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From the Editor

Pharmacogenomics was until recently little more than a mirage for daily clinical practice. In fact it seems to be taking far-reaching strides in the way it may soon come to impact on therapeutic options, as well as on the prevention of adverse drug reactions. The association of an increased risk of serious and potentially fatal adverse skin reactions, which had previously been considered as idiosyncratic, with exposure to allopurinol in the presence of a specific gene allele, is now supported by robust evidence.

One does not need to be wildly imaginative to predict that the generation of the children whose adverse reactions are described in this Boletim issue may come to be a generation of adults whose genetic profile will be brought into the equation as a matter of routine whenever medicines are prescribed or suspected ADRs diagnosed. Even currently unpredictable and catastrophic hypersensitivity reactions such as those resulting from anaphylaxis (another ADR category whose epidemiology and diagnosis are discussed in this number) may one day come to be prevented with the help of future pharmacogenetic insights.

Further in this quarter's Boletim: statins and glucose metabolism changes, the association between oesophageal cancer and prolonged use of bisphosphonates, and drug-drug interactions in the literature.

How can I report an adverse reaction?

- **ADR Portal (Portal RAM):**
  http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage
- **Report Card online printout link:**
  www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM
- **Postage Paid Card**

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Southern Regional Pharmacovigilance Unit
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E-mail: ufc@aibili.pt

Online reporting of adverse drug reactions by health professionals and patients

Portal RAM for ADR reporting.
Online forms for both health professionals or patients.

Allopurinol risk of serious skin reactions in patients with allele HLA-B*5801

In January 2012, the European Pharmacovigilance Working Party (PhVWP) found it relevant to highlight a published article on case-control studies conducted by the US Food and Drug Administration (FDA) which supported the concept that allopurinol should be avoided in patients with the HLA-B*5801 allele, in that they seem to have a higher risk of developing serious cutaneous adverse reactions (SCARs), including DRESS hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and Toxic Epidermic Necrolysis (TEN).[1]

The documentation pertaining to the innovative medicinal product* (Zyloric®) contained pharmacogenomic data in section 4.8 of the SPC in some member states. However, it was not harmonized Europe-wide.

Following the assessment undertaken by the PhVWP on the risk of SCAR, including SJS and TEN, associated with the use of allopurinol in patients who are bearers of the allele HLA-B*5801, it has been decided that information on this association is to be included in the SPCs and information leaflets of all medicinal products containing allopurinol.

The text to be included in the SPC and information leaflets can be accessed here (in Portuguese):
http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/INFORMACAO_SEGURANCA/ALTER_TIPO2_SEGURANCA/MED_USADOS_GOTA

Margarida Guimarães

** "Innovative" refers to the product that was first marketed as a direct outcome of research which was at the time innovative.*

Reference

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What do they stand for?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
PIL	Patient Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

INDEX CARD | **Director:** Alexandra Pego **Editor:** Rui Pombal **Assistant Editor:** Cristina Rocha **Contributors:** Ana Araújo, Catarina Fernandes Costa, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Inês Clérigo, Joana Oliveira, Leonor Nogueira Guerra, Magda Pedro, Margarida Guimarães, Pedro Marques Silva **Publishing Assistant:** Inocência Pinto **Advisory Board:** Conselho Directivo do INFARMED, I.P.; Comissão de Avaliação de Medicamentos **Publisher:** INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P., Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa, Tel.: 217 987 316, correio electrónico: infarmed@infarmed.pt **Design and production:** Letras&Sinais,Comunicação e Imagem, Lda. **Printing:** Rainho&Neves,Lda. **Legal Deposit:** 115 099/97 **ISSN:** 0873-7118 **Print Run:** 49 000 (Portuguese)

ADRs in the Paediatric Age Range reported in Portugal: a bird's-eye view

The paediatric population is especially vulnerable to the effects of medicines. In pharmacovigilance, monitoring ADRs in children is of particular relevance and entails a series of specific issues and problems. For one, safety data for the paediatric population cannot be extrapolated from adults, given the differences in pharmacokinetics, pharmacodynamics and ADR incidence, which account for a drug toxicity profile diverse from the one observed in adults. Those differences can usually be ascribed to relative immaturity of hepatic metabolism and renal function, progressive organ development, growth and sexual maturation, as well as to the epidemiology of illnesses which are characteristic of the younger age groups. The scarcity of research in children due to ethical considerations is another limitation.[1]

In this article we characterise the paediatric population's cases of ADRs received by the Portuguese National Pharmacovigilance System in 2011. These data are then compared with the figures from the three preceding years (2008 to 2010).

ADRs in children in 2011

259 cases of suspected ADRs were reported to the Portuguese National Pharmacovigilance System in 2011. They accounted for **10.3%** of the total number of ADR cases added to the system that year.

Most cases (63%) were reported directly by health professionals, the remainder having been entered by the pharmaceutical industry (indirect reports). Physicians reported over half of the cases (88 cases; 54.3%), followed by nurses (57 cases; 35.2%) and pharmacists (17 cases; 10.5%).

The gender difference was not significant (51.4% of cases affected females). Most cases involved children **up to two years of age**: 33% (n=86). Teens aged **between 16 and 18** came next (15.4% (n=40)), and only then children between 4 and 6 years (12% (n=31)).

The prominence of the 16-18-year age group can probably be explained by a relatively high number of cases associated with human papillomavirus vaccines given to female adolescents. The peak at the younger age groups is likely to be related to the weight of vaccines, since infants and children up to 6 years receive most of the doses of the National Immunization Programme.

Of the 259 cases of ADRs in children in 2011, 202 involved only one suspected drug while the remaining thirty-two were to do with two or more medicines. In total, medicines from 37 different ATC groups were involved, corresponding to 308 different medicines. Of these, 165 (53.6%) belonged to just two ATC groups: ***vaccines*** (112) and ***antibacterials for systemic use*** (53). The most represented group was therefore that of vaccines, which is not surprising given the expected high levels of exposure of children to this pharmacotherapeutic group.

As for organ system distribution (System Organ Categories – SOC) the following SOCs stand out: General disorders and administration site conditions (20.8%), Skin and subcutaneous tissue disorders (18.5%) and Infections and infestations (9.8%).

The greater incidence of **general** and **site of administration** ADRs is probably related to the fact that most local reactions are associated with the administration of vaccines. Indeed, these groups of ADRs include mostly **skin reactions at site of injection** or are associated with **hypersensitivity**.

The **skin** SOC cases are almost all associated with **vaccines** or **antibiotics**, both pharmacological groups with a characteristically relatively high incidence of adverse cutaneous reactions. They also include several cases of hypersensitivity (e.g., angioedema, anaphylaxis) which, though much less frequent, are not unexpected and typically include skin manifestations such as rash, urticaria or pruritus.

Infections come as the third most significant SOC. This is not surprising as a consequence of mostly vaccine failure or other **prophylaxis failure** (e.g., prevention of human respiratory syncytial virus infection in children at risk), or as complications from reactions at the site of inoculation (e.g., skin infection).

Of the total number of cases detected in children, 192 (**74.1%**) were deemed **serious** by the reporting agent. Fatal outcomes (3.6%) were related to the children's background condition in one way or another.

Evolution of ADRs in children between 2008 and 2011

In the table below one can see the evolution of the total number of cases of suspected paediatric ADRs received by the Portuguese National Pharmacovigilance System between 2008 and 2011. The table also shows the most representative ATC groups of medicines and ADR SOCs.

Throughout this four-year period there was a slight growth trend in terms of total number of cases (absolute frequency). The **proportion of ADR cases in children versus the whole population** increased between 2008 and 2010, and stabilized in 2011 at around **ten per cent**.

Vaccines and antibacterials for systemic use are the main ATCs for every year studied. These categories include medicines used in the prophylaxis and/or treatment of the most frequent conditions in the paediatric age groups, namely infections. Aldea A. et al describe a similar pattern: vaccines are the group most frequently associated with ADRs in the paediatric population (67%), followed by antibacterials. [2]

The dominance of the General disorders and administration site conditions and the Skin and subcutaneous tissue disorders SOCs is also in agreement with the data from Aagaard L et al[3,4] and Aldea A et al[2]. Our epidemiology is not only in line with the results from the studies above, it is also coherent with the fact that vaccines are frequently associated with adverse reactions at the site of inoculation.

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ADRs in children between 2008 and 2011

	2008		2009		2010		2011	
ADR cases (paediatric population) and % in relation to population as a whole	136 cases	8,2%	195 cases	9,6%	221 cases	10,3%	256 cases	10,3%
ADR cases (population as a whole)	1654 cases		2038 cases		2141 cases		2521 cases	
SOC – 1st most frequent	*Skin*	32,4%	*General*	38,0%	*General*	23,6%	*General*	20,8%
SOC – 2nd most frequent	*General*	16,4%	*Nervous*	31,0%	*Skin*	19,1%	*Skin*	18,5%
SOC – 3rd most frequent	*Immune*	7,0%	*Skin*	28,0%	*Gastro*	10,9%	*Infect*	9,8%
ATC – 1st most frequent	*Vaccines*	33,8%	*Vaccines*	60,7%	*Vaccines*	47,7%	*Vaccines*	36,4%
ATC – 2nd most frequent	*Antibacterials*	16,6%	*Antibacterials*	4,5%	*Antibacterials*	18,4%	*Antibacterials*	17,2%
ATC – 3rd most frequent	*Nervous System*	11,7%	*Immunosuppr.*	4,0%	*Immunoglob.*	5,3%	*Anti-inflamm.*	5,8%

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2. Aldea A et al. Paediatric adverse drug reactions reported to the Spanish Pharmacovigilance System from 2004 to 2009. Eur J Clin Pharmacol 2012 Sep;68(9):1329-38.
3. Aagaard L et al. Adverse Drug Reactions in the Paediatric Population in Denmark. Drug Saf 2010 33:327-339.
4. Aagaard L et al. Information about adverse drug reactions reported in children: a qualitative review of empirical studies. Br J Clin Pharmacol 2010 70(4):481–491.

Anaphylaxis with medicines
A review of cases reported in Portugal

Anaphylaxis is a rare but potentially fatal systemic adverse drug reaction. It is unpredictable, in most cases independent of the dose given, and occurs little after exposure to the causative medicinal product.

In this paper, the case series of anaphylactic reactions reported over the past decade to the Portuguese National Pharmacovigilance System between 1 January 2000 and 1 November 2012 was retrospectively characterized. The patients' demographics, drugs implicated, reaction seriousness and time intervals, were analysed. For the purposes of this study, anaphylaxis was defined according to the criteria issued by the ***Second Symposium on the Definition and Management of Anaphylaxis.***[1]

Of the 16,157 ADRs reported to the National Pharmacovigilance System during the study period, 918 (6%) met the anaphylaxis criteria adopted. The patients' age range was between 7 days and 91 years; 87 (9%) cases involved patients younger than eighteen. There was an overall predominance of females (67%), but most paediatric patients were male (56%). Throughout the decade under study, there was a **trend towards higher reporting rates** of these episodes and 31% (284) of the cases of anaphylaxis were reported in the last two years of the study period.

Nineteen per cent of the episodes listed involved **hospitalization** and 3% were fatal. **Antibacterials** were the drugs most frequently involved (17%), followed by **nonsteroidal anti-inflammatories/ /paracetamol** (13%), **cytotoxic agents** (12%) and **immunomodulators** (9%). **Vaccines** and **radiological contrast agents** were also reported.

From the above, one can see that most reported episodes were associated with widely used medicines, such as antibiotics and analgesics. Anaphylaxis can supervene at any age and females seem to be more affected, except in the paediatric age range where males predominate.

The annual incidence of cases of anaphylaxis varies worldwide between 3.2 to 49.8 cases per 100,000 inhabitants, a figure which has been increasing in the past few years.[2-6] Medicines are the main cause of anaphylaxis in most studies.[5,7,8]

In this study we found an incidence of 7.9 cases per one million Portuguese inhabitants (**0.79 cases per 100.000**), within the study period. It should be noted however, that this figure corresponds to drug-related anaphylaxis only. Our results also overlap those of other authors regarding patient demographics and drugs most frequently associated with anaphylaxis.[2,8-13]

Inês Ribeiro Vaz, Joana Marques, Pascal Demoly, Jorge Polónia, Eva Rebelo Gomes

References

[1] Sampson HA et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006 Feb;117(2):391-7.

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[11] Star K et al Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Saf 2011 34(5):415–428.

[12] Bohlke K el al. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. J Allergy Clin Immunol 2004 113(3):536–542.

[13] Simons FE et al. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. J Allergy Clin Immunol 2002 110(4):647–651.

NB: *The authors wish to thank the Medicines Risk Management Department at INFARMED for making the data used in this study available. The Northern Portugal Pharmacovigilance Unit has sole responsibility for the analysis conducted and conclusions drawn.*

Clínical criteria for the diagnosis of anaphylaxis*

Anaphylaxis is highly likely when
any one of the following three criteria are fulfilled:

Criterium 1

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
and at the least one of the folowing:

a. Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia)
b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

Criterium 2

Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxaemia)
c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

Criterium 3

Reduced blood pressure (BP) after exposure to known allergen for that patient (minutes to several hours):

a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

***Adapted from**: Sampson HA et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006 Feb;117(2):391-7.*

Statins
Risk of onset of Diabetes / Changes in Glucose Metabolism

Ensuing the publication in 2010 of a meta-analysis which pointed to a slight increase in the risk of development of diabetes associated with therapy with statins,[1] the European Pharmacovigilance Working Party (PhVWP) started an overall review of this safety issue. It concluded in March 2012 an assessment of the risk of onset of diabetes / changes in glucose metabolism associated with HMG-CoA reductase inhibitors – atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Following this assessment a reference to increased risk of onset of diabetes in patients with predisposing risk factors was inserted in sections 4.4 and 4.8 of the SPC of statins.

In fact, from the analysis of all the safety data compiled, it has been concluded that there is sufficient evidence for the association of statin therapy and the onset of diabetes. However, this risk seems to be greater for patients with an increased background risk of diabetes. Raised fasting blood glucose is a major factor for increased risk. Other factors include a history of hypertension, raised blood triglycerides and increased body mass index.

The strength of association varied among statins, but currently available data do not allow for the exclusion of the possibility of any statin being able to exacerbate the risk of diabetes in healthy individuals. Still, studies have clearly shown the benefits of statins in reducing major cardiovascular events in at-risk populations. In any case, patients with identified risk factors should be monitored from both the clinical and biochemical viewpoints, in order for the onset of diabetes to be promptly diagnosed and adequately managed.

Cristina Rocha

Reference

[1] *Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010 Feb 27;375(9716):735-42.*

Risedronate
Risk of Oesophageal Cancer in patients with Barrett's Oesophagus

In 2010, the European Pharmacovigilance Working Party (PhVWP) initiated an assessment on the risk of oesophageal cancer associated with the use of oral bisphosphonates. This review was prompted by the publication of a study conducted on the UK General Practice Research database (GPRD).[1] In Europe and North America, the incidence of cancer of the oesophagus within the 60 to 79 year-old age range is typically of one case per 1000 people per five years. The study mentioned above found an estimated increase to circa 2 cases per 1000 people per 5 years of use of oral bisphosphonates.

From the assessment performed, the PhVWP has concluded that current data cannot exclude the possibility of an association, and that a warning on the use of bisphosphonates in patients with Barrett's oesophagus should be included in every medicinal product containing nitrogenic bisphosphonates. This warning already exists for alendronate and ibandronate and it should therefore be added to products containing risedronate as well.

The text (in Portuguese) to be included in the SPC and information leaflets can be found here:

http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/INFORMACAO_SEGURANCA/ALTER_TIPO2_SEGURANCA/BIFOSFONATOS

Margarida Guimarães

Reference

[1] *Green J et al. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ 2010 Sep 1;341:c4444.*

ADRs in the Literature...

Drug-Drug Interactions in Older Ambulatory Patients

Elderly patients have certain characteristics (such as physiological changes associated with ageing, frailty, comorbidities and polypharmacy) which increase their risk of sustaining ADRs arising from drug-drug interactions (DDIs). On the other hand, the responses of older individuals to drugs can be variable: there may be an increased response to some frequently used medicines (e.g., benzodiazepines, antidepressants, warfarin) and a decreased response to others such as beta-blockers, for instance.

This was a prospective study which was relatively innovative in that the characteristics of DDIs in a cohort of older (≥60 years) Brazilians were studied for over one year in an ambulatory setting rather than during hospital admission. The incidence of DDI-related ADRs was 6% versus 10% for non-DDI-related ADRs. This incidence was considered to be high, since the DDIs corresponded to 39% of all ADRs. The interactions detected more frequently involved warfarin, acetylsalicylic acid, digoxin and spironolactone, and they frequently had clinically serious and avoidable or ameliorable consequences, such as gastrointestinal haemorrhage, hyperkalaemia and myopathy.

Obreli-Neto PR et al. Adverse drug reactions caused by drug–drug interactions in elderly outpatients: a prospective cohort study. Eur J Clin Pharmacol. 2012 Dec;68(12):1667-76

Interaction between a Topical Antifungal agent and an Anticoagulant

The authors describe two cases of interaction between the topical antifungal amorolfine and the cytochrome-P450-metabolized anticoagulant acenocumarol, with resulting raised INR (International Normalized Ratio). The drug interactions most commonly reported for antifungals usually involve oral systemic presentations. Since amorolfine has little systemic absorption and its free fraction seems to be rapidly inactivated, these two cases of a clinically significant interaction are of special interest.

Morales-Molina JA et al. Interaction between amorolfine and acenocoumarol (Letter to the Editors). Eur J Clin Pharmacol. 2012 Dec;68(12):1687-8.

Reversible Hyperpigmentation with Methotrexate

This short paper discusses a case of face, arm and leg skin hyperpigmentation in a 75-year-old female patient with Wegener's granulomatosis who was being treated with methotrexate and corticosteroids, with no change in her adrenal and adrenocorticotropic functions. This ADR supervened four years into the treatment and resolved upon discontinuance of methotrexate. The case illustrates how hyperpigmentation can be a rare but reversible adverse reaction to methotrexate therapy.

BMJ 2012;345:e6359

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