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Editor's Notes

In spite of the prerequisites defined by regulatory authorities for the marketing of medicines, and of all the efforts of research protocols for drug design and effectiveness evaluation, medicines are not rarely withdrawn from the market for safety reasons some time into the phase of widespread clinical use. This is more often due to adverse reactions which had not been previously detected, or whose magnitude or relevance turns out to be more signficant than expected. Furthermore, ADRs may either be ascribed to the drug itself, or to the medicine's excipients, or still to the chemical, physical or biological properties of its pharmaceutical formulation. This is illustrated in the articles in this issue.

Rui Pombal

Rofecoxib
withdrawn

At the 4th and 5th October EMEA Committee for Medicinal Products for Human Use (CHMP) informal meeting in Scheveningen (Netherlands), the EU regulatory authority experts met with the Marketing Authorisation Holder for Vioxx® (rofecoxib). This COX-2-selective non-steroidal anti-inflammatory drug had initially been authorised in the UK in 1999, and later in the remaining EU member states. The MA Holder informed the authorities about the data that had made them **withdraw** this product from the world market on **30 Sep 2004**, namely the results of the ***APPROVe*** clinical trial in patients with intestinal polyposis: an increase in the risk of confirmed thrombotic events (including myocardial infarction and cerebral stroke) compared to placebo, after prolonged use of the drug (longer than 18 months).

The regulatory authorities agreed during the above meeting to review the assessment of long-term data on the cardiovascular safety of all COX-2 inhibitors (rofecoxib, celecoxib, etoricoxib, valdecoxib, and parecoxib).

What do they stand for?!

ADR	Adverse Drug Reaction
CPMP	European Committee of Proprietary Medicinal Products
EMEA	European Medicines Evaluation 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/reaccoes_adversas/fichas_notificacao/index.html

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Portugal em Acção

Modified-Release Oral Formulations

safety problems reported to the National Pharmacovigilance System

During the past two decades, ever more sophisticated pharmaceutical formulations have been developed. This calls for an additional updating effort on the part of health professionals, not only concerning new molecules, but also regarding new ways to make them reach their targets in the human body. These two aspects are interdependent and may both have relevant clinical consequences. The influence of new pharmaceutical formulations, forms and systems of administration on the endogenous action of therapeutical molecules underscores the need for effective post-marketing surveillance. Pharmacovigilance systems must carry out this sort of surveillance. However, for adverse reactions/events to be detected in actual practice those systems are clearly highly dependent on input from health professionals.

For most ADRs reported to the National Pharmacovigilance System (NPS), since it first started operating in 1992, the *suspect* is the drug itself. Reports whose suspect medicines are indeed **excipients** or the **pharmaceutical formulation** are quite rare. Nevertheless, they are particularly important, in that they may just as well change the medicine's risk-benefit ratio, either for one particular patient, or for public health in general.[1]

In this article two safety problems reported to the NPS by health professionals are described. In these cases, the ADRs or adverse events were determined by the oral pharmaceutical formulation, or by its inadequate use.

On Table I two exemplary cases are summarised concerning safety problems with **Modified-Release Oral Formulations (MROFs)**.

In case history 1, an elderly male patient sliced his tablets in order to reduce the dosage. Alfuzosine tablets in OD formulation are made up of three layers containing a total 10 mg of alfuzosine chloride; they are release-controlled and should be swallowed undivided as specified in the SPC and Information Leaflet.

For decades, patients - and health professionals - have been dividing up tablets in order to obtain lower dosages. **With this type of formulation, the opposite occurs: dividing may suddenly release an excessive and potentially toxic dose**.

In case 1, the clinical consequences were in fact adverse reactions already described for alfuzosine, which may have been triggered or amplified by sudden release of the active ingredient. Health professionals and patients should know how to correctly use MROFs in such a way that potentially health damaging events may be prevented. The possibility of dividing up a tablet of an oral formulation varies with the manufacturing technology used, and should be mentioned in the SPC or IL.[2]

As for case history 2, the patient spotted the **tablet's *matrix*** in his faecal matter, which led him to discontinue his therapy. Avoidable anxiety was generated, and he consulted his attending physician to have his medicine switched for another with the same therapeutical indication. The reasons presented for this case of non-compliance were the fact that the patient was persuaded that his "medicine had gone off", or "just wasn't having any effect". Nifedipine in its CR formulation consists of prolonged release tablets so that it may be administered in a relatively constant way by means of a membrane-controlled osmotic pump system. After ingestion, the tablet's biologically inert components remain intact throughout their passage down the gastrointestinal tract, and are finally eliminated in faecal matter under the form of an insoluble capsule. This is detailed in the SPC and is quite explicit in the IL.

	Medicine	Safety/handling problem	Clinical consequences
Case history 1	Alfusozine 10 mg MROF	Patient sliced the tablet into two halves because he was afraid he was taking "such a high dose".	Severe arterial hypotension; uneventful recovery
Case history 2	Nifedipine 30 mg MROF	Detection of the tablet's *matrix* in the patient's faecal matter	Therapy discontinued.

Table I. Two examples of cases reported to the NPS involving Modified-Release Oral Formulations.

Developing MROFs is justified by the clinical goal of increasing **safety, efficacy and compliance** to therapy[3]. These pharmaceutical forms allow for frequency of administration to be reduced, making the dosage regimes more comfortable for patients, which in turn may secure their compliance. Better compliance brings along more accurate therapeutic control and hence greater safety of use.[4] MROFs flatten down plasma level curve ups and downs, thus generating **more stable and continuous pharmacological effects**. This prevents the occurrence of certain adverse reactions which are either related to concentration peaks or to the lack of efficacy of subtherapeutical concentrations.

On the other hand, the disadvantages of MROFs determine a few special precautions with their use. In many cases, MROF **absorption** is altered by food and by the speed of intestinal traffic. In addition, these formulations contain higher quantities of active ingredient (in comparison to immediate-release analogues), and the **loss of integrity** of the active ingredient's modified-release system may entail toxicity problems.

From a technological standpoint, MROFs are diverse according to the mechanism through which the active ingredient is

[1] Uchegbu IF, Florence AT. Adverse drug events related to dosage forms and delivery systems. Drug Saf 1996; 14(1): 39-67.

[2] CPMP/EWP/280/96. Note for Guidance on Modified Release Oral and Trandermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation).

[3] CPMP/EWP/1875/03/Final. Points to Consider on the Clinical Requirements of Modified Release Products Submitted as a Line Extension of an Existing Marketing Authorisation.

[4] Florence AT, Jani Pu. Novel oral drug formulations: their potencial in modeling adverse effects. Drug Saf 1994; 10(3): 233-266.

released, absorbed, and distributed. Frequently, there are broad variations in pharmacokinetic parameters amongst different modified-release formulations of the same active ingredient. Some types of modified-release tablets may be divided to give a "half dose", others however should only be taken strictly undivided. **MROFs may not be crushed, ground or chewed**, in that their modified-release properties may be lost, thus determining a sudden release of the active ingredient with its attending toxicity risks. This problem is especially important in the case of patients who cannot swallow tablets, such as the elderly, or patients with nasogastric tubes.

The use of MROFs should be justified by well-defined clinical benefits when compared to standard immediate-release formulations, the latter being usually much less costly.

Just by looking at the tablet or capsule, or even at the medicine's trademark name, one cannot know for certain the type of pharmaceutical formulation involved. Occasionally, the drug's name may include an acronym (e.g.: XR for ***eXtended Release***; LA for ***Long Acting***; CR for ***Controlled Release***), but its absence does not mean anything by itself. In fact, most MROFs have no such acronyms in their trademark names. This should be checked on the SPC/IL[5], or at the INFARMED site. On the INFOMED database, which can be accessed at **www.infarmed.pt/infomed/inicio.php),** various data can be obtained regarding marketed medicines, and their pharmaceutical formulation can be looked up (Figure 1).

When changing from immediate-release forms to prolonged-release formulations, potential benefits and risks for the patient should be adequately weighed, information on the correct use of the medicine should be conveyed, and benefits anticipated from the change should be ensured. From a therapeutic point of view they are **different medicines,** each with their **specific SPC and IL** clearly stating the peculiarities of each pharmaceutical formulation.

In what concerns **prescribing and dispensing** this type of medicines, special caution is also required. Checking the indication from the prescription and the formulation on dispensing the medicine is crucial for potentially serious errors to be avoided. These recommendations obviously apply to every medicine in general, but they are even more relevant for MROFs, more so when they are Critical Dose Drugs (CDD). The latter are drugs for which a minor change in dosage or concentration will cause a clinically significant alteration in their efficacy or toxicity/safety. Drugs included in this category are usually those which are routinely monitored by blood concentration level measurements (e.g.: carbamazepine, cyclosporin, warfarin). Extremely precise dosages are therefore necessary if one is to obtain the expected therapeutic benefit without any toxic effects.

M Rosário Pereira Rosa

[5] **Centro de Informação do Medicamento e dos Produtos de Saúde - CIMI** (*Centre for Information on medicines and Health Products*) - from 9 am to 6 pm. Green Line - 800 222 444. Ph: 21 798 7373. Fax: 21 798 7316. *Email:* cimi@infarmed.pt

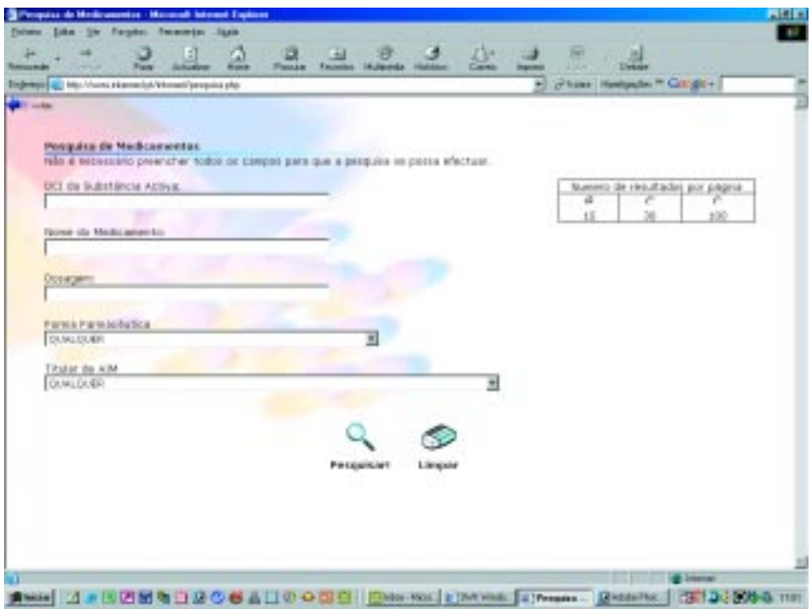

Figure 1. INFOMED database at INFARMED's online site.

Benzalchonium Chloride
rhinitis medicamentosa

Benzalchonium chloride is an **excipient** which is contained in various medicinal products for sterilisation purposes. It may be found in numerous drugs which are administered intranasally, either for a local effect or for systemic effects (osteoporosis, for instance; see Table II).

Benzalchonium chloride present in intranasal medicines has been associated with rhinitis medicamentosa, which is characterised by nasal mucosal oedema and congestion following **prolonged and repeated exposure** to these medicines. Whenever this condition is suspected, **another similar medicine** without this ingredient should be considered. In case there is no alternative, it should be **replaced** by a different pharmaceutical product.

Trademark Name	Pharmaceutical Formulation	Qualitative Composition	Quantitative Composition
Aeromax Nasal®	Nasal spray suspension	Budesonide	1 mg/g
Beconase Inalador Nasal®	Nasal spray suspension	Beclomethasone dipropionate	0.5 mg/g
Bisolspray Nebulicina Adulto®	Nasal spray suspension	Oxymetazoline chlorhydrate	0.5 mg/ml
Calcimon®	Solution for inhalation via nebulisation	Synthetic salmon calcitonin	50 U.I./dose
Calcitar 200®	Nasal spray suspension	Synthetic salmon calcitonin	200 U.I./dose
Calcitonina Wander 200	Solution for inhalation via nebulisation	Synthetic salmon calcitonin	200 U.I./dose
Calsyn 200®	Nasal spray suspension	Synthetic salmon calcitonin	200 U.I./dose
Calsyn Monospray®	Nasal spray suspension	Synthetic salmon calcitonin	100 U.I./dose
Cusicrom Forte Nasal®	Nasal drops solution	Sodium cromoglycate	40 mg/ml
Cusicrom Nasal®	Nasal spray suspension	Sodium cromoglycate	20 mg/ml
Eustidil®	Nasal spray suspension	Fluticasone propionate	50 mg/g
Fenolip®	Solution for inhalation via nebulisation	Sodium cromoglycate	20 mg/ml
Flutaide®	Nasal spray suspension	Fluticasone propionate	0.5 mg/g
Intal®	Suspension for inhalation via nebulisation	Sodium cromoglycate	1 mg/dose
Livostin®	Solution for inhalation via nebulisation	Levocabastine chlorhydrate	0.54 mg/ml
Miacalcic 200 Spray Nasal®	Nasal spray suspension	Synthetic salmon calcitonin	200 U.I./dose
Nasacort®	Nasal spray suspension	Triamcinolone acetate	55 µg/dose
Nasarox®	Nasal drops solution	Oxymetazoline chlorhydrate	0.025 mg/ml
Nasarox®	Solution for inhalation via nebulisation	Oxymetazoline chlorhydrate	0.5 mg/ml
Nasex®	Nasal drops solution	Oxymetazoline chlorhydrate	0.5 mg/ml
Nasex®	Solution for inhalation via nebulisation	Oxymetazoline chlorhydrate	0.5 mg/ml
Nasomet®	Nasal spray suspension	Mometasone furoate	0.5 mg/g
Nasorhinathiol®	Nasal drops solution	Oxymetazoline chlorhydrate	0.5 mg/ml
Neo-Sinefrina®	Nasal wash solution	Phenylephrine chlorhydrate	2.5 mg/ml
Onsudil®	Solution for inhalation via nebulisation	Procaterol chlorhydrate	0.1 mg/ml
Osseocalcina 200®	Nasal spray suspension	Synthetic salmon calcitonin	200 U.I./dose
Otrivina®	Nasal drops solution	Xylometazoline chlorhydrate	1 mg/ml
Otrivina®	Solution for inhalation via nebulisation	Xylometazoline chlorhydrate	1 mg/ml
Rhinolast®	Nasal spray suspension	Azelastine chlorhydrate	1 mg/ml
Rhinospray®	Nasal spray suspension	Tramazoline chlorhydrate	1.18 mg/ml
Rhinospray Plus®	Solution for inhalation via nebulisation	Tramazoline chlorhydrate	1.18 mg/ml
Rinerge®	Solution for inhalation via nebulisation	Oxymetazoline chlorhydrate	0.5 mg/ml
Rinivent®	Nasal spray suspension	Fluticasone propionate	50 mg/g
Rinofluimucil®	Nasal drops solution	Acetylciysteine	10 mg/ml
Robinaz®	Solution for inhalation via nebulisation	Oxymetazoline chlorhydrate + eucaliptol	0.5 mg/ml + 0.075 mg/ml
Rontilona®	Nasal spray suspension	Fluticasone propionate	0.5 mg/g
Rynacrom®	Solution for inhalation via nebulisation	Sodium cromoglycate	20 mg/ml
Suprefact Nasal	Solution for inhalation via nebulisation	Busereline acetate	1.05 mg/ml
Synarel®	Nasal spray suspension	Nafareline acetate	2 mg/ml
Tramazolina Boehringer Ingelheim	Solution for inhalation via nebulisation	Tramazoline chlorhydrate	1.18 mg/ml
Ventilan®	Solution for inhalation via nebulisation	Salbutamol sulphate	5 mg/ml
Vibrocil®	Nasal gel	Dimetindene maleate + phenylephrine	0.25 mg/g + 2.5 mg/g
Vibrocil®	Nasal wash solution	Dimetindene maleate + phenylephrine	0.25 mg/ml + 2.5 mg/ml
Vibrocil®	Solution for inhalation via nebulisation	Dimetindene maleate + phenylephrine	0.25 mg/ml + 2.5 mg/ml
Vibrocil Pediátrico®	Nasal wash solution	Dimetindene maleate + phenylephrine	0.125 mg/g + 1.25 mg/g
VibrocilFen®	Solution for inhalation via nebulisation	Phenylephrine	2.5 mg/ml
VibrocilFen®	Nasal drops solution	Phenylephrine	2.5 mg/ml
VibrocilFen®	Nasal gel	Phenylephrine	2.5 mg/g
Vicks Sinex®	Suspension for inhalation via vaporisation	Oxymetazoline chlorhydrate	0.5 mg/ml
Vicks Vapospray®	Solution for inhalation via nebulisation	Oxymetazoline chlorhydrate	0.5 mg/ml
Xylonas a 0,1%®	Nasal drops solution	Xylometazoline chlorhydrate	1 mg/m

Table II. Medicines for nasal use containing benzalchonium chloride.

A reminder: **Suspected adverse reactions to an excipient should also be reported to INFARMED**.

Paula Roque