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From the Editor

Medication errors make up for an aspect of adverse reactions which is of great practical relevance. They are under the spotlight in two of this issue's articles. The source of error can be the health professional who prescribes or administers the medicine (such as a perfusion of paracetamol for newborns) mixing up the dosage units. The patients themselves can be the source of error by getting the dosage intervals wrong (e.g., daily instead of weekly), which in the case of methotrexate can expose them to a potentially fatal overdose.

It is indeed expected that patients will take on a more active role within the national pharmacovigilance system thanks to new legislation that will be coming into effect later this year. The consumers' role and autonomy are implicitly underscored in another feature on the differences between medicinal products and food supplements. The different ways to report any untoward effects from each type of product are also explained.

On the back page of this issue you will find the hard copy form of the bulletin's index. This will soon be available online on the Infarmed Boletim webpage. This index is searchable by using active ingredients or topics of interest as key words. Each entry gives you the corresponding Boletim's reference links. By clicking on a link you can directly access a pdf file with the relevant data. This index will include every issue starting from 2004 and will be kept current with the latest published Boletim.

Prevention of Medication Errors with Paracetamol IV

Within the EU there have been cases reported of accidental overdose of parenteral paracetamol in infants and children, caused by erroneously administered doses of up to ten times the recommended dosage. Mixing up the **prescription units (mg)** with the **administration units (mL)** was at the root of these cases.

Several measures have consequently been taken by the member states, including an update of the SPCs of medicines containing paracetamol for intravenous administration and the dissemination of recommendations to health professionals. Furthermore, there are plans to disseminate posters with a sum-up of prescription recommendations for children and infants and special precautions concerning double-checking of dose prescription and administration.

In order to avoid these medication errors, which can be associated with serious liver toxicity, it is recommended that the **volume to be administered be clearly spelled out in milliliters (mL) in the prescription**, and that the dosage calculations always be based on the details included in the SPC.

PARACETAMOL 10 MG/ML IV – DOSAGE TABLE

patient's weight	single dose	maximum daily dose
≤ 10 kg	7.5 mg/kg in each administration, i.e., **0.75 ml of solution per kg**	**30 mg/kg** i.e., **3 ml/kg**
> 10 kg and ≤ 33 kg	15 mg/kg in each administration, i.e., **1.5 ml of solution per kg**	**60 mg/kg** i.e., 2 g or **200 ml**
> 33 kg and £ 50 kg	15 mg/kg in each administration, i.e., **1.5 ml of solution per kg**	**60 mg/kg** i.e., 3 g or **300 ml**
> 50 kg	**1 g** in each administration, i.e., 100 ml	**4 g** or **400 ml**
All		ü up to four times a day ü minimum interval between each administration should be 4 hrs

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

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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Exposure to Antipsychotics in the Third Trimester of Pregnancy Risk of Extrapyramidal Manifestations and/or Withdrawal

The SPC of antipsychotic agents (amisulpride, aripiprazole, asenapine, ciamemazine, chlorpromazine, clozapine, droperidol, fluphenazine, flupentixol, haloperidol, levomepromazine, melperone, olanzapine, paliperidone, pimozide, quetiapine, risperidone, sertindole, sulpiride, tiapride, ziprasidone, zotepine, and zuclopentixol) is going to be updated on account of a recently identified risk of increased incidence of adverse reactions in newborns exposed to those drugs during the third trimester of pregnancy, namely extrapyramidal signs and/or withdrawal syndrome. The changes will be as follows:

Section 4.6 – fertility, pregnancy and lactation

Newborns exposed to antipsychotics during the third trimester of pregnancy are at risk of adverse reactions after delivery, including extrapyramidal and/or withdrawal symptoms, which can vary in intensity and duration. Cases of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorders have been reported. Consequently, newborns should be carefully monitored.

Section 4.8 – undesirable effects

Pregnancy, puerperium and perinatal conditions

Unknown frequency: neonatal drug withdrawal syndrome (see section 4.6).

Joana Oliveira

Methotrexate and Risk of Overdose from self medication error

The data (SPC, information leaflets, labels) of medicines containing methotrexate per os with rheumatological and dermatological indications is to emphasize the fact that dosing should be on a **weekly** basis rather than daily, and that patients should be informed on the risk of overdose due to wrongly taking oral methotrexate daily. The text to be included in the SPCs and information leaflets can be found at: http://www.hma.eu/222.html

Margarida Guimarães

Nimesulide therapeutic indications further restricted

The use of medicines containing nimesulide has been subjected in the past to **several restrictions** aiming to reduce the risk of hepatic injury. Those restrictions have included the use of nimesulide as second-line therapy, the use of the minimum effective dose for the shortest possible period of time, and a maximum duration of treatment of 15 days.

A recent risk-benefit reassessment has introduced a **novel important restriction** to ensure that nimesulide is only used in short-term treatments: the indication "**symptomatic treatment of painful osteoarthritis**" has been **withdrawn**.

EMA has concluded that the benefits of nimesulide are no longer greater than its risks when used for the treatment of osteoarthritic pain, on account of the risk of chronic use. On the other hand, there is evidence that nimesulide will have the same efficacy in the treatment of acute pain as other non-steroidal antiinflammatory drugs such as diclofenac, ibuprofen and naproxen.

EMA and Infarmed recommend:

To physicians:

- To not prescribe systemic nimesulide for the treatment of painful osteoarthritis.
- To review the therapy of patients being treated for painful osteoarthritis in order to select an appropriate alternative.
- Nimesulide should only be used as second-line therapy, and for the treatment of acute pain or dysmenorrhoea.

To patients:

- If being treated with systemic nimesulide for painful osteoarthritis, they should see their doctor in order to get an appropriate therapeutic alternative.
- In case of doubt, they should consult their doctor or pharmacist.

Margarida Guimarães

Escitalopram: new recommendations for prescription and use

EMA has recommended an update of the SPCs of medicines containing escitalopram on account of the risk of ECG changes, namely **dose dependent QT interval prolongation**. This safety review was triggered by recent evidence of the above risk for citalopram, escitalopram's enantiomer.

Summary of the changes to be introduced in the SPC:

Section 4.2 – posology and method of administration

Elderly patients (> 65 years)

The initial dose is 5 mg once daily. Depending on the individual patient's response, the dose can be increased up to a maximum of 10 mg per day.

Section 4.3 – contraindications

Prolongation of the QT interval or congenital long QT syndrome.

Section 4.4 – warnings and special precautions for use

Escitalopram is known to prolong the QT interval in a dose dependent fashion. In the post-marketing phase, cases of QT interval prolongation and ventricular arrhythmia, including torsades de pointes, have been reported, mostly in female patients, in hypokalaemic patients, and in patients with preexisting QT interval prolongation or other cardiac conditions.

Special caution is recommended in the case of patients with significant bradycardia, recent acute myocardial infarction or decompensated heart failure.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk of malignant arrhythmia and should be corrected before starting treatment with escitalopram.

An ECG should be considered before starting treatment with escitalopram in stable cardiac patients. Should any sign of cardiac arrhythmia occur during treatment, the latter should be discontinued and an ECG performed.

Section 4.5 – drug interactions and other interactions

The concomitant administration of escitalopram and medicines known to prolong the QT interval, such as class IA and III antiarrhythmics, antipsychotics (e.g., phenothiazines, pimozide, haloperidol), tricyclic antidepressants, some antimicrobials (sparfloxacin, moxifloxacin, IV erythromycin, pentamidine, antimalarials (especially halofantrin)), some antihistamines (astemizole, mizolastine) etc., is contraindicated.

Section 4.8 – undesirable effects

In the post-marketing phase, cases of QT interval prolongation and ventricular arrhythmia, including torsades de pointes, have been reported, mostly in female patients, in hypokalaemic patients, and in patients with preexisting QT interval prolongation or other cardiac conditions.

Section 4.9 – overdose

It is advisable to perform an ECG in at risk cases.

Section 5.1 – pharmacodynamic properties

The results of a double-blind, placebo-controlled trial conducted on healthy subjects showed a change in the baseline QTc interval (Fredericia correction) of 4.3 msec with a daily dose of 10 mg, and of 10.7 msec with a daily supratherapeutic dose of 30 mg.

Joana Oliveira

Gonadotropin Releasing Hormone Agonists Risk of Depression

Gonadotropin releasing hormone agonists (buserrelin, goserrelin, histrelin, leuprorrelin, nafarelin, triptorrelin) are generally indicated for the treatment of prostate cancer, hormone-dependent breast cancer in pre-and perimenopausal women, endometriosis and uterine fibromyomatosis.

Following reports of serious depression, including suicide, from a Japanese trial, and epidemiological studies from the UK, the European Pharmacovigilance Working Party (PhVWP) reviewed gonadotropin releasing hormone agonists and risk of depression. It has concluded that the risk of depression and mood changes should be described, and warnings should be included in the safety information of these medicines in a consistent way and for all indications.

Margarida Guimarães

New Pharmacovigilance Legislation impact on the authority and the public

Pharmacovigilance aims to promote public health by identifying and detecting safety problems concerning medicines. An estimated five percent of hospital admissions are due to ADRs, which are the fifth major cause of intra-hospital death in Europe.[1] A more rational and dynamic legislation that is well adapted to the globalisation of the pharmaceuticals market has become a necessity if we are to increase the efficiency and proactivity of the European system, reduce work duplication, simplify procedures, clarify roles and accountability, increase transparency, and optimise information on medicines that is made available to all stake-holders.

This new legal framework will hopefully enhance the current European pharmacovigilance systems by making them fitter for detecting, assessing and preventing ADRs. It has been adopted by the European Parliament and published on 31 December 2012 in the official EU Journal. It is to be enforced from **July 2012**, and it has been transcribed into the 15 December 2010 Directive 2010/84/EU which altered Directive 2001/83/EC of 6 November 2001, and into Regulation N. 1235/2010 of 15 December, which on its turn alters Regulation N. 726/2004 from 31 March.[2,3] One of the main novel points is **greater involvement of patients**, in that the latter will be **able to report suspected ADRs themselves to their national authority**, thus taking on a more significant role within the pharmacovigilance system.

Reporting will become easier, since both patients and professionals will be able to access an ADR Portal for online submission of adverse drug reactions. Nevertheless, health professionals will still be able to report ADRs through the usual reporting card scheme. A hardcopy card scheme will also be made available to patients.

In order to allow for the collection and sharing of data on the administration of medicines outside their marketing authorisation conditions, the definition of adverse reaction is broadened to include **medication errors**, **overdose**, **misuse**, **abuse**, and **off-label use**. All these adverse reactions are to be reported by health professionals and patients to the regulatory authorities or to the MA Holder, which are to share this information and report it directly to EudraVigilance (the European ADR database) before the deadlines laid out by the new legislation according to the degree of ADR seriousness.

On the other hand, every ADR should be reported, even if they are expected and/or non-serious, although with different legal deadlines for data sharing between MA Holders and regulatory authorities.

In order to increase the transparency of the pharmacovigilance system, **information on every medicine** will be available in a national **web** portal which will be linked to the European medicines portal. It will contain various documents, such as: public assessment reports and their summaries, information leaflets and SPCs, summaries of risk management plans, list of medicines under additional monitoring, and information on how to report suspected ADRs to the national authorities.

Furthermore, whenever deemed appropriate by the PRAC (Pharmacovigilance Risk Assessment Committee), public auditions will be conducted on safety issues in which not only the health professionals, the industry and the authorities, but also the public, will take part.

Still with the objective in mind to improve transparency and communication with health professionals and patients, medicines subjected to additional monitoring will be highlighted by a black label and a relevant, standardised explanatory statement in the SPC and information leaflet. This will provide the medicine's special monitoring conditions with a framework, and will promote reporting of suspected adverse reactions that may appear at any time during its use.

Additionally, active participation of health professionals and patients in the national pharmacovigilance systems will be explicitly requested by means of a standardised text included in the SPC and information leaflet, respectively. This statement will appeal to reports of suspected adverse reactions as a way to contribute towards our knowledge of the safety profile of medicinal products.

This novel legislative package will hopefully make a major contribution towards the protection of the public's health through enhanced resource and medicines safety information management.

Ana Gonçalves, Ana Araújo

References:

1. Lazarou J et al. Incidence of Adverse Drug Reactions in Hospitalized Patients. JAMA. 1998 Apr 15;279(15):1200-5.
2. Directive 2012/84/EU of the European Parliament.
3. Regulation (EU) N. 1235/2010 of the European Parliament.

Medicinal Products and Food Supplements: diverse assessment and monitoring procedures

Following several reports to Infarmed of undesirable effects of food supplements (also known as nutritional or dietary supplements), it became clear that further relevant information on this type of products could be of great usefulness.

The safety of food supplements is **outside** the scope of **pharmacovigilance**. The authority regulating and overseeing those products is the Ministry of Agriculture, Sea, Environment and Spatial Planning Policies Planning Office (GPP – Gabinete de Planeamento e Políticas). According to the GPP site, which can be accessed at **http://www.gpp.pt/RegAlimentar/SupAlimentares.html** (in Portuguese), food supplements are foodstuffs which are presented in pre-packaged unit doses to be taken daily by oral route only. They can be used to complement and/or supplement a normal dietary regime, and they are concentrated sources of nutritional substances, either in isolation or in association.

No curative or preventive properties regarding illnesses or their symptoms in humans can be ascribed to food supplements, since those properties are within the realm of medicinal products proper (Portuguese Law Decree 176/2006). Dietary supplements cannot likewise mention or suggest such properties in their labels and marketing tools. They are under the umbrella of the general legislation on foodstuffs in what pertains to health and nutritional claims. Their labels cannot contain false, wrongful or ambiguous statements. A list of authorised claims for these products is awaiting publication by the EFSA (European Food Safety Authority).

It can sometimes be **difficult to determine** whether a given substance is a medicinal or a nutritional product. In those cases, the GPP requests advice from Infarmed. For instance, lithium salts, no matter their quantity, are now always considered to be medicinal products. On the other hand, dose can also be a determinant factor; e.g, if the melatonin content of a product is lower than 2 mg, it can qualify as a food supplement. However, melatonin in such small doses may not have any proven effectiveness, which would be an issue had it been classified as a medicinal product.

Food supplements are viewed as foodstuffs and, contrarily to medicines, safety, effectiveness and quality studies and assessments are not required pending market introduction. When a manufacturer or a trader intends to place a food supplement in the market, they need only notify the GPP by sending in a copy of the product's label. The GPP is not supposed to assess the product, rather it is the economic agent who is in charge of ensuring the product's safety and quality, as well as other legal requirements such as labeling.

Information for consumers may be included in a leaflet contained inside the product's packaging, but all the labeling information must be visible on the outside packaging and be in accordance with the corresponding relevant legal provisions. In order to avoid mistaking them for medicinal products, it is recommended that the **leaflets of food supplements** be called "information for consumers" rather than "information leaflet".

In short, medicinal products and dietary supplements differ significantly. The latter, though presented as pre-packaged unit doses to be taken on a daily basis, can only be administered orally, may not contain any substances with pharmacological or other effects that may be construed as medicinal, and may not make statements of preventive or curative properties, nor contain pictures suggesting them. Food supplements are a complement or a supplement to a normal diet, not products aiming to alleviate pathological symptoms. Accordingly, their marketing procedures are not dependent on assessment and effectiveness, safety and quality studies, neither are they under the oversight of a specific national vigilance system.

Any undesirable effects occurring with food supplements should therefore not be sent into the national pharmacovigilance system. Instead they should be reported directly by phone, fax or e-mail to the GPP.

For further information: www.gpp.pt

Fátima Bragança

THE BOLETIM'S ONLINE INDEX

In English (from 2004):
http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/PHARMACOVIGILANCE_BULLETIN

MEDICINES

MISCELLANEOUS