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Editor's Notes

According to the European Centre for Disease Prevention and Control (ECDC) the influenza A (H1N1v) pandemic has been spreading in Europe in such a way that it can be viewed as a significant but manageable challenge.[1] The decisions in both individual medical approaches and public health strategies put into practice worldwide involve first-line measures to contain/delay the pandemic and later to mitigate its effects. In certain cases the decision making algorithms may resort to the use of specific medicines aiming for a cure or for a chemo- or immunoprophylactic effect.

Viral neuraminidase inhibitors can be used either for treatment of the disease or for chemoprophylaxis. They inhibit the enzyme that allows the virus to pierce through the mucosal secretion barrier takes part in the release of new viral particles from the infected host cells.[2] The risk-benefit ratio and the indications of oseltamivir and zanamivir have evolved as the pandemic unfolded, together with the acquisition of knowledge on the H1N1v virus and its epidemiological impact.[3] Immunoprophylaxis is to be provided by specific anti-H1N1v vaccine.

Meanwhile, with the start of Autumn in the Northern hemisphere comes the usual time for seasonal flu vaccination, only this time there is a potentially confounding backdrop of overlap with the novel influenza A virus without any likely "cross" protection.[4]

Priority target groups have been defined for seasonal influenza immunization: individuals 65 years or older, chronic and immunocompromised patients (older than 6 months of age), health professionals, and other caregivers.[5]

In this issue, some of the more significant features of the safety profile of the seasonal flu vaccine are reviewed, as well as those regarding the neuraminidase inhibitor anti-influenza agents.

In this issue also: the Northern Regional Pharmacovigilance Unit, the paradoxes of ADR reporting (ADRs in the Literature section), antihypertensive agents in pregnancy and breastfeeding, a safety update reminder for methylphenidate now that kids are going back to school, and serious interactions to bear in mind when using sympathomimetic nasal decongestants.

1. http://ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx [accessed Sep 2009].
2. http://www.bmj.com/cgi/content/full/339/jul24_2/b3046 [accessed Aug 2009].
3. http://www.cdc.gov/h1n1flu/recommendations.htm[accessed Sep 2009].
4. http://www.cdc.gov/h1n1flu/vaccination/ [accessed Sep 2009].
5. Direcção Geral de Saúde [Portuguese General Health Directorate. [Immunization against seasonal influenza 2009/2010]. Circular Informativa Nº: 33/DSPCD. 08/09/2009.

Seasonal Flu Vaccine: Safety Profile Highlights

(trivalent vaccine against seasonal influenza viruses)

Contraindications

- Hypersensitivity to any active ingredient, excipient or residue such as **egg or chicken protein, gentamycin, neomycin, or phormaldehyde** (depending on the vaccine).
- Postpone vaccination in patients with a **fever or anacute infection**.
- A past history of **Guillain-Barré syndrome in the 6 weeks following** a previous dose of vaccine is considered a relative contraindication. The decision whether to use the vaccine should be made on a case by case basis.

Special precautions for use

- Like for any injectable vaccine, appropriate medical surveillance and treatment should be readily available in case an anaphylactic reaction occurs on administration of the vaccine.
- Under no circumstance should the intravascular route be used.
- Antibody production may be insufficient if the patient is endogenously or iatrogenically immunodepressed.*
- The immune response may be decreased by concomitant immunodepressant medication.

Drug interactions

- Can be given simultaneously with other vaccines. Different limbs should be used. Adverse reactions may be more intense.

Interactions with diagnostic tests

- Potential post-vaccination **false positives** with ELISA tests used for detection of antibodies against HIV1, hepatitis C virus, and especially HTLV1 (this may be due to vaccination induced IgM).

Pregnancy and breastfeeding

- The vaccine may be considered from the second trimester. In pregnant women whose clinical condition exposes them to an increased risk of flu associated complications, vaccination is recommended at any gestational age.
- Can be administered during breastfeeding.

Undesirable effects

Frequent or very frequent *(≥1/100)*
Headache, malaise, fatigue, fever, myalgia, arthralgia.**
Local inflammatory reaction or echymosis.**

Infrequent *(≥1/1000 but <1/100)*

Generalized skin reactions, including pruritus, urticaria, and non specific rash.

Rare *(≥1/10.000 but <1/1000)*
Neuralgia, paraesthesia, seizures.
Transient thrombocytopoenia.
Allergic reactions (rarely with shock).

Very rare *(<1/10.000)*
Other neurological disorders, such as encephalomyelitis, neuritis, and Guillain-Barré syndrome.
Vasculitis with transient renal compromise.

Special storage precautions

Refrigerate between +2°C and +8°C (**do not freeze**).
Keep in package to protect from **light**.

** In immunocompetent individuals seroprotection is usually obtained within **2 to 3** weeks. Post-vaccination immunity generally lasts for 6 to 12 months.*

*** These reactions usually disappear within 1-2 days without treatment.*

Cristina Rocha

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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Neuraminidase inhibitors for the treatment and chemoprophylaxis of H1N1v influenza A virus infection: Safety Profile Highlights

	OSELTAMIVIR (Tamiflu®)	**ZANAMIVIR** (Relenza®)
Contraindication	Hypersensitivity to any active ingredient or other component.	Hypersensitivity to any active ingredient or other component. (**lactose** included).
Special precautions for use	Recommended to be taken with **food** (to decrease probability of nausea). In adults with severe **renal** compromise the dose should be adjusted. Not recommended for children younger than 1 year. However, in the context of novel influenza A (H1N1) pandemic, according to EMEA, oseltamivir may be administered in younger children.* See also the guidelines (OT-7) from the (Portuguese) General Directorate for Health.	Patients with **asthma or chronic pulmonary disease** should be informed about the risk of bronchospasm. Patients should have a fast-acting bronchodilator available. Patients on inhaled bronchodilator maintenance therapy should administer the bronchodilator a few minutes before receiving zanamivir. Can be used in adults and children older than 5 years.
Drug interactions	Clinically significant drug interactions are not likely. The effectiveness of the influenza vaccine should not be altered.	
Pregnancy and breastfeeding	Use in pregnancy and breastfeeding only when potential benefit outweighs risk, as may be the case in a pandemic situation.*	
Undesirable effects	**Adults and Adolescents** ***Very Frequent*** *(≥1/10)* Nausea and headache. ***Frequent*** *(≥1/100 but <1/10)* Bronchitis, cough, rinorrhoea, upper respiratory infection. Insomnia, dizziness. **Children** ***Very Frequent*** *(≥1/10)* Vomiting and diarrhoea. ***Frequent*** *(≥1/100 but <1/10)* Nausea, abdominal pain. Upper and lower respiratory infections, asthma (including worsening). Lymphadenopathy. Epistaxis, dermatitis.	***Rare:*** Acute bronchospasm and/or severe decrease of respiratory function in patients with a past history of respiratory illness. ***Very rare:*** Acute bronchospasm and/or severe decrease of respiratory function in patients without a past history of respiratory illness. Allergic reactions.
	In patients **with flu, mainly children and adolescents**, **cases of seizures and delirium** have been reported, including symptoms such as altered consciousness, confusion, abnormal behaviour, delirious ideas, hallucinations – the actual incidence of these events and the contribution of the antiviral agents is not known.	
Special storage precautions	Do not store at a temperature above 30 ºC (powder). **Once prepared**, the suspension can be kept at room temperature (not above 25 ºC) for 10 days, or in the refrigerator (2 ºC to 8 ºC) for 17 days.	Do not store at a temperature above 30 ºC.

* http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/32609509en.pdf

Cristina Mousinho

NB: It is strongly suggested that professionals consult the guidelines issued by the (Portuguese) General Directorate for Health, namely OT-7 and those concerning special cases, such as pregnant women, renal and diabetic patients: **www.dgs.pt** [flu microsite].

I National Pharmacovigilance and Risk Management Congress
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http://www.infarmed.pt/portal/page/portal/INFARMED/EVENTOS/DETALHE_EVENTO?eventoid=1386269

Northern Regional Pharmacovigilance Unit

Strategies against ADR under-reporting

Adverse drug reactions are an important and widely acknowledged cause of morbidity and mortality in developed countries. In Portugal, like in other countries, the rates of spontaneous ADR reporting by health professionals is lower than desirable. Data obtained thus tend therefore not to be representative of the total reality of adverse events resulting from the use of medicines.

The Northern Regional Pharmacovigilance Unit (UFN) has been developing various strategies to promote this pharmacovigilance method amongst the health professionals working in the corresponding region as defined within the National Pharmacovigilance System. This Unit concluded a study in June 2009 aiming to **increase the number and relevance of ADRs reported by pharmacists** working in the North of Portugal, by means of telephone interventions and workshops. This was in fact the second time such a programme was being brought to the region's pharmacists after training received earlier from this Unit between 2002 and 2006, and whose resultshad already suggested a booster intervention would be in order.[1] During the interventions carried out between May and July 2007, the main attitudes preventing these professionals from reporting ADRs were discussed and elaborated on.[2]

The intervention **increased the rate of ADR spontaneous reports three-fold** when compared to the control group in the same period of time. Not only did the number of spontaneous ADR reports increase, but their relevance also rose; the number of serious and unexpected adverse reactions went up, as compared to a control group. This effect **lost statistical significance after 4 months**. We therefore concluded that this professional group needs periodical training in order for their participation in the National Pharmacovigilance System to be kept up.

We further concluded that, for the group studied, **telephone interventions are as effective as face-to-face ones**. The former may be an awareness raising tool to be adopted by this and other regional pharmacovigilance units, to revert under-reporting.

The interventions described are part of a crossover study according to whose protocol those participants who received a telephone intervention in the first phase will later receive a workshop intervention, and vice versa. In this way the UFN will continue to promote spontaneous ADR reporting by health professionals, while pursuing its research activities.

UFN

1. Herdeiro T, et al. Improving the reporting of adverse drug reactions : a cluster randomized trial among pharmacists in Portugal. Drug Safety, 2008; 31(4): 335-44.
2. Herdeiro T, et al. Influence of pharmacists' attitudes on adverse drug reaction reporting: a case-control study in Portugal. Drug Safety, 2006; 29(4): 331-40.

ADRs in the literature...

Under-reporting paradoxes

Generally speaking, medicine is loathe of lack of information. Medicine demands knowledge, detail and accuracy, which can only be obtained with study, observation, and rigorous data collection. It is not socially acceptable to disinvest in this area of human knowledge. This social demand is in contrast with the phenomenon of ADR under-reporting. As in other contexts of medicine, in pharmacovigilance too it is essential for data to be obtained which can be analyzed so that novel adverse reactions and contraindications can be found.

In pharmacovigilance in particular, observation is conducted by the professionals themselves. The generation of new knowledge is thus dependent on their reporting adverse reactions. However, data point to significant under-reporting in this country. The question is, why does this social demand for more medical knowledge not translate into social awareness on the need to report adverse reactions?

In the past, several studies have questioned the reasons for non reporting from a formal perspective. Factors contributing for under-reporting include training, availability of reporting forms time constraints, or others. INFARMED, and the other medicines regulatory authorities, have always tapped into these studies for a rationale for their reporting promotion activities. A lot of effort has been put into more training in pharmacovigilance in the last few years, and web-based reporting tools have become available.

Nevertheless, two facts make one think that the measures inspired in those study results do not entirely account for the under-reporting phenomenon: 1. Most solutions proposed by the studies have not resulted in a sustained increase of reports. 2. These studies did not truly analyze the causes but rather causal components, which means that the factors identified may discourage reporting, but they do not explain the dynamics of reporting in clinical practice.

In relation to this issue, an article by Nichols et al. has recently been published: *Risk Perception and Reasons for Non-compliance in Pharmacovigilance: A Qualitative Study Conducted in Canada*[1]. This research aimed to identify the perceptions of physicians and pharmacists regarding pharmacovigilance, their role in reporting and the consequences of the latter for their professional practice. This study was innovative in that it used a qualitative methodology for the first time. Four factors were identified which the authors called paradoxes. They can be grouped into those that relate to the pharmacovigilance system and those that concern the health professional. These paradoxes merit reflection, even if one allows for varying national contexts.

Paradoxes relating to the reporting system

Paradox of the unrealistic ideal

The professionals who were interviewed actively acknowledge the importance of pharmacovigilance, believe in its usefulness, and seem to be willing to collaborate, but they state they are not totally clear on procedures. On the other hand, they show high expectations regarding information they expect to receive from the pharmacovigilance system.

Paradox of distancing

From the study one is led to conclude that the professionals believe that interaction between them and their pharmacovigilance system is inadequate. They come across as two remote identities without a direct relationship or common goals. While the pharmacovigilance system takes on a public health face, professionals expect it to help them in managing individual cases. Furthermore, reporting to the pharmaceutical industry entails some reluctance due to uncertainty regarding the industry's actual commitment to assessing the safety of medicines.

Paradoxes relating to the health professionals

Paradox of perception

This is the most interesting paradox, and it includes two factors, the first one being **risk perception**. From the interview it became apparent that professionals working in intensive care or other specialties dealing with patients with a dire prognosis are more used to the risk of adverse reactions. In fact, these professionals have to deal with the patient's imminent death, and therefore need to run the risk of an adverse reaction and need to manage it. Whenever the frequency of adverse reactions is high, even if they are serious, risk desensitization may occur, and the number of reports diminish. The second factor is **causality assessment**. Every pharmacovigilance system proposes that the professionals not do an assessment of the causal relationship. However, it seemed all the professionals that were interviewed did, because they believe that they would otherwise generate confounding noise. These professionals look up the literature for previous reports of the reaction they are considering. The paradox is: if no-one reports it is not possible to have a previous record of reports which will help one to assess causality.

Paradox of function

This last paradox arises from the fact that the functions of each health professional are complementary. The physician is essential for the diagnosis, but the pharmacist is seen as more qualified to analyse the implications of ADRs and to explain the phenomenon. Since responsibility within the team is not clear, it is eventually dissipated, and the event ends up not being reported.

From this article one concludes that, additionally to professional training, other activities are essential. Apparently, perception and its subjectivity is as important as knowledge. It seems therefore that if we are to cut down under-reporting, pharmacovigilance needs to be more present, i.e, there have to be more familiarity and trust in it.

Luís Pinheiro

1. Nichols V, Theriault-Dube I, Touzin J, Delisle J-F, Lebel D, Bussieres J-F, Jean-Fra Bailey B, Collin J. Risk perception and reasons for noncompliance in pharmacovigilance: a qualitative study conducted in Canada. Drug Safety, 2009; 32(7):579-590.

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

Antihypertensive agents: Pregnancy and Breastfeeding

The use of **angiotensin converting enzyme (ACE) inhibitors** and **angiotensin II receptor antagonists (ARA II)** during pregnancy has been assessed by the European Pharmacovigilance Working Party (PhVWP), which considered that **their use in the first trimester of pregnancy is not recommended,** and that **they are contraindicated in the second and third trimesters**. Should pregnancy be diagnosed with such therapy already under way, the latter should be discontinued and alternative therapy started, where appropriate.

Available data on the use of ACE inhibitors and ARA II during **breastfeeding** were also evaluated. Limited pharmacokinetic data have shown very small concentrations of **captopril, enalapril, benazepril and quinapril** in mother's milk. Although these data may not be clinically relevant, those active ingredients are not recommended whilst breastfeeding pre-term children and in the first weeks after birth, due to a hypothetical risk of renal and cardiovascular effects, and lack of clinical experience. In the case of older children, the use of the above drugs during breastfeeding may be considered, but the child should be monitored for possible adverse effects. As for the use of **other ACE inhibitors and ARA II** during breastfeeding, lack of data entails that their use is not recommended, especially in newborns and premature children. Therapeutic alternatives with an established safety profile are thus preferable.

The PhVWP also assessed the safety of **hydrochlorthiazide** during pregnancy and concluded that it should not be contraindicated in the second and third trimesters. However, it should not be started in pregnant women with essential hypertension, except in those rare situations where a therapeutic alternative cannot be used. Hydrochlorthiazide should not be given in gestational oedema, pregnancy-induced hypertension or preeclampsia, on account of a risk of decreased plasma volume and placental hypoperfusion weighed against lack of clear beneficial effects for the course of the disease.

The SPCs and Information Leaflets of these medicines have recently been altered in order to include this information. All the changes inserted can be looked up at INFARMED website at:

http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/INFORMACAO_SEGURANCA/ALTER_TIPO2_SEGURANCA
(in Portuguese).

Other safety information issued by the INFARMED Risk Management Department is also available at the site, including **educational materials, safety alerts, the Pharmacovigilance Bulletin, and other safety updates for health professionals**.

Cristina Rocha

Methylphenidate: safety update

Methylphenidate has been available in the EU for several years. In Portugal it is marketed as Concerta®, Ritalina LA® and Rubifen®, and is used for the treatment of attention deficit / hyperactivity disorder (ADHD). This medicinal product is structurally related to amphetamines and is classified as a controlled substance, which entails a number of special restrictions to prescription and use.

Methylphenidate is indicated in ADHD in children older than 6 years in the setting of a broader therapeutic programme in which psychosocial measures have been shown to be insufficient. Treatment should be conducted under the supervision of a specialist in child behaviour disorders, and is usually discontinued in puberty. ADHD is characterized by prominent symptoms of attention deficit and/or impulsivity/hyperactivity, and can be associated with disorders such as opposition behaviour, mood and learning disorders, anxiety, depression, tics, and Tourette syndrome. Children with severe ADHD can have low levels of self-esteem, as well as emotional and social problems, and they frequently show problems regarding school behaviour and performance. These signs may persist into adolescence and adulthood, frequently associated with deficient social interaction, emotional disorders, unemployment, criminality and substance abuse.

The CHMP has issued a report on safety issues of medicinal products containing methylphenidate. Safety data from various sources were analyzed namely from clinical trials, pre-clinical studies, spontaneous ADR reports, and published literature. It was concluded that the **risk-benefit ratio** of methylphenidate is **favourable**, but information in SPCs and Information Leaflets should be further harmonized. Moreover, **additional risk minimization measures** should put into place, including educational materials addressing prescribing physicians. The main conclusions from this assessment at a European level are summed up below.

- **Cardiovascular risk** – There is a potential risk f hypertension, increased heart rhythm and arrhythmia. Patients should be assessed before treatment for blood pressure and heart rhythm disorders. A family history of cardiovascular disorders should also be investigated. Any patient with such problems should not start treatment without first being evaluated by a specialist. Every child on methylphenidate should have their **blood pressure and heart rhythm closely monitored**.
- **Cerebrovascular risk** – Migraine, stroke and cerebral vasculitis: the corresponding SPC and IL sections should be updated and harmonized.
- **Psychiatric risk** – Hostility, depression, psychosis, mania, irritability and suicidal ideation: may be caused or worsened by methylphenidate. Therefore, every patient should be carefully **assessed** concerning this type of disorders **before** treatment is started, then periodically **monitored** for psychiatric symptoms during treatment. **"Excessive concentration" and "repetitive behaviour"** have been observed with methylphenidate and should be added to the SPC and IL list of possible adverse effects.
- **Effects on growth** – In order for eventual effects on growth to be minimized, periodical **monitoring** (height and weight) should be included in the SPCs and ILs, and warnings improved and harmonized.
- **Leukaemia** – The available data have **not been conclusive**. **Cytogenetic studies** are going to be conducted to look into a possible carcinogenic risk of methylphenidate.
- **Effects of long-term treatment** – There are not enough data on the long- -term effects of methylphenidate. In what concerns those patients who have been on this medication for over one year, physicians should **suspend therapy at least once a year** and determine whether it is necessary to continue it.
- **Off-label use, abuse and recreational use** – Safety information should be reinforced and prescribers should receive guidelines on correct use. The MA Holders have agreed to disseminate **educational materials** for clinical guidance.

Joana Oliveira

Interactions to keep in mind Patients using nasal decongestants

- **sympathomimetic vasoconstrictors**

Risk of

- ♦ hypertensive crises and vascular accidents with:
  - other sympathomimetics [including indirect ones, such as bupropion, sibutramine, methylphenidate]
  - other vasoconstritors [bromocryptine, oxytocin, di-hydroergotamine...]
  - MAO inhibitors (also risk of hyperthermia)
- ♦ seizures, with seizure threshold lowering medicines [e.g., neuroleptics, MAO inhibitors, SSRIs, venlafaxine, methylphenidate, opioids, baclofen]
- ♦ arrhythmia, with halogenated anaesthetics
- ♦ decreased effect of alpha-blockers and antiepileptics

Based on: la revue Prescrire