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Editor's Notes

Pharmacovigilance as a cutting-edge scientific field is reflected in e-communication developments described in the opening article. This is followed by a look into antidepressants in children, interactions of angiotensin II receptor antagonists, contraindications of dextropropoxyphene, and the safety profiles of a product of special current interest: the most recent vaccine to be introduced in the National Immunisation Programme – the antimeningococcal C vaccine. The A to Z section on medicinal plants goes through letter A (in Portuguese).

Pharmacovigilance, Information Systems and e-Communication

Pharmacovigilance is a cutting-edge scientific field and this is greatly to do with its public health mission in medicines safety assurance. Accessibility and dissemination of up-to-date information is therefore vital. Reporting cases of suspected adverse reactions to either the regulatory authorities or the pharmaceutical companies is key to keeping up an ongoing medicines safety profiling system.

Until recently, information concerning ADR reports had been moving around mainly in hard copies. Health professionals have essentially used tailor-made ADR reporting forms, although reporting has also been possible by fax, e-mail or even over the phone. ADRs are reported by the pharmaceutical industry mostly through paper documents as well: CIOM I forms are filled out and sent in by fax, snail mail or e-mail. All the above media have in common the following drawbacks: it is not possible to fully standardise the data collected, information safety from the sender all the way to the receptor is hard to guarantee, and paper documents have inherent problems of handling, filing, organisation and analysis.

Th number of ADR reports nationwide and Europe-wide has been steadily increasing, which is leading to an exponential growth of the sheer volume of data being circulated among all the parties involved. In the whole of the EU, 4,516 ADR cases concerning centrally approved products had been reported in 1998; this figure is now over 22,000. In Portugal, the number of reported ADRs has also gone up significantly, now past the 1,500 mark.

Various complex factors have made our current paper-document-centred system clearly insufficient and inadequate: growing concerns about information safety; an increasing number of ADR reports whose data have to be passed on around all the parties involved in the pharmacovigilance process; the need to ensure a fast and effective flow of information, along with its storage and analysis. Electronic communication has therefore become absolutely essential.

Broad discussions among the international partners have made it obvious that a transition period is needed before all paper is banned and totally replaced by fully electronic data transmission, storage and analysis. Integrated data systems are central to this process. Norms and regulations have to be agreed upon at an international level, so that conditions can be created for medicines safety information to become truly universal and updated in real time.

(cont'd overleaf)

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

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Pharmacovigilance, Information Systems and e-Communication

(cont'd from front page)

Portugal, an active participant in the European discussion and decision-making working groups, has successfully implemented the internationally accepted norms and procedures for electronic transmission of pharmacovigilance data. This is currently circumscribed to individual ADR reports, but will be extended to every pharmacovigilance area in the future, thus encompassing the whole life cycle of medicines.

Electronic data transmission is central to an integrated pharmacovigilance data management system. It ensures that standardised information will flow automatically and at all times, and contributes towards the development of data analysis and signal generation tools.

Type of Information to be Transmitted

E-transmission of information is to be adopted for all pharmacovigilance data. However, it has been decided that this process should start with data from ADR reports. Hopefully in the near future this process will be extended to other types of documents, such as periodic safety update reports. Electronic pharmacovigilance data transmission is indeed simple, reproducible, standardised, safe, and reliable, besides being universally accessible full-time.

International Norms

Electronic transmission of pharmacovigilance data complies with internationally accepted norms. Under the aegis of the **International Conference on Harmonisation** (ICH) (www.ich.org) in which the EU, the USA and Japan took part, information to be included in ADR report data transmissions and the technical characteristics of the files to be used were discussed. A new **terminology** was agreed upon, which has been specifically developed to support the technical and scientific activities regarding medicines and health products – MeDRA (Medical Dictionary for Regulatory Activities).

Key documents for process standardisation have come out of the discussions taking place within several working groups that have been set up to discuss the matters above. Those groups include the E2B group (to define the information elements to be included in the transmitted reports), the M2 group (in charge of both norm definition for electronic transmission of information, and structuring of messages), and the M1 group (dealing with MeDRA terminology). From this work common norms for the various international partners and a specific universal terminology have resulted. Furthermore, several fields of controlled vocabulary have been defined beyond those pertaining to the coding of therapeutic indications and adverse reactions.

An attempt has thus been made to standardise the structure of information to be transmitted, in order for data analysis to be reproducible from partner to partner. This is a contribution towards turning pharmacovigilance into a global activity which can leap over national and even intercontinental frontiers.

Confidentiality of transmitted information is guaranteed by complex encryption systems set up amongst data exchange partners. These systems ensure that only the information recipient as intended by the sender actually accesses the information contained in the message. On the other hand, access to data systems sending out and receiving information is limited to restricted and controlled user groups, thus ensuring that the stored data remain confidential.

Flexible as they are these systems allow for diverse access levels to be ascribed to different types of users, and it is even possible to use the internet to make selected, non-confidential information available to the public in general and to health professionals. Internet-embedded electronic data transmission is a key element in pharmacovigilance information management systems, and is critical for permanent access to information, through the creation and use of data search and analysis tools.

Requirements for Electronic Data Transmission

All these developments are meant to be adapted to both the more complex and the most basic of systems, so that every party involved may take up this medium of communication, regardless of their dimension or available resources. In order to implement an electronic data transmission system the following items are required:

- a pharmacovigilance information management system
- an e-communications system
- adoption of internationally accepted norms.

Discussion, Testing and Decision Groups

Aiming to promote and regulate the implementation of the electronic transmission of ADR reports in the EU following internationally accepted norms, discussion and decision groups have been created, which are integrated within the whole process of restructuring and organisation of the European medicines telematics infrastructure.

The main European working groups are the **EudraVigilance Steering Committee, the EudraVigilance Expert Working Group,** and the **EudraVigilance Telematics Implementation Group**. Portugal is represented in all of these groups, which aim to co-operate with other working parties from different but related fields (e.g.: EuroPharm for the medicines database, e-Submission for submission of information on medicines), in order to provide the EU with modern medicines data networks and systems.

The European System

A single communications hub, EudraVigilance-centred ADR report data management, validation, analysis and transmission system is currently implemented and fully operational within the EU. **The EudraVigilance application** (www.eudravigilance.org) can be accessed free of charge by all partners within the European pharmacovigilance system. It consists of an adverse reactions database with a terminology that is very closely related to MeDRA and includes a medicines dictionary. Its gateway allows information to be received and sent out into and from the system, and it is also possible to make direct data submissions online through the above application.

The Portuguese System

The Portuguese pharmacovigilance information management system is fully implemented, and has been tested with EMEA (www.emea.eu.int), which has granted it certification as an effective partner of the EudraVigilance system. Advanced testing with all the pharmaceutical companies that are ready to proceed with the system is ongoing. The Portuguese system is compatible with internationally agreed norms, and allows for electronic sending and receiving of information from adverse reaction reports. Portugal was in fact one of the pioneering partners in Europe to set up and use this type of technology on a regular basis. The system has been developed in order to make it possible for health professionals to report ADRs through the internet in the near future.

Concluding Remarks

Implementing e-transmission of pharmacovigilance information poses great challenges to all the parties involved. It is however already happening and will replace paper-based information exchange in the short run. Advantages are two-fold: the flow of information is standardised, reproducible, fast and safe, on the one hand, and real-time pharmacovigilance information is made available from a permanently up-to-date centralised European database. More than a technical challenge, migration into a system with transparent and real-time information flow is a challenge to our mindsets. This is an example of how pharmacovigilance is a cutting-edge activity, which is centred not only in accurate data collection but also in continuing analysis and criticism of the huge amount of data in which it is immersed.

Luís Pinheiro

Angiotensin II Antagonists: Interactions

Angiotensin Antagonists and NSAIDs

Interaction of angiotensin II antagonists with non-steroidal anti-inflammatory drugs (including acetylsalicylic acid at a dose above 3 g per day) makes biological sense, although it is not yet clear whether the mechanism involved consists of a synergistic reduction of glomerular filtration or of a cumulative nephrotoxic effect.

Due to this interaction, and similarly to angiotensin converting enzyme inhibitors, simultaneous administration of angiotensin antagonists II and NSAIDs may result either in a decrease of the anti-hypertensive effect of the former, or in an increase in the risk of deterioration of renal function. This could lead to acute renal failure and hyperkalaemia in patients with compromised kidney function (e.g.: dehydrated patients, or the elderly with reduced renal function)

Concomitant administration of NSAIDs and angiotensin antagonists is quite common in **elderly patients**, who are indeed a population at greater risk of interactions anyway. These patients should be adequately **hydrated**, and thought should be given to the need for **monitoring** renal function at the start of concomitant therapy and periodically thereafter.

Angiotensin II Receptor Antagonists and Lithium

Similarly to angiotensin converting enzyme inhibitors, concomitant administration of angiotensin antagonists with **lithium** may lead to a reversible increase of lithium blood serum concentration, therefore increasing the **toxicity** of the latter. Should the association of these two medicines be absolutely necessary, then **monitoring lithium's blood serum levels** during therapy is recommended.

Paula Roque

- *Meune C, Mourad JJ, Bergmann JF, Spaulding C. Interaction between cyclooxygenase and the renin-angiotensin-aldosterone system: rationale and clinical relevance. J Renin Angiotensin Aldosterone Syst. 2003. Sep;4(3):149-54.*
- *Matthew R. Weir. Renal effects of nonselective NSAIDs and coxibs. Cleveland Clinic Journal of Medicine 2002, 69(i): si-53-8.*
- *Seelig CB, Maloley PA, Campbell JR. Nephrotoxicity associated with concomitant ACE inhibitor and NSAID therapy. South Med J. 1990 Oct;83(10):1144-8.*
- *Finley PR, O'Brien JG, Coleman RW., Lithium and angiotensin-converting enzyme inhibitors: evaluation of a potential interaction. J Clin Psychopharmacol. 1996 Feb;16(1):68-71.*

Antidepressants in Children and Adolescents: watch out for agressive behaviour

The European Commission has recently decided to adopt the CPMP's conclusions re-evaluating of the potential risk of **suicidal behaviour** associated with antidepressants in children and adolescents. The decision is binding for all Member States. A warning must therefore be included in the SPCs and Information Leaflets on the fact that **suicidal behaviour** (attempted suicide and suicidal ideation) and **hostile behaviour** (mostly aggressive or opposition behaviour, or anger) has been observed more frequently in patients on antidepressants than in patients taking placebo.

The active ingredients evaluated and which are approved in Portugal were: **citalopram, duloxetine, escitalopram, fluoxetine, mianserine, milnacipram, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine.**

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)

MenC – Safety Profile Highlights

Contraindications

- Hypersensitivity to any of the vaccine's components.
- Immunisation should be postponed in case of acute febrile illness.

Special precautions of use

- As for any other parentheral vaccine, and in spite of its rarity, appropriate medical observation and treatment should be available in case an anaphylactic reaction occurs.
- Under no circumstances should the vaccine be given by the intravascular route. It should not be administered either subcutaneously or intradermally.
- Caution is needed when administering the vaccine to patients with **thrombocytopoenia or coagulation disorders.**

Drug interactions

- Should not be mixed with other vaccines in same syringe.
- In case it is given simultaneously with another vaccine, a different injection site should be used.

Pregnancy and breastfeeding

- There are no data available on the use of this vaccine in pregnant women. Vaccine use during pregnancy or while breastfeeding however, should be considered whenever risk of exposure has been clearly identified.

Undesirable effects

Very frequent (>1/10):

- Local reactions: redness, tenderness, swelling.
- Limb pain, headache, crying, crankiness, dizziness, sleepiness/ change in sleep patterns in infants and children from 1 to 3 years of age.
- Vomiting/nausea/diarrhoea and loss of appetite in infants.

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

- Muscle pain in children and adults.

Very rare (<1/10.000)

- Arthralgia.
- Lymphadenopathy.
- Anaphylaxis, hypersensitivity reactions, including wheezing, facial oedema and angioedema.
- Dizziness, seizures (including febrile seizures), fainting, hyposthaesia, paresthaesia, hypotonia in infants.
- Relapse of nephrotic syndrome.
- Skin rash, urticaria, pruritus.
- Petechiae and/or purpura.
- Stevens-Johnson's and erythema multiforme

Special storage precautions

- Should be kept at a temperature of between 2 ºC and 8 ºC; must not be frozen.

N.B.: *For further information and guidance of clinical practice, please refer to product's SPC and national guidelines.*

Dextropropoxyphene: safe use

Dextropropoxyphene is an opioid analgesic approved in Portugal for oral administration in association with paracetamol (co-proxamol). It can be an adjuvant for the treatment of pain, for instance in the acute stages of chronic rheumatic conditions, and as an alternative to other mild opioids, such as codeine and tramadol, which may have more central nervous system adverse reactions. Cancer pain is another important indication.

This medicine has been associated with a high number of fatal overdose cases (accidental and voluntary) in some European countries, suicide being the most significant event. In general, **reported serious ADRs** are to do with **inadequate use** of the medicine (e.g.: interaction with alcohol or with other psychotropic agents). No cases of serious adverse reactions or death have however been reported whenever the drug's safety profile was duly taken into account. According to the literature, dextropropoxyphene and its combinations do not seem to be associated with a higher frequency of adverse events when compared to other opioids in general, and at the recommended dosage adverse events are actually less relevant than with morphine.

Nevertheless, on account of new safety data, the SPC is being reviewed in order to include a warning that this medicine **should not be used in patients with depression**, and it is contraindicated in patients **younger than 18 years, or with alcohol addiction.** The recommended dose should not be exceeded.

In order to avoid overdosage, it is essential that the patient be informed that in case pain persists he/she should not take an additional dose of this medicine, rather another dose of a paracetamol-only product.

João Ribeiro Silva
Paula Roque

- *Goldstein DJ, Turk DC. Dextropropoxyphene: safety and efficacy in older patients. Drugs Aging. 2005; 22(5):419-32.*
- *Collins SL, Edwards JE, Moore RA, McQuay HJ. Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. Cochrane Database Syst Rev. 2000; (2):CD001440. Review.*
- *Collins SL, Edwards JE, Moore RA, McQuay HJ. Single-dose dextropropoxyphene in post-operative pain: a quantitative systematic review. Eur J Clin Pharmacol. 1998 Apr; 54(2):107-12. Review.*

Adverse Reactions to Antimeningococcal (Group C) Vaccination: an overview for Portugal

The Portuguese General Directorate for Health has decided to make changes to the National Immunisation Programme, as a result of current population needs and a recent risk-benefit re-evaluation. The new Programme will start in January 2006, and will include a conjugated vaccine against ***Neisseria meningitidis*** Group C (MenC), whose two doses will be given to infants at **3 and 5 months** of age, followed by a **booster** at **15 months** of age. The vaccines to be included in the Programme are those that were already being marketed in Portugal, namely: Meningitec® (Wyeth Lederle Portugal (Farma), Lda), Menjugate® (Chiron S.r.l.) , and Neisvac C® (Baxter Healthcare, Ltd.).

Between 2000 and the end of 2004, 14 serious and 9 non-serious **ADRs** had been reported. The ADRs reported were: generalised skin reactions (11 cases), high fever (6), meningitis-like signs and symptoms (without meningococcal infection) (2), seizure with or without high fever (2), and lack of effect of vaccine (2), that is, cases of meningitis caused by a strain to which the patient was supposed to have become immune following vaccination.

Every ADR reported is mentioned in the SPC of these vaccines. However, given that the use of MenC in Portugal is relatively recent and its inclusion in the National Immunisation Programme will greatly increase exposure to it, **all health professionals should be reminded of their vital role in reporting every suspected ADR.**

Susana Gonçalves
Isabel Afonso

- *Boletim de Farmacovigilância Vol.6, nº2, 2º trimestre de 2002.*
- *Circular Informativa da DGS n.º 15/DT de 3 de Abril 2002.*
- *Circular Informativa da DGS n.º 23/DT de 31 de Maio de 2005.*

Medicinal Plants from A to Z - described adverse reactions

• **Angelica** *(Angelica archangelica)*
- photodermatitis (furanocoumarins in root oil)
- interaction with coumarinic anticoagulants (increased effect), haemorrhage in pregnancy

N.º of Medline citations (human side effects): 1
Main uses described: antiflatulent; topical antifungal/antibacterial (root oil)

• **Anise** *(Pimpinella anisum)*
- hypersensitivity reactions

N.º of Medline citations (human side effects): 5
Main uses described: antiflatulent, digestive, expectorant; antiseptic (topical)

• **Star Anise** *(Illicium verum)*
- seizures and other neurological reactions in children (tea for abdominal colic)

N.º of Medline citations (human side effects): 12
Main uses described: antispasmodic

• **Arnica** *(Arnica montana)*
- hypersensitivity, contact dermatitis

N.º of Medline citations (human side effects): 20
Main uses described (topical): anti-inflammatory/healing/antiseptic for skin wounds and blunt trauma; osteoarthritis

• **California pepper tree** *(Schinus molle)*
- hypersensitivity, contact dermatitis

N.º of Medline citations (human side effects): 1
Main uses described: anti-inflammatory, skin wound healing; dyspepsia

• **Mugwort** *(Artemisia vulgaris)*
- hypersensitivity
- uterine contractions during pregnancy
- liver toxicity

N.º of Medline citations (human side effects): 42
Main uses described: analgesic (headache), antispasmodic (menstrual pain, intestinal colic)

• **Sheep's sorrel, field sorrel** *(Rumex acetosa)*
- dyspepsia, acute gout, renal stones (contains oxalic acid, oxalates, tannins)

N.º of Medline citations (human side effects): 1
Main uses described: diuretic, anti-inflammatory, skin wound healing, "antidysuric"; antiscorbutic (contains vitamin C)

• **Wood sorrel** *(Oxalis acetosella)*
- dyspepsia, acute gout, renal stones (contains oxalic acid)

N.º of Medline citations (human side effects): 1
Main uses described: antipyrexial, diuretic, "antidysuric"; antiscorbutic (contains vitamin C)

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