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From the Editor

Come the end of the year many patients take a decision to quit smoking. This is probably a good time for a reminder on the main drug interactions to look out for when using medicines to help smokers give up the habit. Pharmacokinetic considerations play an essential role in this area, as well as in other topics reviewed in this number of the Boletim, namely beta-blockers administered in ophthalmology, or allergic reactions caused by long-term inhalatory exposure to psyllium, a commonly used laxative. Among various other safety issues, two articles address quality problems associated with serious adverse effects – lack of effect of a vaccine, and bacterial contamination of dialysis solutions. An agile and effective pharmacovigilance system can thrive only thanks to the continuing awareness of health professionals.

Beta-blockers for ophthalmic use: risk of systemic adverse reactions

Beta-blocking agents are largely used in the treatment of glaucoma and high intraocular pressure. These medicines, when administered topically into the eye, can be absorbed and cause systemic effects (e.g., negative chronotropism, bronchospasm, masking of hypoglycaemia in diabetics), although with an **incidence lower that that associated with systemic administration of beta-blockers**. Following a recent review on this topic, the European Pharmacovigilance Working Party (PhVWP) has detected broad variations in the data contained in SPCs and information leaflets. They are therefore going to be updated, so that the information pertaining to all beta-adrenergic agents for ophthalmic use in the treatment of glaucoma and high intraocular pressure will be harmonised.

For further reading:

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/PhVWP_Recommendations/Beta_blockers/CMDh_PhVWP_030_2011_Rev2_2011_09b.pdf

Margarida Guimarães

What do they stand for?!

ADR Adverse Drug Reaction

CHMP Committee for Medicinal Products for Human Use

EMA European Medicines Agency

PIL Patient Information Leaflet

MA Marketing Authorisation

SPC Summary of the Product's Characteristics

How can I report an adverse reaction?

Postage Paid Card

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

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Domperidone: cardiovascular risk

The cardiovascular safety of domperidone-containing medicines has been monitored throughout the years both at a national and at a European level. Two new epidemiological studies were published in 2010 on the risk of ventricular arrhythmia and sudden cardiac death and its possible association with domperidone.[1,2] The following was concluded:

- The risk of serious ventricular arrhythmia or sudden cardiac death may be increased **in patients older than 60 years or taking doses higher than 30 mg daily**.

The risk of QTc interval prolongation and ventricular arrhythmia is well known and was already mentioned in the SPCs of every medicine containing domperidone. This information will now be updated to include the above.

The risk-benefit ratio of domperidone continues to be favourable. However, this drug should be used in the lowest possible effective dose, both in adults and in children. Health professionals should be especially careful when treating patients with prolongation of cardiac conduction intervals, namely QTc, patients with significant electrolyte disturbances or with serious underlying cardiac conditions, such as congestive heart failure.

Catarina Fernandes Costa

1. Van Noord C. et al. Drug Saf 2010; 33 (11): 1003-1014.
2. Johannes C. et al. Pharmacoepidemiology and Drug Safety 2010; 19:881-888.

INDEX CARD | **Director:** Alexandra Pêgo **Editor:** Rui Pombal **Assistant Editor:** Cristina Rocha **Contributors:** Ana Araújo, Catarina Fernandes Costa, Cristina Mousinho, Fátima Bragança, Joana Oliveira, Magda Pedro, Margarida Guimarães, Pedro Marques Silva. **Publishing Assistant:** Inocência Pinto. **Advisory Board:** INFARMED, I.P. Executive Board; Medicines Evaluation Committee. **Publisher:** INFARMED - National Authority of Medicines and Health Produts, I.P., Parque de Saúde de Lisboa, Av. Brasil, N.º 53, 1749-004 Lisboa, Tel. 217 987 100, Fax. 217 987 316, E-mail: infarmed@infarmed.pt **Design and Prodution:** nsolutions - design e imagem, lda. **Printing:** Peres-Soctip, S.A. **Legal Deposit:** 115 099/97 **ISSN**: 0873-7118 **Print Run:** 49.000 (Portuguese)

Angiotensin II receptor antagonists: no evidence of oncological risk

Angiotensin II receptor antagonists (ARA II) have been authorised in the European Union since the mid 1990s for the treatment of arterial hypertension. They are also used in the treatment of heart failure and renal impairment associated with type 2 diabetes, as well as in the prevention of brain stroke and heart disease.

Following the publication of the results of a metaanalysis,[1] which pointed to a slight ARA II associated increase in the risk of new cases of cancer, namely lung neoplasms, EMA has reassessed the probability of such an association. It has concluded that evidence from the above metaanalysis is limited, mostly by methodological problems related to data quality; the patients included were not followed up for long enough time for an unequivocal causal relation to be established, no data were available on cancer risk before ARA II therapy was initiated, and there may have been some publication bias. The CHMP additionally evaluated data from major population based studies, as well as other metaanalyses exempt of the above methodological problems.

From this reassessment it was concluded that an **association** between ARA II and *de novo* cases of cancer has **not** been **confirmed**. The benefits of using these medicines still outweigh their risks, and the current recommendations continue to be valid.

1. Sipahi I et al. Lancet Oncol. 2010 Jul;11(7):627-36.

Buflomedil (Loftyl®): suspended

Buflomedil is indicated in the symptomatic treatment of lower limb peripheral arterial disease where major artery obstruction occurs. EMA started to review buflomedil's risk-benefit ratio in February 2011, following a decision of the French Medicines Authority to suspend the Marketing Authorisation of these products.

Conclusions:

- The risk of serious untoward neurological and cardiac effects, under normal conditions of use, was not effectively reduced by the implemented minimisation measures, such as reduction of package size, recommendations for dose adjustment on patients with renal problems, and restriction of the drug's therapeutic indications.
- There is a significant risk of adverse reactions due to a narrow therapeutic window, especially in elderly patients or in patients with renal disease.
- Data on the benefits of buflomedil are scarce and of limited quality.

The CHMP has recommended that the MA of these medicines be suspended all over the EU. Thus, in Portugal, marketing of Loftyl 300® and Loftyl Forte® has been suspended.

Pradaxa®: renal function changes

Pradaxa® is authorised for the primary prevention of venous thromboembolic phenomena in adults submitted to elective total hip replacement surgery or to elective total knee replacement arthroplasty, as well as in the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation.

The risk of haemorrhage with anticoagulant agents such as Pradaxa® is well known and reflected in the SPC and information leaflet that have been approved for this medicine, which is contraindicated in various situations, including bleeding and patients with severe kidney failure. It should be used cautiously and with reduced doses in the elderly and in patients with moderate renal failure (depending on indication and context).

Concerning the management of the risk of bleeding, the CHMP has recommended that the following information be included:

- Renal function should be assessed in every patient **before treatment** is started.
- During treatment, renal function should be assessed at least **once a year**, in patients over 75 years of age, and in all patients **whenever renal impairment is suspected**.

Xigris®: lack of effectiveness

Xigris®, whose active ingredient is drotrecogin alfa (activated), has been authorised in the EU under exceptional conditions for the treatment of serious sepsis in patients with multiorgan failure, in association with standard therapy.

Following the 2007 yearly review, the CHMP concluded that the initial effectiveness results from the PROWESS clinical trial were not replicated in later studies. Therefore, no further data on the risk-benefit ratio were deemed necessary. Though not corresponding to the approved indication (severe sepsis with multiple organ failure), the MA Holder was requested to conduct a placebo-controlled clinical trial to confirm whether the benefits from Xigris® outweighed its risks in patients with septic shock. Eli Lilly accepted to carry out this clinical trial, which was called PROWESS-SHOCK.

The results from PROWESS-SHOCK showed that there was no statistically significant reduction of lethality at 28 days in patients treated with Xigris® compared to placebo (26.4% in the Xigris® arm versus 24.2% with placebo, n=1680 patients), nor a reduction in lethality in the population of patients with severe protein C deficiency.

Given that these results do not support a favourable risk-benefit ratio for Xigris®, the CHMP and Infarmed recommend that physicians should not start Xigris® in any new patients, and that any ongoing treatments should be discontinued. The MA Holder will voluntarily call back this medicine worldwide. EMA and Infarmed will continue to monitor this issue and keep health professionals abreast of all new relevant information.

Plantago ovata: allergic reactions associated with prolonged occupational exposure

Subjects under continuing occupational exposure to Plantago ovata seed dust (namely health professionals and caregivers **who prepare laxatives** for administration to patients) may become sensitised and allergic through **inadvertent inhalation**. This is more frequent in atopic subjects. It usually leads to hypersensitivity reactions which can be serious.

The seed husk of Ispaghula/psyllium contains powerful allergens. Exposure to these allergens is possible through oral administration, skin contact or, in the case of powder formulations, through inhalation. Exposed individuals may develop hypersensitivity reactions, such as rhinitis, conjunctivitis, bronchospasm and, in some cases, anaphylaxis. Skin manifestations such as rash and/or pruritus have also been reported.

It is recommended that possible sensitisation of individuals at risk should be clinically assessed. If justified, specific diagnostic tests should be carried out. In case of proven sensitisation causing hypersensitivity reactions, exposure to the product should be discontinued immediately and avoided thenceforth. The text to be included in the SPC and Information Leaflet of these medicinal products can be consulted here:

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/PhVWP_Recommendations/Plantago_ovata_seeds/CMDh_PhVWP_035_2011-Rev0.pdf

Margarida Guimarães

Antipneumococcal vaccine - Prevenar 13®

It is essential to avoid freezing of this vaccine when stored in a fridge, since deep freezing can impair its effectiveness.

(Infarmed Board Circular letter (in Portuguese) at:

http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_ALERTAS/DETALHE_ALERTA?itemid=4892103)

Revlimid®: conclusions from the risk-benefit review

Revlimid® (lenalidomide) is an antineoplastic agent used in association with dexamethasone in the treatment of adults with multiple myeloma who have received at least one previous treatment. The safety data of Revlimid® have been reviewed following three studies which demonstrated a four-fold higher rate of new cases of cancer in patients with a recent diagnosis of multiple myeloma and who were receiving concomitant treatment with Revlimid® and other medicines. The above included both solid and non-solid neoplasms, such as haematopoietic tumours. Although the studies were conducted in patients for whom Revlimid® was not indicated, EMA considered that these results could also be relevant for the population encompassed by the approved indication. From the review performed, it has been concluded that the benefits of lenalidomide still are higher than its risks, especially in what concerns increased survival.

EMA and Infarmed recommend that physicians:

- take into consideration the risk of occurrence of new cases of cancer before they start treatment with Revlimid®,
- assess their patients before and during the treatment with the procedures normally used for detecting *de novo* neoplasms,
- bear in mind that the conclusions reached regarding a continuing positive risk-benefit ratio do not apply to the use of this medicinal product outside its indications,
- report promptly any new cases of cancer.

Citalopram: new recommendations for prescription and use

EMA has recommended an update of the SPCs of medicinal products containing citalopram on detecting that these drugs can cause ECG changes, namely dose-dependent QT-interval prolongation. The studies have **not** demonstrated any **added benefit** with therapy using **daily doses higher than 40 mg**, which will prompt a review of the currently approved dosing regime, as well as the inclusion of new contraindications and precautions of use in patients with risk factors. The changes to be made to the SPC can be summarised as follows:

SPC section 4.2 – Posology and method of administration

Reduction of the maximum daily dose from 40 mg to 20 mg in the elderly, in patients with impaired liver function, and in slow CYP2C19 metabolisers.

SPC section 4.3 – Contraindications

Citalopram is contraindicated in patients with known QT-interval prolongation or congenital long QT syndrome.

Citalopram is contraindicated together with medicinal products that are known to prolong the QT-interval

SPC section 4.4 – Special warnings and precautions for use

QT interval prolongation and ventricular arrhythmia including torsades de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.5, 4.8, 4.9 and 5.1).

Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with citalopram is started.

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started. If signs of cardiac arrhythmia occur during treatment with citalopram, the treatment should be withdrawn and an ECG should be performed.

SPC section 4.5 – Interaction with other medicinal products and other forms of interactions

Contraindicated associations (see 4.3).

QT interval prolongation:

Pharmacokinetic and pharmacodynamic studies between citalopram and other medicinal products that prolong the QT interval have not been performed. An additive effect of citalopram and these medicinal products cannot be excluded. Therefore, co-administration of citalopram with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. fentiazine derivatives, pimozide, haloperidol), tricyclic antidepressants , certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc., is contraindicated.

Influence of other medicinal products on the pharmacokinetics of citalopram:

Cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) caused a moderate increase in the average steady state levels of citalopram. Caution is advised when administering citalopram in combination with cimetidine. Dose adjustment may be warranted.

SPC section 4.8 – Undesirable effects

Frequency unknown: Ventricular arrhythmia including torsades de pointes.

Cases of QT-prolongation and ventricular arrhythmia including torsades de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT prolongation or other cardiac diseases (see sections 4.3, 4.4, 4.5, 4.9 and 5.1).

SPC section 4.9 – Overdose

ECG monitoring is advisable in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

SPC section 5.1 – Pharmacodynamic properties

In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 7.5 (90%CI 5.9-9.1) msec at the 20 mg/day dose and 16.7 (90%CI 15.0-18.4) msec at the 60 mg day/dose (see sections 4.3, 4.4, 4.5, 4.8 and 4.9).

Joana Oliveira

Solutions for peritoneal dialysis: aseptic peritonitis

EMA has concluded a review of Baxter's manufacture procedures at their Castlebar (Ireland) unit, which has raised concerns regarding the production of solutions for peritoneal dialysis (Dianeal®, Extraneal® and Nutrineal®) and of sodium chloride solution for haemodialysis (Monosol®). This investigation was prompted in December 2010 by the detection of endotoxins in the dialysis solutions produced at that factory, which caused adverse reactions in some patients on peritoneal dialysis. At that time, Baxter identified endotoxin producing bacteria in two tanks as the source of the problem; those tanks were removed from the production chain. In spite of this, endotoxins were again detected in new batches and ▶

▶ the manufacturing unit was shut down and all solutions made there withdrawn.

From the analysis conducted, the CHMP concluded that the presence of endotoxins in the production lines had resulted from a combination of factors: fissures in the equipment (which may have allowed for bacterial growth), the factory's design, and the equipment cleaning methods (which may have allowed contamination to disseminate). Changes are now being made and monitored at the Castlebar factory in order to ensure that future dialysis solutions manufactured there will not be contaminated.

In order to avoid supply problems, the CHMP has recommended the use of products imported from four units outside the European Union and has adopted a strategy to ensure regular supply within the EU, should this type of problem recur, by authorising several manufacture sites.

All these measures notwithstanding, health professionals should always be aware of this issue and **report** as soon as possible any symptoms that may point to the development of **aseptic peritonitis**. EMA and Infarmed will continue monitoring and disseminating any new relevant data.

ADRs in the Literature…

Palmoplantar keratoderma associated with influenza immunisation

Palmoplantar keratoderma can have various aetiologies including an adverse drug effect. In this article, the authors describe a case of acquired palmoplantar keratoderma associated with the influenza vaccine and confirmed on reexposure.

Lim D et al. Australas J Dermatol. 2011 Nov;52(4):298-300.

Disulfiram and occupational exposure to solvents

A case is described of an artist under treatment for alcoholism with disulfiram, who presented with symptoms suggesting the reaction expected from concomitant use of alcohol. However, investigation concluded that the cause was occupational exposure to alcohol-containing products and other solvents. Symptoms initially improved with strict exposure eviction measures. This case highlights the importance of bearing in mind possible interactions between disulfiram and occupational exposure to solvents.

Ehrlich RI, et al. Occup Med (Lond). 2011 Nov 7.

Interactions to keep in mind!

Patients trying to quit smoking

Patients who are still smoking

Tobacco is an enzyme inducing agent, especially cytochrome P450 isoenzyme CYP 1A2. This makes certain pharmacokinetic interactions possible, namely by **decreasing the effectiveness** of medicines which are metabolised by the above isoenzyme. Conversely, it can propitiate **overdosing** problems whilst tobacco is being weaned, due to slower elimination of the same medicines.

- **Risk of decreased effectiveness**
  vs. relative overdose of medicines such as:
  - antineoplastic agents such as bortezomib and erlotinib
  - propranolol
  - antiparkinson agents such as ropinirole
  - antimigraine agents such as zolmitriptan
  - neuroleptics such as clozapine
  - theophylline
  - melatonin agonists
  - duloxetine
  - etc.
- **Increased insulin resistance**

Patients using nicotine replacement therapy

Nicotine is rapidly absorbed through skin and mucosa. It is a total acetylcholine agonist and is metabolised mainly by CYP 2A6. Its plasma elimination half-life is of only one to two hours.

- **Risk of:**
  - Antagonising the effect of **antiacids** in dyspepsia.
  - Increased **insulin** resistance (though less than tobacco itself).
  - High blood pressure, with **bupropion**.
  - Nausea, vomiting, headache, vertigo, dyspepsia, weakness, with **varenicline**

Patients taking varenicline

This is a partial acetylcholine agonist with no significant effect on cytochrome P450. It is eliminated in its non-metabolised form almost exclusively through the kidneys.

- **Risk of:**
  - Nausea, vomiting, headache, vertigo, dyspepsia, weakness, with **nicotine**.
  - Potentiation of adverse effects by reducing the elimination of medicines which may **impair renal function**.
  - Potentiation of **depression**, suicidal ideation with:
    - various neuropsychiatric agents
    - antimicrobials such as fluoroquinolones, interferon alfa, ribavirine, antiretrovirals, mefloquine
    - finasteride, dutasteride, flutamide, bicalutamide,...
    - betablockers, nifedipine, diltiazem, disopyramide, ...
    - progestative agents, tibolone, raloxifen, tamoxifen...
    - sitagliptin
    - NSAIDs and corticoids
    - montelukast
    - isotretinoin
    - acetazolamide
    - etc.
  - Potentiation of **seizures** with medicines which can lower the seizure threshold, or through antagonisation of the effect of antiepileptic agents in patients whose seizure activity is otherwise under control.
  - Potentiation of **hallucinations** with medicines which can induce or potentiate psychotic disorders.
  - Potentiation of **hyperglycaemia** and antagonisation of blood sugar lowering agents.

Patients taking bupropion

Bupropion is structurally akin to amphetaminic agents and inhibits catecholamine and serotonin reuptake. It inhibits isoenzyme CYP 2D6, and is metabolised mostly by CYP 2B6 resulting in active metabolites whose half-lives are longer than that of bupropion itself.

- **Risk of:**
  - **Increased effects** of medicines metabolised by CYP 2D6, such as:
    - betablockers
    - loratidine
    - opioids
    - carbamazepine
    - antidepressants such as venlafaxine or mirtazapine
    - various neuroleptic agents
    - duloxetine
    - tamsulosine
    - etc.
  - **Overdose of bupropion** with medicines which inhibit CYP 2B6, such as:
    - antiplatelet agents such as clopidogrel, ticlopidine...
    - etc.
  - Potentiation of **seizures** with seizure threshold lowering medicines.
  - Potentiation of the **sympathomimetic** effects of medicines such as:
    - nasal decongestants
    - adrenaline, noradrenaline
    - amphetaminic agents
  - Potentiation of undesirable **dopaminergic** effects (nausea, vomiting, neuropsychiatric disturbances) with drugs such as levodopa.
  - **Serotoninergic syndrome**: serotoninergic antidepressants, IMAO, etc.
  - **High blood pressure**, with nicotine.

** Based on: la revue Prescrire.*