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Editor's Notes

Underreporting by health professionals is an ongoing problem in our pharmacovigilance system. A good example thereof is the ADR reporting profile of a medicine of very specific and restricted use such as infliximab. We all need to take a more active part in postmarketing (re)definition of the safety profile of the medicines we use.

Special precautions and contraindications when prescribing coxib NSAIDs in patients with significant cardiovascular conditions has triggered recent alerts. "Nothing new" however for the time being in what concerns non-selective NSAIDs. Their use is long standing and their safety profile well-known – usual precautions are always in order. Following the evidence that has been emerging since the Women's Health Initiative started, the new data from the Million Women Study are not especially surprising, although highly relevant. Autumn is nearing, and a reminder is made on the safety profile of the influenza vaccine, a propos its interaction with medicines metabolised in the liver.

In the special section on medicinal plants new items have been added, namely the Latin and English nomenclature of each phytotherapeutic agent, and its common uses from a merely descriptive point of view, not of efficacy/effectiveness criteria. The number of Medline citations at the date the Boletim is issued gives the reader an idea on the magnitude of research published. Whenever reported in the literature, potential drug-plant interactions are mentioned. The contrasting interactions of garlic and avocado with anticoagulants is a good example.

In "standard pharmacopoeia" the use of plant products is obviously neither rare nor irrelevant: closing this issue, an article on medicines containing soy or peanut oil as excipient or active ingredient and their potential for allergic reactions.

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

How can I report an adverse reaction?

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

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Adverse reactions to Infliximab reported to the National Pharmacovigilance System

Infliximab is an anti-TNF monoclonal antibody approved for the treatment of rheumatoid arthritis, Crohn's disease and ankylosing spondilitis. Continuing safety monitoring of this innovative drug of restricted and subspecialist use is especially relevant, in order for potential risks to be more accurately pinpointed. An analysis of all spontaneous reports of serious adverse reactions to infliximab retrieved from the National Pharmacovigilance System (NPhS) database was made aiming to quantify and characterise them for the period **from January 1999 to December 2004.** The main variables studied were: age and sex of patient, origin of report, therapeutic indication, type of ADR, and severity criteria.

Sixty-five reports (1.3% of the NPhS total) were analysed, 9 from physicians and the remainder from the MA holder. Females predominated (68.2%), more so for patients with rheumatoid arthritis ▸

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Portugal em Acção

(83.3%). Concerning ADR characteristics, 31.8% of cases were **infectious conditions (tuberculosis:** 18.2%), 22.7% **allergies,** and 6.1% **lupus-like reactions.** Regarding seriousness, **40.9%** of cases were admitted to **hospital**, and **12.1% were fatal, with diverse relations to drug administration.**

These results illustrate an already previously identified attending risk of infection, especially tuberculosis, in patients treated with infliximab. This medicine is exclusively prescribed and dispensed in the hospital setting by well-informed and highly aware professionals. The role of the MA holder however, has been of the utmost importance, as shown by the high rate of reports from the pharmaceutical industry when compared to the health professionals' input. Given the drug's therapeutic specificity, a greater number of reports would be expected. Underreporting still is one of the main shortcomings of spontaneous reporting systems.

Ana Araújo

Hormonal Replacement Therapy: *new data from the Million Women Study*

In the year 2000 the Women's Health Initiative (WHI) was brought to a halt as it became apparent that hormonal replacement therapy (HRT) does not prevent heart disease, and may even increase its risk during the first year of use. An associated increase in breast cancer risk was also found.

In 2002 the Million Women Study results came out. They confirmed the conclusions from former studies of an **increased risk of breast cancer,** the latter being substantially **higher for combination HRT** (oestrogens + progestagens, either in sequential or continuous regimes) in comparison to isolated oestrogen therapy. Tibolone was also shown to increase the risk of breast cancer, although less so than combination HRT.

New additional data have now come out from this same study, which demonstrate that there is an **increased risk of endometrial cancer in long-term HRT users** of **oestrogen or tibolone-only** therapies, when compared to non-users. These data show a significant reduction in the risk of endometrial cancer when a progestagen is added. Should the latter be added on a daily basis, then the risk is kept below that of non-users of HRT. In the case of tibolone, risk is dependent on duration of use; it is not significant for periods shorter than 3 years, but increases significantly from the third year onwards.

Considering then that the various HRT regimes (combined or isolated) all are associated with varying effects on the risk of breast or endometrial cancer, both types of risk should be thought over when deciding for any one of the possible therapeutic options. Each case should be approached individually, and the woman should be kept fully informed throughout the decision-making process.

Reminder:

- For the **treatment of menopausal symptoms,** the **benefits** from short-term HRT use surpass any potential risks for most women.
- In any case, it is sound clinical practice to use the **smallest effective dose for the shortest possible time,** and to **review** the need to keep the therapy going, at least on an yearly basis.
- In **post-menopausal women who are older than 50,** and who are at an increased risk of bone fractures, **HRT should only** be used as an alternative for the prevention of osteoporosis **in case other therapies are not well tolerated or are contraindicated.**

Isabel Brito Afonso

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Cardiovascular Safety of Non-Selective Non-Steroidal Anti-Inflammatory Agents

In June 2005 INFARMED reported the start of a European assessment on cardiovascular safety of non-selective non-steroidal anti-inflammatory drugs (NSAIDs), including **diclofenac, etodolac, ibuprofen, indometacin, ketoprofen, meloxicam, nabumetone, naproxen, and nimesulide.** This review followed a prior assessment of cardiovascular safety of the class of selective COX-2 inhibitors, which gave rise to a set of recommendations which remain unchanged (see previous issue of the Boletim).

The CHMP evaluated the available data on cardiovascular safety of non-selective NSAIDs, including clinical trials, epidemiological studies, and data from spontaneous reports. Currently available evidence on thrombotic risk – especially myocardial infarct and stroke - was also reviewed. Though depending on the final results of the **ongoing review** regarding other safety issues, the CHMP considered that there is at the moment **no reason to change** the existing recommendations for patients and prescribers.

Thus:

- The prescription of non-selective NSAIDs should be based on their safety profiles (for instance in what concerns potential GI risks), as described in the SPC and Information Leaflet. it should of course be based on individual risk factors as well.
- Every patient should take the lowest effective dose for the shortest possible period of time, as needed to control the therapeutic indication which prompted prescription.

Risk of potential Interactions between Medicines metabolised in the Liver and the Influenza Vaccine

The use of the influenza vaccine has been steadily increasing in the past few years, in order to prevent flu outbreaks, especially in risk groups such as the elderly, chronic and immune deficient patients. Multidrug regimes are frequent in those patient groups, and the risk of potential interactions should always be borne in mind.

Cases of drug toxicity (akin to overdose) have been described in several studies on medicines such as **phenytoin, warfarin, and theophylline,** following influenza vaccination[1,2,3]. In Portugal, the National Pharmacovigilance System database contains at least one related case:

- Eighty-six-year-old, male patient on pentoxyphylline for several years who showed symptoms of overdose (vomiting, vertigo, lethargy) following an influenza jab.

It is suspected that the mechanism for this type of interactions is to do with **inhibition of cytochrome P450 3A4,** thus reducing the clearance of concomitant medicines. However, not all studies back this hypothesis, and some suggest that warfarin's interaction with the flu vaccine, for instance, might be due to a change in the synthesis of coagulation factors rather than to enzyme inhibition[4]. Although advancing age is a risk factor for this type of enzyme inhibition, there is great individual variability, and independently of the degree of inhibition, the vaccine's effectiveness does not seem to be reduced[5].

In general terms, the influenza vaccine is not associated to clinically relevant interactions. The above-mentioned studies however, do indicate that this vaccine may interact with certain medicines with a narrow therapeutic window and whose accumulation may cause adverse reactions.

Health professionals should be vigilant concerning the possibility of toxicity from medicines metabolised by cytochrome P450 3A4 as late as 28 days after influenza immunisation is given. If possible, monitoring of anticoagulation therapy should be performed at shorter intervals. It is also recommended that patients be informed on signs and symptoms of toxicity, especially regarding anticonvulsants.

In any case, patients should report to their physician any symptom following influenza immunisation. Any suspected interaction between the flu vaccine and other medicines should be reported to the National Pharmacovigilance System as a standard ADR report.

The potential risk of interaction however, should not be a reason to keep patients from being vaccinated against influenza.

Susana Gonçalves

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Influenza Vaccine Safety Profile Highlights

Contraindications

- Hypersensitivity to any of the components, including eggs/chicken proteins, and gentamicin.
- Postpone vaccination in patients with febrile or acute infectious condition.

Special Precautions of Use

- As for any injectable vaccines, adequate medical support and treatment should be available, in case a rare anaphylactic reaction occurs.
- Under no circumstance should it be administered intravascularly.

Drug Interactions

- Can be administered simultaneously with other vaccines.
- Vaccination should be applied in different limbs. Adverse effects may be intensified.
- Immunological response may be reduced if patient has endogenous or iatrogenic immune suppression.

Interactions with diagnostic tests

- Following anti-influenza vaccination false positive results have been reported with serological ELISA tests for detection of anti-HIV1, anti-hepatitis C virus, and especially anti-HTLV1 antibodies. The Western Blot technique will sort out the results. Transient false positive reactions may be due to vaccination-induced IgM.

Pregnancy and breastfeeding

- The use of this vaccine may be considered starting from the second trimester. In pregnant women with clinical conditions in which the flu may significantly raise the risk of complications, the vaccine is recommended irrespective of gestational age.
- Can be used whilst breastfeeding.

Undesirable effects

Frequent (>1/100, <1/10):

Local reactions: redness, oedema, pain, echymosis, painful nodule. Systemic reactions: fever, malaise, chills, fatigue, headaches, sweating, myalgia, arthralgia. These reactions subside within 1-2 days without treatment.

Infrequent (>1/1000, <1/100):

Generalised skin reactions, including pruritus, urticaria, and non-specific rash.

Rare (>1/10,000, <1/1000):

Neuralgia, paraesthesia, seizures, transient thrombocytopoenia. Allergic reactions have been reported which, in rare cases, caused shock.

Very rare (<1/10,000):

Vasculitis with transient renal involvement. Neurologic disorders, such as encephalomyelitis, neuritis and Guillain-Barré syndrome.

Special storage precautions

Should be stored at between +2°C and +8°C (in fridge), protected from light. Must not be frozen.

Note: ***Seroprotection*** *is usually obtained* ***2 to 3 weeks after innoculation.*** *Duration of post-vaccination immunity to homologous or similar strains may vary but is usually of* ***6 to 12 months.***

Medicinal Plants from A to Z
described adverse reactions

- **Avocado** *(Persea americana)*
  -interaction with anticoagulants (reduced effect)

  N.º of Medline citations (human side effects): 58
  Main described uses: analgesic; osteoarthritis

- **Artichoke** *(Cynara scolymus, C. cardunculus)*
  - contact dermatitis, allergic rhinitis and asthma

  N.º of Medline citations (human side effects): 10
  Main described uses: antioxydative, functional dyspepsia, acute alcoholic intoxication, hyperglycaemia, hypercholesterolaemia

- **Liquorice** *(Glycyrrhiza glabra, G. uralensis, G. pallidiflora)*
  - hypokalaemia, water and salt retention, hypertension, lethargy, paraesia

  N.º of Medline citations (human side effects): 278
  Main described uses: dyspepsia, cough

- **Rosemary** *(Rosmarinus officinalis)*
  - contact dermatitis, bronchospasm, seizures, abortive
  - reduced absorption of iron from food

  N.º of Medline citations (human side effects): 15
  Main described uses: dyspepsia, hypertension, arthritis

- **Alfalfa** *(Medicago sativa)*
  - interference in antibody synthesis (children, elderly, immune deficient patients)?
  - pancytopoenia
  - cases of infection with S. enterica, E. coli and Listeria, through contamination of seeds or sprouts

  N.º of Medline citations (human side effects): 31
  Main described uses: anti-inflammatory, hypercholesterolaemia

- **Garlic** *(Allium sativum)*
  - allergic reactions, dyspepsia, light-headedness, burns (topical use)
  - interaction with anticoagulants (haemorrhage)
  - interaction with saquinavir (reduction of blood plasma levels)

  N.º Medline citations (human side effects): 256
  Main described uses: dyslipidaemia; hypertension; antiplatelet, antineoplastic?; ear ache

- **Aloe** *(Aloe vera, A. barbadensis, A. ferix, A. perryi)*

  topical
  - burning sensation following application on abraded skin;
  - contact dermatitis

  systemic
  - diarrhoea, colic
  - acute toxic hepatitis, renal toxicity, melanosis coli, risk of colon cancer

  N.º of Medline citations (human side effects): 46
  Main described uses: minor wounds and burns, psoriasis; catharctic

NB: The main uses are those most frequently described in literature irrespective of evidence of effectiveness.

Medicines and Peanut Allergy

The European Commission issued in July 2003 a recommendation regarding the risk of allergic reactions of variable type (predominantly respiratory), and variable severity (some fatal cases reported), in patients sensitive to soy and/or peanut.

Recently, in a cohort of pre-school age children, peanut allergy was associated with a family history of such allergy, with consumption of soy by infants, with early appearance of allergic manifestations (skin or respiratory), and with exposure to topical preparations containing peanut oil[1]. From this article it stands out that consumption of soy is independently associated with peanut allergy. Initial data on **cross-sensitivity involving peanut, soy and other legume foods**[2] is thus confirmed. It is possibly related to some homology existing between the corresponding protein fractions[3], and exposure to a common T-cell epitope[1].

Recent studies have demonstrated that refined peanut oil contains low levels of protein[4], which determines the synthesis of IgE in allergic patients, and positive responses in skin tests or in leukocyte tests (and release of histamine). One should bear in mind that although the manufacture of refined oil does remove polar macromolecules, it does not totally exclude proteins from the final product, often below detection thresholds. The presence of low levels of protein may thus cause sensitisation.

Extremely low antigen levels are sufficient to promote *in vitro* synthesis of IgE, and to trigger production of pro-inflammatory cytokines. This is similar to what happens with egg albumin, whose smallest peptides (aminoacids 323 to 339) are quite sufficient to induce synthesis of IgE in the mouse model of allergic sensitisation. Oils might be immunological adjuvants of the allergic response to proteins.

Taking the above biological background into account, the Committee on Safety of Medicines, although acknowledging that there is insufficient evidence, has recommended that ***"patients allergic to peanut should not use medicines containing peanut oil", the same applying to "patients allergic to soy".*** This recommendation should be widely disseminated – together with its supporting rationale -, and correctly and adequately implemented into the SPCs of every medicine containing soy or peanut oil (as an excipient or as an active ingredient), independently of its gallenic formulation and its mode of administration.

Pedro Marques da Silva

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What should one report?

Every suspected **serious** adverse reaction, even if already previously described. Seriousness criteria include:

- causing death
- life threatening
- prompting hospital admission
- prolonging hospital stay
- resulting in persistent or significant incapacity
- suspected congenital anomaly or malformation
- does not meet any of the above criteria but health professional considers it to be a serious ADR

Every suspected adverse reaction which has thus far **not been described** (unknown thus far), even if not serious or severe.

Every suspected **increase in the frequency** of ADRs (both serious and non-serious)