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Medication Errors

Medication errors as a possible cause of adverse drug reactions (ADRs) are hard to detect and quantify given their intrinsic characteristics. ***"Medication errors" are frequently mistaken for "prescription errors", which are not at all synonymous.*** *In fact, medication errors have various causes and agents, as well as diverse manifestations, whether occurring in hospital or in the ambulatory setting.*

The following are examples of medication errors:

- *Change in dose or switching of medicines by the patients themselves or by their caregivers*
- *Dispensing error at the pharmacist's*
- *Prescription error*
- *Change in route of administration*

Some examples of predisposing factors:

- *Very similar* ***trademark names***
- ***Tablets*** *with identical colours and shapes*
- ***Packages*** *with identical colours and shapes*
- ***Blisters*** *without the medicine's name on the underside of each individual tablet wrapping; sometimes the name can no longer be read after a few blisters have been emptied*
- ***Ampoules for parentheral use*** *with only very minor labelling differences. This is a potentially very serious problem, mainly in the hospital setting, in casualty, intensive care or surgical units, where speed of intervention and pressure from severe conditions are both often at peak levels*
- *Ampoules or tablets stored away in great quantities inside unremarkable drawers or cupboards, mainly in the hospital setting*
- *Poor information given to the patient*
- *Insufficiently trained health professionals*
- *Counterfeited medicines*
- *Electronic medicines sale systems in which health professionals take no part (e.g.: via the internet)*
- *Parallel import of medicines*

Those errors do occur and may originate serious ADRs (including fatal cases) which are mostly avoidable. Errors occurring due to human failure are the most difficult to control, still a great number of the above-mentioned situations should not be tolerated so much so that human lives may be at stake. Hence the question: where and how should one intervene? Awareness is undoubtedly the first step to be taken, followed by informing the consumers, training the health professionals and the pharmaceutical industry, and resorting to the regulatory authorities as law-making bodies. These are the main players in this process, and controlling this public health problem is fully dependent on their contribution.

Regina Carmona

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

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

OR

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Melagatran e Ximelagatran: voluntary withdrawal for safety reasons

Melagatran AstraZeneca® 3mg/0.3ml (parentheral solution of melagatran in preloaded syringes) and Exanta® 24 mg (film-coated ximelagatran tablets) are both anticoagulant drugs indicated for preventing venous thromboembolic disease in patients submitted to elective hip or knee replacement surgery, for up to 11 days. A **serious liver damage adverse event** has recently been reported in a patient who was taking part in a clinical trial on the use of ximelagatran for long-term prophylaxis (up to 35 days) of venous thromboembolism in patients submitted to orthopaedic surgery. Considering that ximelagatran may indeed have to be used for periods longer than 11 days, and that there are therapeutic alternatives for anticoagulation in orthopaedic surgery, the MA holder has decided, as a precautionary measure, to withdraw all marketed batches of this medicine. Ongoing clinical trials have been terminated, and physicians have received information on how to substitute these patients' therapy.

Isotretinoin: Carrying out the Pregnancy Prevention Programme

Isotretinoin is a vitamin A derived, retinoid compound which is used for systemic treatment of severe acne, as second line therapy when systemic antibacterial and topical therapy have both failed.

Similarly to other retinoids, isotretinoin is teratogenic, and is contraindicated in pregnancy, breastfeeding, as well as in women who have a potential to become pregnant whether or not they are sexually active (see also the Boletim's issue 2nd quarter 2005). Women of childbearing age can only receive treatment with isotretinoin provided the **Pregnancy Prevention Programme** is applied. This aims to ensure, by means of effective contraceptive measures, that no woman of childbearing age will be pregnant when treatment is started, nor will they become pregnant throughout its duration and up to as late as one month after therapy has been discontinued.

Isotretinoin should only be prescribed by physicians experienced in the use of systemic retinoids, and who are aware of all the risks associated with them and of all the monitoring requirements. Serious adverse reactions to isotretinoin are recorded in the Portuguese National Pharmacovigilance System database, namely cases of **psychiatric reactions** (including death), and cases of exposure during pregnancy with **spontaneous abortion and congenital malformations.**

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)

Telithromycin: liver toxicity and visual changes

Telithromycin (Ketek®) is a semi-synthetic ketolide antibiotic, closely related to the macrolides, and indicated in the treatment of respiratory infections.

As part of this medicine's continuing safety monitoring, serious cases of **acute hepatitis** have been reported to EMEA, including liver failure and fatal cases. Three of these cases have recently been described in an article published in Annals of Internal Medicine online (20th January 2006). As a precaution, EMEA has asked the MA holder to alter the drug's SPC in order to reinforce the warning on liver changes. This precautionary measure will be dependent on the risk-benefit assessment being carried out within the scope of the MA renewal process. While data are still being analysed, prescribers should use telithromycin **with caution in patients with liver function changes.** You can access EMEA's information on this subject online at: http://www.emea.eu.int/pdfs/human/press/pr/2938606en.pdf

Telithromycin-associated adverse reactions are also recorded in the Portuguese National Pharmacovigilance System database, though none is to do with liver function changes. They consist mostly of cases of **visual changes** (blurred vision, diplopia, and temporary loss of vision). Although these reactions are **already described** in the medicine's SPC, patients who will be **driving or using machinery** should be warned that this type of adverse effects may occur immediately after the first dose of medicine is taken.

Ciprofloxacin, Enoxacin, Norfloxacin and Pefloxacin: inhibition of CYP1A2

Following a safety assessment of the risk of interaction between medicines metabolised by the CYP1A2 enzyme, and taking into account the studies published[1,2], the European Pharmacovigilance Working Party has concluded that the inhibiting effect of some quinolones on CYP1A2 may cause a clinically significant rise in the serum concentrations of other concomitant medicines which are metabolised by the same isoenzyme, such as theophylline, clozapine, tacrine, ropinirol, and tizanidine. The following paragraph has been approved to be included in the SPC and to be adapted to the information leaflets of the medicines containing ciprofloxacin, enoxacin, norfloxacin and pefloxacin:

Section 4.5 – DRUG INTERACTIONS AND OTHER FORMS OF INTERACTION

Ciprofloxacin/enoxacin/norfloxacin/pefloxacin inhibits CYP1A2, which may cause an increase in the **serum concentrations** of other concomitant substances also metabolised by this enzyme **(e.g.: theophylline, clozapine, tacrine, ropinirol, tizanidine).** Patients taking these drugs concomitantly with ciprofloxacin/enoxacin/norfloxacin/pefloxacin should be carefully monitored for clinical signs of overdose; **serum monitoring, especially in the case of theophylline,** may become necessary.

Alexandra Pêgo

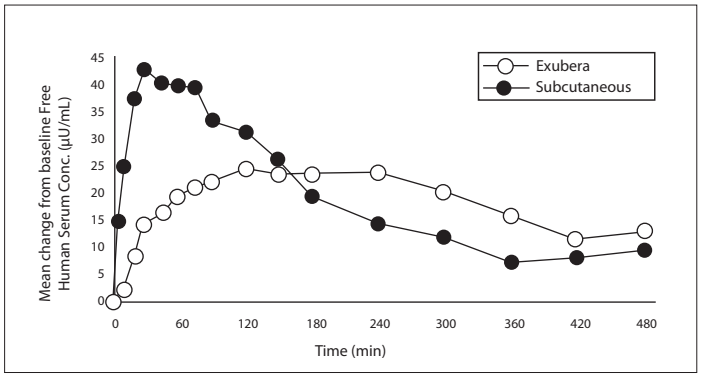
1 Raaska K et al.. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia. Eur J Clin Pharmacol (2000)56:585-589.

2 Fuhr U et al.. Inhibitory potency of quinolone antibacterial agents against cytochrome P4501A2 activity in vivo and in vitro. Antimicrob Agents Chemother(1992)36:942-948.

Inhaled Insulin approved by EMEA

Last January the European Medicines Agency (EMEA) approved Exubera®, the very first inhaled insulin [1]. The US Food and Drug Administration (FDA) also approved this medicine later the same month[2]. This is the first alternative to subcutaneous insulin since it was first discovered in the 1920s, and it is poised to become a reality for thousands of insulin-dependent diabetics in Portugal.

This product has resulted from collaborative work by two pharmaceutical companies aiming for a common goal to create a non-invasive device for the administration of insulin[3]. Out of various alternatives to subcutaneous injection researched within the past few years (patches, intraabdominal pumps, oral gastroresistant preparations), inhaled insulin was the one which has shown the most promising results. Clinical trials have demonstrated higher and faster peak bioavailability through this route of administration comparatively to regular acting insulin given subcutaneously[4].



Mean changes in serum concentration of free insulin (µU/mL) in type 2 diabetic patients after administration of isolated doses of 6 mg of inhaled insulin and regular subcutaneous insulin (18 U)[4].

Norwood et al.[5] have compared the effects of inhaled insulin to those of regular acting insulin in 226 type 1 diabetics, aged 26 to 65 years, for 12 weeks. Glycated haemoglobin levels (HbA1c), which reflect average blood glucose levels within the past 2 months, went down from 7.5% to 7.1% with inhaled insulin, and from 7.5% to 7.0% with regular insulin. A mean 5.5. and 6.8 hypoglycaemic episodes per month, respectively, were recorded. Episodes of severe hypoglycaemia occurred in 9 vs. 17 patients. These figures do not stray from what would be expected from comparing rapid acting to regular acting insulin (both given subcutaneously).

Two weeks into the trial, FEV1 decreased 0.070 L, and DLco went down 0.973 mL/minute/mmHg in the group of patients treated with inhaled insulin. Cough was reported in 31% in this group of patients vs. 8% in the patient group receiving regular subcutaneous insulin. **Cough** occurred within **a few minutes** following administration and was usually mild.

Antibody levels increased after 12 weeks in the patients receiving inhaled insulin. This does not seem to alter the action of inhaled insulin, nor to cause any immunologic adverse reactions, and is apparently similar to antibody production reported on administration of subcutaneous insulin. However, consistent evidence of decreasing DLco has raised concerns that **subgroups of diabetics with respiratory conditions may be at risk of adverse reactions.** Thus, patients currently presenting with asthma, chronic obstructive airways disease (COAD), or who are smokers (or who quit within the last six months) should not use these preparations. In fact, although changes to the alveolar-capillary interface are not characteristic, and there are no apparently significant changes in absorption, there is an increased risk of adverse reactions.

Neither this nor other studies have been able to ascertain the risk of development of pulmonary interstitial disease in subgroups of diabetics with concomitant conditions. Hayes et al. [6] have been the first to study subjective data from 119 patients undergoing therapy with inhaled insulin versus subcutaneous insulin. Patients using inhaled insulin showed **greater satisfaction.** Patients said that inhaled insulin could make travelling easier, reduce embarrassment, and decrease reluctance to use insulin before meals. Given the evidence that inhaled insulin decreases blood glucose levels in the same way that subcutaneous insulin does, patients' objective and subjective satisfaction therefore becomes the main reason for marketing this product. This may boost therapeutic responses and decrease the impact of insulin therapy on the lives of diabetic patients.

Nevertheless, some very relevant issues still under assessment may possibly limit the range of patients able to take this treatment. Those issues include: **complex handling and maintenance** of the drug administration device, which may adversely influence the quality of the insulin administered and raise problems for elderly patients; **the dose cannot be linearly adjusted unit by unit,** which may be a disadvantage for diabetics with intensive and flexible regimes; and there needs to be **an alternative conventional therapeutic regime** at hand whenever there is a change in the patient's respiratory function, especially during seasonal respiratory disorders.

In the USA, the prescription of inhaled insulin will have to be accompanied by a Medication Guide. Pharmacists are indeed required to hand out Medication Guides for medicines for which following accurately the instructions of use is indispensable for the treatment to be effective[2]. In Europe, the introduction of this medicine will go along with specialised information approved by EMEA (and INFARMED in Portugal). The Medication Guide and the specialised information accompanying the medicine contain a good deal of useful information for the patient, but do not make it unnecessary to consult with the health professionals who prescribe and dispense the product.

Once this medicine is introduced into our market, any adverse reactions should be reported to the National Pharmacovigilance System. Spontaneous reporting is essential if we are to continuously monitor the safety of new drugs.

Maria Susana Gonçalves

[1] Information available at http://pharmacos.eudra.org/http://pharmacos.eudra.org/F2/register/2006/2006012410856/decision_exubera_aut_special_mah_en.pdf accessed on 06-03-2006.

[2] Information available at http://www.fda.gov (http://www.fda.gov/bbs/topics/news/2006/NEW01304.html) accessed on 06-03-2006.

[3] http://www.drugdevelopment-technology.com/projects/exubera/accessed on 06-03-2006.

[4] FDA-approved SPC. Available at: http://www.fda.gov/cder/foi/label/2006/021868lbl.pdf accessed on 06-03-2006.

[5] Norwood P, Dumas R, England RD, Riese RJ, Teeter JG; Exubera Phase 3 Study Group. Inhaled insulin (Exubera) achieves tight glycemic control and is well tolerated in patients with type I diabetes. Program and abstracts of the European Association for the Study of Diabetes 41st Annual Meeting; September 12-15, 2005; Athens, Greece. Abstract 73.

[6] Hayes RP, Rosenstock J, Muchmore DB, Stump TE, Silverman B. Patient reported outcomes (PROs) using the Lilly/Alkermes Inhaled Insulin System versus injectable insulin in patients with type 1 diabetes (T1D). Program and abstracts of the European Association for the Study of Diabetes 41st Annual Meeting; September 12-15, 2005; Athens, Greece. Abstract 815.

Leukotriene receptor antagonists - safety profile

Therapeutic indications

Mild to moderate, persistent asthma, as additional therapy.
Prophylaxis of asthma whose dominant component is exercise-induced bronchoconstriction.

Contraindications

- Hypersensitivity to active ingredient or to any of the excipients.
- **Zafirlukast** should not be used in patients with **liver failure,** including cirrhosis, neither should it be used in children **younger than 12 years**.

Special precautions of use

- **Should not** be used for the treatment of **acute asthma attacks.**
- **Should not** be used in **replacement** for corticosteroids or inhaled beta agonists.
- Patients who are hypersensitive to aspirin or to other anti-inflammatory agents should still avoid these drugs even when taking leukotriene receptor antagonists.
- **Serum liver enzymes** should be monitored before and during treatment with **zafirlukast**; the latter should be discontinued if there are any clinical symptoms or signs suggestive of liver impairment.

Drug interactions

- **Montelukast** is metabolised by cytochrome P450 3A4. Caution should be exerted when co-administering it, especially in children, with CYP 3A4 inducers, such as **phenytoin, phenobarbitone and rifampin.** Montelukast is also a CYP 2C8 inhibitor, which calls for caution when co-administering it with drugs metabolised through that route, such as **paclitaxel, rosiglitazone, and rapaglinide.**
- **Zafirlukast** may interact with **aspirin** and with **warfarin,** increasing their concentrations. Monitoring of prothrombin time is therefore recommended whenever it is administered simultaneously with warfarin. Zafirlukast may interact with **erythromycin, theophylline, and terfenadine,** lowering their serum levels.

Pregnancy and Breastfeeding

- These drugs cross the placental barrier and are excreted in human breast milk. Since there are no studies demonstrating their safety for the foetus and breastfed babies, they should not be used unless they are considered to be strictly necessary (category C for montelukast, CM for zafirlukast).

Undesirable effects

Montelukast

Frequent (> 1/100 and < 1/10)

- **Abdominal pain** (adults).
- **Headache** (adults and children from 6 to14 years).
- **Thirst** (children 2 to 5 years).

Very rare (<1/10,000)

- Weakness, malaise, oedema.
- Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, pruritus, rash, and an isolated case of liver eosinophillic infiltration.
- Dizziness, nightmares, hallucinations, somnolence, insomnia.
- Paraesthesia/hypoaesthesia, irritability, agitation (including aggressive behaviour), nervousness, seizures.
- Arthralgia, myalgia, muscle cramps.
- Diarrhoea, dry mouth, dyspepsia, nausea, vomiting.
- Raised serum liver enzymes, cholestatic hepatitis.
- Increased haemorrhagic tendency, palpitations.
- Churg-Strauss syndrome.

Zafirlukast

Frequent (> 1/100 and < 1/10)

- **Nausea, vomiting, diarrhoea, abdominal pain.**
- **Malaise, insomnia, headaches.**
- **Infections** (mostly of the respiratory tract)

Infrequent

- Oedema, rash, pruritus.
- Increased serum liver enzymes.

Rare (>1/10,000 and <1/1,000)

- Symptomatic hepatitis, hyperbillirubinaemia.
- Arthralgia, myalgia.
- Hypersensitivity reactions, including urticaria and angioedema.
- Coagulation disorders.

Very rare (<1/10,000)

- Liver failure, fulminating hepatitis.
- Agranulocytosis.

Medicinal Plants from A to Z described adverse reactions

• **Balsam of Peru** *(Myroxylon peruiferum)*
- Contact dermatitis

N.º of Medline citations: 36
Main uses described: cough, cosmetics.

• **Burdock** *(Arctium lappa)*
- Hypersensitivity reactions

N.º of Medline citations: 2
Main uses described: colleretic, uricosuric diuretic, anti-inflammatory, wound healing.

• **Purslane** *(Portulaca oleracea)*
- caution in patients with renal stones (risk of stone displacement), and in pregnant women (risk of uterine hyper- or hypomotility)

N.º of Medline citations: 0
Main uses described: diuretic, antidyspeptic, antifungal, antioxydative, nutritional.

• **Vernonia condensata**
- ?

N.º of Medline citations: 0
Main uses described: analgesic, antiulcerous.

• **Plectranthus** *(Plectranthus/Coleus barbatus Andrews)*
- ?

N.º citações Medline: 0
Main uses described: antidyspeptic.

• **Boldus** *(Peumus boldus* Molina*)*
- vomiting (in high doses)

N.º of Medline citations: 0
Main uses described: tonic, antidyspeptic, colleretic, diuretic.

NB 1: The main uses are those most frequently described in the literature irrespective of evidence of effectiveness.

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".