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5-Year Trend of Reporting Adverse Drug Reaction: an Italian General Practice Experience

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Abstract

Background: Adverse Drug Reactions (ADRs) underreporting is a serious drawback of the pharmacovigilance system. Spontaneous reporting of ADRs is a valid instrument to enhance pharmacovigilance.

Objectives: To avoid prescribing again to patients the drug that caused them the ADRs, to evaluate spontaneous reporting of ADRs by patients to their General Practitioner (GP); to investigate the most involved Anatomical Therapeutic Chemical (ATC) classes in ADR signaling; to focus on sex-related differences in reporting ADRs; to propose suggestions to increase awareness about the issue.

Methods: All ADRs reports collected by an Italian GP, during a period of five years, had been recorded by himself into his own array of records and then evaluated. The database of case histories in which data were filed allows data mining through queries formulated in SQL (Structured Query Language). We analyzed the numbers of prescriptions for each class of every ATC group in order to demonstrate the most involved ATC classes in ADR signaling.

Results: We observed a total of 1278 ADRs for 11596 medical acts (11.02 ADRs per 100 consultations); four ATC groups (N, J, C, M) were responsible for the majority of ADR reports. Women had a higher reporting aptitude than men; 58% of women versus 38.9% of men has done at least one ADR report.

Conclusion: The autonomous attention of the GP has led to more knowledge about the issue, the importance of reporting ADRs has been stressed in his local community, and, therefore, he has definitely changed the quality of life of his patients. Our study demonstrates that a close collaboration between GPs, patients and Pharmacovigilance Authorities may lead to a better pharmacovigilance practice, and may provide useful data about reporting trend and about unknown drug adverse reactions. We suggest to offer GPs some training courses to raise awareness to the problem of underreporting.

Keywords: *Pharmacovigilance; General Practitioner; ADRs; Sex-Related Reporting Trend; Italian Pharmacovigilance; ATC Classes*

Introduction

Pharmacovigilance is an integral part of drug therapy [1]. In various studies, adverse drug reactions (ADRs) have been implicated as a leading cause of considerable morbidity and mortality [2]. According to WHO an Adverse Drug Reaction (ADR) is defined as a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man, whilst an adverse event or experience is defined as any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment [3].

Pre-marketing trials are, generally, predictive of a new drug efficacy for the approved indications; patients are treated in hospital, according to specific and restrictive protocols and they are part of a selected population. After marketing, the drug is prescribed by doctors

with different experiences and, above all, it is given to a heterogeneous population (that includes men and women, elderly patients and children, pregnant women, people with concomitant diseases). Besides, the drug is often used together with other drugs, so the possibility of negative interactions arises. This is why ADRs that are not common during pre-marketing trials, often become relevant, in some groups of patients, after the marketing. Eventually, in pre-marketing trials, patients are treated for short periods so long-latency ADRs can't be evidenced.

Pharmacovigilance, as defined by WHO (WHO Guidelines, 2000), is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem; moreover, its aim is to disseminate information and education [4]. Methods in Pharmacovigilance are: spontaneous reporting, prescription event monitoring, case control surveillance and record linkage (automated population databases; 'data mining').

As told above, spontaneous reporting of ADRs is a valid instrument for Pharmacovigilance: it is the simplest and cheapest method to prematurely identify an alert signal related to drugs toxicity. As claimed by Rajakannan., *et al*. the reported incidence of ADRs ranges from 3.7% to 30%; in studies where ADRs documentation depends on voluntary reporting by physicians, it was observed that underreporting was a major obstacle in the estimation of the true incidence of ADRs. ADRs adversely affect quality of life and results in direct and indirect cost to the health care system [5].

Spontaneous reporting is the most widely employed method for monitoring entire populations for the safety of drugs in real life use [6].

Compared to other methods, spontaneous reporting is very cheap to enhance and with this system, all medicines may be monitored in a population on an ongoing basis [7]. Despite inherent limitations, spontaneous reporting of ADRs by Physicians remains the only surveillance system capable of routinely monitoring the safety of drugs. This approach allows not only identification of iatrogenic risks or syndromes, but may also permit comparison of ADRs characteristics between groups of patients [8]. As recently claimed by Tandon., *et al*. the lower reporting from indoor patients can be overcome by monitoring computerized medical records or by developing a system of active screening of all medical records of inpatients for ADRs [9]. Factors that discourage reporting include uncertainty about the causal relationship between the ADR and the drug, forgetfulness, diffidence in reporting known ADRs and lack of time [10]. Unfortunately, it must be said that the amount of time dedicated to teaching of PV in undergraduate and postgraduate courses in Pharmacology is low [11].

In July 2012, new pharmacovigilance legislation come into effect across the EU [12]. In developing the new guidance, the MHRA (Medicines and Healthcare products Regulatory Agency) has been working closely with other Member States and the EMA, who have set up six project teams to lead on various areas to help oversee implementation. The project teams are focused on: audit and inspection, Periodic Safety Update Reports (PSURs), Adverse Drug Reaction (ADR) reporting and signal management, risk minimization, Risk Management Plans (RMPs), and post-authorization studies, committees and referrals, communications and transparency, including web portals.

The major change for the reporting of suspected ADRs will be the centralized reporting to the Eudravigilance database at the EMA. Another major change is the inclusion of reports from patients as valid, reportable ADRs.

Aim of the Study

Our study aims are to measure the reporting trend of ADRs spontaneously referred from patients to their General Practitioner (GP); to demonstrate the most involved Anatomical Therapeutic Chemical (ATC) classes (WHO-Anatomical Therapeutic Chemical Classification System used for the classification of drugs) [13,14] in ADR signaling; to analyze the ADRs reporting trend focusing on sex-related differences; to emphasize the importance of make GPs aware of the problem of underreporting; to propose suggestions to sensitize GPs.

Methods

Study design

The Study was carried out by the GP himself who decided to carefully record all the ADRs reported by his patients during a long period of time. His primary aim was to note and record his patients' tolerability towards the drugs he commonly prescribed, to avoid prescribing them again in case of suspected adverse reactions.

After this 5-years recording period he officially requested the approval for data elaboration to his patients (informed written consent obtained by his patients) and to the local Ethical Committee. His proposal was approved during the local Ethical Committee session held on March 7th, 2008.

The data elaboration, therefore, has been performed with the approval of the local Ethic Committee (San Martino Hospital, Genoa - Ethic Committee). The study was designed, and performed in accordance with the Ethical Principles laid down in the Declaration of Helsinki.

Study Population

From January 2002 to May 2007, a Genoese (Genoa, Liguria, Italy) General Practitioner (GP) collected by himself into his own array of records, all drugs adverse effects spontaneously reported by his own patients. According to the Italian law, a GP is allowed a maximum of 1,500 (1,800 in some special cases) patients on his or her list. Citizens are entitled to the choice of general practitioner. The choice can be achieved within the municipality of residence or domicile in health. In May 2007 the Genoese GP (G-GP), who took an active part in the study, had 1091 patients in his list, 52% of them were females (573/1091) and 48% were males (518/1091).

During the study period, the GP annually saw 90% of his patients; each of whom usually came to the doctor's practice an average of 11 times per year.

Each patient has the reporting of 17 health diseases (chronic, on-going or resolved). Annually about 22,100 drugs were prescribed.

Data collection

The ADR reports were inserted in a computerized database; drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The computerized database used was programmed to record ADR reports every five years. Data concerning the period 2007 - 2012 are not available yet. The computerized database of case histories in which data were filed allows data mining through queries formulated in SQL (Structured Query Language). Its main properties are: problem-oriented subdivision of case histories, automatic registration and printing of prescriptions and clinical investigations, continuative-therapy management, reporting of adverse reactions (to the active principle or to the drug class), automatic signaling of well-known interactions (by blocking prescriptions system), completely automatic management of medical exemptions, prevention and management of chronic diseases, automatic updating of the annual Drugs Handbook.

This survey takes account of all ADR reports, even of those that are considered not serious, not health-threatening and already known, but important in the daily management of a single patient. Every ADR reported by patients was collected and classified as either serious or not serious and as labeled or unlabeled.

G-GP collected ADRs reports during his clinical activity, so the process of inserting ADRs into a computerized database did not interfere with his practice and did not take time for diagnosis activity and patients' care. Patients had been educated by the GP to report any ADR appeared; ADR reports were assessed according to the physicians' opinion of the relationship between the suspect drug and the adverse event. GP remained in contact with pharmacologists for all the period in study in order to ask for advice when reported ADRs were not so clearly attributable to a specific therapy or in case of poly-therapy or co-morbidities. When more suspect drugs were indicated as responsible for causing ADRs, judgments made by physicians were compared with the scores obtained for each drug by a causality assessment method (Algorithm of Naranjo).

To demonstrate the most involved Anatomical Therapeutic Chemical (ATC) classes in ADR signaling, the Anatomical Therapeutic Chemical Classification System was used.

Therefore, the GP analyzed the number of ADRs occurred during his clinical practice, he also investigated the most involved ATC drug classes and he evaluated the differences in reporting related to sex.

Results

During the five-year study period, the average value of the total patients in the care of the G-GP was 1054.1. As described in table 1, patients have been subdivided per year; we have considered the average number of men and women in care, which was respectively of 52.6% (554.8/1054.1) and of 47.4% (499.3/1054.1). Every year, women were more than men.

Table 1 shows the distribution of G-GP's patients per year.

	2002	2003	2004	2005	2006	2007	Average of total patients
Females	533	535	550	567	571	573	554.8
Males	468	491	494	509	516	518	499.3
Total per year	1001	1026	1044	1076	1087	1091	1054.1

Table 1: *Number of patients, subdivided by sex: distribution per year.*

Besides, 72% of them were aged less than 65, while 28% were aged more than 65 years.

We observed a total of 1278 ADRs for 11596 medical acts (11.02 ADRs per 100 consultations). During the study period, women reported 939 ADRs (73.5% of the total ADRs number) and men reported 339 ADRs (26.5%).

Table 2 shows the number of ADRs reported for each ATC group. Number of ADRs reports has been compared to the number of prescriptions (boxes), giving a ratio which represents the effective ADRs burden for each ATC group.

ATC Group	Number of ADR Reports	Number of Prescriptions (Boxes)	ADR/Boxes (%)
A - Alimentary tract and metabolism	91	21987	0.4
B - Blood and blood forming organs	50	7117	0.7
C - Cardiovascular system	245	45426	0.5
D - Dermatologicals	28	1698	1.6
G - Genito-urinary system and sex hormones	62	7430	0.8
H - Systemic hormonal preparations, excluding sex hormones and insulins	30	4311	0.7
J – Anti-infectives for systemic use	210	9344	2.2
L - Antineoplastic and immunomodulating agents	7	740	0.9
M - Musculo-skeletal system	202	5331	3.8
N - Nervous system	267	15012	1.8
P - Antiparasitic products, insecticides and repellents	6	153	3.9
R - Respiratory system	54	6107	0.9
S - Sensory organs	17	2288	0.7
V – Various	9	82	11.0
Total	1278	127026	

Table 2: *ADRs reports for each ATC group compared with the number of drug boxes prescribed.*

Data are expressed as a ratio (%).

Table 2 shows that 4 ATC groups are responsible for the majority of ADRs reports: N (neurological drugs) 267 reports, C (cardiovascular drugs) 245 reports J, (anti-infective drugs) 210 reports, M (musculoskeletal drugs) 202 reports.

We have more specifically analyzed N, C, J and M ATC groups in table 3, which reports the number of ADRs for each class compared to the total number of ADRs reports of the ATC group, giving a ratio.

The same calculation has been made for the number of boxes prescribed. We have analyzed the numbers of prescriptions (number of boxes) for each class of every ATC group. The ratio has been obtained comparing the number of prescriptions for each class to the total number of boxes prescribed for each ATC group. Besides, in the last column, we have also calculated the number of ADRs compared to the number of prescriptions for each group and for each class of the same group, giving a ratio. This ratio shows the proportions of ADRs reporting based on the prescriptions and could give a realistic estimation of what GPs may expect to deal with, during their clinical practice.

The choice of the four classes examined in table 3 was made on the basis of the most prescribed drugs or of the statistical significance performed using chi-square test.

Classes		Number of ADR reports	% ADR	N. of prescriptions	% prescriptions	% ADR/ prescriptions
Analgesics (N02)	**ATC Group N**	131	49.1	2123	14.1	6.2(*)
Antiepileptics (N03)		27	10.1	2651	17.7	1
Antiparkinsonians (N04)		2	0.7	347	2.3	0.6
Psycholeptics (N05)		47	17.6	3929	26.2	1.2
Psychoanaleptics (N06)		54	20.2	5076	33.8	1
Others		6	2.2	886	5.9	0.7
Total Group N		**267**		**15012**	**1,8**	
Cardiac therapy (C01)	**ATC Group C**	13	5.3	1941	4.3	0.7
Antihypertensives (C02)		5	2	1255	2.8	0.4
Diuretics (C03)		16	6.5	3244	7.1	0.5
Peripheral vasodilators (C04)		8	3.3	118	0.3	6.8(*)
Vasoprotectives (C05)		20	8.2	688	1.5	2.9(*)
Beta-blocking agents (C07)		14	5.7	3511	7.7	0.4
Calcium-channel blockers (C08)		46	18.8	9509	20.9	0.5
Agents acting on the renin- angiotensin system (C09)		72	29.4	20444	45	0.4
Lipid modifying agents (C10)		51	20.8	4716	10.4	1.1
Total Group C		**245**		**45426**	**0.5**	
Antibacterials (J01)	**ATC Group J**	193	91.9	8606	92.1	2.2
Antimycotics (J02)		2	1	347	3.7	0.6
Antivirals (J05)		3	1.4	203	2.2	1.5
Immune Sera and Immunoglobulins (J06)		1	0.5	92	1	1.1
Vaccines (J07)		11	5.2	96	1	11.5(*)
Total Group J		**210**		**9344**	**2.2**	
Anti-Inflammatory Products (M01)	**ATC Group M**	162	80.2	3798	71.2	4.3(*)
Topical Products (M02)		17	8.4	155	2.9	11(*)
Muscle Relaxants (M03)		2	1	265	5	0.8
Antigout Drugs (M04)		2	1	272	5.1	0.7
Bisphosphonates (Mo5ba)		19	9.4	841	15.8	2.3
Total Group M		**202**		**5331**	**3.8**	

Table 3: *Number of ADRs for each class, number of prescriptions and ratios (%).*

(*): Statistical significance $p < 0.05$, performed with chi-square Test, for single ATC Group.

Discussion

Strengths and limitations of the study

Data analyzed are not recent and does not examine the latest years. This survey refers to data collected during a five-year period, from 2002 to 2007. Data processing took a long time due to the huge number of reports received by the GP, and also because the database used was programmed to record ADR reports every five years. Our study aims for a retrospective assessment, in part forced by the computerized program used; and in part planned and projected to provide a wider and more truthful evaluation.

Obviously, data are affected by evident biases due to several reasons: the different patients' inclination in reporting ADRs (e.g. sex-related ADRs reporting trend, see below); the fact that patients in study had been encouraged to report ADRs, may have made them particularly sensitive and suitable to report; last but not least, ADRs were firstly evaluated by the G-GP so final data derived also from his personal judgment. The interpretation of spontaneous ADR reports, potentially subject to inherent biases and confounding factors, depends heavily on reliable estimates of the population exposed to drugs. It is also fundamental to read our results taking into consideration that all the ADRs reported by patients were recorded without any distinction, for obvious reasons of real clinical practice, including short-term therapies (such as pesticides or dermatological products) and chronic therapies (anti-hypertensives, anti-epileptics etc).

ADRs reporting trend

Unfortunately, in Italy, many GPs are not used to reporting every spontaneous or not spontaneous ADR to the pharmacovigilance authorities. A possible reason of ADRs under-reporting might be that GPs usually think that ADRs are already well-known; they do not want to alarm Authorities for no reason, and they work autonomously attempting to ease Pharmacologist and local pharmacovigilance authorities' burdens. They are probably not sufficiently aware that their contribution is essential. This fact drastically reduces awareness and knowledge about drugs and possible interactions.

Obviously, the relationship between GPs and patients influences the collection of ADR: motivated GPs sensitize their patients to the issue, and make them more suitable to report ADRs. However, we believe that the type of relationship could influence not only the reporting process, but particularly the daily clinical practice. Our research sets out from the assumption that a trusting relationship should exist independently of anything else inasmuch as it represents the basis of the clinical activity.

In 2007 Italian reports of suspected adverse drug reactions (ADRs) raised of 49% compared the previous 2 years (2005 and 2006), equal to 9740 reports per year and to a reporting rate of 165 reports per million inhabitants [15,16].

Overall, in 2010, Italian reporting raised to 300 reports per million inhabitants. This rate is considered by the World Health Organization (WHO) as the gold standard for an efficient pharmacovigilance system. In 2007, two Italian regions, Tuscana (386 reports) and Lombardia (370 reports), even exceeded this value. However, almost all Italian regions recorded an increase of reporting compared to the previous years, and, in the case of 5 regions (Lombardia, Toscana, Lazio, Piemonte, Puglia, and Campania), the result of 2007 was the best ever reached in those regions. The reports of 2011 confirmed the growing trend of recent years.

Liguria region recorded a low value of ADR reporting in 2007 (< 100 ADR reports per million inhabitants), lower than WHO gold standard of 300 reports per million inhabitants and lower than other Italian regions. Although this reporting value has risen during the next years, these data show the need to improve and enhance ADRs reporting quality and quantity in Liguria region.

Analysis of the most involved Anatomical Therapeutic Chemical (ATC) classes

Considering the number of ADRs in relation to the drug boxes prescribed, class V, P and D drugs show the highest percent (11.0%; 3.9%; 1.6%, respectively) of ADR reports. This datum, however, is not reliable by the fact that most of these drugs are over-the-counter (OTC); reports are probably over-esteemed because they refer also to drugs not prescribed by the G-GP, but bought by the patients themselves without prescription.

Collected data allow us to observe that 49.1% of the total ADRs for N group could be referred to Analgesics. Data about Psychoanaleptics are quite relevant too (20.2%); ADRs reported could be considered "common adverse reactions" (e.g. headache, dry mouth…).

Although the numbers of ADR reports due to class C drugs is quite high, the presence of many prescriptions gives a not so significant ratio (0.5%).

Class C drugs analysis has evidenced unexpected results. It's surprising an incidence of 8.2% of ADRs relating to vasoprotective agents (C05; active principle: diosmin, which is an OTC drug). These drugs should improve the micro-circulation and they are considered well-tolerated, but, in our study, they've been connected to symptoms like: heartburn, fainting, hives, cough with expiratory whistles, asthma and also an isolated case of inferior limbs pain with increased CPK.

A ratio of 20.8% of ADRs emerges from our data in regard to "drugs on lipidic metabolism" (C10 - statins, in particular) and this fact calls for measures in limiting their use. On the other hand the high incidence of ADRs induced by peripheral vasodilators (C04) is very predictable (3.3%).

We have avoided focusing on those J group drugs, prescribed rarely. We have noticed that vaccines cause adverse reactions very commonly. In some cases serious reactions have occurred (life-threatening reactions or reactions that have implied hospitalization). In particular a 55 years-old woman developed, after flu vaccine administration, facial angioedema and hives. Another woman (77 years old) developed high temperature (more than 38 degrees), fainting and she has been hospitalized. High temperature is frequently reported after flu vaccination.

Concerning M group, it's really surprising the high incidence of ADRs (8.4%) related to topical products relieving musculoskeletal pain (M02). These topical products, usually considered safe for their route of administration, are not so harmless. Some cases of local rash have been described, sometimes associated with angioedema, aphthous stomatitis, periorbital and facial oedema. Even if these reported ADRs were generally not serious, we should keep into consideration that pruritus could be very annoying for the patient and may lead to a rejection of the ongoing therapy.

Sex-related reporting trend

Collected data show that women have a higher reporting aptitude than men. It emerges from our standardized data that women are more predisposed to signal ADRs: 58% of women versus 38.9% of men has done an ADR report.

This fact can be ascribed to many factors: the first one is the higher dose assumed in proportion compared to males; sex differences in pharmacokinetics and pharmacodynamics, as function of multiple physiologic and body composition characteristics, may contribute to individual differences in drug efficacy and toxicity [17,18]; however, how these differences result in an increased risk of ADRs is not clear [19]. Several scientific articles indicate that females experience a higher incidence of adverse drug reactions (ADRs) than does the males; as affirmed by Zopf., *et al*. female patients (aged more than 55) have a higher ADR risk compared to males [20]. This study also affirms that neither age nor number of prescriptions is related to the distinctly higher incidence of ADRs in female subjects.

Besides all, women take drugs more frequently; a recent survey by Athanasopoulos., *et al*. [21] has assessed that that Greek women consume more drugs and present different medication patterns, as compared to men. This study confirms what had been already affirmed by Simoni-Wastila in 2000: women are 48% more likely than men to use any abusable prescription drug, controlling for demographics, health status, economic status, and diagnosis [22].

An interesting study carried out by Montastruc., *et al*. have confirmed that gender is an important factor for ADRs related to some classes of drugs [23]. As they affirm, several other factors could explain these gender-related differences: body weight, hormonal levels and drug consumption, higher consulting rates or rates of complaints, and even better compliance with drugs for women.

Our data, performed with statistical analysis (chi-square test), reveal a statistical significance ($p < 0.05$) between women ADRs reporting trend and men one.

Conclusion

Our survey demonstrates that a close collaboration between GPs and patients and between GPs and National Health Pharmacovigilance Authorities may enhance ADRs reporting.

Underreporting is a serious drawback of the Pharmacovigilance system for several reasons, most of which have been described before and concern our personal experience. Biagi C., *et al*. [24] affirm that causes of underreporting may include the belief that: very serious ADRs are well documented by the time a drug is marketed; that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction; that reporting an ADR should only be done if there is certainty that it is related to the use of a particular drug; that a single case that an individual physician might observe could not contribute to medical knowledge, and that it is only necessary to report serious or unexpected ADRs.

The fact that we fell in with an "ideal GP", concentrated on the problem of underreporting, might make our research a theoretical digression about an idyllic pharmacovigilance practice which could be not achievable in other contexts. We think that, instead of considering our study as an unfeasible model of pharmacovigilance practice, it could be more valuable to take our experience as an example to follow.

It would be interesting to investigate, in future researches, some qualitative aspects as the influence of the culture, the context and the doctor-patient relationship in collecting ADR.

In our opinion GPs should take an active part in improving Pharmacovigilance system and they should be aware of the importance of this issue. A possible solution we suggest is to educate GPs, offering them training courses to raise awareness to the problem. After a proper sensitization program, motivation should arise spontaneously.

The autonomous attention of the GP has led to more knowledge about the issue, the importance of reporting ADRs has been stressed in his local community, and, therefore, he has definitely changed the quality of life of his patients. Our study demonstrates that a close collaboration between GPs, patients and Pharmacovigilance Authorities may lead to a better pharmacovigilance practice, and may provide useful data about reporting trend and about unknown drug adverse reactions. We suggest to offer GPs some training courses to raise awareness to the problem of underreporting.

The foresight, attention and dedication of the GP resulted in significant improvements in his clinical practice; our suggestion is therefore to take as an example the model described to provide the scientific community with new information and improve the quality of life of patients and the national health costs.

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