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Adverse Reactions Induced by NSAIDs and Antibacterials

Analysis of Spontaneous Reports from the Sicilian Regional Database

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Abstract

Objectives: To (i) evaluate the suspected adverse drug reactions (ADRs) related to NSAIDs and antibacterials that were reported to Sicilian local health officers by healthcare professionals; and (ii) to detect new or serious potential signals of alarm related to these two widely used drug categories.

Methods: We selected all the spontaneous reports of ADRs sent between January 1998 and June 2004 and analysed those attributed to NSAIDs and systemic antibacterials, applying proportional reporting ratio (PRR) methodology. PRRs >2, χ^2 >4 and >3 ADRs were regarded as signals.

Results: During the period considered, 1585 reports of ADRs were received overall (42.6% serious), with an annual reporting rate of approximately 49.1 reports per million inhabitants on average; 351 referred to systemic antibacterials, and 179 to NSAIDs. There were 174 (49.6%) reports of serious ADRs associated with antimicrobials and 108 (60.3%) associated with NSAIDs. Disproportionality was observed, in particular for anaphylactic shock induced by ceftriaxone (all reports were associated with off-label use of the drug), photosensitivity reaction induced by lomefloxacin (administered in the summer), hepatitis induced by nimesulide (three cases leading to liver transplantation) and vasculitis induced by nimesulide.

Conclusion: Our analysis highlighted several signals of alarm deserving further investigation or measures to influence prescribing. This study underlines the value of a regional centre in identifying local factors (such as prescribing patterns) that may increase the prevalence of serious ADRs.

Background

Pharmacovigilance involves the activities and methods for detecting, assessing, informing on and preventing adverse drug reactions (ADRs).[1] In 1975, Italy joined the WHO Drug Monitoring Programme for spontaneous reporting of ADRs, and set up a centralised system in which all reports are collected and stored by the Italian Ministry of Health. However, given the high rate of under-reporting, in May 2003 the new Italian Pharmacovigilance Directive[2] encouraged the setting up of regional centres, with the aim of imple-

menting an effective national pharmacovigilance system. The system remains centralised from an administrative point of view, but these regional centres should play a crucial role in evaluating and analysing potential early warnings of hazards, arising from collected spontaneous reports (signal generation). Prior to this directive (since January 2003), the Sicilian Health Authority had been promoting a project for the re-organisation of the spontaneous reporting system in Sicily, Italy. The major goals of the project are to improve the number and the quality of ADR reports from Sicilian health professionals and to foster the rational and safe use of drugs in the region.

In fact, up until 2002, Sicily ranked among the areas in Italy with the lowest reporting rates for ADRs (5.2 reports per 100 000 inhabitants/year versus 12.3 reports for the entire nation).[3] Furthermore, the national drug consumption annual report for the year 2003 revealed expenditure for prescription drugs in Sicily that was 25% higher than the national average.[4] The same report also underlined that this discrepancy was mainly due to different prescription patterns for two classes of drugs: NSAIDs and antibacterials. For instance, ceftriaxone was the top ranked antibacterial in Sicily in terms of expenditure for reimbursement (3rd in overall drugs ranking versus 13th in Italy).[4] Moreover, these two drug categories accounted for >45% of ADRs reported in Sicily in the year 2003, putting them in first and second place on the list of drugs most frequently implicated in ADRs. However, looking at the international situation, NSAIDs and antibacterials are two classes of drug that account for an important proportion of ADR reports received by the WHO Uppsala Monitoring Centre, thus indicating an intrinsic hazard linked to their use, even though this risk is well documented.

Spontaneous reporting has proven to be valuable in generating signals for new or rare ADRs in postmarketing surveillance. In regards to NSAIDs and antibacterials, this was the case for tendonitis and Achilles tendon rupture after fluoroquinolone use, temafloxacin syndrome and hepatotoxicity due to bendazac.[5-9]

Given this background, the aim of this study was to evaluate the spontaneous reporting of suspected ADRs to Sicilian local health officers by healthcare professionals between 1 January 1998 and 30 June 2004, paying particular attention to those related to NSAIDs and antibacterials and trying to identify signals of previously undiscovered and/or serious adverse events.

Methods

The regional database that has collected all spontaneous reports of ADRs from the region of Sicily since January 2003 has been recently supplemented with data from 1998 to 2002. Drugs involved in ADRs were first categorised according to the anatomical therapeutic chemical (ATC) classification. We then selected and analysed reports that included at least one NSAID (ATC code M01A) or an antibacterial for systemic use (ATC code J01). Reports were then classified according to the Naranjo algorithm for causality assessment.[10] Only reports with 'certain', 'probable' or 'possible' associations were included.

The ADRs were codified according to the WHO Adverse Reaction Terminology, and classified as 'serious' or 'nonserious' events on the basis of the WHO Critical Term List.[11] We regarded the reports as serious when at least one ADR reported was included in the WHO Critical Term List. The following information was also considered: reporter category, patient's age and sex, the reporter's diagnosis of the disorder, drug exposure (indication, duration of treatment and dosage) and concomitant therapies (including the indication for their use, when available). All ADRs occurring in association with antibacterials or NSAIDs reported in the period considered by the study were analysed in detail by an *ad hoc* panel of experts including pharmacists, medical doctors, pharmacologists and toxicologists. Each specialist performed their own validation of the ADRs. Every time there was a discordance in the judgements of the experts, decisions were made on a consensus basis after a collective discussion.

To identify the potential signals among the suspected ADRs reported (i.e. ADRs either not previ-

Table I. Calculation of proportional reporting ratio

	Drug of interest	All other drugs in database
Reaction(s) of interest	a	b
All other reactions	c	d

ously recognised or underestimated), we applied proportional reporting ratio (PRR) methodology.[12] This represents a measure of disproportionality that involves calculation of the proportions of specified reactions or groups of reactions for drugs or a class of drugs of interest, where the term of comparison is all other drugs in the database. The PRR is the result of a/(a+c) divided by b/(b+d) in a two-by-two table (table I). This measure of disproportionality was combined with an estimator of the statistical association, i.e. a Chi-squared (χ^2) test at one degree of freedom with Yate's correction. An equivalent alternative to χ^2 test might have been the calculation of the 95% confidence interval around the PRR. From the statistical perspective, a signal was empirically defined as a PRR of ≥2, χ^2 of ≥4 and ≥3 cases reported. These cut-off values are those usually applied by the UK Medicines and Healthcare products Regulatory Agency to routinely scan the Adverse Drug Reactions On-line Information Tracking database of spontaneous reports for signals.[13]

The χ^2 test was used to perform statistical analysis; differences with p-values of <0.05 were considered significant. All calculations were performed using Epi Info™, a standard statistical software program.

Results

During the study period, a total of 1585 reports of ADRs were received (42.6% serious), with an average annual reporting rate of approximately 49.1 reports per million inhabitants. Fifty-three percent of the reports were sent by general practitioners, whereas 29.3% were from doctors working in hospitals. The remaining 17.2% of reports were filed by specialists or pharmacists (the source was unknown for the residual 0.5%). Patients with ADRs were 47.5 years old on average (SD ± 24.4) and 55.9% were women.

Since more than one drug might be implicated in a single report, 1761 drugs were present in our database (1.1 drugs per report). When applying the Naranjo algorithm, 59.2% of ADRs were judged as being 'probable', and 40.6% 'possible'. The remaining 0.2% were judged as being 'certain'. Figure 1 shows the drug categories involved in reports according to the 1st level ATC classification (serious and nonserious events were also split).

In almost one-third of reports received (512, 32.3%), a systemic anti-infective (ATC code J) was implicated, whereas musculoskeletal drugs accounted for 13.5% (214) of the total number of reports. When considering only serious ADRs (675), systemic antimicrobials and musculoskeletal drugs accounted for 37.8% and 18.5% of reports, respectively. Table II shows the ADR reports classified by system or organ involved. Disorders affecting the skin or appendages were the most frequently reported ADRs for all drugs (37.6%), followed by disorders affecting the body as a whole (20.2%) and gastrointestinal events (18.4%).

Antibacterials

A total of 351 reports were related to systemic antibacterials (both orally and parenterally administered drugs were included with ATC 2nd level code J01) and 174 (49.6%) reported at least one serious ADR.

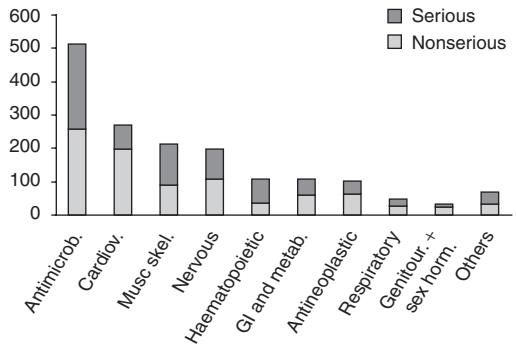

Fig. 1. Drugs implicated in the reports, classified according to anatomical therapeutic chemical 1st level code and to serious or nonserious events. **Antimicrob.** = antimicrobials; **Cardiov.** = cardiovascular; **Musc skel.** = musculoskeletal; **Genitour. + sex horm.** = genito-urinary and sex hormones; **GI and metab.** = gastrointestinal and metabolism.

Table II. Organs/systems affected by suspected adverse drug reactions (% of reports)[a]

Organ/system	Database	Antibacterials	NSAIDs
Skin and appendages	37.6	57.3	42.5
Disorders affecting the body as a whole	20.2	23.4	13.4
Gastrointestinal	18.4	14.2	20.1
Respiratory	12.4	10.3	5.6
Cardiovascular	12.4	10.8	16.8
Nervous system	11.9	8.8	7.8
Psychiatric	7.3	7.4	3.9
Musculoskeletal	6.1	4.0	0.6
Genitourinary	5.2	4.0	11.2
Haematopoietic	5.0	3.7	3.9
Metabolic-endocrine	4.0	1.7	3.4
Liver and biliary	3.8	2.6	8.9
Sensory effects	2.7	4.0	0.6
Immunological	0.6	0.3	0.0
Others	0.9	0.9	0.0

a Columns do not sum to 100% as some reports included >1 adverse drug reaction.

The mean age of the patients who experienced antibacterial-related ADRs was 39.9 years (SD ± 26.1); 53.2% were women. General practitioners filed 46.7% of reports, whereas 45.9% were sent by hospital doctors. The remaining 7.4% of reports were sent by pharmacists or specialists. According to the Naranjo algorithm, 63.6% of ADRs were judged as being 'probable', 36.1% 'possible' and the remaining 0.3% 'certain'. The number of antibacterial active principles reported was 62. Table III shows the antibacterials involved, classified by drug category (ATC 3rd level code) and by the seriousness of the adverse reactions. The cephalosporins and penicillins (β-lactams) were the two classes of antibacterials most frequently implicated in reports. Furthermore, when comparing the proportion of serious ADRs reported for each specific antibacterial class with that for all other antibacterials, a statistically significant increase was found only for cephalosporins ($p = 0.0032$). Table II shows the ADRs due to systemic antibacterials classified according to systems or organs involved. Skin and appendages were the organs most frequently affected by ADRs involving antibacterials (57.3%).

Table IV shows the ten antibacterials most frequently implicated in ADR reports (an 11th was also included because it had the same number of reports as the tenth).

Among antibacterials, the active principle with the highest number of reports was ceftriaxone, which also accounted for the highest proportion in terms of serious ADRs reported ($p = 0.038$ versus all other antibacterials). Regarding the outcomes of ADRs, 259 patients (73.8%) recovered after drug withdrawal, but there were also six fatal cases, four of which were associated with ceftriaxone (three due to anaphylactic shock and one due to disseminated intravascular coagulation), one with ciprofloxacin (toxic epidermal necrolysis), and one with clarithromycin (sudden death). Table V shows the serious ADRs reported that were associated with the top ten antibacterials for ADRs.

The 15 cases of ceftriaxone-induced anaphylactic shock (PRR: 17.09; χ^2: 163.52) all occurred in patients without positive history of penicillin or other drug allergies. Two out of three cardiac arrests associated with ceftriaxone occurred concomitantly with anaphylactic shock (PRR: 14.10; χ^2: 24.20). Table VI shows the indications for which ceftriaxone was

Table III. Antimicrobials involved in adverse drug reactions (ADRs) distinguished by tertiary level anatomical therapeutic chemical (ATC) code and by seriousness

Antimicrobials (ATC)	Reports		Proportion of serious reactions (%)	p-value[a,b]
	overall	serious		
Cephalosporins (J01D)	118	72	61.0	0.0032
Penicillins (J01C)	94	44	46.8	NS
Quinolones (J01M)	79	36	45.6	NS
Macrolides (J01F)	46	18	39.1	NS
Others[c]	25	14	56.0	NA
Total	351	174	49.6	

a χ^2 test.

b Comparison of the proportion of serious adverse events between the specific class of antibacterials and all antimicrobials.

c tetraciclines, amfenicolis, sulfonamides, aminoglicosides, combinations of antibacterials and others.

NA = not applied; **NS** = not significant.

Table IV. Antimicrobials implicated in reports of adverse drug reactions

Drug	Reports		Proportion of serious reactions (%)
	overall	serious	
Ceftriaxone	59	37	62.7
Amoxicillin/ clavulanic acid	37	15	40.5
Amoxicillin	29	11	37.9
Levofloxacin	21	12	57.1
Ciprofloxacin	21	9	42.9
Clarithromycin	18	8	44.4
Moxifloxacin	12	3	25.0
Lomefloxacin	11	7	63.6
Ceftazidime	9	4	44.4
Azithromycin	9	6	66.7
Cotrimoxazole (trimethoprim/ sulfamethoxazole)	9	5	55.6
Others	130	67	51.5
Total	351	174	49.6

prescribed in the 15 patients who experienced anaphylactic shock.

Of the four reports of purpura associated with amoxicillin/clavulanic acid (PRR: 8.61; Chi-squares 18.33), none were associated with a positive history of hepatitis, any other hepatic adverse reaction or thrombocytopenia; in two cases the patients were concomitantly receiving aspirin and niflumic acid, respectively. Unfortunately, none of these reports included data on the administration of the drugs; therefore, a causal relationship is very difficult to assess. Three cases of lomefloxacin-induced photosensitivity reaction occurred (PRR 73.92; Chi-squares 108.93); with regards to these, the patients were not taking any concomitant drugs. Lomefloxacin is a known photosensitiser.

NSAIDs

A total of 179 reports were related to NSAID use (ATC 3rd level code M01A) and, among these, 108 (60.3%) concerned a serious ADR.

The mean age for the patients who experienced NSAID-associated ADRs was 49.5 years (SD ± 22.2), and 65.9% were women. General practitioners were responsible for 55.9% of reports, 31.8% were sent by hospital doctors, whereas the remaining 12.3% were sent by pharmacists or specialists. When applying the Naranjo algorithm, 56.3% of ADRs were judged 'probable', and 43.7% 'possible'.

In our analysis, the proportion of serious ADRs reported that were associated with NSAIDs was significantly higher than for other drugs ($p < 0.001$).

The total number of active principles implicated was 18. Table VII shows the top ten NSAIDs associated with ADR reports (an 11th was also included because it had the same number of reports as the tenth).

Table II shows system and organs implicated in the reports of ADRs associated with NSAIDs. Skin and appendages were the organs most frequently involved in ADRs associated with NSAIDs (42.5%). Other than the skin and appendages, the only other system for which the proportion of NSAID-induced ADRs was significantly higher than the proportion of ADRs affecting this system in entire database was the genitourinary system. Other differences between the proportion of NSAID-related ADRs the proportion of events in the entire database, that were not statistically significant however, concerned the cardiovascular and hepatobiliary systems.

When considering the outcomes of ADRs, 116 patients (64.8%) recovered after drug withdrawal, whereas 3 cases, (two associated with nimesulide [hepatitis and gastrointestinal haemorrhage] and one associated with rofecoxib [gastrointestinal haemorrhage]) were fatal; in the remaining reports the outcome was not specified. Table VIII shows the serious ADRs associated with NSAIDs.

Disproportionality was only seen for hepatitis in association with nimesulide use (PRR: 14.20; Chi-squares 82.48). However, looking at the nine reports of hepatitis associated with nimesulide, three reports contained biopsy results (massive necrosis), while other causes (such as hepatitis viruses) were excluded in all cases. It must be noted that all reports of liver transplants came from one highly specialised hepatology unit. In one case, there were two concomitant, potentially hepatotoxic drugs (clarithromycin and simvastatin) co-implicated with nimesu-

lide in the report. Nimesulide was also associated with two cases of Stevens-Johnson syndrome (SJS); in one of these cases the patients was also receiving amoxicillin/clavulanic acid. Although there have been several reports of vasculitis associated with different NSAIDs, disproportionality was only seen for vasculitis in association with nimesulide (n = 4; PRR: 7.72; Chi-squares 11.09); the latency of onset of this reaction ranged from 1 to 9 days after beginning the therapy. In one of these cases, ketoprofen was co-suspect with nimesulide; in another case, ketoprofen was the only drug suspected to have caused the vasculitis. Finally, there was a high proportion of hypertension associated with celecoxib (n = 8; PRR 15.40; χ^2: 70.77), which is significant; this was also seen with rofecoxib, although it was less frequent (n = 3; PRR 6.64; χ^2: 8.11).

Discussion

The rationale for using the PRR approach for signals generation is that the composition of different types of reaction in the data set of a spontaneous reporting system database is relatively constant.[12] In our database, this constancy is confirmed when comparing the reports received from 1998 to 2004 in terms of the class of drugs implicated in ADRs, the organ/systems involved and the sources of reports, as shown in the articles and periodical reports published by the Sicilian Health Authority since 1998.[14-17] Therefore, small differences in the reporting profile of drugs may represent signals worthy of investigation. Of course, the strength of these signals will be strictly related to their clinical relevancy in terms of the severity, seriousness or potential preventability of the ADRs.[12] However, it will also depend on the dimensions of the database, and this is a limitation of small databases like the one for Sicily. Nevertheless, some results might be considered as valuable elements for the signal-detection process and to enable definition of the framework in which adverse reactions occur. Furthermore, since this analysis was derived from data acquired before the Regional Centre was formally established, its value is expected to increase with the further development of the Centre.

Table V. Serious adverse drug reactions (ADRs) associated with top 10 antibacterials reported

Drugs (no. of reports)	Serious ADRs according to the WHO Critical Term List (no. of reports)
Ceftriaxone (37)	Anaphylactic shock (15), cardiac arrest (3), anaphylactoid reaction (2), angioedema (2), bronchospasm (2), oedema of the mouth (2), laryngismus (2), aplastic anaemia (1), bullous eruption (1), circulatory failure (1), DIC (1), face oedema (1), hallucination (1), hyperpyrexia (1), larynx oedema (1), respiratory insufficiency (1)
Amoxicillin and clavulanic acid (15)	Purpura (4), SJS (2), face oedema (2), anaphylactic shock (1), angioedema (1), colitis (1), generalised oedema (1), gastrointestinal haemorrage (1), oedema mouth (1), SJS (1)
Levofloxacin (12)	Larynx oedema (2), bronchospasm (2), bullous eruption (1), circulatory failure (1), face oedema (1), rectal haemorrhage (1), hallucination (1), neuralgia (1), oedema of the mouth (1), purpura (1)
Amoxicillin (11)	Angioedema (2), bronchospasm (2), hepatitis (2), SLE (2), anaphylactic shock (1), bullous eruption (1), larynx oedema (1)
Ciprofloxacin (9)	Asthma (2), circulatory failure (1), convulsions (1), exfoliative dermatitis (1), TEN (1), hyperkinesia (1), larynx oedema (1), vasculitis (1)
Clarithromycin (8)	Oedema mouth (3), hepatitis (2), hepatitis cholestatic (1), laryngismus (1), death (1)
Lomefloxacin (7)	Photosensitivity reaction (3), face oedema (2), circulatory failure (1), hypertension (1)
Azithromycin (6)	SJS (2), anaphylactoid reaction (1), photosensitivity reaction (1), purpura thrombocytopenic (1), thrombocytopenia (1)
Cotrimoxazole [trimethoprim/ sulfamethoxazole] (5)	Erythema multiforme (2), vasculitis (2), SJS (1)
Ceftazidime (4)	Bronchospasm (1), circulatory failure (1), face oedema (1), hyperpyrexia (1)
Moxifloxacin (3)	Asthma (1), hallucination (1), hyperkinesia (1)

DIC = disseminated intravascular coagulation; **SJS** = Stevens-Johnson syndrome; **SLE** = systemic lupus erythematosus; **TEN** = toxic epidermal necrolysis.

Table VI. Indications for treatment reported by prescribers of ceftriaxone to patients who developed anaphylactic shock

Indication	Number of cases
Chronic obstructive pulmonary disease	4
Surgical prophylaxis	2
Febrile pharyngo-tracheitis	1
Acute bronchitis	1
Infected bedsores	1
Dental abscess	1
Convulsive fever	1
Chronic tonsillitis	1
Asthma	1
Not reported	2

The analysis of our database showed that skin is the most frequently involved organ in reports of ADRs concerning antibacterials and NSAIDs, accounting for 57.3% and 42.5% of reports, respectively. These results are in line with those published in a study by Naldi et al.[18] on spontaneous reports of cutaneous ADRs in four Italian regions, where skin reactions were the most common clinical manifestation reported, and the most frequently involved drugs were antimicrobial agents and NSAIDs.

These reactions ranged from mild manifestations, such as rashes, to serious life-threatening events, such as SJS. In particular, our database contains 11 suspected cases of SJS; three of these were reported in connection with an NSAID (nimesulide in two cases and niflumic acid in one) and five with an antibacterial (amoxicillin/clavulanic acid in two cases, azithromycin in two cases, cotrimoxazole [trimethoprim/sulfamethoxazole] in one). To our knowledge, there is only one published case of azithromycin-induced SJS[19]; this occurred in a 5-year-old patient with herpes simplex virus who had acute pharyngitis, a known predisposing factor to drug-related SJS. SJS is documented, although rare, for the other drugs involved.

In our analysis of serious cutaneous reactions, we also noticed a strong predominance of photosensitivity reactions in association with lomefloxacin use (table V). All fluoroquinolone antibacterial agents are known for causing phototoxicity, although at low frequencies.[6,20-22] The actual mechanism of such photosensitivity remains unknown, although it has been hypothesised that it is connected with the substitution at places 5 and 8 of the quinolone skeleton.

However, lomefloxacin seems to be the fluoroquinolone with the greatest potential for the induction of phototoxic reactions[23,24] and, in a randomised clinical trial, the frequency of photosensitivity attributed to the drug was about 1%.[25] Furthermore, all of the three reported events occurred during the summer. It has been suggested that an evening administration strategy could reduce the risk of inducing phototoxic effects.[26] One report of a phototoxic event was also associated with azithromycin, whereas no reports were received for NSAIDs.

Penicillins and cephalosporins were the drugs most frequently associated with anaphylactic shock, with 17 reports of such an effect. Interestingly, ceftriaxone was the only cephalosporin involved, accounting for 15 of these events, three of which led to the patient's death. This higher frequency probably reflects both the increased use of this cephalosporin and parenteral administration of the drug.[27] In fact, ceftriaxone is a systemic third-generation cephalosporin, indicated for treating serious infections, and this generation appears to be more sensitising than others.[28] Numerous cases of anaphylactic shock and IgE-mediated responses to

Table VII. Top ten NSAIDs implicated in adverse drug reactions reports

Drug	Reports		Proportion of serious reactions (%)
	overall	serious	
Nimesulide	50	32	64.0
Celecoxib	31	15	48.4
Rofecoxib	23	13	56.5
Ketoprofen	22	13	59.1
Diclofenac	13	7	53.8
Ketorolac	7	5	71.4
Ibuprofen	6	3	50.0
Niflumic acid	5	4	80.0
Diclofenac + misoprostol	4	2	50.0
Piroxicam	4	1	25.0
Meloxicam	4	2	50.0
Others	17	16	94.1
Total	179	108	60.3

Table VIII. Serious adverse drug reactions (ADRs) associated with NSAIDs

Drugs (no. of reports)	Serious ADRs according to the WHO critical term list (no. of reports)
Nimesulide (32)	Hepatitis (9; one with encephalopathy), angioedema (6), vasculitis (4), face oedema (3), SJS (2), hepatic failure (2), bronchospasm and bullous eruption (1), circulatory failure [with GI haemorrhage and respiratory insufficiency] (1), hyperkinesia (1), melaena, multiple organ failure and purpura (1), generalised oedema (1)
Ketoprofen (15)	Face oedema (3; 1 with oedema of the mouth), anaphylactic shock (2), angioedema (2), vasculitis (2), bronchospasm and laryngismus (1), bullous eruption (1), erythema multiforme (1), hepatitis (1), hypertension (1), leucopenia [with thrombocytopenia] (1)
Rofecoxib (13)	Hypertension (3), GI haemorrhage (2), hepatitis (2; one with face oedema), haemorrhagic gastric ulcer and peritonitis (1), hallucination and hyperkinesia (1), melaena (1), generalised oedema (1), oedema of the mouth (1), leg thrombophlebitis (1)
Celecoxib (13)	Hypertension (8; 1 with albuminuria), angioedema (2), anuria (1), delirium and hallucination (1), face oedema (1)
Diclofenac (7)	Angioedema (3; 1 with larynx oedema), hypertension (2; one with hyperkinesia), larynx oedema [with anaphylactoid reaction] (1), hepatitis [with decrease in coagulation factor, paralytic ileus and acute renal failure] (1)
Ketorolac (5)	Angioedema (3), hepatitis and melaena (1), vasculitis (1)
Niflumic acid (4)	Angioedema (2; 1 with laryngismus), purpura (1), SJS (1)
Etoricoxib (4)	Angioedema (1), generalised oedema (1), hypertension (1), thrombocytopenia (1)
Ibuprofen (3)	Angioedema (3; 1 with oedema of the mouth)
Indomethacin (3)	Hyperkinesia (1), purpura (1), abnormal renal function (1)
Morniflumate (3)	Angioedema (2), oedema of the mouth (1)
Diclofenac + misoprostol (2)	GI haemorrhage (1), melaena (1)
Meloxicam (2)	Angioedema (1), face oedema (1)
Dexketoprofen (1)	Anaphylactoid reaction (1)
Ketoprofen + sucralfate (1)	Larynx oedema (1)
Piroxicam (1)	GI haemorrhage (1)
Tenoxicam (1)	Vasculitis (1)

GI = gastrointestinal; **SJS** = Stevens-Johnson syndrome.

ceftriaxone have already been described.[29,30] However, in our opinion, these cases might at least partially reflect inappropriate drug use (both qualitative and quantitative) by Sicilian prescribers. In fact, ceftriaxone is the first-placed antibacterial in terms of costs, as reported above, and all 15 reactions appear to have occurred in patients where the drug was prescribed in an off-label setting. Although the reasons for these prescriptions have not been investigated in depth, we think they were made, at least in part, with an unfavourable risk/benefit ratio, where effective and safer alternative drugs might have been used. It must also be underlined that approximately half of the cases occurred in outpatients. An observational study published in 2003 analysed antibacterial prescribing in primary care in Italy.[31] Great variability in antibacterial prescription was found by the authors, with frequent use of cephalosporins and fluoroquinolones and only approximately 40% of these drug classes were being appropriately prescribed as first-choice treatments. The use of third-generation cephalosporins was particularly frequent in southern Italy, with a positive association between prescriptions of parenteral antibacterials and patients' aged >65 years or the presence of concurrent diseases, thus supporting the authors' hypothesis that Italian GPs consider parenteral and newer antibacterials more effective in high-risk patients. Different views of Italian general practitioners rather than different patterns of bacterial resistance may, at least partially, explain this prescribing behaviour.[32,33]

Moreover, none of the 15 report forms featuring ceftriaxone-related anaphylactic shock mentioned a history of penicillin or other drug allergy for the patients involved. This would make these cases of

anaphylactic shock unpreventable ADRs; therefore, in these cases, only a more rational use of the drug might have reduced the number of these serious events.

Overall, we collected 14 reports of cases of hepatitis induced by NSAIDs, accounting for 23% of all hepato-biliary reactions reported. Two cases of hepatitis were associated with rofecoxib and 12 with traditional NSAIDs (nine with nimesulide, one with ketorolac, one with ketoprofen and one with diclofenac). In general, the risk of hepatopathy among patients taking NSAIDs was small. The results of two large cohort studies provided a rate ratio of 9 per 100 000 persons per year for the development of hepatotoxicity associated with NSAID use.[34,35] An Italian cohort study published by Traversa et al.[36] in 2003 suggested that nimesulide, when compared with the other NSAIDs, was associated with only a small increase in the risk of serious hepatic reactions. However, although our nine reports appear to be few in relation to the large use of nimesulide in Sicily, our database shows a high level of disproportionality for the reports referring to serious hepatitis. Moreover, there have also been two additional cases of nimesulide-induced hepatic failure (table VIII). The molecular mechanisms underlying the idiosyncratic hepatotoxicity of nimesulide are not yet fully understood; genetic and/or acquired patient factors can play a crucial role, but it has been also suggested the contribution of reactive metabolites generated in the liver may be critical for the development of this adverse reaction.[37] In our database, the characteristics of the patients who developed hepatotoxicity showed that their ages ranged from 27 to 65 years, and that the reactions were similarly distributed between males (4) and females (5). Six patients developed hepatotoxicity after 1 or 2 days of therapy and five were receiving therapy with only nimesulide when the ADR occurred. Three patients developed fulminant hepatitis and thus required liver transplantation. Although only one of the nine reports was received before the withdrawal of nimesulide from the Finnish and Spanish markets, suggesting a potential publicity bias, the seriousness of the ADR and the examination of liver biopsies of the three transplanted patients strengthen the causal association between use of this drug and hepatotoxic events. Furthermore, in these three cases, no predisposing factor (e.g. alcohol consumption, hepatic viral infections or concomitant use of hepatotoxic drugs) was present and the drug had always been taken for few days at normal doses as a painkiller.

Seven cases of vasculitis were associated with the following NSAIDs: nimesulide, ketoprofen, ketorolac, and tenoxicam. To our knowledge, there are no published reports of vasculitis induced by these drugs, although several cases of this ADR have been reported in association with ibuprofen,[38] aceclofenac,[39] naproxen[40] and celecoxib.[41] Our data seem to indicate that vasculitis may be a class-effect of NSAIDs. Two possible mechanisms have been suggested for this reaction: an allergic response linked to the chemical structure of several NSAIDs; or an interaction of the drugs with the synthesis of endothelial eicosanoids leading to an imbalance between vasoactive end products, resulting in a widespread rise in local thrombosis.[41]

Finally, we observed several cases of hypertension induced by celecoxib (8) and rofecoxib (3). The influence of NSAIDs on blood pressure is well documented, with average increases in systolic blood pressure of between 3 and 5 mmHg.[42,43] Although this adverse effect was initially thought to be less for the specific cyclo-oxygenase 2 (COX-2) inhibitors, molecular studies and clinical data suggest that this is not the case. The hypertensive effects of NSAIDs arise as a result of the inhibition of prostaglandins, particularly PGE2 and PGI2, in the kidney.[44,45] PGE2 reduces sodium and water resorption in the collecting duct and thick ascending limb of the loop of Henle. The relative contribution of COX-1 and COX-2 to the production of prostaglandins and its importance in regulating fluid retention is not precisely known. However, it now appears that this effect is mostly COX-2 mediated, with clinical studies demonstrating similar levels of sodium retention in patients on nonspecific NSAIDs and those on COX-2-specific agents, with a frequen-

cy of clinical oedema of between 2% and 5% for both groups.[46]

Conclusions

This study reviews the case reports of suspected ADRs to medicines, as received in a 5-year period by the Sicilian Regional Pharmacovigilance Centre. Two groups of drugs emerged as the most frequent causes of serious ADRs in outpatients: NSAIDs and antibacterial drugs. Predominating individual drugs were, in particular, ceftriaxone, nimesulide and lomefloxacin. The evidence indicates that such reactions often occurred in connection with off-label or inappropriate drug use (e.g. unfavourable benefit-risk profile, or better alternatives available). Better prescribing will prevent unnecessary and serious ADRs. Our results show that regional pharmacovigilance centres can identify inappropriate drug use and other factors underlying the occurrence of adverse reactions, which in turn can be used to influence prescribing and lead to a safer and more rational use of drugs.

Spontaneous reporting is not able to estimate the frequencies of ADRs because of under-reporting and, in Sicily, the absence of drug exposure data. Nevertheless our results show that a regional and relatively small database can detect important risk determinants. Whenever there is a disproportionate reporting of a remarkable – rare or serious – event, this needs special attention and may require in-depth investigation.

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