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From the Editor

Never taking things for granted is probable a good motto to always keep in mind. Features like the shape and colour of a medicines container, not reading the Information Leaflet, and communication gaps between patients and health professionals, can all contribute to significant medication errors. Instances when Caladryl®, a topical skin product, was given per os, are a vivid example of the above. They remind us not to take for granted the knowledge patients have on how to take medicines. What may seem obvious to physicians, pharmacists and nurses, is often obscure or confusing to patients, even those with a solid educational background.

In this Number of the Boletim you will also be able to keep up to date with other safety issues, including changes in the SPCs of several antidepressants.

Concomitant use of Thiazolidinediones (Pioglitazone) and Insulin: risk of Heart Failure

Literature data indicate that the simultaneous use of insulin and thiazolidinediones can be associated with an increased incidence of cardiac failure, oedema and weight gain. This information has been included in the Summary of the Product's Characteristics of pioglitazones (SPC section 4.4 – Warnings and Special Precautions for Use). The SPCs and Information Leaflets of insulins are also going to be updated.
In spite of the above risk, combining thiazolidinediones with insulin still is a therapeutic option for diabetes, provided the attending risk-benefit ratio is adequately weighed.

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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Non-Steroidal Anti-inflammatory Drugs (NSAIDs): risk of Cardiovascular adverse reactions

The European Pharmacovigilance Working Party (PhVWP) has discussed the findings of a recently published metaanalysis of studies on the cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs).[1] The active ingredients included in the metaanalysis were: diclofenac, ibuprofen, naproxen, as well as celecoxib and other selective COX-2 inhibitors, etricoxib, lumiracoxib, and rofecoxib (MA withdrawn in the EU).

The PhVWP has concluded that the metaanalysis confirms that the risk of cardiovascular events associated with NSAIDs is increased in comparison to placebo, and that diclofenac and ibuprofen are associated with a relatively higher risk than naproxen. These data however, are in accordance with previous Europe-wide reviews on the safety of NSAIDs, including COX-2 inhibitors. Therefore, no regulatory action based on these more recent data has been considered necessary at this time.

Meanwhile, the previously established warning to use **the lowest possible dose** of NSAIDs **for the shortest possible period of time** necessary to treat symptoms, keeps current and relevant.

Trelle S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. Br Med J. 2011; 342: c7086.

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

Caladryl®: incorrect route of administration

Caladryl® skin lotion (diphenhydramine + calamine + camphor) is a local anaesthetic and an antipruritus agent, which is indicated in adults and children older than 12 years, to abate and relieve skin irritation associated with urticaria, contact dermatitis, other mild skin conditions such as lichen and minor rashes, insect bites, and sunburns.

In 2010, following a safety assessment conducted by Infarmed's Medicines Risk Management Dept. (DGRM) on medicines containing camphor as active ingredient, problems were identified to do with incorrect use of the route of administration.

According to data from the Portuguese Antipoison Information Centre (*Centro de Informação Antivenenos* - CIAV) on cases occurred in Portugal of accidental ingestion of various medicines containing camphor, it stood out that patients were especially prone to incorrectly use the route of administration of Caladryl® topical skin lotion. In fact, several cases were identified in which patients took the medicine orally, either because they did not know how to use the product, or simply by mistake.

Caladryl® skin lotion is a medicine of exclusively external use to be applied topically on affected skin. Health professionals are therefore urged to reinforce **advice on the correct route of administration** whenever prescribing or dispensing this medicine.

This message has also been directly disseminated by the MA Holder to every pharmacy and over-the-counter medicines dispensing outlet in this country.

Cristina Mousinho

Avastin® (bevacizumab): association with Paclitaxel only

EMA recommends that Avastin® (bevacizumab) in the treatment of patients with metastatic breast cancer be used **only in association with paclitaxel**. Docetaxel should not be used. A proposal to use Avastin® with capecitabine in those patients has also been turned down.

Bevacizumab is used in the treatment of various types of cancer, namely colon, rectum, breast, lung and kidney cancers, in association with other antineoplastic agents. In metastatic breast cancer it has been used in association with the taxans paclitaxel or docetaxel. Within the scope of a request for authorisation of a novel indication of Avastin® for use in association with capecitabine in the treatment of metastatic breast cancer, data comparing this association with that with taxans were taken into consideration. Those data suggested that the association of Avastin® with docetaxel could have a negative impact on patients' overall survival post-treatment initiation. This triggered an in-depth review of the various drug associations used for breast cancer.

In conclusion:

Association with capecitabine: Although data show a slight increase in disease progression free survival, no improvement was seen for other equally important parameters, such as overall survival or quality of life. Benefits were thus not considered sufficient to offset this association's high level of toxicity. This new indication has therefore **not** been authorized.

Association with docetaxel: This association can have a negative impact on overall survival, which renders its risk-benefit ratio unfavourable. It should therefore **not** be used in breast cancer treatment.

Association with paclitaxel: The benefit of Avastin® in association with paclitaxel outweighs its risk, since available data show that disease progression free survival is prolonged without a negative impact on overall survival. This association is therefore still a **valid** therapeutic option.

Pandemrix®: causal link between vaccine and narcolepsy not established

EMA has analyzed the additional data obtained in Finland about a possible relation between a number of cases of narcolepsy reported in children and adolescents, and immunization with Pandemrix® (anti-influenza A pandemic vaccine). Preliminary results from the epidemiological study conducted in Finland, comparing the incidence of narcolepsy in individuals aged between 4 and 19 years who had been immunized with Pandemrix® between 1 January 2009 and 31 December 2010, with the incidence of narcolepsy in non-vaccinees of the same age range, suggested a risk of narcolepsy which was nine-fold higher for the vaccinated population, i.e. an increase from a baseline of one to nine cases per 100,000 vaccinated individuals. It should be noted that even if this increase is confirmed, the overall incidence of narcolepsy will still be very low.

In Sweden, the number of cases of narcolepsy reported after immunization with Pandemrix® has also been higher than expected. Results from a study in this member State are still pending and they will hopefully further illuminate the Finnish observations.

Nevertheless, **no increase** in the number of cases of narcolepsy reported has been so far seen **in other non-Nordic countries**, for example in Canada, where a high proportion of children and adolescents were vaccinated.

The CHMP considers that it is **important to collect more data** on the use of Pandemrix® and related vaccines in other countries, so that it may definitely be possible to determine whether or not there is a relation between this immunization and narcolepsy. An epidemiological study conducted by the European Centre for Disease Control and Prevention (ECDC) in nine European Union member States is under way. Its final results are expected to be known until the end of June 2011.

Since no definitive conclusion can be reached at this stage, EMA has decided that, at this time, it is not necessary to alter the profile of use of the Pandemrix® vaccine.

Antidepressants: new safety information

The European Pharmacovigilance Working Party has conducted an assessment of the risks of persistent pulmonary hypertension of the newborn (PPHN), birth defects, and bone fractures, associated with the use of several antidepressant drugs. It has concluded for the introduction of new **safety information in the SPCs** according to the risks identified for the various active ingredients:

RISK OF BIRTH DEFECTS

fluoxetine

section 4.6 – fertility, pregnancy and lactation

Some epidemiological studies suggest an increased risk of cardiovascular malformations associated with the use of fluoxetine during the first trimester of pregnancy. The mechanism is still unknown. Overall, data indicate that the risk of a newborn presenting cardiovascular malformations following maternal exposure to fluoxetine is 2/100, whereas the expected rate for these malformations in the general population is of approximately 1/100.

RISK OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

section 4.6 – fertility, pregnancy and lactation

citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline

Epidemiological data suggest that the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy, especially during its later stages, can increase the risk of persistent pulmonary hypertension of the newborn (PPHN). The observed risk was of approximately 5 cases per 1,000 pregnancies. In the general population one to two cases of PPHN occur per 1,000 pregnancies.

venlafaxine

Epidemiological data suggest that the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy, especially during its later stages, can increase the risk of persistent pulmonary hypertension of the newborn (PPHN). Although there are no studies regarding the relation between PPHN and treatment with serotonin/noradrenaline reuptake inhibitors, this potential risk cannot be excluded for therapy with this medicine, given its related mechanism of action (serotonin reuptake inhibition).

mirtazapine

Epidemiological data suggest that the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy, especially during its later stages, can increase the risk of persistent pulmonary hypertension of the newborn (PPHN). Although there are no studies concerning the relation between PPHN and treatment with mirtazapine, this potential risk cannot be excluded, given the related mechanism of action (increased serum serotonin concentration).

RISK OF BONE FRACTURES

citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amitriptyline, clomipramine, dosulepine, doxepine, imipramine, lofepramine, nortriptyline, and trimipramine

section 4.8 – undesirable effects

Class effects:
Epidemiological data, namely from studies conducted in patients aged 50 years or older, show an increased risk of bone fractures in patients taking selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. The mechanism underlying this risk is still unknown.

Joana Oliveira

Thelin® (sitaxsentan): market withdrawal

Thelin® (active ingredient sitaxsentan) is an endothelin receptor antagonist (ERA). It had been authorized within the European Union in 2006 for the treatment of pulmonary arterial hypertension.

The CHMP at EMA has analyzed three **fatal cases of liver injury**; one occurred in the UK in 2009, two during clinical trials carried out in India and Ukraine in 2010. Two of these cases had a direct causal nexus with Thelin®. Data suggest that serious liver toxicity cannot be prevented in all patients. The toxicity cases were not associated with identifiable risk factors, they are not detectable through liver function monitoring, and once therapy was discontinued, affected patients did not recover.

Furthermore, **other treatment alternatives** are available, including other endothelin receptor antagonists: bosentan (Tracleer®) and ambrisentan (Volibris®). Liver toxicity can be a common effect to other medicines of the same class, but its frequency and intensity may vary. Recommended doses should be strictly followed and liver function monitored.

A cumulative review of the hepatotoxic profile of ERAs has been initiated in the meantime in order to confirm whether they still are a therapeutic option for the treatment of pulmonary hypertension.

ADRs in the Literature…

In utero exposure to carbamazepine and birth defects

Cohort studies corresponding to a total of 2,680 pregnancies with exposure to carbamazepine in monotherapy, as well as the EUROCAT database, were reviewed by the authors. The overall prevalence of major birth defects obtained in association with exposure to carbamazepine in monotherapy during the first trimester of pregnancy was 3.3% (CI 95%: 2.7-4.2). Spina bifida was the only major malformation that was specifically and significantly associated with carbamazepine monotherapy exposure, even though still with a risk that was lower than that associated with valproate. Other preliminary data suggest there could be an increased risk of atrioventricular septal defect and single ventricle. These data however need further elaboration.

Jentink J et al. Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. BMJ 2010; 341:c6581.

Report of a very rare adverse reaction: fever with an antibacterial agent

An ADR has recently been reported to the Portuguese National Pharmacovigilance System which presented features of special interest. Firstly, the approved dose and therapeutic indication are unusual for antibiotics (prophylactic oral administration on alternate days). On the other hand, the clinical picture was particularly interesting in terms of pharmacovigilance.

The case was reported by a physician and involved a male adult patient who had presented with fever with chills and myalgia upon taking co-trimoxazole for *Pneumocystis jirovecii (*ex-*Pneumocystis carinii)* prophylaxis at a dose of 960 mg every Monday, Wednesday and Friday. Axillary temperature had risen to 38-39 ºC and had prompted hospital admission on account of a suspected infection. However, no pathogen was isolated in either the blood or urine cultures. Symptoms worsened as therapy progressed, and it eventually became notorious that the patient's complaints coincided with the days of the week he took co-trimoxazole. The latter was discontinued for this reason and the patient's fever and myalgia disappeared. These adverse reactions are very rare but they are described in the medicine's Summary of the Product's Characteristics (SPC).

The SPC is an official document for use by health professionals, which can be accessed at the INFARMED webpage. If you look up co-trimoxazole you will find under *4.8 Undesirable effects*, fever and myalgia described with a frequency lower than 1:10,000. This incidence, according to the WHO scale, means they are indeed very rare reactions. It is worth noting that, depending on clinical practice findings and the number of cases reported, among other factors, the ADR frequency stated in SPCs can be altered, making the SPC an up-to-date reflection of the medicinal product's safety profile at each time. The fact that a given ADR is described as very rare or, conversely, as frequent, may change the health professional's prescribing and preventive attitudes. Precise data on ADR frequency can be yet another diagnostic modulation tool for health professionals.

This case study is moreover a good example of how even very rare adverse reactions do occur in "real-world" clinical practice. The health professionals' effectiveness in identifying and reporting them is a precious contribution to the National Pharmacovigilance System and to public health in general.

Fátima Bragança

With thanks to the reporting doctor.

Alendronates: risk of oesophageal cancer

The European Pharmacovigilance Working Party has reviewed the risk of oesophageal cancer associated with the use of orally administered biphosphonates, following spontaneous reports and published data suggesting an increased risk (which further rises with treatment duration) of the above type of cancer, associated with oral biphosphonates.[1]

Warnings on the use of alendronates in **patients with Barrett's oesophagus** (a significant risk factor for oesophageal cancer) are thus going to be included in the SPCs and Information Leaflets of alendronates.

Margarida Guimarães

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…

Gastric acid secretion suppressing drugs and risk of pneumonia

Following several studies with inconclusive results, the authors conducted a systematic review and a metaanalysis (including 31 studies) to investigate the potential association between the use of acid secretion suppressing agents (namely proton pump inhibitors and anti-H_2) and risk of pneumonia. They concluded that there may in fact be an association with either community or hospital-acquired pneumonia.

They therefore propose that clinicians should carefully ponder on the decision to prescribe proton pump inhibitors or anti-H_2, especially in patients with a significant baseline risk of pneumonia. Since it is usually not necessary to obtain total achlorhydria, they recommend that the strictly minimum dose should be used which is needed to reach the therapeutic goals.

Eom CS, et al. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ. 2011 Feb 22;183(3):310-9. Epub 2010 Dec 20.

Interactions to keep in mind!

Patients with Gastroesophageal Reflux*

Risk of:

Interaction between antacids and other medicines

- Antacids decrease the absorption of numerous medicines. It may be prudent to systematically leave an interval of about 2 to 3 hours between taking antacids and the administration of any other medicines.

Interaction between proton pump inhibitors and medicines whose absorption greatly depends on gastric pH

- Decreased absorption of **azole antifungals** such as ketoconazole or itraconazole.
- Decreased bioavailability of the antiretroviral **atazanavir** by about 75%.

NB

- Since proton pump inhibitors are metabolized by cytochrome P450 isoenzyme CYP2C19, some competition could be expected with the metabolism of drugs such as diazepam or warfarin, but pharmacokinetics studies suggest interaction should be minimal.
- Generally speaking, **proton pump inhibitors** are **not usually** major players in drug **interactions**.

** Based on: la revue Prescrire*