

Accepted Manuscript

Title: Allergic reactions to oral drugs: A case/non-case study from an Italian spontaneous reporting database (GIF)

Authors: Francesco Salvo, Giovanni Polimeni¹, Paola Maria Cutroneo, Roberto Leone, Anita Conforti, Ugo Moretti, Domenico Motola, Marco Tuccori⁵, Achille Patrizio Caputi



PII: S1043-6618(08)00129-1
DOI: doi:10.1016/j.phrs.2008.07.003
Reference: YPHRS 1900

To appear in: *Pharmacological Research*

Received date: 18-4-2008
Revised date: 2-7-2008
Accepted date: 3-7-2008

Please cite this article as: Salvo F, Polimeni¹ G, Cutroneo PM, Leone R, Conforti A, Moretti U, Motola D, Tuccori⁵ M, Caputi AP, Allergic reactions to oral drugs: a case/non-case study from an Italian spontaneous reporting database (GIF), *Pharmacological Research* (2007), doi:10.1016/j.phrs.2008.07.003

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title:

Allergic reactions to oral drugs: a case/non case study from an Italian spontaneous reporting database (GIF).

Authors:

Francesco Salvo¹, Giovanni Polimeni^{1,2}, Paola Maria Cutroneo¹, Roberto Leone³, Anita Conforti³, Ugo Moretti³, Domenico Motola⁴, Marco Tuccori⁵, and Achille Patrizio Caputi^{1,2}

Affiliations:

¹Department of Clinical and Experimental Medicine and Pharmacology, School of Medicine, University of Messina, Messina, Italy

²Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Centro Neurolesi "Bonino-Pulejo," Messina, Italy

³Clinical Pharmacology Unit, Reference Centre for Education and Communication Within the WHO Programme for International Drug Monitoring, University of Verona, Verona, Italy

⁴Department of Pharmacology, Interuniversity Research Centre for Pharmacoepidemiology,
University of Bologna, Bologna, Italy

⁵Tuscan Regional Centre for Pharmacovigilance, Division of Pharmacology and Chemotherapy,
Department of Internal Medicine, University of Pisa, Pisa, Italy

Name and address for correspondence

Dr. Francesco Salvo

Section of Pharmacology

Dept. of Experimental and Clinical Medicine and Pharmacology

University of Messina

Torre Biologica - Policlinico Universitario

Via Consolare Valeria – Gazzi

98125 Messina - Italy

E-mail: fsalvo@unime.it

Tel: +39 090 2213878

Fax: +39 090 2213300

Number of text pages (title, references and tables excluded):

10

Number of tables:

5

Number of Figures:

3

Allergic reactions to oral drugs: a case/non-case study from an Italian spontaneous reporting database (GIF).

Abstract

Despite the wide number of studies investigating on drug-induced allergy, limited data focused on allergies associated with orally administered drugs are available.

The aim of the study is to evaluate allergic drug reactions associated with oral drug use, using an Italian spontaneous reporting database of adverse drug reactions (ADRs).

Spontaneous reports associated with oral drugs retrieved from seven Italian regions (GIF research group), collected from 1988 to 2006, were analysed. Association between drugs and allergic adverse reactions was assessed using the case/non-case method, calculating the ADR reporting odds ratio (ROR) as a measure of disproportionality.

Overall, 27,175 reports of adverse reactions related to oral drug use were analysed; of these, 3,143 (11.6%) were judged as allergy cases. Paediatric patients (≤ 15 years) and in-patients ($p < 0.001$) were more represented in cases than in non-cases. Antibiotics and Non-Steroidal Antinflammatory Drugs (NSAIDs) were the only two drug classes associated with a significant increase of ROR. Regarding antibiotics, cinoxacin (6.88; 95%CI 4.19-11.29) and moxifloxacin (4.20; 95%CI 3.19-5.55) were related to the highest ROR values, while propionic acid derivates (ROR 2.75; 95%CI 2.30-3.28), and in particular ibuprofen (4.20 95%CI 3.13-5.63), have shown the highest ROR values among NSAIDs.

The results of the present paper confirm the higher frequency of allergic reactions with oral antibiotics and NSAIDs, although more data are needed. Given the widespread use of these drug classes (some of them being purchased as over the counter drugs), awareness should be raised among patients and prescribers about these risks.

Introduction

Despite a wide number of papers evaluating drug-induced allergy being available, its magnitude is particularly difficult to estimate (1-3). In fact, clinical manifestations are very heterogeneous, ranging from non-serious adverse reactions (e.g. localized erythema or rash) to potentially life-threatening reactions (like anaphylactic shock or laryngeal oedema). In addition, many adverse drug reactions (ADRs) suggesting an immunologic origin might be linked to a non-allergic aetiology (4). Moreover, every drug may cause an allergic reaction, including those used for treatment of allergies, like antihistamines and glucocorticoids (5,6). Available data regards in particular either serious drug allergies like anaphylaxis or bullous reactions, or single classes of drugs related to allergy (e.g. beta-lactams) (7-8). From this data, it has been found that allergic reactions are frequently associated with antibiotics (beta-lactams and quinolones in particular), and Non-Steroidal Antinflammatory Drugs (NSAIDs) (9-11).

It is well known that an increased frequency of hypersensitivity reactions is associated with parenteral administration of drugs, mainly due to specific components of parenteral formulations (e.g. stabilizers) (12-14). However, every administration route has been related to allergic reactions (7). Nevertheless, limited data focusing on allergies associated with oral administration of drugs is available in the literature (15).

Thus, the aim of this study was to evaluate allergic drug reactions due to orally administrated drugs, using an Italian spontaneous reporting database of adverse drug reactions.

Methods

The database of the Italian Interregional Group of Pharmacovigilance (GIF) was analysed. This database collects all spontaneous reports of suspected ADRs from seven regions of Italy: the Veneto, the Autonomous Province of Trento, Lombardy, Sicily, Emilia-Romagna, Friuli-Venezia-Giulia, and Tuscany.

The GIF activities are focused on research and educational programmes in the field of pharmacovigilance. The participating regions have their own Regional Pharmacovigilance Centre and represent together a population of about 19 million inhabitants (48.9% of the total Italian population); however, about 75% of all Italian reports come from these regions, with a reporting rate three times higher compared with other Italian regions (167 reports per 100,000 inhabitants/year versus 54). Analyses of the GIF database are performed every 6 months, with the aim to identify potential alarm signals.

All reports of adverse reactions associated with oral drug use, collected between 1988 and 2006, were selected. Drugs were grouped according to the Italian ‘Sistema Codifa’, that is linked to the Anatomical Therapeutic Chemical (ATC) classification. Reactions were classified according to the WHO Adverse Reaction Terminology (16). Reports involving at least one parenteral drug, either those associated with vaccines or not describing the administration route of suspected drugs were excluded from the analysis.

Each report was classified according to the WHO criteria for causality assessment and only reports with a ‘certain’, ‘probable’ or ‘possible’ causality assessment were included in the analysis (17).

The study design consisted in a case/non-case approach, a validated method used in spontaneous reporting analyses since 2002 (13).

Patients were defined as “cases” if their clinical manifestation complied with at least one of these criteria:

1. Reports with “preferred term” of anaphylactic shock or anaphylactoid reactions (defined according to WHO-ART dictionary). Patients with at least 2 symptoms of shock (e.g.

diaphoresis, itching or dispnoea) associated with a blood pressure reduction were also included.

2. Adverse reactions with a time of event onset suggesting an allergic reaction, involving at least two of the following systems/organs: skin and appendages, respiratory system, gastrointestinal system, central nervous system and cardiovascular system.
3. Cutaneous reactions, with a time to onset of the event suggesting an allergic reaction in patients not included in the previous categories.

All of the cases were analysed in detail and validated by an *ad hoc* panel of experts including toxicologists, clinical pharmacologists and pharmacists. All other reports included in the GIF database were defined as “*non-cases*”.

The frequency of the association between allergy and the suspected drug was calculated using the ADR reporting odds ratio (ROR) as a measure of disproportionality (18-20). Odds ratios and their 95% confidence intervals (CIs) were calculated using Epi Info TM1 (Version 6) software.

Characteristics of the two groups of patients were compared using the χ^2 or Student's t-test, when appropriate.

Results

At the time of the analysis, the GIF database contained 45,673 reports of suspected ADRs. Of these, 28,002 were associated with orally administered drugs; 827 were excluded from the analysis, 700 because they were incomplete, and 127 because of ‘unlikely’, ‘unclassified’ or ‘unclassifiable’ causality assessment according to WHO criteria. Therefore, the study was conducted using 27,175 reports, representing 59.4% of total reports collected in GIF database.

Overall, 3,143 (11.6%) cases were identified. **Table 1** shows allergic reactions according to the three different categories described above.

Table 2 shows the characteristics of patients both for cases and non-cases. Cases were more often paediatric patients (≤ 15 years) or inpatients ($p < 0.001$) compared to non-cases. Conversely, fatal reactions were more frequent in non-cases than in cases ($p < 0.001$). **Figure 1** shows cases and non-cases stratified by age (paediatric patients, then by decade). Patients up to 54 years old were more often cases than non-cases as compared to those aged above. Moreover, 53.1% of cases belonged to one of the first three age groups.

Table 3 shows the drug classes (coded by first ATC level) implicated in a minimum of 30 allergic reaction reports. Anti-infectives for systemic use (ROR 2.92; 95%CI 2.71-3.15) and musculo-skeletal system drugs (plus aspirin) (ROR 1.65; 95%CI 1.51-1.81) were the only two drug classes significantly involved in cases, accounting for more than 70% of the total number of cases. In particular, antibiotics and NSAIDs were the only two classes associated with a significant increase of ROR. Furthermore, despite all classes of antibiotics being positively associated with allergy, the highest rate regarded “other quinolones” (ATC code J01MB that includes cinoxacin and pipemidic acid), while macrolides (ATC code J01FA that includes clarithromycin and erythromycin) showed the lowest association (**Table 4**). **Figure 2** reports ROR values for single antibiotics involved in at least 20 cases. The highest ROR values were related to cinoxacin (6.88; 95%CI 4.19-11.29) and moxifloxacin (4.20; 95%CI 3.19-5.55).

Table 5 reports different NSAIDs plus aspirin associated with at least 20 cases of allergy, classified according to their fourth ATC level. Propionic acid derivatives (M01AE) were the most frequently involved chemical class of NSAIDs (ROR 2.75; 95%CI 2.30-3.28), while oxicams (M01AC) were not associated with allergic reactions in comparison with the other drugs collected in the database (ROR 0.86; 95%CI 0.58-1.29). **Figure 3** reports ROR values for single NSAID molecules (with at least 20 cases) and aspirin; ibuprofen was associated with the highest ROR (4.20; 95%CI 3.13-5.63). Celecoxib (ROR 1.30; 95%CI 0.95-1.77) and rofecoxib (ROR 0.99; 95%CI 0.67-1.44) were not found to be connected with allergic reactions (the latter was withdrawn from the market in 2004).

Discussion

To our knowledge, this is the first study investigating allergies related to orally administered drugs using data from spontaneous reporting of suspected ADRs. The results suggest that allergic reactions were rather frequently associated with oral drugs (11.6% of adverse reactions reported for orally administered drugs), most of which being antibiotics (in particular cinoxacin and moxifloxacin) and NSAIDs (in particular propionic acid derivatives, ibuprofen and ketoprofen), with younger patients being most frequently involved.

Weaknesses of ROR methodology are well documented in literature (21). Indeed, a quantification of risks is not possible, because adverse events are always under-reported. However, since underreporting is supposed to be more or less of the same magnitude for all drugs, it is possible to identify those drug-adverse event pairs that emerge from comparison of their frequency with respect to others within the same data source (22). Furthermore, disproportionality in the analysis of spontaneous reports can be lessened if one drug or drug class-specific reaction is widely reported, because this attenuates the association by increasing the frequency of the drug in non-case reports (23,24).

Another problem occurs in the selection of cases from a spontaneous reporting database. In this study, a part of drug allergies reported by caregivers may have been missed because of the selection criteria applied. Moreover, in spite of the evaluation of single cases by physicians, pharmacists, and pharmacologists, it is impossible to confirm hypersensitivity mechanisms in selected reactions. Finally, even if some drugs were withdrawn from the market on the base of spontaneous reports analysis only (25,26), usually a definite association cannot be provided using only such studies, but requires complementary post-marketing safety assessment (e.g. cohort and case-control studies). However, given the clinical features of allergies (generally occurring soon after drug exposure and resolving after its withdrawal) we are quite confident that cases included in the analysis were indeed immuno-mediated reactions.

The study reports no difference in terms of gender between cases and non-cases, but shows a considerable difference in mean age (48.0 years for cases and 55.0 for non-cases), cases being significantly more often under 15 years of age than non-cases ($p < 0.001$). This result could be explained by a higher susceptibility in younger patients to develop allergic drug reactions (27) but may also be due, at least in part, to a possible selective over-reporting of this kind of reaction in paediatric patients, who are strictly cared for by parents that tend to report every unusual finding to their paediatricians during the first stages of treatment (28). In this context, a possible distortion of safety data must be taken into account when drug allergies regarding children are considered.

In line with previous studies, inpatients were more associated with drug allergy than outpatients (24, 29-31). This finding is probably due to intensive diagnostic and therapeutic procedures, but it has been suggested that nearly 10% of ADRs occurring in hospitalised patients are directly due to poor appreciation of drug allergies (32).

Allergy induced by oral drugs showed lower frequency of mortality than other reactions. This result is certainly influenced by case selection, including also non-serious reactions such as urticaria or cutaneous rash. Moreover, this result supports previous reports suggesting that fatal allergies are more frequent when drugs are parenterally administered (13,24).

Results on drug classes are in accordance with all previous findings, indicating that antibiotics and NSAIDs are those most frequently associated with allergic reactions. Among antibiotics, the strongest association was found for “other quinolones” (ATC code: J01MB), with cinoxacin strongly contributing to this result. This drug is known to cause hypersensitivity reactions, and is particularly associated with anaphylactic shock (10,24,33,34). Stricker et al. (1988) reported that a possible increase of drug allergies related to quinolones might be expected, noting the constant rise in their use and the commercialisation of several newer antibiotics of the same class (10). Interestingly, moxifloxacin, the latest fluoroquinolone marketed in Italy, showed a significant association with allergies. However, despite contradictory findings reported in the literature (35,36), the Italian Regulatory Agency (AIFA), in accordance with Bayer, recently issued a “Dear Doctor

Letter” to increase the awareness of caregivers on the risk of serious and potentially fatal hypersensitivity adverse reactions [e.g. Fulminant hepatitis, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)] associated with moxifloxacin **(37)**.

Regarding beta-lactams, all available oral classes showed similar frequencies for allergic reactions, but combinations of penicillins (amoxicillin plus clavulanic acid) showed the highest ROR value. A recent study performed on GIF database has noted an increased risk towards developing drug related hepatitis, SJS and TEN when compared to non-protected amoxicillin **(20)**. Hautekeete et al. (1999) found a significant association between a human leukocyte antigen (HLA) haplotype and drug-induced immuno-allergic hepatitis, suggesting an ‘immunologic idiosyncrasy’, at least partially mediated through HLA class II antigens **(38)**. This explanation might be applied also to amoxicillin/clavulanic acid-induced SJS and TEN and other hypersensitivity reactions, and may explain, at least in part, its higher value. These findings should be taken into account before prescribing this drug, in particular in high-risk situations, such as a convincing allergic reaction to penicillin having occurred within the previous 1-5 years **(39,40)**. Moreover, it may be interesting to apply the same precaution in the presence of atopy or asthma although these are not unanimously recognised risk factors **(4,43)**.

Regarding oral cephalosporins, cefaclor accounted for the highest number of cases, largely occurring in paediatric patients (data not shown), and its ROR value was similar to that of other beta-lactams. However, further investigation is required because these findings may be due to a more frequent utilization of this drug in childhood, where a probable higher susceptibility to allergic drug reactions (and a selective over-reporting) has been suggested, as discussed above **(28,42)**.

This study confirms the association between NSAID use and allergies **(11,13,24,43,44)**. Interestingly, oral propionic acid derivatives were associated with a noteworthy higher frequency of allergic reactions. Ibuprofen and ketoprofen were associated with the highest ROR among NSAIDs, indicating a possible class-effect. Díaz Jara et al. (2001) have previously considered selective allergic properties related to propionic acid derivatives, including ibuprofen and ketoprofen **(45)**. A

retrospective study performed on children showed that a large part of reactions associated with ibuprofen was based on an allergic mechanism of action (46). Another study showed that in 55,785 children treated with ibuprofen, 44 developed asthma, 20 gastritis, 8 low white cell count, 4 abdominal pain and 3 erythema multiforme, as a result of treatment (47). Moreover, to date ibuprofen is the only NSAID associated with delayed multiorgan hypersensitivity reactions (48,49). Several studies evidence the sensitisation property of ketoprofen, with contact dermatitis and photoallergy being the most common reactions when applied topically (15,50,51). It has been hypothesized that the diphenylketone group of ketoprofen plays a key role in contact sensitization or photocontact sensitivity (52).

It is also important to note that phenylpropionic acid derivative group of NSAIDs (ibuprofen, ketoprofen, oxaprozin, naproxen and nabumetone), are reported to be associated with pseudoporphyria (53).

The present study seems to confirm the hypothesis regarding propionic acid derivatives are at a higher risk of inducing allergies compared to other NSAID classes. In the absence of more complete information, prescriptions of propionic acid derivatives should be carefully considered in patients with a positive history of NSAID allergy, atopy and asthma (46, 54-57).

Finally, although two previous studies indicated a higher frequency of anaphylaxis with diclofenac (13,24), the present study did not confirm this risk. The differences may be due to the case selections, comprehending not only anaphylactic reaction but also other allergic reactions, or may be due to the exclusion of parenteral diclofenac administration.

In conclusion, the analysis of spontaneous reports of adverse reactions to oral drugs collected in the GIF database indicates that 11% of cases have an allergic basis. Drug classes mostly related to allergies are NSAIDs and antibiotics. In particular, among the former, a class effect involving propionic acid derivatives clearly emerges, while within the antibiotic class quinolones appear to be more frequently implicated, with cinoxacin and moxifloxacin being the two active principles associated with the highest ROR values. Further investigation is required to confirm these results

and, possibly, to evaluate the contribution of single molecules to the occurrence of allergic reactions. Furthermore, given the widespread use of these drug classes (some of them being purchased over the counter), awareness should be raised among patients and prescribers about these risks. For instance, the incidence of these and other severe drug-induced adverse events should always be reported in the Summary of Product Characteristics. In addition, despite a considerable number of post-marketing studies comparing the relative risk of developing immuno-mediated adverse reactions among different drugs of the same class are today available, often this information is not adequately brought to the attention of prescribers. Generally speaking, we think that providing adequate information and improving communication with health professionals and patients is a crucial issue. An important role may also be played by continuing medical education training courses, that should be more addressed toward the safety and the appropriate use of drugs, rather than their efficacy, in order to increase adherence to practice guidelines and avoid preventable adverse reactions.

Acknowledgment

We are very grateful to the Pharmaceutical Departments of Emilia-Romagna, Friuli-Venezia-Giulia, Lombardy, Sicily, the Autonomous Province of Trento, Tuscany, and the Veneto and their local Health Districts, for collecting the adverse reaction forms. The authors thank Philip Robinson for help in manuscript preparation. This study was partially funded through a grant from Valeas S.p.a.

References

1. Haddi E, Cherpin D, Taffareau M, et al. Atopy and systemic reactions to drugs. *Allergy* 1990; 45: 236-9.
2. Hamzaoui A. Allergy to antibiotics. *Rev Mal Respir* 2006; 23: 10S70-10S72.
3. International Collaborative Study of Severe Anaphylaxis. An epidemiologic study of severe anaphylactic and anaphylactoid reactions among hospital patients: methods and overall risks. *Epidemiology* 1998; 9: 141-6.
4. Leviton I. Separating fact from fiction: the data behind allergies and side effects caused by penicillins, cephalosporins, and carbapenem antibiotics. *Curr Pharm Des* 2003; 9: 983-8.
5. Vythoulka A, Pitsios C, Kompoti E. Allergic reactions due to mizolastine. *Ann Allergy Asthma Immunol* 2006; 97: 262-3.
6. Compalati E, Guerra L, Rogkakou A, Zanella C, Scordamaglia A, Passalacqua G. Angioedema after administration of methylprednisolone to treat drug allergy. *Allergy* 2007; 62: 1346-8.
7. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 2005; 60: 443-451.
8. Antúnez C, Martín E, Cornejo-García JA, Blanca-Lopez N, R-Pena R, Mayorga C, Torres MJ, Blanca M. Immediate hypersensitivity reactions to penicillins and other betalactams. *Curr Pharm Des* 2006; 12: 3327-33.
9. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. *J Allergy Clin Immunol* 2002; 110: 341-8.
10. Stricker BH, Slagboom G, Demaeseneer R, Slootmaekers V, Thijs I, Olsson S. Anaphylactic reactions to cinoxacin. *BMJ* 1988; 3: 1434-5.

11. Kidon MI, Kang LW, Chin CW, et al. Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, Atopic children. *Pediatrics* 2005; 116: e675-80.
12. Ewan PW. Anaphylaxis. *BMJ* 1998; 316: 1442-5.
13. van Puijenbroek EP, Egberts AC, Meyboom RH, Leufkens HG. Different risks for NSAID-induced anaphylaxis. *Ann Pharmacother* 2002; 36: 24-9.
14. Bigliardi PL, Izakovic J, Weber JM, Bircher AJ. Anaphylaxis to the carbohydrate carboxymethylcellulose in parenteral corticosteroid preparations. *Dermatology* 2003; 207: 100-3.
15. Lee P, Shanson D. Results of a UK survey of fatal anaphylaxis after oral amoxicillin. *J Antimicrob Chemother* 2007; 60: 1172-3.
16. Anonymous. WHO Adverse Drug Reaction Dictionary. Uppsala: WHO Centre for International Drug Monitoring, 1995.
17. Olsson S. The role of the WHO programme on International Drug Monitoring in coordinating worldwide drug safety efforts. *Drug Saf* 1998; 19: 1-10.
18. Motola D, Vargiu A, Leone R, Cocci A, Salvo F, Ros B, Meneghelli I, Venegoni M, Cutroneo PM, Vaccheri A, Velo G, Montanaro N. Hepatic adverse drug reactions: a case/non-case study in Italy. *Eur J Clin Pharmacol* 2007; 63:73-9.
19. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf* 2004; 13: 519-23.
20. Salvo F, Polimeni G, Moretti U, Conforti A, Leone R, Leoni O, Motola D, Dusi G, Caputi AP. Adverse drug reactions related to amoxicillin alone and in association with clavulanic acid: data from spontaneous reporting in Italy. *J Antimicrob Chemother* 2007; 60: 121-6.
21. Edwards IR. Adverse drug reactions: finding the needle in the haystack. *BMJ* 1997; 315: 500.

22. Pierfitte C, Begaud B, Lagnaoui R et al. Is reporting rate a good predictor of risks associated with drugs? *Br J Clin Pharmacol* 1999; 47: 329-31.
23. Moore N, Kreft-Jais C, Haramburu F, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; 44: 513-8.
24. Leone R, Conforti A, Venegoni M, Motola D, Moretti U, Meneghelli I, Cocci A, Sangiorgi Cellini G, Scotto S, Montanaro N, Velo G. Drug-induced anaphylaxis : case/non-case study based on an italian pharmacovigilance database. *Drug Saf* 2005; 28: 547-56.
25. Davidson MH. Controversy surrounding the safety of cerivastatin. *Expert Opin Drug Saf* 2002; 1: 207-12.
26. Blum MD, Graham DJ, McCloskey CA. Temafloxacin syndrome: review of 95 cases. *Clin Infect Dis* 1994; 18: 946-50.
27. Pilzer JD, Burke TG, Mutnick AH. Drug allergy assessment at a university hospital and clinic. *Am J Health Syst Pharm* 1996; 53: 2970-5.
28. Lange L, Koningsbruggen SV, Rietschel E. Questionnaire-based survey of lifetime-prevalence and character of allergic drug reactions in German children. *Pediatr Allergy Immunol* 2008; Epub ahead of print, DOI: 10.1111/j.1399-3038.2007.00702.x.
29. Radford A, Undre S, Alkhamesi NA, Darzi SA. Recording of drug allergies: are we doing enough? *J Eval Clin Pract* 2007; 13:130-7.
30. Thurmann, PA. Detection of drug-related adverse events in hospitals. *Expert Opinion on Drug Safety* 2003; 2:447-449.
31. National Audit Commission Spoonful of Sugar Report - Medicines Management in NHS Hospitals. ISBN 1 86240 321 X. London: National Audit Commission 2001.
32. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. *Journal of the American Medical Association* 1997; 277: 312-317.

33. Quercia O, Rafanelli S, Emiliani F, Stefanini GF. Anaphylactic reaction to cinoxacin: report of one case associated with inferior acute myocardial infarction. *Allerg Immunol* 2003; 35: 61-3.
34. Burt RA. Review of adverse reactions associated with cinoxacin and other drugs used to treat urinary tract infections. *Urology* 1984; 23: 101-7.
35. Sachs B, Riegel S, Seebeck J, Beier R, Schichler D, Barger A, Merk HF, Erdmann S. Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. *Drug Saf* 2006; 29: 1087-100.
36. Johannes CB, Ziyadeh N, Seeger JD, Tucker E, Reiter C, Faich G. Incidence of allergic reactions associated with antibacterial use in a large, managed care organisation. *Drug Saf* 2007; 30: 705-13.
37. Agenzia Italiana del Farmaco. Nota Informativa Importante su moxifloxacina (Avalox/Octegra/Actira/Proflox), February 2008
http://www.agenziafarmaco.it/allegati/nota_moxifloxacina_120208.pdf.
38. Hautekeete ML, Horsmans Y, van Waeyenberge C et al. HLA association of amoxicillin-clavulanate-induced hepatitis. *Gastroenterology* 1999; 117: 1181-6.
39. Greenberger PA. 8. Drug allergy. *J Allergy Clin Immunol* 2006; 117(2 Suppl Mini-Primer): S464-70.
40. Grammer LC, Greenberger PA. Drug allergy and protocols for management of drug allergies. 3rd ed. Providence (RI): Oceanside Pubs; 2003: 1-42.
41. Sullivan TJ, Wedner HJ, Schatz GS, Yecies LD, Parker CW. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981; 68: 171-80.
42. Segal AR, Doherty KM, Leggott J, Zlotoff B. Cutaneous reactions to drugs in children. *Pediatrics* 2007; 120: e1082-96.

43. Palma-Carlos AG, Palma-Carlos ML. Drug allergy and asthma. *Allerg Immunol (Paris)* 2007; 39: 193-4.
44. Strom BL, Carson JL, Schinnar R. The effect of indication on the risk of hypersensitivity reactions associated with tolmetin sodium versus other nonsteroidal antiinflammatory drugs. *J Rheumatol* 1988; 15: 695-699.
45. Díaz Jara M, Pérez Montero A, Gracia Bara MT, Cabrerizo S, Zapatero L, Martínez Molero MI. Allergic reactions due to ibuprofen in children. *Pediatr Dermatol* 2001; 18: 66-7.
46. Titchen T, Cranswick N, Beggs S. Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. *Br J Clin Pharmacol* 2005; 59: 718-23.
47. Lesko SM, Mitchel AA. An assessment of the safety of pediatric ibuprofen. *JAMA* 1995; 273: 929-933.
48. Mou SS, Punaro L, Antón J, Luckett PM. Severe systemic hypersensitivity reaction to ibuprofen: a presentation of systemic lupus erythematosus. *J Rheumatol* 2006; 33: 171-2.
49. Williams C, Highet AS. Drug-induced delayed multiorgan hypersensitivity (DIDMOHS). *Clinical Exp Dermatol* 2006; 31: 452-482.
- Vythoulka A, Pitsios C, Kompoti E. Allergic reactions due to mizolastine. *Ann Allergy Asthma Immunol* 2006; 97: 262-3.
50. Hindsén M, Zimerson E, Bruze M. Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis* 2006; 54: 150-7.
51. Diaz RL, Gardeazabal J, Manrique P, Ratón JA, Urrutia I, Rodríguez-Sasiain JM, Aguirre C. Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006; 54: 239-43.
52. Serrano G, Fortea JM, Latasa JM et al. Photosensitivity induced by fibric acid derivatives and its relation to photocontact dermatitis to ketoprofen. *J Am Acad Dermatol* 1992; 27: 204-8.

53. Meggitt SJ, Farr PM. Pseudoporphyria and propionic acid non-steroidal anti-inflammatory drugs. *Br J Dermatol* 1999; 141: 591-2.
54. Sánchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000; 84: 101-6.
55. Asero R. Risk factors for acetaminophen and nimesulide intolerance in patients with NSAID-induced skin disorders. *Ann Allergy Asthma Immunol* 1999; 82: 554-8.
56. Palma-Carlos AG, Clode MH, Ferreira AM, Palma-Carlos ML. Drug allergy and pollinosis. A short report. *Eur Ann Allergy Clin Immunol* 2007; 39: 200-1.
57. Stevenson D. Aspirin and NSAID sensitivity. *Immunol Allergy Clin North Am* 2004; 24: 491-505.

Tables

Table 1. Cases according to definitions.

Definition	Number (%)
Anaphylactic shock or anaphylactoid reactions	280 (8.9)
ADRs suggesting allergic reactions involving two systems/organs	888 (28.2)
Other skin reactions suggesting allergic reactions	1975 (62.8)
Total	3143 (100.0)

Table 2. Characteristics of cases and non-cases.

Pt Characteristics	Cases (n=3143)	Non-cases (N=24032)
Female, n (%)	1933 (61.5)	14569 (60.6)
Mean Age*, years ($\pm$ SD)	48.0 (21.4)	55.0 (20.8)
≤ 15 years**, n (%)	228 (7.2)	1076 (4.5)
Inpatient**, n (%)	1378 (43.8)	9197 (38.3)
Fatal ADRs**, n (%)	9 (0.3)	248 (1.0)
Polytherapy*, n (%)	1312 (41.7)	10535 (43.8)

*p<0.05; **p<0.001

Table 3. Cases and non-cases per drug classes (1° level ATC).

Class Drug (1 Level ATC code)*	Cases 3143 (%)	Non-cases 24032 (%)	ROR (95%CI)
Anti-infectives for systemic use	1437 (45.7)	6436 (26.8)	2.92 (2.71-3.15)
Musculo-skeletal system plus aspirin	798 (25.4)	4102 (17.1)	1.65 (1.51-1.81)
Nervous system	484 (15.4)	3906 (16.3)	0.94 (0.85-1.04)
Cardiovascular system	237 (7.5)	6288 (26.2)	0.23 (0.20-0.26)
Alimentary tract and metabolism	209 (6.6)	1800 (7.5)	0.88 (0.76-1.02)
Respiratory system	159 (5.1)	698 (2.9)	0.18 (0.15-0.21)
Blood and blood forming organs	46 (1.5)	1090 (4.5)	0.31 (0.23-0.42)
Genito urinary system and sex hormones	42 (1.3)	757 (3.1)	0.42 (0.30-0.57)

*Class drug with at least 30 reports of hypersensitivity reactions.

Table 4. Reports with Antibiotics in cases and non-cases (at least 20 cases).

Definition (ATC code)	Cases	Non-cases	ROR (95% CI)
Fluoroquinolones (J01MA)	387	1513	2.09 (1.85-2.36)
Narrow-spectrum penicillins (J01CA)	272	998	2.19 (1.90-2.52)
Combinations of penicillins (J01CR)	271	855	2.56 (2.21-2.96)
Macrolides (J01FA)	183	984	1.45 (1.23-1.71)
Combinations of sulfonamides and trimethoprim (J01EE)	90	449	1.55 (1.22-1.96)
Second-generation cephalosporins (J01DC)	51	176	2.24 (1.61-3.09)
Other quinolones (J01MB)	41	62	5.11 (3.37-7.73)
Third-generation cephalosporins (J01DD)	38	156	1.87 (1.29-2.71)

Table 5. Reports with NSAIDS (plus aspirin) classes (at least 20 cases).

Definitions (ATC code)	Cases	Non-cases	ROR (95% CI)
Other anti-inflammatory and antirheumatic agents, non-steroids (M01AX)	190	792	1.89 (1.60-2.23)
Propionic acid derivatives (M01AE)	182	526	2.75 (2.30-3.28)
Aspirin (B01AC06 and N02BA01)	171	901	1.48 (1.24-1.75)
Acetic acid derivatives and related substances (M01AB)	85	379	1.73 (1.36-2.22)
Oxicams (M01AC)	29	256	0.86 (0.58-1.29)

Figures

Figure 1. Cases and non-cases group age.

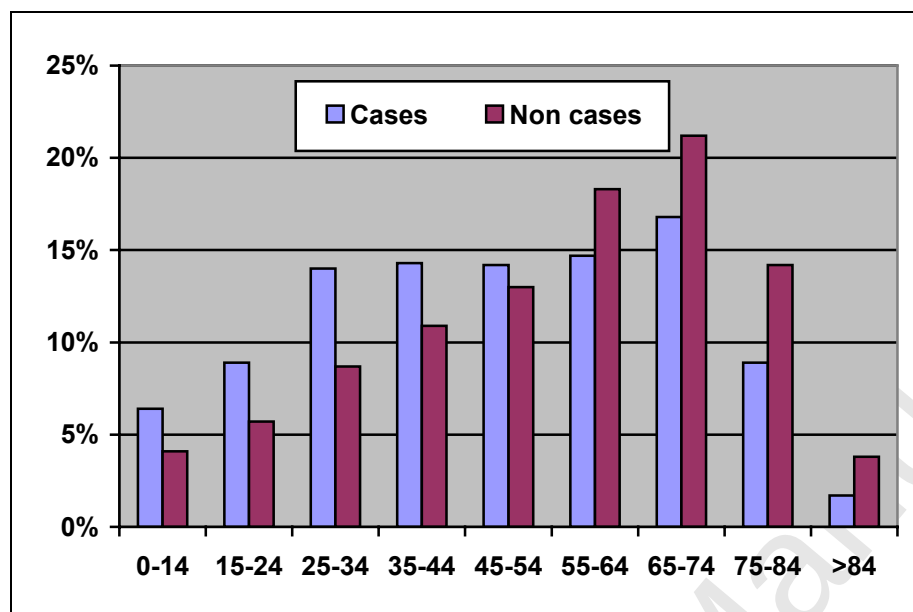
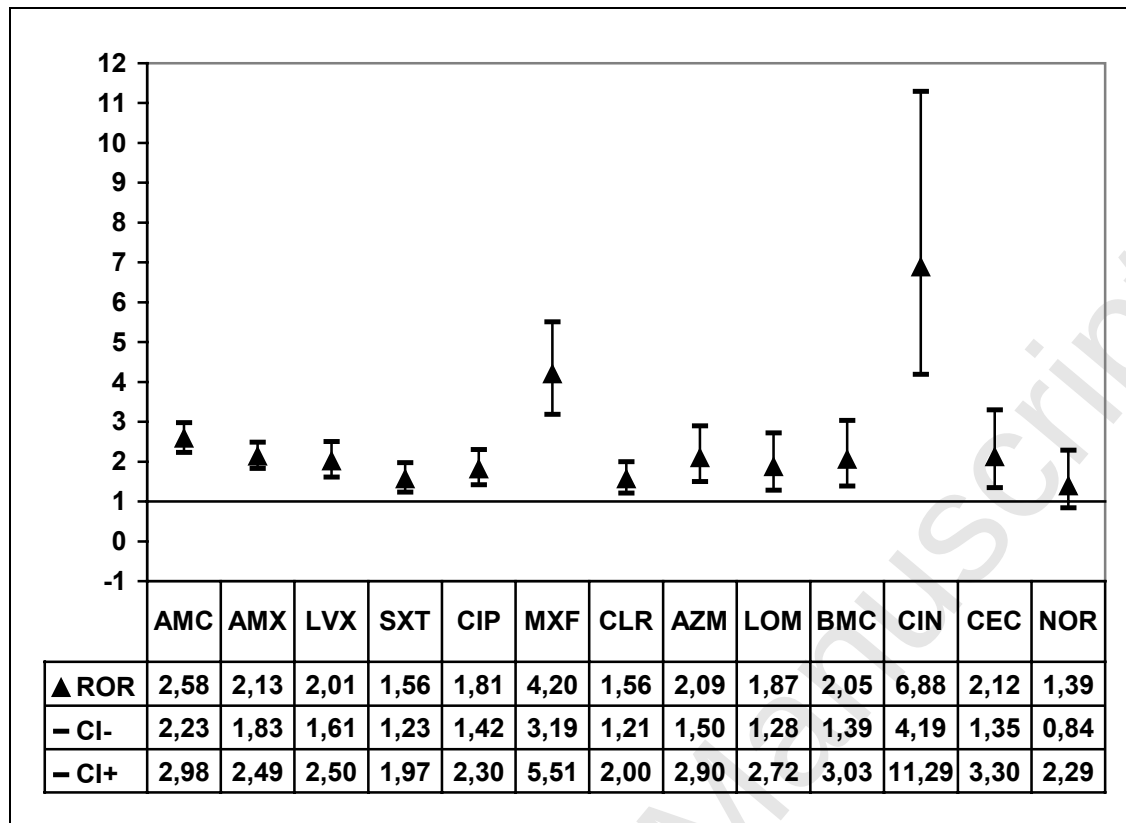
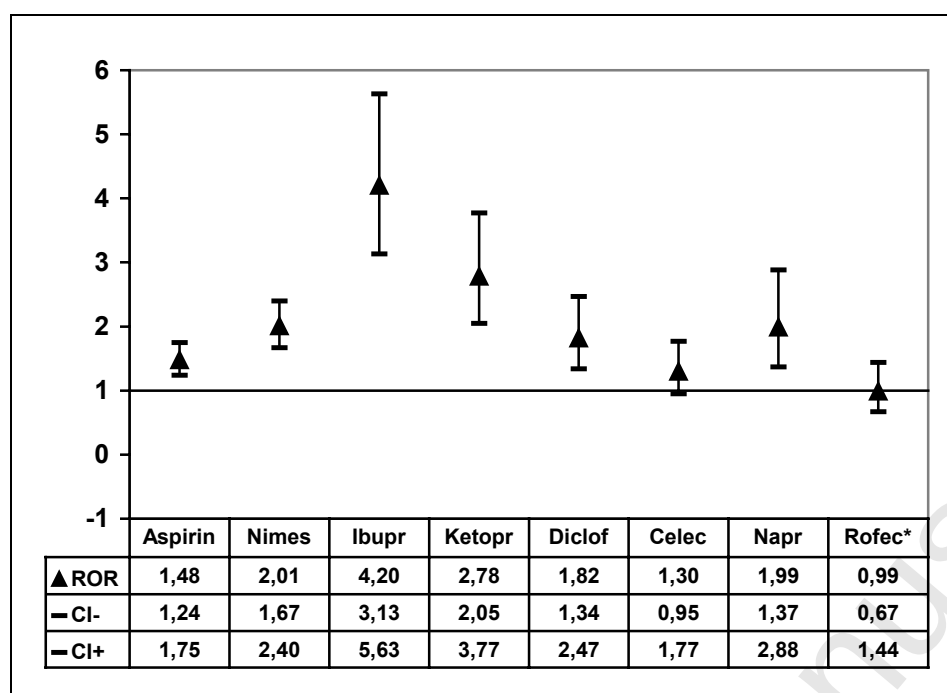


Figure 2. Antibiotics ROR and 95%CI of with at least 20 cases.

AMC: Amoxicillin/clavulanic acid 270 cases and 844 non-cases; AMX: Amoxicillin 226 cases and 842 non-cases; LVX: Levofloxacin 190 cases and 423 non-cases; SXT: Sulfamethoxazole/Trimethoprim 90 cases and 446 non-cases; CIP: Ciprofloxacin 89 cases and 381 non-cases; MXF: Moxifloxacin 86 cases and 160 non-cases; CLR: Clarithromycin 79 cases and 391 non-cases; AZM: Azithromycin 49 cases and 181 non-cases; LOM: Lomefloxacin 37 cases and 152 non-cases; BMC: Bacampicilline 35 cases and 131 non-cases; CIN: Cinoxacin 33 cases and 37 non-cases; CEC: Cefaclor 27 cases and 98 non-cases; NOR: Norfloxacin 20 cases and 110 non-cases.

Figure 3. NSAIDS (with aspirin) and 95%CI of with at least 20 cases.

Aspirin 171 cases and 901 non-cases; Nimesulide 162 cases and 634 non-cases; Ibuprofen 75 cases and 139 non-cases; Ketoprofen 61 cases and 170 non-cases; Diclofenac 55 cases and 233 non-cases; Celecoxib 50 cases and 296 non-cases; Naproxen 38 cases and 147 non-cases; Rofecoxib 33 cases and 256 non-cases (*withdrawn from the market in 2004).