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Editor's Notes

A new cycle starts in this Boletim with a special focus on drug interactions. This is a highly relevant topic in pharmacovigilance and medicines risk management, which however often goes underestimated. A typical example given in one of this issue's articles is potentiation of QT interval prolongation with attending risk of serious cardiac arrhythmia.

A background article on drug interactions by Prof Luz Rodrigues certainly is an excellent starting point for this subject. The author gives us a brief rundown on the difficulties posed by pharmacological interactions in the daily practice of prescribing health professionals, as well as on the problem of effectively communicating risk in this field.

How can I report an adverse reaction?

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yellow *(physicians)*, **purple** *(pharmacists)* **or white** *(nurses)*

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Drug Interactions and risk minimisation

The need to administer more than one medicine simultaneously has arisen from the complexity of pathophysiological mechanisms and the attempt to zoom in on the various pathways involved. Moreover, the fact that one patient may be affected by more than one concomitant condition often prompts the prescription of medicines which may in some way interact. This means that administering more than one drug may modify another's pharmacological effect and therefore result in a drug-drug interaction, the probability of which increases as the number of concomitant medicines rises. The result obtained can either be desirable and synergistic, therefore enhancing the therapeutic effect, or undesirable by reducing the therapeutic effect or by causing an adverse reaction.

The elderly are especially vulnerable to the untoward effects of drug interactions, in that they are often prescribed a number of medicines, and partly also because their renal clearance is reduced and their response to medicines may be altered.

Nevertheless, many of the drug interactions described, namely those of a pharmacokinetic nature, have little or no clinical relevance and do not impact on the therapeutic result aimed for. Other interactions, due to their seriousness, can on the other hand justify that the simultaneous use of two drugs be contraindicated or that their doses be adjusted.

Pinpointing the causal link of medicines involved in a suspected interaction in a patient who is receiving several drugs can at times be quite challenging. Two factors can be of assistance in determining the probability of the drugs' role: the **time course** of the reaction and **biological plausibility**.

Interactions reported in the medical literature are sometimes hard to transpose to clinical practice, in that they do not forcibly occur in every patient receiving drugs that have a potential to interact. Broad **interindividual variation** in pharmacokinetic and pharmacodynamic terms is partly at the root of clinical effect variability.

Generally speaking, drug interactions are classified into two classes: **pharmacokinetic interactions** (whenever a drug interferes in another's absorption, distribution, metabolism or elimination processes), and **pharmacodynamic interactions**, when drugs act on the same receptors, sites of action or physiological systems. *In vitro* drug interactions, i.e. precipitation associated with mixing solutions for intravenous administration, are called **pharmaceutical incompatibilities**, and are usually not viewed as drug interactions proper, since they occur before the drug enters the body.

Drugs can interact at various pharmacokinetic stages. This renders ascribing an interaction to a sole mechanism difficult. For instance, amiodarone increases the serum levels of digoxin mainly through renal excretion inhibition, but it also inhibits the hepatobilliary excretion and tissue bonding of the latter, apart from increasing its absorption.

In a pharmacodynamic interaction the drug's kinetics is not altered, but the effect of one drug is changed by the other. Aminoglycosides, for example, potentiate the neuromuscular blocking effect of succinylcholine or of a non-depolarising muscle relaxant.

It is often seen that an interaction observed with a medicine is **extrapolated** to others of the same pharmacotherapeutic class. Should the interaction involve **pharmacodynamic mechanisms**, then it is acceptable and possibly relevant to make an extrapolation, but the same does not apply to pharmacokinetic interactions. H_2 histamine receptor antagonists, for example, have similar effects ▶

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as far as reducing acid gastric secretion is concerned. However, pharmacokinetic interactions with propranolol are frequent for cimetidine (a CYP inhibitor) but rare for the others.

Sources of information

It is not easy to clinically manage all possible drug interactions and their clinical significance. Several computer-based systems and quick reference guides have been published to help practitioners. Their use contributes towards reducing pharmacological prescription errors. However, a host of factors hinder the effectiveness of access to these data sources, rendering their actual use in healthcare rather infrequent. This type of physician behaviour is due to reasons such as the fact that their use comes in the way of the efficiency of daily clinical practice. Furthermore, an excessive proliferation of warnings on interactions of dubious or even null significance is not of any help either.

A comparative analysis of four different sources of information – the British National Formulary, the French Vidal's Interactions médicamenteuses, and the US Drug Interaction Facts and Micromedex Drug–Reax System, shows that differing systems are used to describe drug interactions of relevance.

The **British National Formulary** uses a highlighting system for potentially dangerous drug associations, which should either be altogether avoided, or used with caution and appropriate monitoring.

Vidal's Interactions médicamenteuses uses four seriousness levels to which recommendations for clinical practice are attached: contraindication (absolute contraindication), avoid (relative contraindication), caution (drugs may be associated provided recommendations are heeded), and ponder (no specific recommendation).

Drug Interaction Facts and **Micromedex Drug–Reax System** classify interaction seriousness into three classes – major, moderate, and minor – but describe the degree of supporting evidence in different ways: established, probable, suspected, possible, and unlikely, in the case of the former, excellent, good, fair, poor, and unlikely, in the latter. Based on this, Drug Interaction Facts further ascribes a level of 1 to 5 to describe interaction relevance.

Differences among these four sources are significant. An analysis of interactions classified as major for 50 medicines in any one of the four publications, shows that 14% to 44% of the interactions described in one of the sources are not mentioned in the others. For instance, 80 interactions classified as dangerous and 18 tagged to be avoided or contraindicated in the British National Formulary fail to be mentioned in any of the other three sources. Inclusion and seriousness criteria therefore lack consistency from one source to another.

These discrepancies may be explained by several factors, namely inclusion criteria, inclusion or exclusion of differing sources of evidence (e.g., articles in different languages, non-published data from drug manufacturers), differing approaches to so-called class effects, lack of consensus regarding severity classification and the best way to evaluate an interaction's clinical relevance.

These differences cannot be explained by deficient analyses made by the sources mentioned. Instead, they probably reflect the lack of standardisation of terms used to classify drug interactions, and the absence of consistent epidemiological evidence on which to base the assessment of the interactions' clinical relevance. The **discrepancies** found seem to underscore how difficult it is to provide prescribing professionals with useful and reliable information.

Ideally, data on any given medicine should list all potential interactions, including for each its mechanism of action, relation with drug doses, time evolution, factors that may modify an individual's susceptibility to that interaction, seriousness, and probability of occurrence. In practice however, these data are seldom available.

Many drug interactions are described based on anecdotal cases or on small studies. A great number of anecdotal cases are not confirmed by subsequent studies. Besides, even when an interaction is well established it may be difficult to predict an individual patient's specific risk.

From all the above it ensues that **standardised sources of information** are needed to communicate in simple terms to the prescribing professionals about the risk of drug interactions and the quality of the evidence on which the described association is based. A broad consensus on how this information should be spelled out could go a long way to make physicians more aware of drug interactions, and to help them to better interpret and act on them. Once a consensus of this source is reached, information can be made accessible online in a matter of seconds, for example at the INFARMED site.

H. Luz Rodrigues
Professor of Pharmacology, Lisbon University School of Medicine

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)

The Lisbon and Tagus Valley Regional Pharmacovigilance Unit

The Lisbon and Tagus Valley Regional Pharmacovigilance Unit (UFLVT) started out its activity in 2001, and operates from the Lisbon University School of Medicine Clinical Pharmacology and Therapeutics Laboratory. Prof Cristina Sampaio heads the Unit, and Dr Mário Miguel Rosa is the medical co-ordinator. The team in its whole includes a broad range of necessary and relevant technical and scientific skills in pharmacovigilance.

The UFLVT is part of the Portuguese National Pharmacovigilance System, and as such shares in the common goal to more effectively collect, process and analyse pharmacovigilance data, in order to make it possible for the medicines regulatory authorities to have a timely intervention regarding the quality and safety of medicines. The **population covered** by the Unit's activities overlaps that served by the **public and private health service units under the Lisbon and Tagus Valley Regional Health Authority**.

One of the Unit's priorities is to **raise awareness of the National Pharmacovigilance System** and promote spontaneous ADR reporting by health professionals and potential report originators within the catchment area. In order to do this, the UFLVT has consistently been carrying out activities aimed at potential ADR report originators, namely concerning fields and subjects of relevance for ADR detection, diagnosis and reporting.

Another of the Unit's priorities is to provide its collaborators and potential report originators with **training and information**. Training and information activities are being regularly rolled out on specific subjects aiming for target populations and including subjects of relevance for the rational use of medicines. Throughout the years these activities have always been enthusiastically welcomed by health professionals.

Right from its inception, and on a par with the dissemination of the National Pharmacovigilance System, the UFLVT's objectives have also been to **develop scientific methods and protocols** applicable to pharmacovigilance, as well as to **get the region's hospital units involved in close cooperation**. The Unit has thus developed several protocols and conducted various pharmacoepidemiological studies at the Santa Maria Hospital in the fields of internal medicine and paediatrics. Other studies have also been under way, such as metaanalyses of pharmacoepidemiology articles published. For six years now, since it first started operating, the Unit has moreover given support to several Master's and PhD works.

The more routine activity of the UFLVT consists of spontaneous, health professional originated **ADR report processing**. Reports are checked in, classified, validated, fed into the National Pharmacovigilance System, and their nexus of causality assessed.

The Unit aims to go on optimising the critical mass of data and skills it has created by expanding its activity into novel pharmacoepidemiology fields which are now emerging in this country.

UFLVT

Rasilez® and other medicines containing Aliskiren caution: angioedema

Aliskiren, the first antihypertensive drug in the pharmacological class of direct renin inhibitors, was granted Marketing Authorisation within the EU in August 2007 for the treatment of essential hypertension, under the trademark names of **Rasilez®, Enviage®, Sprimeo®, Tekturna®** and **Ripraz®**.

Following reports of cases of angioedema and similar adverse reactions with medicines containing aliskiren, EMEA's CHMP has evaluated the available data and concluded that the **benefits** of aliskiren in the treatment of essential hypertension **are still higher than its risks**.

However, the inclusion of a new contraindication in the safety information of aliskiren has been recommended, namely that it should not be used in patients who have previously sustained **angioedema** when taking aliskiren. EMEA further recommends that a warning be included regarding the need to discontinue therapy and seek medical advice in case patients show any signs of **angioedema**.

Raptiva® (efalizumab) suspension recommended

Raptiva® (efalizumab) was authorised in the EU in 2004 for the treatment of adult patients with moderate to severe chronic plaque psoriasis, who do not respond, have a contraindication, or do not tolerate other systemic therapy modalities, including cyclosporin, methotrexate, and PUVA (psoralen and UVA). Following reports of serious adverse reactions associated with Raptiva®, the European Commission has asked the CHMP to review the available safety and effectiveness data. It has been concluded that the risks of this medicine outweigh the benefits, therefore a recommendation to suspend its MA in the EU has been issued.

Recommendations for prescribing professionals:

- Do not prescribe Raptiva® to new patients. Review the treatment of patients already on this drug in order to find a more adequate **therapeutic alternative**.
- **Do not stop the treatment abruptly**, since this may cause the disease to flare up or recur, rather consider alternative treatment modalities.
- **The effects of Raptiva® on the immune system last for about 8 to 12 weeks. Therefore, doctors should continue carefully monitoring all their patients who have taken Raptiva® for neurological and infection signs and symptoms, even after the therapy has been discontinued!**

Fareston® (toremifen): beware of QT interval prolongation

Fareston® (toremifen) – a non-steroidal derivative of triphenylethylene of predominantly antioestrogenic effects – has been authorised within the EU since 1996 for first line hormonal therapy of hormone-dependent, metastatic breast cancer in postmenopausal women.

The CHMP has conducted a review of this medicine's safety data, namely concerning its cardiac effects, due to a suspicion raised that its use might cause QT interval prolongation, which in turn is associated with a risk of ventricular arrhythmia. It has been concluded that the benefits of Fareston® still outweigh its risks. Its conditions of use however, should be narrowed down.

Fareston® (toremifen) **should not** be used in patients with:

- Prolonged **QT** interval.
- Serum electrolyte changes, especially **hypokalaemia**.
- Clinically relevant **bradycardia**.
- Clinically relevant **heart failure**, with decreased left ventricular ejection fraction.
- A history of **symptomatic arrhythmia**.
- Toremifen should not be used concomitantly with **other medicines which might cause QT interval prolongation**.

Comorbidity is a better predictive factor of ADR-associated hospital readmittance than advancing age

In this study in the universe of all public and private hospitals of Western Australia, the authors tried to find predictive factors of hospital readmittance motivated by ADRs in elderly patients. They concluded that increasing age had no significant effect on occurrence of readmittance. In contrast, comorbidity factors such as the following were strongly associated with a higher risk for readmittance: congestive heart failure, peripheral vascular disease, chronic pulmonary disease, rheumatologic disease, liver disease of varying severity, either mild or complicated diabetes, renal disease, and oncologic disease of several types and stages. On the other hand, conditions requiring continuing care such as cerebrovascular disease, dementia and paraplegia, were associated with lower probability of readmittance.

Zhang M, Holman CDJ, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. BMJ 2009;338:a2752

"Natural products" also naturally cause adverse reactions…

The Italian Pharmacovigilance System received between April 2002 and September 2008 a total of 315 spontaneous reports concerning adverse reactions to so-called natural products, including medicinal herbs, homoeopathic products, food supplements and similar products. Twenty of these reports regarded **propolis**, including children, usually in the context of upper respiratory disease or local use on skin or oral mucosa; 18 were allergic reactions, sometimes with serious manifestations which prompted seeking emergency medical care.

Menniti-Ippolito F. Bollettino di Farmacovigilanza: 5, No. 54, Dec 2008

Unexpected outburst of cases of hypoglycaemia

In a letter to the Editor, this group from Singapore draws attention to a bizarre outburst of cases of hypoglycaemia associated with the use of illegally marketed **medicinal herbs** for the treatment of erectile dysfunction, which were **contaminated with gliburide** (an oral antidiabetic agent). Several cases of severe neuroglycopenia were reported, including four deaths. In view of a presentation of hypoglycaemia that cannot be easily accounted for, it may be advisable to look for the possibility of use of counterfeited products contaminated with a hypoglycaemic agent.

Kao SL, Chan CL, Lim CCT, Dalan R, Gardner D, Pratt E, Lee M, Lee KO. N Engl J Med 360;7 nejm.org february 12, 2009 734-5

Don't shake yourself before use?

Body posture can influence physiological parameters such as perfusion, digestive function, and plasma volume, which in turn may interact with other factors of importance for the pharmacokinetics of medicines (dissolution, absorption, distribution, metabolism, excretion). Postures that favour gastric emptying – sitting, standing or lying on the right side – speed up the absorption of orally administrated medicines. Changes in hepato-splanchnic blood flow may also affect the metabolism of oral drugs. For instance, it is estimated that comparatively to lying supine (on one's back), standing is associated with a reduction in liver perfusion of about 37%. The authors conclude that **patient positioning** can be an effective strategy to **promote or retard the absorption of some medicines in certain clinical contexts** (e.g., toxic ingestion, bed-ridden patients). Could it be argued that positional factors might have some influence on the occurrence of ADRs whose mechanism is significantly dependent on pharmacokinetic variables?

Queckenberg C, Fuhr U. Eur J Clin Pharmacol (2009) 65:109–119.

Spontaneous ADR Reports from Health Professionals Portuguese National Pharmacovigilance System 2008

Total n. of reports received	840
Northern Region	***318***
Physicians	*149*
Pharmacists	*129*
Nurses	*40*
Central Region + Madeira and Azores islands	***129***
Physicians	*50*
Pharmacists	*53*
Nurses	*26*
Lisbon and Tagus Valley Region	***318***
Physicians	*161*
Pharmacists	*124*
Nurses	*33*
Southern Region	***75***
Physicians	*28*
Pharmacists	*42*
Nurses	*5*

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
PIL	Patient Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics