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Original Research

Type B adverse drug reactions reported by an immunoallergology department

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Abstract

Objective: Characterization of the adverse drug reactions (ADR) reported by the immunoallergology department (IAD), Centro Hospitalar de São João (Porto), to the Northern Pharmacovigilance Centre (NPC).

Methods: An observational, descriptive and retrospective study was conducted, based in a spontaneous report system. Participants were all the patients from the IAD, with suspected ADR, reported to NPC by specialists after the study was completed.

Results: Studied population had a median age of 41 years, with the predominance of the female gender (73.2%). Allergic rhinitis and asthma were the most frequent comorbidities. All studied ADR were type B, 89.6% were serious, 86.4% unexpected and 2.6% associated with drugs that presented less than 2 years in the market. The most represented drug classes were the non-steroidal anti-inflammatory drugs (NSAIDs) (52.6%) and antibiotics (25.2%). Skin symptoms represented 61.2% of the reported complaints. About 52.9% of these ADR occurred in less than one hour after intake. The most frequent ADR treatment at the time of the reaction was drug interruption (86.2%), followed by the prescription of anti-histamines (42.2%).

Conclusions: Reported ADR to NPC by the Drug Alert Unit were mainly serious, unexpected, associated with NSAIDs and antibiotics and related with marketing authorization medicines older than two years. These results could be very useful to develop strategies to prevent the clinical and economic consequences of ADR.

Keywords

Drug-Related Side Effects and Adverse Reactions; Adverse Drug Reaction Reporting Systems; Inpatients; Anti-Inflammatory Agents, Non-Steroidal; Anti-Bacterial Agents; Portugal

INTRODUCTION

The awareness that "any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects", is the foundation of the adverse drug reaction (ADR) concept.[1] The World Health Organization (WHO) defines ADR as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man".[2] The European directive 2010/84/EU states that the definition of 'adverse reaction' should be amended to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.[3]

ADR are a worldwide public health problem. The incidence of ADR as cause of hospitalization ranges between 1% and 5,3%.[4,5] In a meta-analysis of prospective studies from USA hospitals, in hospitalized patients the incidence of serious ADR was 6,7% and fatal ADR was 0,32%, placing ADR between the fourth and sixth cause of death.[6] It has been estimated that approximately ADRs cause 197,000 deaths annually throughout the EU.[7,8] In general population, fatal ADR can represent the seventh death cause.[9]

According to drug-induced allergies, there are some studies, related to specific drugs[10] or to specific age groups[11] concluding that reported allergic reactions should be further explored. The ADRs clinical, economic and public health consequences enhance the need to persist with pharmacoepidemiologic studies and pharmacovigilance systems. Drug hypersensitivity reactions are typically unpredictable and potentially life-threatening. They may cause or prolong patient's hospitalization, and may constraints future therapeutic options.[12]

In this context, we conducted a pharmacoepidemiologic study aiming to characterize the ADR reported by the Immunoallergology Department (IAD) of the Centro Hospitalar de São João (Porto) to the Northern Pharmacovigilance Centre (NPC) that deals particularly with evaluation of possible drug hypersensitivity reactions (DHR after suspicion of an allergic reaction.

METHODS

A pharmacoepidemiologic retrospective study was conducted, descriptive and based in a spontaneous ADR report system.

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Participants

All patients from the IAD of Centro Hospitalar de São João (Porto) with reported ADR by the IAD to the NPC were included in the study. These reported ADRs have one feature in common. All were previously considered compatible with a drug hypersensitivity reaction (DHR), with the suspicion of an allergic reaction and reason why the patients were referred to the IAD of the Centro Hospitalar de São João, for further study.

In order to achieve the study objectives, the extracted data were organised in two different groups of variables:

1.Patient characterization: Age, gender, and co-morbidities (asthma, rhinitis, dermatitis, chronic urticaria, food allergy, latex allergy, house dust mite allergy, hymenoptera allergy, pollen allergy, ADR history associated with surgical acts, and ADR history associated with complementary diagnostic exams).

2.ADR characterization:

- Seriousness: according to the Guidelines on Pharmacovigilance for Medicinal Products for Human Use, a serious ADR is any occurrence that causes: death; can be life threatening; requires hospital admission or causes delay in hospital discharge or results in persistent or significant disability/incapacity and congenital anomalies.[11]
- Expected vs unexpected: according to the same Guidelines, unexpected ADR are the ones partially or totally not described in the summary of products characteristics.[13] Expected ADR are the ones totally described in the summary of products characteristics.
- Recent placing on the market: the threshold of 2 years was established for the characterization of recent placing on the market. This limit considered the community regulation[14] for semiannual drug safety reports during the first 2 years of market authorization.
- Drug class: drugs suspected of ADR were classified according with the pharmaceutical classes, referred in the summary of products characteristics, and then aggregated in accordance with common characteristics (e.g., beta-lactams, macrolides and quinolones form the class of antibacterials).
- ADR characterization: described according with the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Symptoms were grouped in accordance with the body system.
- Time elapsed until ADR: the time between drug administration and the occurrence of the first symptom(s). Data were then grouped in immediate and non-immediate ADRs. Immediate ADR were those occurring within the first hour after the last drug administration, and the non-immediate occurred more than one hour after the last drug administration.[15-17]
- ADR duration: time between the first ADR symptom(s) and to-tal remission of symptoms.
- ADR treatment: the treatment interventions studied were: drug withdraw; adrenalin administration; anti-histamines; corticosteroids and non-steroidal anti-inflammatory (NSAIDs) administration.
- Drug reintroduction: re-administration of the suspected drug after the reported ADR episode.

An ADR recurrence was considered, when the adverse event was reproducible with the drug reintroduction.

Data collection and analysis

Data were collected from the report forms sent to the NPC by the IAD, between the 1st of January 2006 and the 31st of December 2010. The descriptive statistical analyses were performed using the software SPSS version 20.0.

RESULTS

Between January 2006 and December 2010, among the patients followed in the Drug Alert Unit, 117 developed ADR originating 125 reports to the NPC.

The patients' median age was 41 years, ranging from 8 months to 78 years of age, and 72% were female (Table 1). In total, 25.7% of participants had no comorbidities and the most common comorbidities were: rhinitis (25.7%); asthma (17.8%); and chronic urticaria (5.9%).

Report forms with data for ADR history to the same or other drug(s) were respectively 42 and 51. ADR history to the same drug occurred in 14.3%, and to other drug(s) in 88.2%. The drugs reported were: NSAIDs (44.7%), antibacterials (44.7%), proton pomp inhibitors (2.1%), analgesics and antipyretics (2.1%), antitussives (2,1%), antiepileptics and anticonvulsants (2,1%), sulfonamides and associations (2,1%), local anesthetics (2,1%), and thiocolchicoside (2,1%).

ADR characterization is summarized in Table 2. All reported ADR were classified as type B because the studied population was composed exclusively by patients with suspected drug allergy studied in the DAU of IAD. Type B reactions include hypersensitivity drug reactions, that can be distinguished in allergic (drug allergy) and non-allergic hypersensitivity reactions (Table 2).

According to the ADR seriousness, 89.6% of the reported ADR were considered serious, with 41.1% causing hospitalization and 4.5% considered life-threatening. 86.4% of the reported ADR were classified as un-expected, according to the guidelines.

For recent placing on the market, 11 ADR reports were excluded, be-cause they presented the suspected active substance instead of the drug name. Drugs up to 2 years of placing on the market were identified in 2.6% of the reported ADR. The remaining 97.4% were drugs marketed for more than two years.

The most frequent drug classes involved in the reported reactions were NSAIDs (52.6%) and antibacterials (25.2%).

In this study, 81 different symptoms were identified, corresponding to a total of 338 occurrences. The skin symptoms were the most frequent, corresponding to 61.2% of the occurrences. The most common cutaneous

Table 1. Sociodemographic and clinical practice characteristics of the patients		
	n	**%**
Age (years)		
[0;35	36	32.4
35;50	44	39.6
50;78	31	27.9
NI	14	-
Gender		
Female	90	73.2
Male	33	26.8
NI	2	-
Comorbidities		
Asthma	17	17.8
Chronic urticarial	5	5.9
Dermatitis	2	2.2
Food allergy	2	2.2
House dust mite allergy	14	14.9
Hymenoptera allergy	1	1.1
Latex allergy	1	1.1
Pollen allergy	3	3.2
Rhinitis	24	25.7
No comorbidities	24	25.7
NI	24	-
ADR history to the same drug		
Yes	6	14.2
No	36	85.7
NI	83	-
ADR history to a different drug		
Yes	45	88.2
No	6	11.8
NI	74	-
*ADR means Adverse Drug Reaction; *NI means No Information available		

Table 2. Reported Adverse Drug Reactions characterization.		
	n	**%**
Seriousness		
Serious	112	89.6
Hospitalization	46	41.1
Life threatening	5	4.5
Other	66	58.9
Not serious	13	10.4
Expected vs Unexpected		
Expected	17	13.6
Unexpected	108	86.4
Recent placing on the market		
Up to 2 years	3	2.6
More than 2 years	111	97.4
Drug Class		
Non-steroidal anti-inflammatory	71	52.6
Antibacterials	34	25.2
Corticosteroids	7	5.2
Others	23	17.0
Symptoms		
Cutaneous	207	61.2
Respiratory	48	14.2
Gastrointestinal	35	10.4
Cardiovascular	10	3.0
Anaphylaxis	7	2.1
Other	31	9.2
Total	338	100
Beginning time		
Immediate	45	52.9
Non-immediate	40	47.1
Treatment		
Anti-histamines	49	42.2
Anti-inflammatory	28	24.2
Corticosteroids	27	23.3
Non-steroidal	1	0.9
Adrenaline	3	2.6
Drug withdraw	100	86.2
Drug re-introduction		
Yes	7	41.2
With ADR recurrence	6	85.7
Without ADR recurrence	1	14.3
No	10	58.8
*ADR means Adverse Drug Reaction.		

complaints were: urticaria (2.6%), rash (24.6%) and pruritus (8.7%). Respiratory symptoms represented 14.2%, and dyspnea was the most reported respiratory symptom (47.9%). Gastrointestinal symptoms were present in 10.4% of the reported occurrences.

For the characterization of ADR beginning time, 40 reports were excluded, because of incomplete information. In 85 reports, 52.9% of the ADR were immediate and 47.1% were non- immediate.

For the study of ADR duration and total remission, 83 report forms were excluded, because of incomplete information. In 42 ADR, 24 (57%) had a duration up to 24 hours. The remaining 18 (43%) ADR lasted for more than 2 days.

Considering the characterization of ADR treatment, 9 reports were excluded, because of incomplete information. The most frequent ADR treatment at the time of the reaction was drug withdraw (86.2%), followed by the administration of anti-histamines (42.2%), corticosteroids (23.3%) and NSAIDs (0.9%). Adrenalin injection was reported in 3 (2.6%) ADR. In this sample drug provocation with the suspected culprit was per-formed in seven patients with a recurrence of ADR of 85.7%.

DISCUSSION

This was an observational retrospective study, based in a spontaneous report system. According to our results, we can characterize the ADR reported by the IAD of Centro Hospitalar de São João (Porto) has being mainly serious, unexpected, associated with NSAIDs and antibacterials, and related with drugs marketed for more than two years.

These results can be very useful to characterize the type and severity of the reactions, the most involved drugs, alert patients about their problem and call the attention of health care providers about the direct and indirect costs involved and to create a universal informatics alert system about specific reactions, to one or more drugs for each patient.

The studied population was composed by the patients with ADR, referred to the DAU, with suspected drug allergy. The median age was 41 years, mainly of the female gender (73.2%), data that is consistent with other studies.[18,19]

ADR are more frequently described in older populations.[19-27] The most represented comorbidities in this study were rhinitis, asthma. Although these diseases have already been reported in one study[28], other concomitant diseases states associated with an increased risk for drug allergy, like viral causes: HIV, Epstein-Barr virus, Human Herpes virus 6, Human Herpes virus 7 and Cytomegalovirus infections have been described.[18,29] The HIV patients was not included in this study.

The most frequent drug classes reported in ADR history were NSAIDs and antibacterials, with predominance of NSAIDs. Considering all the patients studied with DHR, the results are consistent with other studies where NSAIDs, followed by antibacterials are the most frequent drugs involved in DHR.[30-32]

This study focused only in type B ADR, because all the patients presented ADR suspected of DHR. According with the classification proposed by Hunziker *et al*.[33], the allergic drug reactions are included in the type B reactions.

Serious ADR were the most frequent (89.6%), 41.1% caused hospitalization and 4.5% were life threatening. These results are consistent with the characteristics of type B reactions, which tend to be more serious[25], and should alert health professionals and patients about the importance of drug use surveillance and pharmacovigilance.

The majority of the ADR were related to drugs that presented a marketing authorization with more than 2 years. Our results may be explained by the specific characteristics of the type B studied ADR.

The most frequent drug classes were NSAIDs (52.6%) and the antibacterials (25.2%). Usually, antibacterials are the most represented drug class (18, 34, 35, 36) In a self-report drug allergy study, beta-lactams and NSAIDs were the most frequently involved drugs.[37] In an analysis of spontaneous reports from a regional database, there were 49.6% reports of serious ADRs associated with antimicrobials and 60.3% associated with NSAIDs[38] other study performed for paediatric population based in a national database, vaccines were the most represented group (42%) followed by antibacterials for systemic use (17%).[39]

The most common ADR complaints were related to skin (61.2%), as expected when compared with other studies.[18,28,34,35,40] In drug-induced allergic reactions, cutaneous symptoms or signs are the most common physical manifestations.[34]

Concerning the duration of ADR, 43% lasted for more than 2 days. This is important in different aspects, one of them is the negative influence in the patient's quality of life, but also, because it raises the importance of ADR economic negative impact, contributing to the increase of direct and indirect costs.[41]

The most frequent ADR treatment at the time of the event was drug withdraw (86.2%), followed by the administration of anti-histamines (42.2%), corticosteroids and NSAIDs. Surprisingly adrenalin injection was reported only in 3 (2.6%) patients. These results are in accordance with the management of the acute drug reactions: withdraw of the suspect drug, treatment of acute reaction according to the severity and the referral to a specialized Center for study.[29]

Drug reintroduction, either accidental or not has presented a very high risk of a similar or even worse ADR (85.7%). This is of outmost importance concerning prevention.[42]

As described in other studies[26,30], the probable and possible ADR were the most represented causality assessment results.

The main limitations of the study were: (i) information bias, including the incomplete data presented in the spontaneous report system[43]; (ii) the participants' selection, (important bias referring to the studied sample, exclusively composed by the patients studied in a Drug Allergy Units (DAU) with suspected DHR).

CONCLUSIONS

The DAU of IAD reported ADR that were mainly serious, unexpected, associated with NSAIDs and antibacterials, and related with drugs marketed for more than two years. It is very important to analyze, characterize and report ADR from different hospitals and departments to allow health professionals, patients and health authorities to develop strategies to ensure drug safety knowledge, and its benefit/risk balance.

CONFLICT OF INTEREST

None.

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None.

References

1. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-1259. doi: 10.1016/S0140-6736(00)02799-9
2. WHO. Safety of Medicines - A guide for detecting and reporting adverse drug reactions - Why health professionals need to take action. Geneve: WHO; 2002.
3. Directive 2010/84/EU http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF (accessed Jul 9, 2017).
4. Amann C, Hasford J, Stausberg J. [Hospital Admission due to Adverse Drug Events (ADE): An Analysis of German Routine Hospital Data of 2006]. Gesundheitswesen. 2012;74(10):639-644. doi: 10.1055/s-0031-1286275
5. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother. 2008;42(7):1017-1025. doi: 10.1345/aph.1L037
6. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279(15):1200-1205.
7. European Commission. Proposal for a regulation amending, as regards pharmacovigilance of medicinal products for human use. Regulation (EC) No 726/2004. Impact assessment. 2008. Available at: http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf (accessed Nov 17, 2017).

8. Bouvy JC, De Bruin ML, Koopmanschap MA. Koopmanschap Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf. 2015;38(5):437-453. doi: 10.1007/s40264-015-0281-0
9. Wester K, Jonsson AK, Spigset O, Druid H, Hagg S. Incidence of fatal adverse drug reactions: a population based study. Br J Clin Pharmacol. 2008;65(4):573-579. doi: 10.1111/j.1365-2125.2007.03064.x
10. Gomes E1, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004;34(10):1597-1601. doi: 10.1111/j.1365-2222.2004.02070.x
11. Rebelo Gomes E, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: from self-reporting to confirmed diagnosis. Clin Exp Allergy. 2008;38(1):191-198. doi: 10.1111/j.1365-2222.2007.02870.x
12. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, Khan DA, Lang DM, Park HS, Pichler W, Sanchez-Borges M, Shiohara T, Thong BY. International Consensus on drug allergy. Allergy. 2014 Apr;69(4):420-437. doi: 10.1111/all.12350
13. European Comission. Volume 9A Guidelines on Pharmacovigilance for Medicinal Products for Human Use, in The Rules Governing Medicinal Products in the European Union. 2008.
14. European Community Regulation. Nº 726/2004 of The European Parlamiament And The Council of 31 March 2004.
15. Romano A, Torres MJ, Castells M, Sanz Ml, Blanca M. Diagnosis and management of drug hypersensitivity reactions. J Allergy Clin Immunol. 2011;127(3 Suppl):S67-S73.
16. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wüthrich B; EAACI (the European Academy of Allergology and Cinical Immunology) nomenclature task force. revised nomenclature for allergy: An EAACI position statement from the EAACI nomenclature task force. Allergy. 2001;56(9):813-824.
17. Bousquet PJ, Demoly P, Romano A, Aberer W, Bircher A, Blanca M, Brockow K, Pichler W, Torres MJ, Terreehorst I, Arnoux B, Atanaskovic-Markovic M, Barbaud A, Bijl A, Bonadonna P, Burney PG, Caimmi S, Canonica GW, Cernadas J, Dahlen B, Daures JP, Fernandez J, Gomes E, Gueant JL, Kowalski ML, Kvedariene V, Mertes PM, Martins P, Nizankowska-Mogilnicka E, Papadopoulos N, Ponvert C, Pirmohamed M, Ring J, Salapatas M, Sanz ML, Szczeklik A, Van Ganse E, De Weck AL, Zuberbier T, Merk HF, Sachs B, Sidoroff A; Global Allergy, Asthma European Network (GALEN) and Drug Allergy and Hypersensitivity Database (DAHD) and the European Network for Drug Allergy (ENDA). Pharmacovigilance of drug allergy and hypersensitivity using the ENDA-DAHD database and the GALEN platform. The Galenda project. Allergy. 2009;64(2):194-203. doi: 10.1111/j.1398-9995.2008.01944.x
18. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol. 2011;71(5):684-700. doi: 10.1111/j.1365-2125.2010.03774.x
19. Fattinger K, Roos M, Vergères P, Holenstein C, Kind B, Masche U, Stocker DN, Braunschweig S, Kullak-Ublick GA, Galeazzi RL, Follath F, Gasser T, Meier PJ. Epidemiology of drug exposure and adverse drug reactions in two swiss departments of internal medicine. Br J Clin Pharmacol. 2000;49(2):158-167.
20. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15-19. doi: 10.1136/bmj.329.7456.15
21. Wu TY, Jen MH, Bottle A, Molokhia M, Aylin P, Bell D, Majeed A. Ten-year trends in hospital admissions for adverse drug reactions in England 1999-2009. J R Soc Med. 2010;103(6):239-250. doi: 10.1258/jrsm.2010.100113
22. Hopf Y, Watson M, Williams D. Adverse-drug-reaction related admissions to a hospital in Scotland. Pharm World Sci. 2008;30(6):854-862.
23. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci. 2002;24(2):46-54.
24. Alexopoulou A, Dourakis SP, Mantzoukis D, Pitsariotis T, Kandyli A, Deutsch M, Archimandritis AJ. Adverse drug reactions as a cause of hospital admissions: a 6-month experience in a single center in Greece. Eur J Intern Med. 2008;19(7):505-510. doi: 10.1016/j.ejim.2007.06.030
25. Patel H, Bell D, Molokhia M, Srishanmuganathan J, Patel M, Car J, Majeed A. Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998-2005. BMC Clin Pharmacol. 2007;7:9.
26. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One. 2009;4(2):e4439. doi: 10.1371/journal.pone.0004439
27. Ventura MT, Napolitano S, Buquicchio R, Cecere R, Arsieni A. An approach to urticaria in the elderly patients. Immunopharmacol Immunotoxicol. 2012;34(3):530-533. doi: 10.3109/08923973.2011.631549
28. Ensina LF, Amigo MH, Koch T, Guzman E, Paoli R, Nunes IC. Drug hypersensitivity in students from São Paulo, Brazil. Clinics (Sao Paulo). 2010;65(10):1009-1011.
29. Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugué P, Friedmann PS, English JS, Huber PA, Nasser SM; BSACI. BSACI guidelines for the management of drug allergy. Clin Exp Allergy. 2009;39(1):43-61. doi: 10.1111/j.1365-2222.2008.03155.x
30. Green CF, Mottram DR, Rowe PH, Pirmohamed M. Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study. J Clin Pharm Ther. 2000;25(5):355-361.
31. Cornejo-Garcia JA, Blanca-López N, Doña I, Andreu I, Agúndez JA, Carballo M, Blanca M, Canto MG. Hypersensitivity reactions to non-steroidal anti-inflammatory drugs. Curr Drug Metab. 2009;10(9):971-980.
32. Doña I, Blanca-Lopez N, Cornejo-Garcia JA. NSAIDs are the most frequent medicaments involved in hypersensitivity drug reactions. Eur Ann Allergy Clin Immunol. 2014;46(1):63.
33. Hunziker T, Bruppacher R, Kuenzi UP, Maibach R, Braunschweig S, Halter F, Hoigné RV. Classification of ADRs: a proposal for harmonization and differentiation based on the experience of the Comprehensive Hospital Drug Monitoring Bern/St. Gallen, 1974-1993. Pharmacoepidemiol Drug Saf. 2002;11(2):159-163. doi: 10.1002/pds.669

34. Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S126-S137. doi: 10.1016/j.jaci.2009.10.028
35. Park CS, Kim TB, Kim SL, Kim JY, Yang KA, Bae YJ, Cho YS, Moon HB. The use of an electronic medical record system for mandatory reporting of drug hypersensitivity reactions has been shown to improve the management of patients in the university hospital in Korea. Pharmacoepidemiol Drug Saf. 2008;17(9):919-925. doi: 10.1002/pds.1612
36. Buccellato E, Melis M, Biagi C, Donati M, Motola D, Vaccheri A. Use of antibiotics in pediatrics: 8-years survey in Italian hospitals. PLoS One. 2015;10(9):e0139097. doi: 10.1371/journal.pone.0139097
37. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004;34(10):1597-1601. doi: 10.1111/j.1365-2222.2004.02070.x
38. Polimeni G, Salvo F, Cutroneo P, Morreale I, Patrizio Caputi A. Adverse reactions induced by NSAIDs and antibacterials: analysis of spontaneous re-ports from the Sicilian regional database. Drug Saf. 2006;29(5):449-459.
39. Nogueira Guerra L, Herdeiro MT, Ribeiro-Vaz I, Clérigo MI, Rocha C, Araújo A, Pêgo A, Rebelo Gomes E. Adverse drug reactions in children: a ten-year review of reporting to the Portuguese Pharmacovigilance System. Expert Opin Drug Saf. 2015;14(12):1805-1813. doi: 10.1517/14740338.2015.1105214
40. Gruchalla R. Understanding drug allergies. J Allergy Clin Immunol. 2000;105(6 Pt 2):S637-S644.
41. Demoly P, Pichler W, Pirmohamed M, Romano A. Important questions in Allergy: 1--drug allergy/hypersensitivity. Allergy. 2008;63(5):616-619. doi: 10.1111/j.1398-9995.2008.01693.x
42. Ensina LF, Fernandes FR, Gesu G, Malaman MF, Chavarria ML, Bernd LAG. Reações de hipersensibilidade a medicamentos. Rev Bras Alerg Imunopatol. 2009;32(2):42 -47.
43. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18(6):427-436. doi: 10.1002/pds.1742