boletim de FARMACOVIGILÂNCIA

Ministério da Saúde

infarmed
Instituto Nacional da Farmácia e do Medicamento

VOLUME 11
NUMBER 1
1ST QUARTER 2007

Editor's Notes

The Boletim has been online for some time now. If you are looking for an article on a given medicine or specific subject published in the past, or if you just want to look up the Boletim on the net, you are invited to go to:

http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH

and click on

Publications

There you will find the Boletim's issues published since 2003 in pdf format. All the issues since 1998 are available in Portuguese only at:

http://www.infarmed.pt/portal/page/portal/INFARMED/PUBLICACOES/TEMATICOS/BOLETIM_FARMACOVIGILANCIA

Soon a medicine-by-medicine and subject-by-subject primary index referring back to all articles published since 2000 will also be available at the same link (in Portuguese only).

Botulinum Toxin – risk of ADRs caused by toxin diffusion outside the site of administration

Botulinum toxin is a protein produced by *Clostridium botulinum*, a Gram-positive anaerobic bacterium which causes botulism. It synthesises 7 different toxin serotypes known by the letters from A to G. These toxins block the release of neurotransmitters at cholinergic nerve endings, especially acetylcholine (which causes muscular contraction, and salivary and sweat secretion). **Type A and B neurotoxins** have been used in clinical practice, and there currently are four medicinal products approved in the EU which contain botulinum toxin: Botox®, Vistabel®, Dysport® (type A), and Neurobloc® (type B). Approved indications vary according to product and country, and include: **spastic torticollis, hemifacial spasm, cerebral palsy in children, blepharospasm, arm and leg spasticity in adults, hyperhydrosis, and cosmetic use**. The neurotoxin is injected locally into the muscles, or intradermally in the case of axillary hyperhydrosis. It causes a partial and reversible nerve block of the muscles or sweat glands injected.

Serious adverse reactions, including fatal cases, have been reported in association with **diffusion of the toxin out of the site of administration**, namely marked and prolonged muscle weakness. **Marked muscle weakness** is in fact in most cases related to neurotoxin diffusion, the risk being higher in case of incorrect administration or overdose. Secondary to neck muscle weakness, **dysphagia and aspiration** have been described. Reactions caused by toxin diffusion are more frequent in patients with dystonia or spasticity. Identified **risk groups** are children, elderly patients with compromised respiratory function, and patients with clinical evidence of neuromuscular transmission disorders.

After reviewing the known data on the botulinum toxins available in the market, it was concluded that information on these medicinal products should be updated. The objective is indeed to raise health professionals' and patients' awareness of the possibility of ADRs away from the site of administration, namely marked muscle weakness, dysphagia, aspiration/aspiration pneumonia, and/or significant weakness. In order to avoid those untoward reactions, **special caution** should be exerted when giving botulinum toxin to patients with neurological disorders, including deglutition problems, since they are at higher risk for the above ADRs. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

Botulinum toxin must **always be used under the supervision of a specialist physician**, for the approved indications only, and following the written recommendations, especially in what concerns dose and administration. Immediate medical help should be sought in case of difficulty swallowing, talking or breathing, following the administration of botulinum toxin.

Madalena Arriegas

How can I report an adverse reaction?

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

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

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Tramal® solution – mind the forms of presentation

Tramal® oral drops solution, whose active ingredient is tramadol chlorhydrate, is an analgesic agent indicated for moderate to intense pain. It is authorised in Portugal in the dose of **100 mg/ml**, and is presented as packages each containing one 10 ml, 30 ml, or 100 ml vial.

Ten-millilitre vials contain a **dropper** that allows for drops to be counted one by one, whereas **30 ml and 100 ml vials** come as a spray dosage device which releases a quantity of solution with **each puff** that **corresponds to 5 drops**. In order to avoid mix-ups between the two different forms of presentation and administration (drops versus puffs), special attention should be paid to the instructions of use included in the package and package insert. For the medicine to be correctly given, it must be ensured that the prescription is adapted to the type of presentation, either dropper or spray.

Paula Roque

Ceftriaxone in new-borns - EMEA benefit-risk evaluation

Ceftriaxone is a beta-lactamic antibiotic, more specifically a third-generation cephalosporin which has a bactericidal effect on a series of Gram-positive and Gram-negative bacteria by inhibiting their cell wall mucopeptides. When given parenterally, ceftriaxone penetrates almost every body tissue, including the cerebrospinal fluid. Ceftriaxone's effectiveness in various types of clinically relevant infections has been established by over ten years of therapeutic use.

Regarding new-borns, most studies in this age group have used a dose of 50 mg/kg per day, and there are limited data on the use of higher doses for conditions other than meningitis. Within the first few weeks of life, ceftriaxone elimination capacity is altered, although the exact moment that change occurs has not been determined. In spite of limited and relatively recent data, no scientific evidence has been found that makes it necessary to change the currently recommended doses, which were authorised years ago and have not shown any associated problems in the various member states. The proposed **dosing interval** of **20-50-80 mg/kg per day** is in line with long-term clinical experience and supported by recommendations from academia.

However, ceftriaxone is **contraindicated** in **hyperbillirubinaemic and premature new-borns**, since *in vitro* studies have demonstrated that it can displace billirubin from serum albumin, possibly paving the way for billirubin encephalopathy. Moreover, ceftriaxone is **contraindicated** in new-borns requiring **concomitant calcium therapy**, due to rare cases of serious, sometimes fatal ADRs that have occurred in both premature and term babies. These new-borns had been treated with IV ceftriaxone and calcium, and some had received ceftriaxone and calcium at different times and through different IV drips. In premature babies who died, ceftriaxone-calcium salt precipitates were observed in their lungs and kidneys. The reduced blood volume of new-borns accounts for a high risk of precipitation. Furthermore, the drug's half-life is longer than in adults.

The scientific background and rationale for the European Commission's Decision can be accessed at:

http://ec.europa.eu/enterprise/pharmaceuticals/register/2006/2006082112129/anx_12129_pt.pdf

Alexandra Pêgo

Baraclude® – resistant strain of HIV in a patient coinfected with hepatitis B virus

The MA Holder of Baraclude® (entecavir) has reported a case to EMEA of selection of an HIV strain containing the M184V mutation during therapy with entecavir in a patient coinfected with HIV/HBV who was not receiving HAART concomitantly. The M184V mutation confers a high level of resistance to lamivudine and emtricitabine.

Baraclude® has not been evaluated in patients with HIV/HBV coinfection who are not simultaneously receiving effective treatment for HIV. When considering therapy with Baraclude® in a patient coinfected with HIV/HBV who is not receiving HAART, he or she should be informed about the risk of HIV acquiring resistance to antiretrovirals. Until new data become available, the use of Baraclude® in this clinical context should only be an option under exceptional circumstances.

Madalena Arriegas

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

Systemic Nephrogenic Fibrosis associated with Gadolinium -containing contrast agents used in magnetic resonance imaging

See Boletim de Farmacovigilância Vol. 10 n. 3 (3rd quarter 2006) page 4.

Based on available data, the Committee on Human Medicinal Products (CHMP), recommends:

- Omniscan® (gadodiamide) should not be used in patients with severe renal failure [i.e. GFR (glomerular filtration rate) <30ml/min/1.73m^2] or in patients undergoing or awaiting a liver transplant.
- Due to renal function immaturity in new-borns (i.e. <4 weeks) and in children up to 1 year, gadodiamide should only be used in these age groups following careful consideration.
- In patients with severe renal failure (i.e. GFR <30ml/min/1.73m^2) the use of other gadolinium-containing contrast agents should be carefully pondered.

Alexandra Pêgo

Volume 9A now published - pharmacovigilance for medicinal products for human use

The World Health Organization defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or of any other drug-related problem.

Within the European Union, norms providing guidance for pharmacovigilance activities are compiled in **EudraLex Volume 9**. Following on EU Regulation 726/2004 and Directive 2001/83/CE, Volume 9 has been extensively reviewed and updated, and split into two volumes:

- Volume 9B, relating to pharmacovigilance of veterinary medicines, has not yet been finished, therefore Volume 9 Part II (June 2004) is still in force.
- Volume 9A, pertaining to pharmacovigilance of medicinal products for human use, was published by the European Commission in January 2007, following consultation in 2005 and 2006 and a close working connection between the member states and the EMEA; it is to be enforced immediately.

Volume 9A brings together general guidelines on requirements, procedures and obligations of the various participants, and includes the international consensus conclusions reached at the **International Conference for Harmonisation (ICH)**. Its goal is to ensure that information exchange on ADR suspicions obtained by the member states' and the MA Holders' pharmacovigilance systems is effective, that the parties involved comply with their obligations and are made accountable, that duplication is avoided, and that confidentiality and the quality of the systems and of the data ensured.

Norms included in Volume 9 A apply to **every medicinal product for human use** that is **authorised within the EU**, irrespective of their authorisation procedure. **Homoeopathic medicines** are an exception in that they are subjected to a simplified recording procedure.

The new EudraLex Volume 9 (January 2007) - ***Guidelines on Pharmacovigilance for Medicinal Products for Human Use*** – can be accessed on the INFARMED website at:

http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_NOVIDADES/DETALHE_NOVIDADE?itemid=451894

Catarina Martins

Pharmacovigilance in clinical trials

Protecting participants in clinical trials involves an integrated techical-scientific and ethical assessment system, to secure the individual's dignity and interests in relation to those of society and science, and to monitor any risks emerging from participation in experimental studies.

Right from the initial steps of clinical development, the need to ensure the safety of participants in clinical trials and of prospective users of the medicinal product calls for close monitoring of ADRs through effective detection, assessment and understanding of adverse reactions and drug interactions. In Portugal, pharmacovigilance obligations in clinical trials are harmonised with European regulations by means of **Law n. 46/2004 (19th August)**, and include **researchers**, **promoters**, the **Clinical Research Ethics Committee (CEIC)**, and **INFARMED**. They are additionally complemented by the European Commission guidelines included in **Chapter II of EudraLex Volume 10 – Clinical Trials**.

Of suspected serious ADRs sent through by the researchers to the promoters, the ones that are unexpected (**SUSAR**) are reported in expedited form to INFARMED, the CEIC, and remaining researchers. INFARMED keeps a record of those SUSARs on a national database (SVIG), which communicates with the clinical trials module of the European EudraVigilance clinical trial database. Risks are thus monitored in collaboration with the remaining EU competent authorities.

The trial's promoters send to INFARMED and to the CEIC an annual safety report (listing all suspected serious ADRs), as well as a report on the safety of use of the experimental medicine and of participation in the clinical trial, so that all safety data meeting seriousness criteria, irrespective of how expectable they are, may be available for assessment.

The current adverse experimental drug reactions monitoring system has a clear definition of accountability of every participant in clinical trials, and ensures that information on the safety profiles of experimental medicines is shared. This has boosted trust in clinical trial safety and in the introduction of new medicinal products in the marketplace.

Catarina Martins

You can contact us by e-mail for any queries concerning pharmacovigilance in clinical trials:
farmacovigilancia.ec@infarmed.pt

Key points in drug interactions... the patient with hyperlipidaemia

- In a patient who is on statins and/or fibrates, **myalgia**, muscle cramps, or muscle weakness, should raise a suspicion of rhabdomyolysis – **serum creatine-phosphokinase** should be assessed.
- Patients treated with a **statin + fibrate** association are at greater risk of rhabdomyolysis.
- **Ezitimibe** increases the frequency of **statin-associated muscle ADRs**.
- In patients on **chronic therapy with an enzyme inducer or inhibitor (e.g., anticonvulsants, antiretrovirals, rifampin)**, pravastatin has a relatively low risk of interactions, since it is hardly metabolised by the cytochrome P450 system. Enzyme inducers tend to **decrease the efficacy of statins**. On the other hand, when the former are discontinued, the risk of ADRs (especially muscle ADRs) associated with the latter is increased. The effects from introducing or withdrawing an enzyme inducer take approximately **2 to 3 weeks** to become openly manifest.
- **Fibrates** lower blood sugar levels; special care should be taken in patients simultaneously receiving oral antidiabetic agents, due to the risk of **hypoglycaemia**.

The following promote **hyperlipidaemia**:

- androgens, tamoxifen
- oral oestroprogestative contraceptives, hormonal menopausal replacement therapy
- corticosteroids
- immunosuppressants
- HIV protease inhibitors

Adapted from La Revue Prescrire

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)

Medicinal Plants from A to Z
described adverse reactions

- **Comfrey** *(Symphytum officinale)*
  - Liver toxicity, possibly including carcinogenesis and veno-occlusive disease (ingested comfrey)
  - Pancreatic carcinogenesis? (studies in animals)

Nº of Medline citations: 9
Main uses described: topically for bruises, burns, and sprains

- **Feverfew** *(Chrysanthemum parthenium)*
  - withdrawal-like syndrome after several years of use (rebound symptoms, sleep disorders, muscle and joint stiffness)
  - tachycardia
  - mouth mucosal ulcers
  - dermatitis
  - possibly increased effect of anticoagulants
  - emenagogue effect; must not be used by pregnant or lactating women, or small children

Nº of Medline citations: 35
Main uses described: antipyrexial; relief of migraine, menstrual aches, arthritis, dermatitis; asthma

- **Danshen** *(Salvia miltiorrhiza)*
  - coagulation abnormalities
  - potentiation of warfarin

N Nº of Medline citations: 13
Main uses described: vasodilator; menstrual irregularities, symptoms associated with hepatitis, insomnia

- **Dandelion** *(Taraxacum officinale)*
  - contact dermatitis
  - epigastralgia
  - potential toxicity associated with high potassium and magnesium content (high doses)
  - potentiation of anticoagulant effect

Nº of Medline citations: 5
Main uses described: diuretic, appetite stimulant, blood sugar level lowering; dyspepsia, hepato-billiary conditions

NB 1:
The main uses are those most frequently described in the literature irrespective of evidence of effectiveness. Their presentation herein is factual and does not mean that the therapeutical uses mentioned are approved or implicitly condoned in any way by this publication.

NB 2:
The number of Medline citations is merely intended to give an idea of the magnitude of publications on adverse reactions associated with the product. Key-words used: "human side effects", "toxicity in humans", "adverse reactions".