Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions

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Aims Cutaneous manifestations are frequently reported in association with drug use. The aim of this study was to analyse the skin reactions reported to the spontaneous surveillance systems of four Italian regions (Friuli Venezia Giulia, Lombardy, Sicily and the Veneto), and correlate the reports with estimated drug consumption during the same period, paying particular attention to the reactions to antimicrobial agents and nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods All of the adverse drug reactions (ADRs) reported spontaneously between January 1996 and December 1997 to the surveillance systems of four Italian regions (a total population of about 20 million people) were analysed by a panel of experts including dermatologists. On the basis of the Critical Term List of the World Health Organization (WHO), the reactions were classified as either serious or nonserious events. Drug consumption was expressed as a daily defined dose (DDD)/1000 inhabitants/day.

Results A total of 2224 adverse skin reaction reports (44.7% of all of the reported ADRs) were identified, making a reporting rate of about 5.5 per 100 000 inhabitants/year. The female/male ratio was 1.58, and the reporting rate progressively increased with age. The drug categories with the highest number of cutaneous reactions were antimicrobials, followed by NSAIDs, analgesics and radiology contrast media. There was a total of 372 (16.9%) serious reaction reports, the most frequent being angioedema (171 cases), erythema multiforme (68 cases) and photosensitivity (37 cases). Co-trimoxazole, followed by the cephalosporins and fluoroquinolones, were associated with the highest consumption-related reporting rate among the antimicrobials, and aspirin and dipyrrone among the NSAIDs and analgesics.

Conclusions Spontaneous reports from four Italian regions revealed that the skin was the organ most frequently affected by ADRs. The paper shows the validity of a regional decentralized system in Italy.

Keywords: adverse drug reaction, skin, spontaneous reporting

Introduction

In recent years many advances have been made in pharmacovigilance by expanding drug safety monitoring systems and by developing education and information activities [1, 2]. Sixty-three countries are currently participating in the WHO International Programme for

Adverse Reaction Monitoring which analyses spontaneously reported suspicions of adverse drug reactions (ADRs) collected within each country [3]. In this database cutaneous manifestations are the most common clinical pattern and account for about 18% of all reported reactions. Skin reactions may range from generally trivial manifestations such as pigmentation, to severe life-threatening events such as toxic epidermal necrolysis [4]. It is widely recognized that their clinical characterization may be unsatisfactory if specialist assessment is lacking [5]. Their impact may be far from negligible in terms of health service use and costs [4, 6].

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Despite their frequency, there is a limited information concerning the spontaneous reporting of skin reactions. In Italy spontaneous reporting of ADRs has been mandatory since 1987. Doctors and pharmacists have to send all suspected ADRs to the Local Health Districts (around 200 in whole country), that forward reports to Ministry of Health [7]. Up to now, the national government has made only a little effort in favour of the system. So four Italian regions (around 80 Health Districts) have organized their reports in a common database for analysis and to provide feedback information to the health professionals.

The aim of this study was to analyse the skin reactions reported to the spontaneous surveillance systems of these four regions and correlate the reports with estimated drug consumption during the same period, paying particular attention to the reactions to antimicrobial agents and nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods

The data were obtained from a database that holds all of the spontaneous reports of adverse drug reactions from four Italian regions (Friuli Venezia Giulia, Lombardy, Sicily and the Veneto). The four regions had an estimated 19 850 000 inhabitants in December 1996 (about 34% of Italian inhabitants), and are the principal contributors to the Italian spontaneous surveillance system (accounting for about 65% of all Italian reports). We analysed the spontaneous reports collected between January 1996 and December 1997. The following information was taken into consideration: reporter category, patient's age and sex, the reporter's diagnosis of ADR, the characteristics of the underlying disease and drug exposure (indication, duration of treatment and dosage).

The drugs were codified following the Italian System Codifa and the Anatomical Therapeutic Chemical classification (ATC). The reactions were codified according to the WHO Adverse Reaction Terminology, and the reports with an ADR belonging to the System Organ Class (SOC) called skin and appendices were selected (SOC code 0100). The reactions were also classified as serious or nonserious events on the basis of the WHO Critical Term List. For the purposes of this analysis, the serious reactions included angioedema, bullous eruptions including specific patterns such as Stevens-Johnson or toxic epidermal necrolysis and less characterized bullous manifestations, pustular rashes, lichenoid dermatitis, erythema nodosum, exfoliative dermatitis, vasculitis including erythema nodosum-like syndrome, and skin necrosis.

The reports were analysed by a panel of experts constituted *ad hoc* for this study and including dermatologists, internists, pharmacologists and pharmacists. Its main task was to check the completeness of the reports

and the terminology of ADRs. The reports with two or more cutaneous symptoms were reviewed by the team and where possible a unique dermatological diagnosis was formulated (e.g. itching and wheals became urticaria or recurrent erythema with vesicle became fixed eruption). If further clinical data were necessary to reach a diagnosis the reporting doctor was contacted. The reports with no temporal correlation between drug exposure and disease onset, a doubtful ADR diagnosis or relating to events obviously due to the underlying disease were excluded.

Drug consumption data were expressed as daily defined dose (DDD)/1000 inhabitants/day. In the case of antimicrobial agents, data were derived from National Health Service drug prescriptions (data not available for Sicily), whereas the data relating to NSAIDs and analgesics were based on pharmacy sales and hospital consumption, therefore including both prescription and nonprescription (self-medication) drug use. In fact many pharmaceutical formulations in these two last categories are available without prescription or are over the counter (OTC) remedies.

Results

During the period under consideration 4974 events were reported to the system, making a mean annual reporting rate of approximately 12.5 per 100 000 inhabitants (female: 14.7; male: 10.1). A total of 2224 reports (44.7%) involved the skin as the target organ, a mean annual reporting rate of 5.5 per 100 000 inhabitants (female: 6.6; male: 4.4). The reported reactions were 7704 (about 1.5 per patient) and of these skin reactions were 2537 (33%) with a mean of about 1.1 per patient. Four hundred 22 patients have simultaneously reactions of the skin and of other organs. Only 20 reports were excluded by the expert panel, mainly because the dates of drug administration and/or of reaction onset were lacking. Therefore the analysis was made on 2204 reports.

About 60% of the reports were sent by hospital doctors (7% by emergency rooms), 37% by general practitioners, and the remaining 3% by specialists and pharmacists; during the same period, about 59% of the reports regarding organ systems other the skin were reported by general practitioners and 32% by hospital doctors (5% by emergency rooms). On the basis of reporter categories, it was estimated that about 53% of reports involved inpatients and 47% outpatients. We did not observe any significant difference (e.g. reaction pattern, involved drugs and severity) between the two groups.

The female/male ratio of 1.58 was similar to that (1.55) observed in the case of reactions affecting other organ systems. The ratio was 0.9 in children aged under 10 years, 1.05 in those under 14 years and 1.63 in adults. The age-specific reporting rate of skin and other organ

system reactions is shown in Figure 1. The total annual reporting rate tended to increase with age, and this is more evident for nonskin organ system.

On the basis of the reporting doctor's judgement and temporal relationship (drug administration and reaction onset dates), one drug was suspected in 1869 reports, two in 279 reports, and three in 56 reports. The drug categories involved (according to the second level of the ATC classification) are listed in Table 1. The most frequently involved categories were antimicrobial agents and NSAIDs. Three hundred and seventy-two (16.9%) of the 2204 analysed reports related to serious adverse reactions and the clinical patterns and suspected drugs are reported in Table 2.

Few of the severe reactions collected by our surveillance system have not been reported before, including pemphigoid reactions to fosinopril, domperidone and hyoscine butylbromide, a bullous eruption associated with clonidine, and lichenoid dermatitis attributed to ramipril. Of the three patients with pemphigoid reactions, two were admitted to the hospital because of the severity of reaction and one of them was a child, 4 years old, treated once with a domperidone suppository. Lichenoid dermatitis occurred after 2 months of treatment with ramipril and the report came from a department of dermatology. In the case of bullous eruption by clonidine a rechallenge was made with the event reappearance.

The reporting rate of reactions to antimicrobials per

Figure 1 Age-specific reporting rates per 100 000 inhabitants/year of cutaneous (■) and nonskin (□) organ system reactions.

Table 1 Distribution of cutaneous ADRs by drug categories and most common clinical patterns. Drug categories with at least 50 reports.

Drug categories	Number of reports (%)	Exanthema n (%)	Urticaria n (%)	Other reaction patterns	
				Non-serious n (%)	Serious n (%)
Antimicrobial agents	1002 (38.6)	359 (35.8)	303 (30.2)	198 (19.8)	142 (14.2)
NSAIDs	499 (19.2)	94 (18.9)	179 (35.9)	108 (21.6)	118 (23.6)
Analgesic drugs	161 (6.2)	38 (23.6)	57 (35.4)	44 (27.4)	22 (13.6)
Radiology contrast agents	71 (2.7)	9 (12.7)	36 (50.7)	18 (25.3)	8 (11.3)
Topical preparations	70 (2.7)	14 (20.0)	13 (18.6)	28 (40.0)	15 (21.4)
Agents acting on the renin-angiotensin system	56 (2.2)	13 (23.2)	5 (8.9)	17 (30.3)	21 (37.6)
Antiepileptics	55 (2.1)	24 (43.6)	6 (10.9)	14 (25.6)	11 (19.9)
Antacids and drugs for peptic ulcer	54 (2.1)	8 (14.8)	22 (40.7)	17 (31.5)	7 (13.0)
Cough and cold preparations	50 (1.9)	20 (40.0)	13 (26.0)	9 (18.0)	8 (16.0)
Others*	577 (22.3)	147 (25.5)	148 (25.6)	198 (34.3)	84 (14.6)
Total**	2595 (100)	726 (28.0)	782 (30.1)	651 (25.1)	436 (16.8)

*Including the following main drug categories: antithrombotic agents (46 reports); vaccines (32); antispasmodics (30); calcium channel antagonists (28); diuretics (28); antifungal agents (27); antigout preparations (21); antiasthmatics (19); antineoplastics (19); antivirals (19); serum lipid reducing agents (19); antihistamines (17). **The total is more than the 2204 reports because 279 reports involves two suspected drugs, and 56 three.

Table 2 Serious adverse skin reactions: suspected drugs. Number of reports in brackets.*Angioedema (171)**

Aspirin (23); nimesulide (12); amoxycillin (8); cotrimoxazole (7); ketoprofen (7); losartan (6); naproxen (6); paracetamol (6); ceftriaxone (5); ampicillin (4); azithromycin (4); niflumic acid (4); ciprofloxacin (3); diclofenac (3); dipyron (3); hydrochlorothiazide (3); iopromide (3); propyphenazone (3); spiramycin (3)

*Erythema multiforme (68)**

Amoxycillin (16); nimesulide (9); aspirin (4); cotrimoxazole (4); ketoprofen (3); naproxen (3)

*Photosensitivity reaction (37)***

Lomefloxacin (9); ketoprofen (6); nimesulide (3); pefloxacin (3); aspirin (2); cotrimoxazole (2); fenofibrate (2); piroxicam (2); promethazine (2)

*Bullous eruption (34)***

Piroxicam (7); clonidine (2); ketoprofen (2); propyphenazone (2); hyaluronidase (2)

*Stevens–Johnson syndrome (26)***

Naproxen (3); paracetamol (3); aspirin (2); amoxycillin (2); carbamazepine (2); ketoprofen (2)

*Exfoliative dermatitis (16)***

Amoxycillin (3); carbamazepine (2)

Vasculitis and erythema nodosum-like syndrome (5)

Ethinylestradiol (2); methimazole (1); miocamycin (1); ticlopidine (1)

Toxic epidermal necrolysis (5)

Allopurinol (2); phenobarbital (1); sulphasalazine (1); vancomycin + piperacillin (1)

Penphigoid reaction (4)

Aspirin (1); domperidone (1); fosinopril (1); hyoscine butylbromide (1)

Lichenoid dermatitis (3)

Captopril + hydrochlorothiazide (1); methyldopa (1); ramipril (1)

Pustular rash (2)

Bacampicillin (1); ciprofloxacin (1)

Chemical burn (1)

Iodine (1)

*Drugs with at least three reports. **Drugs with at least two reports.

DDD/1000 inhabitants/day is shown in Figure 2: cotrimoxazole was associated with the highest reporting rate, followed by cephalosporins, fluoroquinolones, penicillins and macrolides. There were only eight reports of reactions to tetracyclines. Exanthema was the most frequently

Figure 2 Reporting rates of serious (■) and nonserious (□) cutaneous reactions to antimicrobials per DDD/1000 inhabitants/day in Friuli Venezia Giulia, Lombardy and the Veneto. Drug categories with at least 10 reports. Consumption figures derived from prescription data. Total number of reports in brackets.

reported reaction. The most frequently reported serious reactions to antimicrobials were angioedema (61 reports) and erythema multiforme (36), followed by photosensitivity reactions (14), Stevens–Johnson syndrome (12) and bullous eruptions (7). There were no striking differences in terms of the reporting rate and reaction profile of individual drugs in the various antimicrobial categories with the possible exception of the fluoroquinolones. The reaction reporting rate (reports/consumption) was 176.4 for pefloxacin (seven reactions), 92.1 for ciprofloxacin (51), 84.6 for lomefloxacin (28), and less than 60 for ofloxacin, rifloxacin and norfloxacin. As a whole, phototoxic reactions accounted for three out of seven reactions (43%) to pefloxacin and 9 out of a total of 28 reactions (32%) to lomefloxacin; no phototoxic reactions to the other fluoroquinolones were reported. As for aminopenicillins, a similar reaction rate was observed for amoxycillin alone (49.6 reports/DDD/1000 inhabitants/day) and the amoxycillin–clavulanic acid combination (42.4 reports/DDD/1000 inhabitants/day).

Figure 3 shows the reporting rate of reactions to

Figure 3 Reporting rates of serious (■) and nonserious (□) cutaneous reactions to NSAIDs and analgesics per DDD/1000 inhabitants/day in Friuli Venezia Giulia, Lombardy, Sicily and the Veneto. Drugs with at least 10 reports. Consumption figures derived from pharmacy sales and hospital prescriptions. Total number of reports in brackets.

NSAIDs and analgesics per DDD/1000 inhabitants/day. Aspirin and dipyrrone were associated with more than twice the number of reactions compared with the other NSAIDs. Fewer than 10 reactions were reported in the case of tenoxicam (8), flurbiprofen (7), indomethacin (6), nabumetone (3) and meloxicam (1) and these drugs are not considered in Figure 3. Urticaria was the most frequently reported reaction; the most frequently reported serious reactions were angioedema (60 reports) and erythema multiforme (21), followed by photosensitivity reactions (14), Stevens–Johnson syndrome (11) and bullous eruption (11).

Discussion

Our analysis confirms that skin reactions are the most frequent clinical manifestations reported in the context of a spontaneous surveillance system, accounting for more than 30% of all the reported adverse events. The proportion is higher than in other countries, where skin reactions usually represent 10% to 20% of all reported reactions [8–13]. This may reflect the over-reporting of skin reactions *per se* or the under-reporting of other organ reactions. The latter is the most likely explanation. The four analysed regions are the principal contributors to the Italian spontaneous surveillance system (65% of all Italian reports) and are representative of the Italian population. Nevertheless the overall reporting rate was rather low being only one-third of that in the United Kingdom [3]. It is easier to recognize and report cutaneous adverse reactions than those involving other organ systems and

they may be less likely to be under-reported. Nevertheless, some indications that skin reactions may have been under-reported did emerge from our survey. In particular, only five cases of toxic epidermal necrolysis were collected from a population base of about 20 million people. This is clearly below the expected number of cases since the incidence of the reaction in Italy has been estimated at about one case per million people per year [14], suggesting that only about one in 10 severe reactions may actually be reported. This observation should caution the reader about the limitations of data obtained from spontaneous surveillance systems [15]. These systems should be viewed as *signal* generation tools [16] which do not allow reliable estimates of reaction rates and which involve a degree of aetiologic inaccuracy as documented in our survey by the number of reports with more than one drug suspected. In spite of these limitations, the analysis of spontaneous reports may provide useful indications for reaction patterns.

As for the reporting pattern, at variance with reactions to other organ systems, hospital doctors contributed a higher proportion of skin reaction reports than general practitioners. Cutaneous reactions are frequently observed in a hospital setting. In the Boston Collaborative Drug Surveillance Program, it was found that skin reactions involved about 2% of over 37 000 hospitalized patients [17], and a comprehensive hospital-based monitoring system in Berne recorded a total of 1317 definitely or probably drug-induced skin reactions occurring during the hospitalization of 48 005 consecutively admitted patients [18]. It has been suggested that the rate of skin reactions in inpatients may be higher compared with outpatients [19]. Hospitalized patients may have more concurrent diseases (e.g. severe systemic infections or immunological disorders), which may interact to cause skin reactions [20–22].

In agreement with the data published in a number of other studies [8–12, 18, 23] the reporting rate in our surveillance system tended to increase with age. The increased consumption of drugs with age may at least partially account for age-related variations [19, 24–26] but there are analyses suggesting that, depending on the drug involved, age *per se* may or may not be an independent risk factor for the development of adverse drug reactions [24–26]. Our data suggest that this last observation is more evident for nonskin organ system reactions.

In accordance with the experience of other surveillance systems [8–12], there was a remarkable preponderance of females, the female/male sex ratio being about 1.6. A ratio of 1.5 was reported in the Boston Collaborative Drug Surveillance Program surveying a defined base of hospitalized patients [17]. The greater consumption of medications by women and the unbalanced sex ratio in

the elderly population may at least partly account for the excess of reports in women. Interestingly, we found that the female/male ratio of reported skin reactions in children aged under 10 years was about 0.9.

Antimicrobial agents were most frequently reported as being responsible for cutaneous reactions; together with NSAIDs and analgesics, they accounted for more than 70% of all of the reported reactions. With few exceptions [27, 28], antimicrobial agents are generally the most frequent cause of adverse skin reactions reported in spontaneous surveillance [8–12] or hospital incidence systems [17, 18]. A higher proportion of minor events was reported in association with antimicrobial agents than with NSAIDs; moreover, exanthematic reactions accounted for more than 35% of all the reactions to antimicrobial agents and only 19% of the reactions to NSAIDs. It is frequently difficult to distinguish the role of drugs from that attributed to the underlying disease in febrile patients developing an exanthematic reaction and taking antimicrobial agents. An interaction between infection and drug exposure has been proposed as a possible mechanism for the development of drug-related exanthematic reactions in the course of some viral infections [19, 29–31], the prototype of such an interaction being ampicillin-associated exanthema in patients with infectious mononucleosis [29].

When adjusted for drug prescriptions, our data suggest higher reaction rates for cotrimoxazole, cephalosporins and fluoroquinolones. The limitations of relative reaction rates based on spontaneous reporting and drug sales figures are well known [32], but it is reassuring to find that our data are roughly in agreement with a recent survey of the incidence rates for skin reactions to antimicrobial agents based on computerized data from Dutch general practitioners [19], which showed higher adjusted incidence density rates for sulphonamides, followed by aminopenicillins and fluoroquinolones. No reaction to cephalosporins was observed in the Dutch study, but the population base was relatively small and it can be expected that cephalosporins are not widely prescribed among outpatients. Furthermore, in accordance with our study, a remarkably low reaction rate to macrolides was estimated. Interestingly, as in our study, the Dutch survey documented similar reaction rates for amoxycillin alone and the amoxycillin-clavulanic acid combination.

Interestingly, a high proportion of photosensitivity reactions was reported in association with lomefloxacin and pefloxacin. This is not unexpected as surveillance data put these two agents at the same level in the hierarchy of phototoxicity [33, 34]. In an animal model, lomefloxacin seemed to be the quinolone with the greatest potential for inducing phototoxic reactions [35] and, in a recent randomized clinical trial, the frequency

of photosensitivity attributed to the drug was about 1% [36]. It has been suggested that an evening dosing strategy may reduce the risk of inducing phototoxic effects [37].

NSAIDs and analgesics accounted for more than 25% of all of the reported reactions and were considered responsible for a higher percentage of severe reactions than antimicrobial agents. Within NSAIDs, aspirin and dipyrrone (which is usually prescribed in Italy as an antipyretic and headache remedy) were associated with the highest rate of skin reactions, followed by ketorolac, niflumic acid and a number of arylalkanoic acid derivatives, including ketoprofen and ibuprofen; lower and remarkably similar rates were observed in the case of piroxicam, naproxen and diclofenac. Urticaria, which is a common affliction with a lifetime incidence of 15–20% [38], was the most reported reaction for aspirin in our study. Aspirin may produce urticaria and/or angioedema through interactions with the arachidonic acid metabolic pathways and inhibition of prostaglandin synthesis [38]. Few data are available for dipyrrone: the overall incidence of skin rash during dipyrrone therapy was 2.4% in an epidemiologic study [39]. Further, our data do not support the assumption that phenamates have fewer side-effects than other NSAIDs as niflumic acid appeared to cause even more cutaneous reactions; these included urticaria-angioedema and exanthema, but also one case of erythema multiforme and one case of Stevens–Johnson syndrome.

In terms of the profile of severe reactions to NSAIDs, it is worth noting the reports of vesiculo-bullous reactions to piroxicam and Stevens–Johnson syndrome attributed to paracetamol. It cannot be excluded that bullous manifestations associated with piroxicam were part of a more specific and undiagnosed reaction pattern such as Stevens–Johnson syndrome or photosensitivity, but an excess of not otherwise specified bullous reactions to piroxicam has previously been reported in a specialist-based surveillance program [40], which found that they frequently occurred in sun-exposed areas.

Case reports and a recent international case-control study [21] have suggested that Stevens–Johnson syndrome and toxic epidermal necrolysis may be associated with paracetamol. Interestingly, in the case-control study, there was a documented heterogeneity in the risk estimates: no association was found in France, but there was a nine-fold increased risk in Germany, Italy and Portugal in comparison with nonusers. Confounding by indication cannot be excluded because paracetamol was mainly used as an antipyretic in Germany, Italy and Portugal, and as an analgesic in France. Infectious diseases *per se* may be a risk factor for Stevens–Johnson syndrome. The classification of erythema multiforme and Stevens–Johnson syndrome has recently been reviewed [41]. It has been

suggested that erythema multiforme major (characterized by acral polycyclical lesions and mucous membrane involvement) is a separate entity from Stevens–Johnson syndrome, which is characterized by a similar mucosal involvement but more widespread vesicular and bullous lesions. Erythema multiforme is frequently associated with herpes and other viral infections, whereas Stevens–Johnson syndrome is usually drug-induced [42]. Since this classification is not widely accepted, it is quite possible that the two terms were used interchangeably by doctors in our study. At any rate, the reports concerning paracetamol in our survey indicate the need for more formal studies of this issue.

Among widely prescribed drug categories for which a remarkably low number of adverse reactions was reported, drugs for peptic ulcer and antacids are noteworthy [43] since our data confirm their good skin safety profile [44, 45]. As expected [46–48], the agents acting on the renin-angiotensin system were the most frequently reported cardiovascular drug class.

The detection of new adverse drug reactions is the major aim of pharmacovigilance. We found some skin events not previously reported, thus showing that an accurate data base can be useful for detecting unknown severe ADRs and for improving the knowledge of the safety profile of drugs.

In conclusion, in spite of its limitations, our analysis documents an acceptable degree of clinical characterization of the events reported to the Italian spontaneous surveillance system, and confirms that, with a reporting rate of 5.5 per 100 000 inhabitants/year, skin manifestations represent the most common clinical patterns. The reactions were most frequently associated with antimicrobial agents, NSAIDs and analgesics. About 17% of them were severe and sometimes life-threatening events; even in the case of severe events, our survey suggests a degree of under-reporting and indicates that there is room for improving the system in terms of reporting rates. In Italy, despite legal requirements, a spontaneous reporting system is lacking. The Ministry of Health has not been able to provide any information on ADR reports, either in quantitative or qualitative terms. In our experience a regional system represents a better approach for analysing and spreading the spontaneous reporting data. Furthermore, regional centres could play an important role in the education of health-care providers in pharmacovigilance. As stated by the 'Erice Declaration' [49], every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and made accessible to all; for the cutaneous reactions to drugs, this is a task in which dermatologists should clearly play a role.

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