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From the Editor

In this Number the suspension of marketing authorization for an immune globulin and an oral antidiabetic agent illustrates the relevance of pharmacovigilance activities in the prevention and early detection of potentially serious problems, thanks to an ongoing process of continuing risk assessment.

Yet another example of pharmacovigilance in action is the current investigation in Europe on a suspected association between anti-influenza A H1N1 vaccine and narcolepsy, a nosological entity whose diagnosis is often complex and probably seldom considered. On a different note, the safety profile of modafinil is highlighted. Modafinil is a drug used in the treatment of narcolepsy in adults.

A safety profile review of modified release opioids, especially in what concerns interaction with alcohol, could well be a reflex of the changing panorama of the use of these drugs, possibly associated with a welcome expansion of effective and more proactive palliative care strategies.

Light is under the spotlight in this issue: phototoxicity problems with a topical anti-inflammatory drug, and in the ADRs in the Literature section, a serious but rather interesting interaction between a drug and a medical device is described.

Octagam® (human immune globulin) MA suspended

The CHMP at EMA has started a safety review on Octagam, following an unexpected increase in reports of thromboembolic reactions, including stroke, myocardial infarction and pulmonary embolism, which is thought to be associated with problems in the manufacturing process (http://www.ema.europa.eu/.

Based on the available information, EMA has recommended the suspension of Marketing Authorization for Octagam 5% and 10% solution, with immediate recall of all lots within the European market. Infarmed I.P. has decided accordingly: http://www.infarmed.pt/portal/pls/portal/docs/1/4808244.PDF (in Portuguese).

Since these medicines will no longer be available, doctors should replace them with an alternative treatment. A list of alternative medicines available in the market can be found at the above link.

Cristina Rocha

Suspension revisited...

Every medicinal product has a potential to cause adverse reactions. Known undesirable effects are described in official documents approved by INFARMED, I.P., and in certain cases by the European Commission as well. Those documents target both the health professionals (Summary of the Product's Characteristics – SPC), and the general public (Information Leaflet). They can be easily accessed at ***www.infarmed.pt/INFOMED***.

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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Within the National Pharmacovigilance System, health professionals report adverse drug reactions from their daily clinical practice, which contributes towards monitoring the safety profile of the medicines that make up the therapeutic armamentarium available in the country. Reports of serious or unexpected ADRs are especially relevant for continuously assessing and monitoring the risk-benefit ratio of medicines since it is methodologically impossible to know every single possible adverse reaction while the drug is undergoing clinical trials before it is finally launched into the market.

The Portuguese National Pharmacovigilance System participates in the European Pharmacovigilance System as well as in the World Health Organization's Drug Monitoring Program, namely by feeding ADRs occurring in Portugal into the corresponding databases.

ADRs are considered **serious**, according to the WHO definition and current EU legislation, when they cause death, are life threatening, cause or prolong the patient's hospital stay, result in significant disability, cause any congenital anomalies, or prompt the intervention of a health professional to prevent the ADR to rapidly evolve to any of the other seriousness criteria.

ADRs which are not described in the SOC are considered to be **unexpected**. They are evaluated in what concerns seriousness and severity, frequency, therapeutic alternatives, and other data relevant for the drug's safety. ADRs which are unexpected may end up being included in the drug's official documents (SPC and/or Information Leaflet) and, similarly to serious ADRs, lead to the other measures being rolled out. The latter may go as far as the recall of specific batches or even market withdrawal of the drug.

Fátima Bragança

INDEX CARD | **Director:** Júlio Carvalhal **Editor:** Rui Pombal **Assistant Editor:** Alexandra Pêgo **Contributors:** Ana Araújo, Cristina Mousinho, Cristina Rocha, Fátima Bragança, João Ribeiro Silva, Joana Oliveira, Luís Pinheiro, 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

HMG-CoA reductase inhibitors precautions and undesirable effects update

The European Pharmacovigilance Working Party (PhVWP) at EMA has reviewed the class of HMG-CoA reductase inhibitors (**atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin**) taking into account data from clinical trials, from spontaneous reports and from published literature. It has decided that **SPC and Information Leaflet** safety data need to be harmonized across Europe in what concerns the following adverse reactions: sleep disturbances, memory loss, sexual dysfunction, depression, interstitial lung disease.

SPC Section 4.4 – Special warnings and precautions for use

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

SPC Section 4.8 – Undesirable effects

The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares [where this is not already listed]
- Memory loss
- Sexual dysfunction [where this is not already listed]
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

Cristina Rocha

Topical Ketoprofen
Mind the sun!

Ketoprofen is a non-steroidal anti-inflammatory drug which with both oral and topical formulations. The latter is indicated in the relief of musculoskeletal pain and inflammatory symptoms. Although alternative topical drugs exist within the EU, ketoprofen is the sole topical non-steroidal anti-inflammatory drug authorized for the treatment of acute lumbar pain.

The risk-benefit ratio of medicines containing ketoprofen for topical use has been evaluated in relation to reports of **phototoxicity/ photoallergy**. The CHMP has decided that the **incidence** of ADRs including photoallergy is **low** across the EU, and that the risk of these adverse reactions can potentially be reduced through appropriate minimization measures.

Recommendations

- These drugs should become **prescription-only**.
- Warnings on solar exposure should be included in the product's information documents, together with data on skin adverse reactions arising when ketoprofen is used concomitantly with octocrylene, an organic compound used as an ingredient in sunscreens and cosmetics.
- The risk of photoallergy associated with the use of ketoprofen should be clearly communicated to health professionals and patients. To ensure this and that instructions on how to prevent photoallergy are also give an action plan has been indicated.

The effectiveness of the risk minimization measures will be evaluated after a period of three years, and the health professionals are to be informed periodically..

Margarida Guimarães

Pandemrix safety review

Cases of **narcolepsy** have been spontaneously reported in temporal association with the use of Pandemrix®, mostly in Sweden and Finland. The European Medicines Agency, at the European Commission's request, has started an investigation into whether there is an link between those cases of narcolepsy and the vaccine. Knowing the actual background incidence of the condition, i.e. the number of cases that are usually diagnosed in the population in a given period of time, is one of the data that will have to be taken into account.

Pandemrix, which was approved in September 2009 for immunization against the influenza A H1N1 virus, has been used in about 30.8 million people in Europe. Narcolepsy is a rare sleep disorder that causes people to fall asleep suddenly and unexpectedly. Its cause is not completely known, but it is thought that it may be triggered by a combination of genetic and environmental factors, including infections.

Although a possible temporal link with the use of Pandemrix has been detected, it is not clear whether the vaccine has in fact triggered the cases. The CHMP at EMA, together with experts from across the EU, is going to assess this safety issue and its possible impact on the risk-benefit ratio of Pandemrix.

Joana Oliveira

Modafinil
for narcolepsy only

EMA recommends that medicinal products containing modafinil should be used only for sleep disturbances associated with narcolepsy, a chronic sleep disorder characterized by excessive daytime sleepiness.

Modafinil promotes alertness and has been used to counter sleep under various circumstances. It is authorized in 21 European countries, including Portugal. Besides **narcolepsy**, modafinil is indicated in other countries for the treatment of **idiopathic hypersomnia**, excessive sleepiness associated with **obstructive sleep apnoea**, and **shift work** sleep disorder.

EMA (CHMP) Recommendations

- The benefit of modafinil only clearly outweighs its risks in the case of **narcolepsy**. In the remaining conditions the risk of skin, hypersensitivity and neuropsychiatric reactions does not make up for the medicine's benefit.
- Modafinil should **not** be prescribed to **children**, since the potential risk of serious skin and hypersensitivity reactions is higher in this population.
- Modafinil should be **contraindicated** in patients with uncontrolled hypertension, or with cardiac arrhythmia.
- Despite the fact that modafinil is being used off label for recreational purposes, available data does not enable a corresponding risk assessment to be made. Therefore, companies marketing products containing modafinil should continue to provide information that allow the unduly use of this drug to be monitored.

In Portugal, the medicinal products containing modafinil (Modiodal and Modafinil Generis) already are approved for the treatment of narcolepsy only, and are not recommended for the paediatric population. Thus patients taking modafinil within the expected indications need not discontinue their therapy.

Joana Oliveira

Narcolepsy*

- Age of onset usually between the first and second decades of life.
- Essential narcolepsy symptoms are cataplexy and excessive sleepiness.
- Cataplexy is defined as sudden, recurrent and reversible attacks of muscle weakness triggered by emotions.
- Accessory symptoms are hypnagogic hallucinations, sleep paralysis and nocturnal fragmented sleep.
- Full in-lab polysomnography followed by a multiple sleep latency test is recommended for the confirmation of the diagnosis and co-morbidities.
- A positive HLA-DQB1*0602 with lower than 110pg/mL level of hypocretin-1 in the cerebrospinal fluid is required for the final diagnosis of cataplexy and sleep-onset REM period -free narcolepsy.

** Aloé F et al, 2010*

Rosiglitazone suspended

Fluid retention caused by rosiglitazone and its attending increased risk of heart failure have prompted cardiovascular safety monitoring of this drug since 2000. Its use had already then been restricted to second-line therapy as well as contraindicated in cardiac failure. Furthermore, data obtained within the past three years have pointed to an increased risk of coronary ischaemic disease in patients on rosiglitazone leading to additional warnings and a contraindication for that patient group. Still more recently, studies have confirmed an increased cardiovascular risk associated with rosiglitazone, and the CHMP has concluded that the benefits of this active ingredient do not supersede its risks.

In Portugal, two medicines containing rosiglitazone for type 2 diabetes mellitus have been marketed: Avandia® (rosiglitazone) and Avandamet® (metformin + rosiglitazone). Both will no longer be available in Europe within few months, according to EMA's recommendation to suspend their MAs.

Infarmed recommends:

- Physicians should **stop prescribing rosiglitazone** and **review** the treatment plan of all their patients currently on this medicine.
- **Patients** currently on rosiglitazone should not discontinue their medication before **first talking to their doctor**.

Further information on line (Portuguese):
http://www.infarmed.pt/portal/pls/portal/docs/1/4800248.PDF

Prolonged Release Oral Opioids No alcohol!

EMA has concluded a review of the available safety data concerning the interaction of alcohol with third step WHO analgesic ladder modified release oral opioids: **morphine, oxycodone and hydromorphone**. Conclusions:

- The risk-benefit ratio of these medicinal products is still favourable. Therefore, they can go on being used in the treatment of pain that is not amenable to control with other drugs.
- Warnings in the information datasheets approved for modified release opioid medicines should be harmonized and reinforced in what concerns their interaction with alcohol, namely an augmented sedative effect of opioids caused by rapid release of the active ingredient and consequent increase of the circulating dose.
- Patients on modified release opioids should not consume alcoholic beverages.

Joana Oliveira

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

Contrast Agents containing Gadolinium risk minimization of Systemic Nephrogenic Fibrosis

As previously published (Boletim's 1st Quarter 2010 issue) the European Medicines Agency CHMP has reviewed the risk of Systemic Nephrogenic Fibrosis (SNF) associated with gadolinium-containing contrast agents used in magnetic resonance imaging and in magnetic resonance angiography. The European Commission has issued its Decision in July confirming the CHMP's Opinion.

Based on available evidence, the CHMP has agreed on a classification of gadolinium-containing contrast agents into 3 risk categories for SNF:

I. **High risk**: Omniscan (gadodiamide), Optimark (gadoversetamide), Magnevist, Magnegita, and Gado-MRT ratiopharm***** (gadopentetic acid)

II. **Medium risk**: MultiHance (gadobenate dimeglumine), Primovist (gadoxetic acid), and Vasovist (gadofosveset)

III. **Low risk**: Gadovist (gadobutrol), ProHance***** (gadoteridol), and Dotarem (gadoteric acid)

Measures to minimize the risk of **high-risk** gadolinium-containing contrast agents

- Prior to using these medicines, every patient, especially those 65 years of age or older, should have their **renal function** assessed.
- **Contraindicated** in patients with severe renal insufficiency (glomerular filtration rate – GFR < 30 ml/min/1,73m^2), in patients who are awaiting or who have recently been submitted to liver transplantation, and in newborns.
- Both in patients with moderate renal insufficiency (GFR 30-59 ml/min/1,73m^2), and in infants, use a **single dose** at the **lowest possible dosage**.
- Women should suspend **breastfeeding** at least 24 hours after the contrast agent has been administered.
- Use in **pregnancy** is not recommended, unless clinically indispensable.
- There is **no** evidence supporting starting **haemodialysis** to prevent or treat SNF in patients not already on haemodialysis.
- The **stick-on label** on the vials or the syringes should be stuck on the patient's file with an exact record of the contrast agent used. The dose given should also be recorded in the patient's clinical file.

Warnings applicable to **medium risk** gadolinium contrast agents are less strict than the above but stricter than those to be applied to **low risk** agents. The datasheets for each of these agents should be consulted.

The SPCs and Information Leaflets of gadolinium-containing contrast agents will be updated in accordance with the above safety data within the scope of the implementation of the corresponding European Commission Decision. Health professionals involved in the use of these medicines should look out for adverse reactions, which should be promptly reported to Infarmed.

Magda Pedro

** Gado-MRT-Ratiopharm and ProHance have no MA in Portugal.*

ADRs in the Literature...

Acyclovir e Valacyclovir in the first trimester of pregnancy

Herpes simplex and herpes zoster infections are common and often treated with antiviral drugs including acyclovir, valacyclovir, and famciclovir. However, safety of these antivirals when used in the first trimester of pregnancy is insufficiently documented. The first trimester is when women may be more likely to inadvertently take potentially teratogenic medicines.

In this study in a large Danish cohort, 1.804 pregnancies were identified as having been exposed to the above drugs. Exposure to either acyclovir or valacyclovir was **not** associated with an increased **risk** of major congenital malformations. Exposure to famcyclovir was too uncommon to allow for more conclusive data.

Björn P, Anders H. JAMA. Use of Acyclovir, Valacyclovir, and Famciclovir in the First Trimester of Pregnancy and the Risk of Birth Defects 2010;304(8):859-866.

Adverse reaction with photosensitizing drug in patient monitored with pulse oxymeter

This article describes the case of a 58-year-old woman sustained gangrene of the right index and middle fingers from non-thermal injury resulting from the use of pulse oximetry. She had received an injection of temoporfin, a photosensitizing agent, before elective photodynamic treatment for local control of an axillary metastasis from breast carcinoma. The wavelength of light produced by a standard oximeter is in close proximity for the activation of temoporfin, which caused photo-activation and hence excessive tissue destruction.

The author suggests that healthcare professionals should be aware of the risks and apply pulse oximetry for the minimum amount of time and, if needed, reposition on different digits. The SPC of medicines containing temoporfin includes a description of potentially frequent occurrence of **skin necrosis**. **Repositioning the oxymeter** at intervals of at least 10-15 minutes is recommended to avoid the risk of localized skin burns.
Luk S. BMJ 2010;340:c3102

Ultra-fast CYP2C9!

The cytochrome P450 enzyme CYP2C9 metabolizes several commonly used drugs, such as warfarin and oral antidiabetic drugs. The enzyme is polymorphic but ultra-high activity had not yet been reported until this Swedish article came out.

The case concerned a patient with Behçet's disease who was on high doses of phenytoin. When fluconazole, a potent inhibitor of CYP2C9, was added to the treatment regimen, the patient developed signs and symptoms of phenytoin intoxication: ataxia, tremor, fatigue, slurred speech and somnolence. On A phenotyping test for CYP2C9 confirmed a higher activity of CYP2C9 than any of the healthy controls.

Hellden A et al. Eur J Clin Pharmacol. Eur J Clin Pharmacol. 2010 Aug;66(8):791-5.

Interactions to keep in mind!

Patients with Hypothyroidism*

Risk of:

Poor control of hypothyroidism (insufficient hormonal compensation)

- Drugs that decrease the absorption of levothyroxine in the gut - e.g., iron salts, antiacids, sucralfate. Levothyroxine should be taken at least 2 hours away from the above drugs.
- Enzyme inducers which increase the metabolism of levothyroxine – e.g., antiepileptics such as carbamazepine or phenytoin, anti-bacterials such as rifampin, antiretrovirals such as efavirenz, nevirapine, lopinavir, nelfinavir, ritonavir.
- Oestrogens: they decrease the free (active) plasma fraction of thyroidal hormone.

Haemorrhage

- Association of anticoagulants (anti-vitamin K) with levothyroxine, when starting therapy or increasing the dose of the latter.

Hyperglycaemia

- Possible increase in insulin or oral hypoglycaemic drug needs on starting therapy with levothyroxine.
- Potentiation of hyperglycaemia when associating levothyroxine with drugs such as corticosteroids, thiazide diuretics, beta-agonists, HIV protease inhibitors, etc.

Worsening of cardiac failure

- Association of thyroid hormones (especially when in excessive doses) with digoxin, which leads a decrease in the plasma concentration of the latter.
- Association of thyroid hormones with sympathomimetics (increased cardiac workload and increased sensitivity of catecholamine receptors).

Anginal pain in patients with coronary ischaemic disease

- Association of thyroid hormones (especially when therapy is being started or dose augmented) with medicines that induce tachycardia and/or vasoconstriction, e.g., nasal decongestants, theophylline, beta-agonists, prostaglandins, atropinic agents, triptans, levodopa, antidepressants of the imipramine type, venlafaxine, bupropion.

NB

- Levothyroxine has a plasma elimination **halflife** of **6 to 7 days** in normothyroid patients, longer in hypothyroidal states. Its total therapeutic effect therefore can only be obtained after several weeks of continuous administration, and responses to dosage changes are accordingly slow. Analogously, even after levothyroxine has been suspended, its effects may last for several weeks still.
- Gut absorption of levothyroxine is variable and is slowed down by simultaneously ingesting **food**.

** Based on: la revue Prescrire*