boletim de FARMACOVIGILÂNCIA

VOLUME 25
NUMBERS 11 AND 12
NOVEMBER/DECEMBER
2021

November/December highlights from the Pharmacovigilance Risk Assessment Committee (PRAC)

Conclusions on the risk of pericarditis/myocarditis with COVID-19 mRNA vaccines

The PRAC assessment on the risk of myocarditis and pericarditis following vaccination with Comirnaty® and Spikevax® included two major European epidemiological studies – one with data from the French healthcare system and another based on data from registries from Nordic countries. In general, the risk of myocarditis and pericarditis was confirmed. This had already been previously reflected on both vaccines' SmPCs and PLs. These reactions are very rare, affecting **one in 10,000 vaccinees** and appearing a few days after immunization, mostly within the first 14 days.

For **Comirnaty®** the French study demonstrated that, in a period of 7 days following administration of the second dose of the vaccine, an excess occurred of around 0.26 cases of myocarditis per 10,000 vaccinated males aged between 12 and 29 years, when compared with individuals who had not been exposed to the vaccine. In the Nordic study, in a period of 28 days following administration of the second dose of the vaccine, an excess occurred of around 0.57 cases of myocarditis per 10,000 vaccinated males aged between 12 and 24. This means that, overall, **one to two cases of myocarditis "too many" occurred out of 40,000 vaccinated men and boys** than would have been expected without vaccination.

For **Spikevax®**, the French study showed an excess of around 1.3 cases of myocarditis per 10,000 vaccinated males aged between 12 and 29 years, in a period of 7 days following administration of the second dose of the vaccine. In the Nordic study, in the 28 days post administration of the second dose of the vaccine, an excess was seen of around 1.9 cases of myocarditis per 10,000 vaccinated males aged between 12 and 24. This means that, overall, **per 40,000 vaccinated men and boys, around five to fewer than eight "too many" cases of myocarditis** occurred than would have been expected without vaccination.

Myocarditis and pericarditis are inflammatory conditions affecting the heart. Symptoms vary but usually include chest pain, breathlessness or increased and even irregular heart rhythm. Available data suggest that the clinical course of myocarditis and pericarditis following vaccination is not different than the usual clinical evolution of those conditions.

The PRAC has recommended that the SmPCs and PLs of these vaccines be updated. EMA will keep intensively monitoring the safety and efficacy of COVID-19 vaccines. The benefits of these vaccines continue to outweigh their risks, namely as observed in the decreased number of deaths and hospitalizations.

Márcia Silva

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ISSN: 0873-7118

Vaccine-Induced Thrombotic Thrombocytopenia: clinical features

The authors of this study published in the New England Journal of Medicine describe the **first 220 cases of VITT (Vaccine-Induced Immune Thrombocytopenia and Thrombosis)** reported in the United Kingdom between 22nd March and 6th June 2021 in association with the ChAdOx1 nCov-19 vaccine (non-replicating viral vector (chimpanzee adenovirus) COVID-19 vaccine).

The nomenclature that was chosen for this new syndrome (VITT) underscores its clinical similarity with heparin-induced thrombocytopenia. Cases of VITT have been defined according to **five criteria**:

- symptoms beginning 5 to 30 days after vaccination
- presence of thrombosis
- thrombocytopenia (platelet count below 150,000/mm3)
- D-dimer levels above 4,000 FEU (fibrinogen equivalent units)
- presence of ELISA-detected anti-PF4 antibodies

The causal relation of cases meeting all five criteria was considered as definitive. A decreasing number of applicable criteria implied probable, possible or improbable causality.

A total of 170 definitive and 50 probable cases of VITT were identified. All the patients presented **between 5 and 48 days (median: 14) after the first dose of ChAdOx1 nCov-19 vaccine**. The **median age was 48 years, ranging from 18 to 79 years. No clinical risk factors or gender predominance** were observed.

In this cohort of patients with VITT **multiple location thrombosis and arterial events** were common. The cerebral veins (in 50%) were the most frequent presenting location for thrombosis, over one third of these patients having had venous sinus thrombosis complicated by secondary intracranial bleeding. Deep leg veins and pulmonary arteries were affected in 37% of the 220 patients, while 19% presented splanchnic vein thrombosis (more often of the portal vein).

Overall mortality was 22%, mostly associated with **platelet counts below 30,000/mm³ and intracranial haemorrhage.**

• Pavord S, Scully M, Hunt BJ, Lester W, Bagot C, Craven B, Rampotas A, Ambler G, Makris M. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. N Engl J Med. 2021 Oct 28;385(18):1680-1689. doi: 10.1056/NEJMoa2109908. Epub 2021 Aug 11

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics

Excipients: safety information in patient leaflets – part 2

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Benzyl alcohol	All	*This medicine contains x mg benzyl alcohol in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.* *Benzyl alcohol may cause allergic reactions.*	• Preserving agent with antimicrobial properties also used in cosmetics and in the food industry. • Higher volumes should be used with caution and only when necessay, especially in individuals with liver or kidney impairment, on account of risk of build-up and toxicity (metabolic acidosis). • Minimum toxic quantities are not known. • Increased risk in small children due to accumulation.
	Oral, parentheral	*Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build up in your body and may cause side effects (called "metabolic acidosis").* *Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.* *Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor.* *Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.*	
	Topical	*Benzyl alcohol may cause mild local irritation.*	
Cetyl alcohol, cetostearyl alcohol, stearyl alcohol	Topical	*May cause local skin reactions (e.g. contact dermatitis).*	• Cetyl alcohol is widely used in cosmetics and in various pharmaceutical formulations. In suppositories, it raises the product's melting point, and in solid modified-release forms it can be used as a permeable coating. In lotions, creams and ointments, its emollient properties are due to retention in the epidermis; the latter is lubricated and smoothed, acquiring a "silky" texture. • Stearyl alcohol, nowadays a synthetic product, used to be prepared from spermwhale oil. It is employed in cosmetics and pharmacy, in creams and ointments, for increased viscosity and hardening. • Cetostearyl alcohol is an alcohol mixture containing mostly stearyl and cetyl alcohol in variable proportions. It is used in cosmetics and in topical pharmaceutical formulations. It is white and oily. It increases viscosity and acts as an emulsifier - used in creams, sticks and foamless shaving creams.

To be continued ►

▶ *Cont´d*

Excipients: safety information in patient leaflets – part 2

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Wheat starch (containing gluten)	Oral	*This medicine contains only very low levels of gluten (from wheat starch)<.* *It is regarded as 'gluten-free'*> and is very unlikely to cause problems if you have coeliac disease.* *One <dosage unit> contains no more than x micrograms of gluten.* *If you have wheat allergy (different from coeliac disease) you should not take this medicine.*	• The statement 'gluten-free' applies only if the gluten content in the medicinal product is less than 20 ppm. • Wheat starch is a versatile excipient used as a tablet agglutinating, diluent and disintegrating agent. • Starches are good vehicles for amorphous formulations and can improve the bioavailability of poorly soluble drugs.
Aprotinin	Topical (sites that may have access to the circulation - e.g. wounds, body cavities etc.)	*May cause hypersensitivity or severe allergic reactions.*	• Broad-spectrum protease inhibitor with fibrinolytic properties.
Aspartame (E 951)	Oral	*This medicine contains x mg aspartame in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.* *Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly*	• Sweetening agent in drinks, foods, artificial sweeteners and pharmaceutical formulations such as tablets, etc. • Its sweetening power is 180 to 200 times higher than that of sacarose. • It is metabolized by the body, contrarily to other intense sweeteners, thus having minimal nutritional value (1 g provides around 4 kcal); this is in practice irrelevant since aspartame is consumed in small quantities. • When ingested orally it is hydrolized in the GI tract, phenylalanine being one of the main resulting susbtances. • Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

To be continued ▶

▶ *Cont´d*

Excipients: safety information in patient leaflets – part 2

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Balsam of Peru	Topical	*May cause skin reactions.*	• A resin extract from the tree Myroxylon balsamum var. pereirae. • In the past it was also used in cosmetics and as a flavouring agent in food (it contains a volatile oil – benzyl cynnamate). • It also contains benzyl benzoate, which has scabicidal properties. • There are insufficient data to support its medicinal use. • In the literature, it is one of the commonest contact allergens.
Benzalkonium chloride	Ocular	*Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards.* *Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.*	• This is a quaternary ammonium compound with antimicrobial, disinfecting, solubilizing, moisturizing and preserving properties. • It can cause eye irritation and dryness and affect the tear film and the surface of the cornea. Patients should be monitored in case of prolonged ocular use. • Long term nasal use can cause mucosal oedema. • Use during pregnancy and lactation is not expected to be associated with harmful effects for the mother, since skin aborption is minimal.
	Nasal	*Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time.*	
	Inhalation	*Benzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially if you have asthma.*	
	Cutaneous	*Benzalkonium chloride may irritate the skin.* *You should not apply this medicine to the breasts if you are breast-feeding because the baby may take it in with your milk.*	
	Oromucosal, rectal and vaginal	*Benzalkonium chloride may cause local irritation.*	
	All	*This medicine contains x mg <benzoic acid/benzoate salt> in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.*	

To be continued ▶

▶ *Cont´d*

Excipients: safety information in patient leaflets – part 2

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Bronopol	Topical	*May cause local skin reactions (e.g. contact dermatitis).*	• Antimicrobial preserving agent in powder form. It is very stable at room temperature and is also used in cosmetics.
Butylated hydroxyanisole (E 320) and Butylated hydroxytoluene (E 321)	Topical	*May cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.*	• Butylated hydroxyanisole is an antioxidant with a mild characteristic aromatic odour and some antimicrobial properties. It is often used in combination with butylated hydroxytoluene. • They delay or prevent the oxidative rancidity of fats and oils, and prevent liposoluble vitamins from losing their active properties.

Communications to Healthcare Professionals published on the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Communication Online publication date
Brolucizumab *Beovu*	**Physicians:** ophthalmologists treating retinal conditions	Updated recommendations to minimize the known risk of intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion 05-11-2021
Dinoprostone *Propess* *Prostin E2*	**Physicians:** heads of obstetrics departments	Reminder of recommendations on dose, contraindications, warnings and precautions regarding risks of uterine hyperstimulation, uterine rupture and foetal/neonatal death 29-11-2021
Verteporfin *Visudyne*	**Physicians:** ophthalmologists **Pharmacists:** hospital **Patients:** patient organizations supporting eye disease	Information on restrictions to uninterrupted availability until the end of the first quarter of 2022 17-11-2021

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Educational Materials published on the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials Online publication date
Asfotase alfa *Strensiq*	**Patients**	**Self-injection guide** **Injection guide for parents and guardians** 18-11-2021
Fenfluramine *Fintepla*	**Physicians:** neurology, paediatric neurology **Patients**	**Prescriber's guide** **Guide for patients and caregivers** 16-11-2021
Micafungin *Micafungina Hikma*	**Physicians:** heads of department of infectious diseases, intensive care, internal medicine, general surgery, microbiology, transplant unit, and paediatrics	**Prescriber's checklist** 16-11-2021
Quetiapine *Quetiapina Sandoz*	**Physicians:** psychiatry, neurology, general/family medicine, internal medicine	**Prescriber's guide** 30-11-2021
Tolvaptan *Jinarc*	**Physicians:** nephrology **Pharmacists:** hospital	**Information guide** 09-11-2021
Upadacitinib *Rinvoq*	**Physicians:** rheumatology, internal medicine, dermatology, allergy and immunology **Patients**	**Guide** **Alert card** 09-11-2021

Compiled by Patrícia Catalão

Teaching and learning pharmacovigilance in health sciences courses in Portugal

Pharmacovigilance stands out for its continuing impact on the increment of knowledge on medications and on patient safety. It is of great relevance for the activities undertaken by healthcare professionals, suspected ADR reporting being its main facet.

Prevailing underreporting may be palliated through **continuing professional development programmes** and by reinforcing theoretical and practical knowledge imparted by the curricula of health science courses. In general, either at a national or an international level, **higher education syllabi have had reduced emphasis on pharmacovigilance topics**, which may help to explain poor healthcare professional ADR reporting rates.

We conducted a research project aiming to describe and characterize pharmacovigilance teaching and learning processes in Portugal. We analyzed healthcare professional and student knowledge, perceptions and attitudes, as well as the main barriers and facilitating factors that professionals identified concerning spontaneous ADR reporting. We used a mixed methodology consisting both of **direct analysis**, including online social media and an email survey to several organizational contact points and student groups, and **indirect analysis** through an explicit review of the curricula of health sciences courses, including a search using 43 key words into the syllabi of seventeen state-run higher education courses. The results of both analyses are presented in the **Table** overleaf.

Considering the survey's results and the fact that few health sciences courses teach any pharmacovigilance content, there is a clear need for greater thought to be given to the inclusion of pharmacovigilance in graduate and postgraduate programmes, as well as in continuing education programmes addressing active professionals working in various healthcare organizations and facilities.

Margarida Perdigão, Anabela Afonso,
Manuel José Lopes, Ana Margarida Advinha

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<table>
<tr><td rowspan="3">INDIRECT ANALYSIS</td><td colspan="3">98 syllabi identified for possible pharmacovigilance content out of 17 courses
93 syllabi included in the study in Portugal (5 syllabi could not be accessed, hence not included)</td></tr>
<tr><td>3 mandatory specific syllabus units only in Pharmaceutical Sciences, Pharmacy and Biomedical Pharmacy courses, and 1 optional syllabus unit taught in the Pharmaceutical Sciences course</td><td rowspan="2">Courses offering the least training in pharmacovigilance:
Audiology
Orthoptics and Vision Sciences
Speech Therapy
Occupational Therapy</td><td rowspan="2">Courses offering the most training in pharmacovigilance:
Biomedical Pharmacy
Medicine
Nursing
Pharmaceutical Sciences
Pharmacy</td></tr>
<tr><td>39 syllabus units (42%) did not include any of the key words searched</td></tr>
<tr><td>DIRECT ANALYSIS (n=650)</td><td>Health sciences students (62%)</td><td>Healthcare professionals (38%)</td></tr>
<tr><td>Any spontaneous suspected ADR reported</td><td>10% YES
84% NO
(6% did not remember or did not know)</td><td>41% YES
55% NO
(4% did not remember or did not know)</td></tr>
<tr><td>Course syllabus includes a specific pharmacovigilance teaching unit</td><td>29% YES
55% NO
(16% did not remember or did not know)</td><td>23% YES
68% NO
(9% did not remember or did not know)</td></tr>
<tr><td>Perceptions on the relevance of pharmacovigilance</td><td colspan="2">Pharmacy, Dental Hygiene and Dentistry students and professionals agreed the most with including pharmacovigilance in teaching curricula and with considering pharmacovigilance course topics as valuable to practical professional activities.</td></tr>
<tr><td>Perceptions on overall training in pharmacovigilance</td><td colspan="2">Pharmaceutical Sciences, Nursing and Pharmacy students totally agreed that pharmacovigilance should be part of healthcare professional continuing training curricula, that pharmacovigilance should be included in health sciences course syllabi, and that this would motivate them further to report suspected ADRs.</td></tr>
<tr><td rowspan="2">Basic knowledge and perceptions on pharmacovigilance teaching/learning</td><td colspan="2">Health sciences students</td></tr>
<tr><td colspan="2">Most Pharmaceutical Sciences, Nursing and Pharmacy students were aware of pharmacovigilance, knew the relevance of spontaneous ADR reporting and identified general pharmacovigilance-related content in their courses.
On the other hand, a minority reported being familiar with clinical pharmacovigilance resources and not having participated in educational events that could have increased their knowledge in pharmacovigilance; 84% would be interested in participating in such educational sessions.</td></tr>
<tr><td rowspan="3">Main determinants of spontaneous suspected ADR reporting</td><td colspan="2">Healthcare professionals</td></tr>
<tr><td colspan="2">Most frequently identified hurdles: little continuing education in pharmacovigilance and little ADR reporting experience (e.g., little experience in filling out forms).</td></tr>
<tr><td colspan="2">Most frequently identified facilitating factors: viewing ADR reporting as a professional duty, receiving official information regarding pharmacovigilance topics, receiving continuing training in pharmacovigilance.</td></tr>
</table>