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Editor's Notes

Information from and to health professionals on ADR risk and prevention is essential for risk management activities. The impact of risk communication probably depends on how effective pharmacovigilance activities are. These concerns have motivated a study presented by the INFARMED Pharmacovigilance Department at the 22nd ICPE International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Another study presented aimed to assess the impact of the creation of Regional Pharmacovigilance units within the Portuguese National Pharmacovigilance System. Promoting the training of health professionals and raising their awareness of the system itself, in order to increase adverse reaction reporting rates was the main goal of the creation of those centres, which dates back to 2000. Both studies are briefly presented in this issue.

Other highlights: floppy iris syndrome associated to cataract surgery in patients on tamsulosin, the risk of oral clefts associated to lamotrigine during the first trimester of pregnancy, nephrogenic systemic fibrosis as a rare but significant ADR in renal failure patients who are submitted to MR imaging with gadolinium for contrast agent, and a bird's-eye view on the safety profile of a group of immunostimulants of long-standing use but controversial clinical usefulness.

How can I report an adverse reaction?

Postage Paid Card
yellow *(physicians),* **purple** *(pharmacists)* **or white** *(nurses)*

Also online at:
www.infarmed.pt/pt/vigilancia/medicamentos/reacções_adversas/fichas_notificação/index.html

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Patient listed for cataract surgery and taking Tamsulosin? Beware of Intraoperative Floppy Iris Syndrome

Tamsulosin (an alpha1 adrenergic receptor antagonist) is approved for the treatment of lower urinary tract symptoms associated with benign prostatic hypertrophy. In some patients under treatment or previously treated with tamsulosin, a clinical syndrome designated as Intraoperative Floppy Iris Syndrome (IFIS) was observed associated with **phakoemulsification cataract surgery**. According to current data, tamsulosin has been the medicine more often associated with IFIS. However, **a few cases** of IFIS **with other alpha1 adrenergic receptor antagonists** have been reported as well.

Safety information for medicinal products containing tamsulosin will accordingly be updated in order to include the following warnings: *Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, has been observed during cataract surgery in some patients under treatment or recently treated with tamsulosin. IFIS can lead to increased complications of the surgical procedures.* ***It is recommended that patients listed for cataract surgery should not be started on tamsulosin***.

It has been reported that **discontinuing tamsulosin one to two weeks before surgery might be useful**. However, its actual benefit and the best moment to discontinue therapy have not been established. During the patient's **pre-operative assessment** it should be checked whether he is or has been treated with tamsulosin, so that appropriate measures to deal with IFIS be taken during surgery.

Madalena Arriegas

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
IL	Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

Lamotrigine in the First Trimester of Pregnancy: Increased Risk of Cleft Lip/Palate

A recent analysis of data from the North American Antiepileptic Drug Registry in the US and Canada on women who took anticonvulsant medicines whilst pregnant points to a possible increase in the risk of cleft lip/palate associated with the use of lamotrigine during the first trimester of pregnancy. Of children whose mothers had been on lamotrigine monotherapy during their first months into pregnancy (n=564), five were born with a **cleft lip/palate**, with an **incidence of 8.9:1000**, which is significantly higher than the 0.37:1000 expected rate. The total incidence of **major congenital malformations** however, was not higher than expected. Although these results have not been confirmed by other studies, information on medicinal products containing lamotrigine will be updated in order to include the above recent safety data.

Sudden discontinuation of antiepileptic therapy on the other hand, may lead to an increase in the number of fits, which in turn may be seriously deleterious for both mother and child. The possible risk of congenital malformations associated with lamotrigine should therefore be weighed against the drug's benefits for the maternal condition. Women who are pregnant or wish to become pregnant and are taking this anticonvulsant which is indicated for the treatment of epilepsy and bipolar disease, should seek advice from their doctor.

Bacterial Lysates used as Immune System Stimulants Safety Profile Highlights

The therapeutic effect of bacterial lysates used for the treatment and prevention of recurrent bacterial upper respiratory tract infections derives from stimulation of the mucosal immune system. Once the antigens contained in these medicinal products are absorbed and processed, both specific and non-specific stimulation of the immune system are expected to occur, with an attending rise in IgA secreting cells, an increase in serum IgA and/or IgG, increased phagocytic activity, increased production of gamma-interpheron, increased production of interleukins, and reduced pulmonary inflammatory reaction.

Choosing an appropriate bacterial lysate should depend on the patient's age and clinical profile, as well as on the type of intended treatment or prophylaxis, since there are various therapeutic alternatives in the market each with its own specific composition. The strains more frequently included in these immunotherapeutic agents are: *Staphylococcus aureus*, *Neisseria catarrhalis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*. Therapeutic indications include acute stage coadjuvant therapy, treatment of chronic and/or recurrent infections, and prophylaxis of respiratory or ENT tract infections. The conditions for which these medicines are indicated are mainly bronchitis, rhinitis, sinusitis, otitis, tonsillitis, and pharyngitis.

A few studies have been published showing favourable results with these products but **additional evidence is required** if one is to reach any definitive conclusions about their clinical usefulness - see *Prontuário Terapêutico 6* (February 2006) (a Portuguese national formulary published by INFARMED).

Bacterial lysates can be used in any age group older than 6 months, and there are paediatric formulations available in the market. Adult formulations can be used in the elderly in general. The products however, **should not be used** in patients with a pre-existing **autoimmune condition** (risk of flare-ups), with **acute gastroenteritis**, or in case of **hypersensitivity** to any of the product's components. There is a theoretical risk of decreased therapeutic effect when given concomitantly with immunosupressants. **Untoward effects** described for these immunotherapeutic agents include GI disturbances, skin reactions, pharyngeal irritation, headache, vertigo, worsening of pre-existing cough, fatigue.

Any suspected adverse reaction should be reported to INFARMED by filling out a yellow, blue or white card, by phone or by e-mail. Co-operation from all health professionals is crucial for keeping our knowledge of the safety profile of medicines current, relevant and up to date.

Maria Susana Gonçalves

An example of the Impact of Risk Communication: Zoledronic Acid associated Jaw Osteonecrosis

Following on the identification in April 2005 of a signal of jaw osteonecrosis and osteomyelitis in patients treated with biphosphonates, which emerged from the literature and from spontaneous ADR reports, the Portuguese and European ADR databases were reviewed. Most cases were associated with the administration of zoledronic acid in patients with malignancy. In order to make the health professionals aware of this potential safety problem, a *Dear HealthCare Professionals Letter (DHCPL)* was sent out in August 2005 by every EU member state.

The number of reports received six months before and six months after communication of the above risk to health professionals, was analysed. The databases were searched using as keywords the following MEDRA terms: *osteonecrosis*, *osteomyelitis*, and *aseptic bone necrosis*. Of a total of 505 cases identified in Portugal, **21% had been received before, and 79% after the DHCP letter**. This paralleled the **total data for Europe: 30% and 70%, respectively**.

The increased number of ADR reports may be explained by **greater risk awareness resulting from the safety communication** to health professionals, which is of the utmost relevance for any risk minimisation/management plan. Moreover, measuring the impact of risk communication on ADR reporting and on the safer use of medicines is paramount if we are to know whether our efforts are indeed going in the right direction.

Madalena Arriegas, Fátima Bragança, Regina Carmona, Inês Clérigo, Alexandra Pego, Paula Roque, João Ribeiro da Silva, Isabel Sobral.

Edited summary from the paper presented at the 22nd ICPE International Conference on Pharmacoepidemiology and Therapeutic Risk Management
Lisbon, 24-27 August 2006
"Has risk communication a direct impact on pharmacovigilance activities?"

Pharmacovigilance Regional Centres

The Suitable Model for Small Countries?

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ABSTRACT

A Study on the evolution of the Reporting Rate per District was performed. A strong relationship between Healthcare Professionals training activities and the Reporting Rate was found. It appears that the four Regional Pharmacovigilance Centres present different evolution patterns, and only one of them seems to have contributed to a significant increase on the Reporting Rate in their influence area.

CONFLICT OF INTERESTS

The authors have no conflict of interests to declare.

BACKGROUND

The Portuguese Pharmacovigilance System was established in 1992. In 2001, 4 Regional Pharmacovigilance Centres (RPCs) were created with the main purposes of promoting healthcare professionals (HPs) training and divulging the Pharmacovigilance System, in order to increase the reporting rate.

OBJECTIVES

The aim of this study was to analyse the impact of the creation of RPCs in the Portuguese Pharmacovigilance System.

METHODS

An observational retrospective study of all spontaneous reports of ADRs occurring in Portugal and received from HPs between 1996 and 2005, either by Pharmacovigilance System Headquarters only (1996-2000) or by the RPC and Headquarters (2001-2005), was performed.

The evolution of reporting rates (RepR) (number of reports per million inhabitants) of serious ADRs, the geographical distribution of RepR and the number of ADR reports received following training activities were studied, using descriptive statistics and linear regression.

RESULTS

Although a linear increase in the RepR of serious ADR was observed between 1996-2000 and 2001-2005, this evolution was more relevant in the second period.

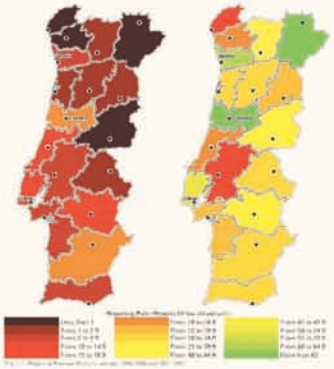
A strong relationship between the number of HP trained and the number of reports received was observed, as expected, more so in the North RPC.

The intensive training of HPs resulted in a major increase in the RepR of serious ADRs, which influences the growing pattern observed nationally in the period 2001-2005.

Region	Growth
North	28.47
Centre	-29.95
Lisbon/Tagus Valley	1.26
South	5.84
Azores Islands	-11.58
Madeira Island	0.00
National	2.68

For all other regions an increase similar or inferior to the national average or even a decrease was observed.

The highest RepR in 1996-2000 were observed in the south and central coastal and, in 2001-2005 in the centre and northern hinterland.



The steepest increase was observed in the Oporto and Coimbra districts (both headquarters of RPC). In Lisbon (other RPC headquarters and the district with more central hospitals) only a very slight increase, below the national average, was noticed.

The area with the smallest increase over the national average was the South, which can be due either to the recent implementation of the RPC or to headquarters existence outside of the influence area.

CONCLUSIONS

Although the creation of RPC contributed to the increase of the RepR from 1996-2000 to 2001-2005, it was mainly due to the North RPC and strongly related to intensive training of HPs. For all other regions the implementation of RPC did not account for a significant increase in the RepR in Portugal. After 5 years of experience, these data call for a benefit-cost re-evaluation of this decentralized model.

Poster presented at the 22nd ICPE International Conference on Pharmacoepidemiology and Therapeutic Risk Management
Lisbon, 24-27 August 2006

Gadolinium: Nephrogenic Systemic Fibrosis and Renal Failure

Nephrogenic systemic fibrosis (NSF) is a fibrosing condition usually occurring in terminal renal failure patients. It consists of more or less symmetrical thickening and induration of the skin, with hyperpigmentation, nodules and papules on the lower and upper limbs, sometimes with a *peau d'orange* effect (**scleromyxedema**). This fibrosis affects the deeper tissues (tendons and periarticular tissues may hinder joint motion and cause flexion contractures) and the dermis, which is why it was first designated as nephrogenic fibrosing dermopathy (NFD).

The lesions in the affected limbs are clinically very similar to those of eosinophillic fasceitis. Contrary to the latter however, they mostly affect the **distal extremities** (hands and feet), sometimes the torso, but never the face and neck.

In spite of **musculoskeletal** involvement and of internal organs such as the **lung and heart**, there is no Raynaud syndrome or autoantibodies (although antinuclear antibodies usually with a homogeneous pattern can be detected in some cases). Muscle biopsy shows increased myofibroblasts, and an increased number of CD34+ dendrocytes can be seen on skin biopsy specimens. The skin's histopathological pattern is indeed peculiar and characteristic of this condition, with thick collagen bundles, mucin deposits and proliferation of fibroblasts and elastic fibres, but with **no signs of inflammation.**

Most patients with NFD are **around fifty years old** and on dialysis for terminal renal disease. The cause of this condition is unknown; no aetiological agents or factors have been identified, namely medicines or specific components of the dialysis solution. Some authors suggest a circulating fibrocyte (CF) might play a role; this is a recently identified bone marrow leukocyte which expresses a unique combination of leukocyte and antigen markers, as well as types I and III collagen. These cells, which are able to expose TGF-β, take part in physiological healing processes and are intimately connected to fibrosis in several organs and systems. It is thus probable that a given *allergen* (some medicinal or contrast product), on being deposited in peripheral tissues, may be able to trigger a fibrogenic response from this type of cells (renal disease > allergen deposition > CF release and cross reaction > TGF-β dependent fibrotic response).

In fact, contrast products with **gadolinium** (Omniscan® especially) used in **magnetic resonance imaging techniques** have for some time been associated with the appearance of cases (25 up to now) of nephrogenic systemic fibrosis in renal failure patients (with metabolic acidosis), **two to four weeks after the exam**.

Gadolinium (Gd-DTPA) was first used as an paramagnetic imaging contrast product in 1998, and **sporadic adverse effects of relatively little significance** have been ascribed to it, such as headache, nausea, pain and sensation of cold in the puncture site, dizziness, vasodilatation, and lowered seizure threshold. It is usually considered to be quite safe, even in patients with kidney failure.

Although in a subject with normal kidney function contrast products containing gadolinium are rapidly cleared from the circulation (with a half-life of around 2 hours), in patients with chronic renal failure its half-life is prolonged up to as long as 30 to 120 hours. In such conditions it is therefore possible that the **Gd-ligand complex** is destabilised and dissociated, leading to the appearance of **free gadolinium**. In renal failure, metabolic acidosis and a marked delay in complex clearance both promote this effect. Free gadolinium is not very soluble, it **may precipitate** with anionic salts (such as phosphate, which is usually raised in patients on dialysis), and **form interstitial deposits** in muscle tissue, bone, liver, skin, and other organs, **triggering infiltration by fibrogenic response mediator cells** of the CF kind.

Awareness of this newly identified entity for which no effective treatment is available is essential:

- One should be **alert and report** any possible cases of NSF/NFD, namely in patients who have been exposed to gadolinium. One should especially look out for systemic fibrosing conditions with *atypical* presentation or manifestations.
- Imaging contrast products containing gadolinium should be used **with extreme caution** and only when absolutely indicated, especially when used in high doses, in **patients with renal failure** with glomerular filtration rates ≤ 15 ml/mm or on dialysis.
- Renal failure patients, **immediately after** they have been exposed to the contrast product, **should be put on dialysis** (which can achieve gadolinium excretion rates above 70-80%), even though there is no definitive evidence of the usefulness of this strategy for preventing or improving NSF/NFD.
- Further data on nephrogenic systemic fibrosis can be obtained at the International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR) site: **www.icnfdr.org**

Pedro Marques da Silva

Medicinal plants from A to Z described adverse reactions

- **Cocoa** *(Theobroma cacao)*
  - allergy
  - decreased seizure threshold?

N.º of Medline citations: 10
Main uses described: emollient (chapped hands and lips), stimulant, diuretic

- **Cashew nut** *(Anacardium occidentale)*
  - skin abrasion

N.º of Medline citations: 31
Main uses described: diuretic, antiseptic, skin exfoliant

- **Marigold** *(Calendula officinalis)*
  - allergy, including anaphylaxis
  - reduced iron absorption

N.º of Medline citations: 4
Main uses described: wound healing, eye inflammation, dyspeptic conditions

- **Chamomile** *(Matricaria chamomilla)*
  - allergic reactions (including contact dermatitis and anaphylaxis)
  - decreased gastric absorption of medicines
  - vomiting (in high doses)
  - increased effect of anticoagulants?

N.º of Medline citations: 21
Main uses described: anti-inflammatory, dyspeptic conditions, antispasmodic (GI, gynaecological)

- **Camphor** *(Cinnamomun camphora)*
  - skin irritation
  - seizures
  - hyper/hypotension (?)

N.º of Medline citations: 33
Main uses described: antiseptic, analgesic, anti-inflammatory, ansiolytic

NB 1: The main uses are those most frequently described in the literature irrespective of evidence of effectiveness. No therapeutic indication or endorsement of use by this publication should be inferred.

NB 2: The number of Medline citations is merely intended to give an idea of the magnitude of publications on adverse reactions associated with the product. Key-words used: "human side effects", "toxicity in humans", "adverse reactions".