serious, expected and unexpected) from all vaccines and medicines under intensive monitoring.

Voluntary reporting is a communication on occurrence of an adverse reaction that is suspected occurred after taking a drug. It is a simple, practical and cost applicable to all types of patients and all drugs, which can detect potential signs of alarm.
The quality and completeness of the information are essential.
The quality is determined by the adequacy of the data, their completeness and accuracy with which they appear. Each section of the reporting form must be properly completed. Incomplete data makes impossible to assess the causal link between drug and reaction.
A single model form is established for the reporting of suspected adverse reactions to all drugs, including vaccines, in order to quickly identify and correct any errors in the immunization program to ensure a more efficient and safe sanitary system.

The intensive monitoring

Legislative Decree 95/2003 introduced the concept of "intensive monitoring", with the first list of drugs under greater attention on the basis of their recent introduction in marketing.
Indeed, the categories of drugs with innovative mechanisms of action or belonging to new chemical or biological classes can be characterized by a non-predictable risk of serious reactions.
In these situations, monitoring of security is based primarily on the collection of spontaneous reports of ADR and the conduct of studies of Pharmacovigilance.
In November 2003 was published the first list of drugs that have to be monitored intensively, according to Lgs. D. 95/2003. This list has been updated several times in recent years, with the inclusion of new drugs, but also of drugs with new indications, new posology or new mode of administration, to increase surveillance for all situations with limited experience in clinical trials in pre-marketing.
Particular interest concerns vaccines: these drugs are under constant monitoring by national authorities and international companies: in fact, they may show variability in their production and it also has strong interest in the monitoring of the safety of immunization programs.
ADR could also be the light of an error in the program of immunization in one of its phases: from the preparation of the product (lack of quality due to lot), during handling and preparation (vaccines administered without having shaken the package before the administration or the use of frozen vaccines that can increase the risk of local reactions and abscesses), finally, in the phase of administration (too superficial injection).

The priority of the monitoring of ADR to vaccines is, therefore, related to identification of the errors of the program of immunization and their timely correction.

Objectives

The appropriate use of medicines requires, in management of drug, attention of sanitary professions not only to the economic aspects, but especially to the parameters of tolerability and toxicity to use drug as safe as possible for the health of the patient.
Pharmacovigilance is a key instrument for enhancing information on security and on related clinical use of medicines.
The voluntary reporting of suspected adverse drug reactions is the foundation of systems of Pharmacovigilance (9).
The assessment of reporting lead to acknowledge the risks of iatrogenic disease and represents for all sanitary professions a valuable stimulus to pay attention to the proper use of medicines (10).
We have analysed, through the monitoring of local and national data, reports of suspected adverse reactions in ASL Sa/2, pointing out similarities or deviations from the national and regional data.

Methods

The data collected are derived from the database of Pharmacovigilance, available on the website of the Ministry of Health, following the inclusion of appropriate password. The National Network of Pharmacovigilance is an effective tool for improving the monitoring of adverse reactions to medicines, because allows, through the input on telematic ways, the management boards of reporting suspected adverse reaction, their display and editing, and research of data in clinical studies.
To get useful data in this research we extrapolated all adverse reactions reported since January 2005 to December 2008 relating to the national territory, in Campania and ASL Sa/2. Therefore, from each reported ADR we obtained: date of reaction, age, sex, region, severity, outcome, ATC code on drug suspicion, the source of reporting. The results have been developed and incorporated in Excel tables.

Results

Reports of suspected adverse reactions to drugs registered in the National Network of Pharmacovigilance in 2005 were a total of 5958, corresponding to a signalling rate of 8,65/100.000 inhabitants. In the following year, the number of reports has increased to 6647 (with a corresponding rate of

reporting of 9,69/100.000 inhabitants), in 2007 there was a further increase of the alerts, with a total of 9433 and a signalling rate equal to 13,64 reports/100.000 inhabitants and in 2008 the total number of records was 9922, with a rate equal to 14,44 reports/100.000 inhabitants (Figure 1).

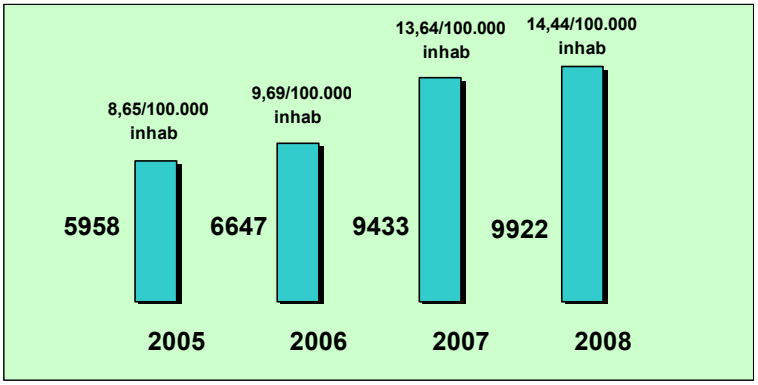

Figure 1 – ADR and their signalling rate

According to WHO, the optimal rate of reported adverse drug reactions, so that the community can be reasonably sure that important ADR are identified in a sufficiently short time, is 30 reports/100.000 inhabitants (11).

From the evidence we can observe a general under-reporting in Italy, with values far from gold standard. However, the increasing number of reports received by the National Network of Pharmacovigilance is a positive data to reach in the near future optimal signalling rates.

From Classification of ADR by gravity response (Figure 2), there is a prevalence of non-serious reactions (73% of total ADR in 2008), the serious represent 24% of total, deaths 1.2%.

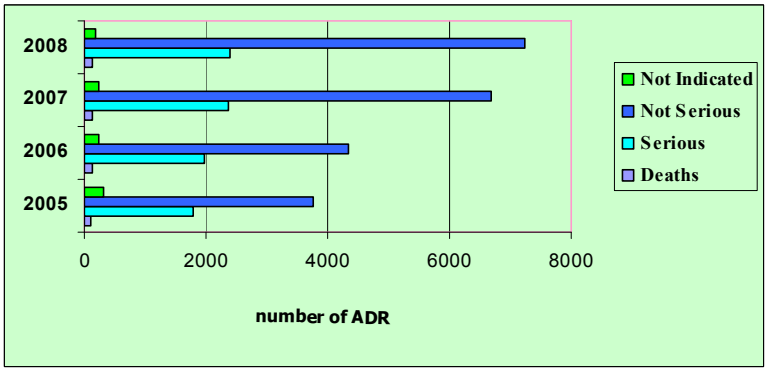

Figure 2 – Classification of ADR by gravity response

Whereas the WHO states that a system of Pharmacovigilance is effective if 30% of reports concerning serious ADR, since in this case we can easily identify important ADR, this value is particularly important in achieving the gold standard.
In relation to the source (Figure 3) the largest number of reports were filed by hospital (5219 records), and 1690 reports were received from doctors in general medicine, 1014 by specialists and 553 records from other medical (doctors of prevention districts, military doctors, doctors of medical services).

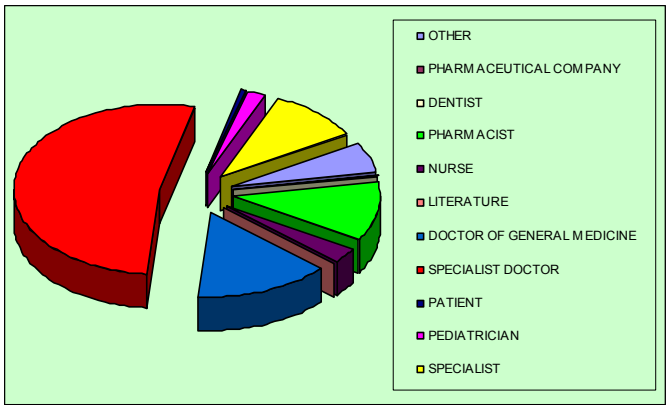

Figure 3 – Sources of ADR in 2008

In recent years we have found in Campania an increase in the number of reports of suspected adverse reactions (Figure 4).

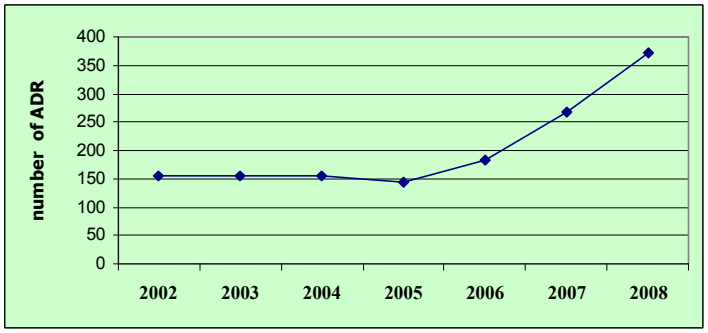

Figure 4 – ADR in Campania

The upward trend is correlated with the training activities at national level (by the Ministry of Health) and regional or individual health care facilities, targeting all health professionals involved in the management of drugs, and also with the Regional Center of Pharmacovigilance, whose activities started since 2005.

The spontaneous reportings of suspected adverse reaction in ASL Sa/2 received by the National Network of Pharmacovigilance in 2008 were 31, including 6 serious and 25 non serious. Compared to other ASL of Campania, ASL Sa/2 presented the highest number of ADR in the year 2008, with a signalling rate equal to 6,76 reports/100.000 inhabitants.
If we consider the optimal level defined by WHO of 30 reports/100.000 inhabitants, it is evident the phenomenon of under-reporting (12), observed in general in Italy, but ASL Sa/2 has a rate alert, strong growth in recent years (an increase of over 30% between 2007 and 2008), above the average of the region (Figure 5).

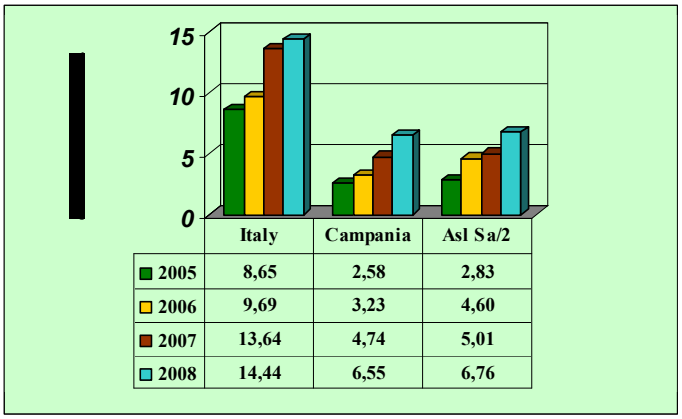

Figure 5 – Signalling rates of ADR in Italy, Campania, Asl Sa/2

We then evaluated data reporting in ASL Sa/2 in the period 2005/2008 in relation to the source (Figure 6).

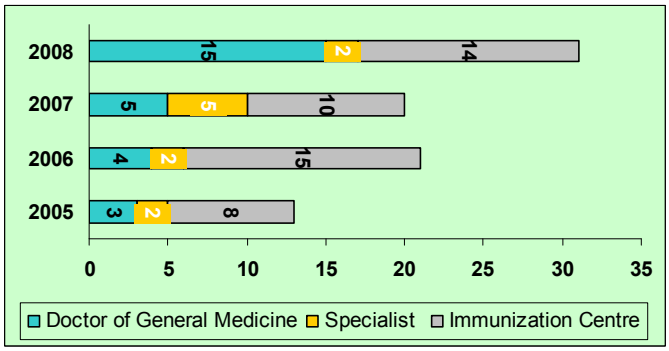

Figure 6 – The sources of ADR in ASL Sa/2

The highest number of ADR comes from vaccination centers, reflecting medical reports of suspected adverse reaction to vaccines, drugs under

intensive monitoring, related to any reaction, whether serious or not serious, expected or unexpected.
In the period 2005/2008, the increased frequency of reporting was found for age less than one year and in the age group between 1 and 15 years, reflecting the high number of reports related to vaccines (Figure 7). The predominance of reports covered the women (63%).

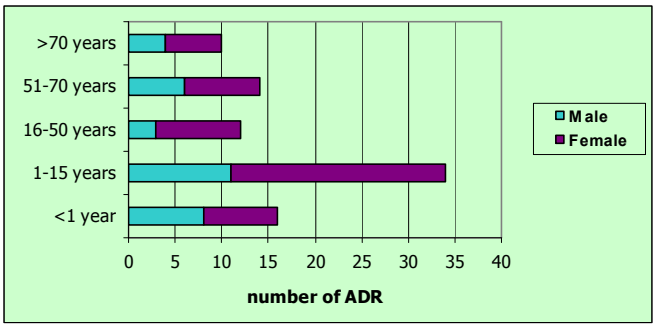

Figure 7 – Classification of ADR for age and sex

The reports received during the period 2005/2008 in ASL Sa/2 were mainly related to vaccines (92% in 2005, 77% in 2006, 50% in 2007, 51% in 2008) of which, under intensive monitoring, was reported all adverse reaction (the most frequent: fever, vomiting, nausea, asthenia, exanthematic reactions, redness at the inoculation).
However, there are increasing reports for other ATC categories, especially J (antibiotics), M (anti-inflammatory), A (gastric protectors). Reports received in the period 2005-2008 for adverse reactions of serious nature are 24%, not serious are 86% of cases.

Discussion

All medicines, including those for the treatment of simple illnesses (colds, pain of various kinds, etc...), represent a risk, in varying degrees, to cause adverse reactions (13). It is desirable, therefore, in use of all drugs, to consider the risk-benefit ratio, understanding the potential adverse event and comparing the severity of the disease for which medication is administered (14).
It is also necessary to make a close surveillance on the true incidence of adverse events that may occur during drug therapies. In ASL Sa/2, we observed, in recent years, an increase in number of reports of suspected ADR from a minimum of 13 reports in 2005 to 31 reports received in 2008. These results were possible thanks to the activities of training and informations implemented by ASL itself, which led to greater awareness

among health professionals and citizens around the importance of reporting of adverse reactions following the administration of drugs, leaving hope for a further increase in the future.
Among the initiatives in this regard, we realised a "Project for Education for the proper use of the drug", in 2008, with a competition on the subject for students of high schools, distribution of material (brochures and CD) and sample surveys, but also information for the adult citizens of local communities (elderly, hospitalized patients, sports). In addition, procedures were implemented to encourage the participation of doctors of general medicine, of pediatricians and pharmacists, such as training and study on pharmacovigilance.
Through these activities in ASL Sa/2, there has been an encouraging increase of reporting of ADR in recent years and, at the same time, a greater effort in promoting the right to health also represented by an effective system of Pharmacovigilance.
In conclusion, therefore, it can be said that the development of an efficient and capillary system of Pharmacovigilance allows not only to establish the incidence of adverse drug reactions in a population, but also to have greater attention and implement all appropriate measures to prevent damage from drugs in the population.

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