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Vigilance News

Edition 23 – November 2019

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Impressum

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We would like to thank all colleagues for their contribution to producing this edition of Swissmedic Vigilance News.

Contact
Please send any suggestions or feedback on this issue of Swissmedic Vigilance News to news.vigilance@swissmedic.ch.

Report of an adverse drug reaction (ADR)

Swissmedic recommends using the reporting portal (direct-entry or XML file upload).

Online reporting portal ElViS

Contents

Editorial

Dear Reader

In drug safety, the question sometimes arises of how valid spontaneous pharmacovigilance reports are compared with trial data from clinical research.

The adverse events that occur during pivotal trials of medicinal products are recorded in a precisely defined collective and under controlled conditions. The medicinal products in question are tested against placebo or a known comparator product. Both the identified and potential risks are described in a risk management plan (RMP).

Once a medicinal product has been authorised, pharmacovigilance studies known as post-authorisation safety studies (PASS) are used to assess risks on an ongoing basis, for example in specific patient populations such as children or pregnant women. This often involves generating and evaluating data from registries or observational studies and provides a way of gaining fresh knowledge in the real-life environment that could not be obtained in a randomised controlled trial, where inclusion and exclusion criteria apply. One example of this is described in the article entitled "Morbidity and mortality associated with the use of oral anticoagulants under real-world conditions".

In addition to trial data, the data from spontaneous reports submitted under the pharmacovigilance system are a further important source of information on the potential risks associated with medicinal products.

Case reports describe patients' data and medical history, the medicinal products they have taken and the course of the adverse drug reaction (ADR) they have experienced. The severity (serious or non-serious), outcome (recovering, not recovering, fatal) and course between administration and the occurrence of the ADR (latency) all play a key role here. The description of the ADR in the case narrative is followed by the medical evaluation. When categorising risks, reference can be made to the Information for healthcare professionals, which is openly accessible at www.swissmedicinfo.ch.

It is thus possible to detect rare ADR such as that described in the "Cortical blindness after cerebral digital subtraction angiography" case report. One article in this edition of Swissmedic Vigilance News deals with haemophagocytic lymphohistiocytosis (HLH), a rare and severe ADR that can occur during treatment with immune checkpoint inhibitors.

However, spontaneous reporting can also draw attention to ADR in certain patient populations, such as the elderly (see article on "Adverse drug reactions in the elderly"). Individual case reports concerning specific groups of medicinal products, such as vaccines, provide a further example. You will find more information in the 2018 statistics for vaccines and human medicinal products.

We wish all our readers a happy festive season and a successful start to the new decade.

Eva Eyal

Pharmacist / editor of Swissmedic Vigilance News
Safety of Medicines division, Swissmedic

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Drug safety and signals

New data on morbidity and mortality associated with the use of oral anticoagulants under real-world conditions

In randomised controlled trials (RCT) of direct oral anticoagulants (DOACs), the substances dabigatran, rivaroxaban, apixaban and edoxaban (1, 2, 3, 4) have proved to be at least as effective as – or slightly more effective and safer than – dose-adjusted treatment with vitamin K antagonists (VKAs).

Data on everyday use from three German health insurance funds now reveal a different picture (5). This study involved 37,439 insured patients with atrial fibrillation who were treated either with a DOAC or a VKA. The average age in both cohorts was 78 years. After one year of treatment, significantly more patients in the group treated with DOACs compared to the group treated with VKAs

- had died (Incidence Rate Ratio [IRR] 1.22; 95% CI: 1.17-1.28) or
- had suffered an ischaemic stroke (IRR 1.90; 95% CI: 1.69-2.15),
- a non-specified stroke (IRR 2.04; 95% CI: 1.16-3.70),
- a transient ischaemic attack (IRR 1.52; 95% CI: 1.29-1.79),
- a myocardial infarction (IRR 1.26; 95% CI: 1.10-1.45),
- an arterial embolism (IRR 1.75; 95% CI: 1.32-2.32) or
- severe bleeding events (IRR 1.92; 95% CI: 1.71-2.15).

Haemorrhagic stroke was the only outcome for which no statistically significant difference was observed between DOAC and VKA treatment (IRR 0.94; 95% CI: 0.76-1.17).

One of the reasons for the discrepancies between these two data analyses could be the differing patient populations. In RCTs, the patients are relatively uniform and have lower morbidity than is the case for real-world data. Roughly a quarter of the patients analysed here would have been denied access to RCTs due to pre-existing illnesses such as endocarditis, heart valve disease, pulmonary embolisms or previous cardiac interventions (6). It should also be borne in mind that sicker patients are generally associated with a longer list of concomitant drugs, with the potential for interactions with DOACs.

Moreover, a study commissioned by the European Medicines Agency (EMA) also revealed differing bleeding risks within the DOAC substance class (7). In this study, apixaban, rivaroxaban and dabigatran were administered in routine clinical use as alternatives to conventional oral anticoagulants (OACs) such as phenprocoumon and warfarin. To this end, four cohorts from Denmark, Germany, the United Kingdom and Spain, with a total of 251,719 patients, were assessed. The patients had an average age of 75 years. Only in Denmark was the bleeding risk significantly lower for DOACs, with 16% fewer major bleeding events, than for OACs (Hazard Ratio [HR]: 0.84; 95% CI: 0.79-0.90). A different picture emerged in the United Kingdom, where DOACs were 13% more often associated with major bleeding events (HR: 1.13; 95% CI: 1.02-1.25). Gastrointestinal bleeds were observed more frequently, to a statistically significant extent, for dabigatran and rivaroxaban, by 48-67% and 30-50% respectively, than for OACs. This was reported by all countries, with the exception of Denmark. For apixaban, the risk of gastrointestinal bleeding events in Germany and Denmark was 20% lower than for OACs. No differences were observed here for Spain or the United Kingdom.

Intracranial bleeds tended to occur less frequently with DOACs than with OACs, although rivaroxaban proved to be an exception in the United Kingdom, where these types of bleeding events were much more frequent than with OACs (HR: 2.37; 95% CI: 1.19-4.71). Possible causes, for example related to patient selection or the failure to observe contraindications, are currently under investigation (7).

Literature

(1) Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in non-valvular atrial fibrillation. N Engl J Med. 2009 Sep 17; 361:1139-51.

(2) Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8; 365:883-91

(3) Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15; 365(11):981-92

(4) Giugliano RP, Ruff CT, Braunwald E et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov 28; 369(22):2093-104.

(5) Mueller S, Groth A, Spitzer SG, et al. Real-world effectiveness and safety of oral anticoagulation strategies in atrial fibrillation: a cohort study based on a German claims dataset. Pragmatic and Observational Research 2018. 9:1-10

(6) Eckert N. Wenn Studienergebnisse und die reale Welt divergieren. Deutsches Ärzteblatt 2019. 116:257-258

(7) Gardarsdottir H. Characterising the risk of major bleeding in patients with Non-Valvular Atrial Fibrillation: noninterventional study of patients taking Direct Oral Anticoagulations in the EU. EU PE&PV Research Network. EUPAS Register Nr: 16014 vom 6.02.2019

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Adverse drug reactions in the elderly

Introduction

Under the current Therapeutic Products Act, adverse drug reactions that are observed in the course of everyday medical practice have to be reported to Swissmedic. Serious adverse drug reactions, as yet unknown adverse drug reactions or reactions that are poorly described in the information for healthcare professionals for the medicinal product in question and adverse drug reactions with a particular clinical relevance have to be reported to the Agency.

The case history below, which was taken from a report in Swissmedic's "VigilanceONE Ultimate" database, is one of many examples of adverse drug reactions in the elderly.

Case Narrative

The case concerns a 96-year-old female weighing 54 kg, with a history of asthma, hypertension, atrial fibrillation and heart failure. Following the death of her husband at an unspecified date, the patient went into cognitive decline, experiencing difficulty in caring for herself at home and becoming malnourished.

Her normal treatment comprises the following medicinal products:

- acenocoumarol, as dictated by monitoring,
- digoxin, 0.25 mg daily, five days out of seven,
- torasemide, 2.5 mg daily,
- lisinopril, 10 mg daily,
- simvastatin, 20 mg daily,
- inhaled budesonide, 200 micrograms twice daily.

At the end of June 2017, the patient was admitted to hospital in an acute confusional state but with no nausea or vomiting; it was not possible to gather a case history for eye-related symptoms. On admission, both blood pressure and heart rate were normal. An electrocardiogram showed a regular sinus rhythm of 85 beats a minute with only one anomaly – a cup-shaped ST segment depression. Laboratory tests showed creatinine of 246 micromol/l (previous known value: 83 in September 2011), potassium of 5.3 mmol/l, a digoxin level (taken on admission, the date and time of the last sample not being known) of 4.6 microgrammes/l for a reference interval of 0.8–2.0 in the indication of atrial fibrillation. Finally, the INR (international normalised ratio) was in excess of 6. The remaining electrolytes – including sodium – were within the normal range.

A diagnosis of digoxin and acenocoumarol intoxication with acute renal failure in the context of high ambient heat levels was made. All medication was suspended and the patient was hospitalised.

The acenocoumarol was resumed some time later. The subsequent course was favourable, with an INR of 2.7, creatinine of 122 micromol/l and potassium of 4.5 mmol/l at the beginning of July 2017.

This patient presents the classic risk factors for digoxin intoxication: advanced age, low body weight, female, excessive dosage, heatwave, isolation, cognitive problems with probable poor compliance, malnutrition and dehydration (accompanied by renal failure and resulting in a vicious circle). Co-medication with a diuretic (although probably ineffective given the low dosage and level of kidney failure) and angiotensin-converting-enzyme (ACE) inhibitor is an aggravating factor. The ACE inhibitor may have been implicated in the hyperkalaemia.

The acenocoumarol intoxication can be attributed to poor compliance and malnutrition.

Given the clinical picture, course of events and absence of other more convincing causes, digoxin is certain to have caused the intoxication and may possibly have caused the (multifactorial) acute confusional state, in which torasemide and lisinopril played a contributory role through pharmacodynamic interaction.

Discussion

Although any patient may experience an adverse drug reaction, the elderly exhibit certain characteristics that make them more susceptible. Age-related factors modify pharmacodynamics and pharmacokinetics in the elderly, thereby increasing the risk of adverse reactions. Certain classes of medicinal product – such as antidepressants, hypnotics, anxiolytics, anticoagulants, hypoglycemics and cardiac glycosides – are currently implicated. Treatment with digoxin de facto requires regular clinical and biological monitoring by virtue of the medicinal product's narrow therapeutic index and the significant risk of adverse drug reactions, drug interactions and intoxication.

Since the elderly often take a larger number of medicinal products (polypharmacy), they are particularly vulnerable to drug interactions, which can sometimes be difficult to predict. Moreover, concomitant use of more than one medicinal product with similar or comparable adverse reactions may increase the risk of those effects manifesting.

A medicinal product administered to treat one condition may exacerbate another, especially in the elderly. Distinguishing barely perceptible adverse drug reactions from the effects of the disease is difficult and may result in a prescribing cascade.

It is also important to remember that under-prescribing may increase morbidity and have a detrimental impact on quality of life. Examples of medicinal products that are under-prescribed in the elderly include anti-depressants, analgesics and blood pressure treatments. It is therefore essential to prescribe adequate doses of medication.

Regular prescribing in the elderly provides a way of determining the potential benefits of treatments compared with their toxicity. Supervising the use of medicinal products in the elderly and efficient communication with healthcare professionals are conducive to good compliance in elderly patients.

Conclusion

Adverse drug reactions occur particularly frequently among the elderly. For that reason, it is crucial for healthcare professionals to ensure smooth communication and optimal supervision among elderly patients, particularly when delivering care. It is important to avoid prescribing cascades as far as possible. Strict vigilance is therefore indicated when an adverse drug reaction is suspected in elderly patients. Regular re-evaluation of elderly patients' prescriptions and treatments is an opportunity to discontinue non-essential, inappropriate or poorly dosed medicinal products and, above all, to remind each patient which treatments are vital for their health.

Reporting adverse drug reactions

Swissmedic recommends using its specially designed online portal (Electronic Vigilance System, ELViS) for reporting adverse drug reactions (ADR). All the necessary information can be found at www.swissmedic.ch.

Literature

- Product information: www.swissmedicinfo.ch
- "Tools" provided by the Clinical Pharmacology and Toxicology Department at Geneva University Hospitals (HUG) (French only): https://www.hug-ge.ch/pharmacologie-toxicologie-cliniques/outils
- Stuck A. Nouveautés concernant les médicaments connus chez les personnes âgées ; Forum Med Suisse 2018. 18(03):46-48 (German and French only)

Véronique Ditesheim, MD

Safety of Medicines division, Swissmedic

Haemophagocytic lymphohistiocytosis (HLH) as an adverse drug reaction

Haemophagocytic lymphohistiocytosis (HLH) is the term given to a group of rare syndromes characterised by excessive immune activation. HLH is potentially life-threatening due to the progressive organ damage it may cause. Patients with HLH present with non-specific symptoms, such as persistent high fever, increased tendency to bleed, hepatosplenomegaly and lymphadenopathy. As the condition progresses, liver function diminishes, ultimately resulting in multiple organ failure. A distinction is made between primary (inherited) and secondary (acquired) HLH. Acquired HLH is generally caused by multiple external triggers. Examples of such external stimuli are infections and the administration of immunomodulatory agents. In addition, the risk of HLH is elevated by underlying autoimmune disease and neoplasms.

To date, 16 cases of medication-related HLH have been reported in Switzerland. Eight of these were fatal (50.00%). The average age of the patients was 41 (5–84 years). Seven patients (43.75%) were female, eight (50.00%) were male. The gender of the five-year-old child was not specified. Medicinal products in the antineoplastic and immunomodulating agents group (Anatomical Therapeutic Chemical / Defined Daily Dose Classification group L) have most frequently been associated with HLH. Of these, seven belonged to the antineoplastic subgroup, and seven to the immunosuppressive subgroup.

HLH in association with checkpoint inhibitors

Immune checkpoint inhibitors are substances that inhibit key molecules involved in combating inflammation. These include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, also called CD152), for example, as well as programmed cell death protein 1 (PD-1) and the associated ligand (PD-L1). Checkpoint inhibition is now being used in cancer treatment as a way of activating the immune system and stimulating anti-tumour activity. In clinical trials, patients who were treated with checkpoint inhibitors for a wide range of tumour entities lived longer on average than patients who did not receive checkpoint blockade therapy. CTLA-4 is inhibited by ipilimumab (Yervoy®). Nivolumab (Opdivo®) and pembrolizumab (Keytruda®) inhibit PD1, while atezolizumab (Tecentriq®), durvalumab (Imfinzi®) and avelumab (Bavencio®) blockade PD-L1. Shortly after the checkpoint inhibitors had been launched, it became clear that the elevated immune activity is capable of causing immune-mediated adverse drug reactions (ADR) in all organ systems, but frequently in the gastrointestinal tract, endocrine glands, skin and liver. Cases of HLH associated with the use of checkpoint inhibitors have now been reported worldwide. However, the number of reports varies greatly from region to region. High reporting rates have been observed in France, Germany and Japan, while the lowest rate was found in the USA.

Case report

A good example is the case of a 74-year-old Swiss male patient who was treated with ipilimumab and nivolumab as adjuvant chemotherapy for adenocarcinoma of the lung following surgical resection. Approximately four months after starting treatment, the patient developed leukocytosis and fever of unknown origin. This prompted the attending physician to discontinue the checkpoint inhibitors. Once an infectious origin for the fever and leukocytosis had been ruled out, treatment with steroids was initiated. While following the course of steroids, the patient continued to experience severe fever accompanied by anxiety and confusional states. The patient was readmitted

to hospital, where he was found to have extremely high levels of C-reactive protein and interleukin 6, as well as splenomegaly, anaemia and thrombocytopenia. His neutrophil count, D-dimers, ferritin and liver enzymes were all elevated. A PET-CT scan that showed disease progression in the skeleton, muscles, liver, spleen and subcutaneous lymph nodes, as well as the existence of highly concentrated tumour cells in the bone marrow and spleen, led to a suspicion of HLH. A PET-CT is a combination of positron emission tomography (PET) and computed tomography (CT) in the same device. The two complementary imaging technologies are thus able to generate an accurate image that simultaneously depicts both body structure and function. The patient died approximately four months after the onset of the HLH.

Summary

Although rare, HLH is nevertheless a serious ADR, producing a fatal outcome in approximately 50% of cases. With the arrival of a significant number of new medicines, particularly for the treatment of cancer, the number of cases could rise substantially in the future. HLH should always be considered when treating non-specific symptoms such as persistent high fever in patients whose immune system has been stimulated by medication. Two factors play a role in treatment: suppressing the excessive inflammatory reaction and treating the underlying disease. In 2011, Trottestam et al. published long-term results of a treatment protocol for HLH, comprising etoposide, corticosteroids, ciclosporin A and intrathecal methotrexate if indicated.

Literature

- Brisse E, Matthys P, Wouters CH. Understanding the spectrum of haemophagocytic lymphohistiocytosis: update on diagnostic challenges and therapeutic options; British Journal of Haematology. 2016; 174
- Daver N, Kantarjian H. Malignancy-associated haemophagocytic lymphohistiocytosis in adults; Lancet Oncology. 2017; 2
- Esteban YM, de Jong JLO, Tesher MS. An Overview of Hemophagocytic Lymphohistiocytosis; Pediatric Annals. 2017; 46
- Noseda R, Bertoli R, Müller L, Ceschi A. Haemophagocytic lymphohistiocytosis in patients treated with immune checkpoint inhibitors: analysis of WHO global database of indivudual case safety reports; Journal for Immunotherapy of Cancer. 2019; 7
- Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade; New England Journal of Medicine. 2018; 378
- Ramos-Casals M, Brito-Zéron P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome; Lancet, 2014; 383
- Thomas W, van't Veer M, Besser M. Haemophagocytic lymphohistiocytosis: an elusive syndrome; Clinical Medicine. 2016; 16
- Trottestam H, Horne AC, Aricò M, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood. 2011;118(17):4577-4584

Kira Vanessa Blankenbach, MD

Safety of Medicines division, Swissmedic

Current case report: Transient cortical blindness after cerebral digital subtraction angiography

A working group at Cantonal Hospital St. Gallen has reported on a 57-year-old female patient who was diagnosed with an aneurysm of the basilar tip at another hospital, which subsequently transferred her to the Cantonal Hospital St. Gallen for further investigation. The patient's only pre-existing disease was arterial hypertension, for which she was taking bisoprolol.

After the patient had been examined on admission, lumbar puncture was carried out, which revealed antecedent subacute subarachnoid haemorrhage. Subsequent digital subtraction angiography (DSA) confirmed the diagnosis of aneurysm, which was treated by endovascular coiling. 230 ml Visipaque 320 was administered for the DSA and endovascular embolisation.

After the patient had returned to the intensive care unit, she complained of being almost totally blind in both eyes and only able to distinguish between light and dark. There were no other neurological deficits. Intracranial haemorrhage and thromboembolic complications were ruled out. Given the temporal relationship with the DSA, transient cortical blindness was suspected, and treatment with heparin and nimodipine (to prevent vasospams) was initiated. The patient regained full vision 36 hours after onset. Follow-up investigations showed complete elimination of the aneurysm and no impairment of vision.

Conclusion

Transient cortical blindness is a very rare complication of cerebral or coronary angiography. Embolic or haemorrhagic causes must be excluded prior to diagnosis. The underlying mechanism has not yet been elucidated and is surrounded by controversy. The contrast medium probably becomes neurotoxic as a result of the blood-brain barrier being breached. No specific treatment is available, and the authors take the view that none is necessary given the spontaneous remission. However, steroids and anticoagulants are frequently used as supportive medication.

This literature report was submitted to us by GE Healthcare of Opfikon, the company that distributes Visipaque in Switzerland. The Information for healthcare professionals describes transient cortical blindness as a very rare (less than 1 in 10,000 cases) undesirable effect of Visipaque. Like traditional spontaneous reports, Swissmedic continuously assesses literature reports and reviews them in particular for their signal impact.

Literature

Weiss A, Den Hollander J, Pietsch U. Transient Cortical Blindness: a Rare Complication After Cerebral Digital Subtraction Angiography; SN Comprehensive Clinical Medicine 2019. 1:567-570

Thomas Schwartz, MD

Safety of Medicines division, Swissmedic

Statistical Review 2018

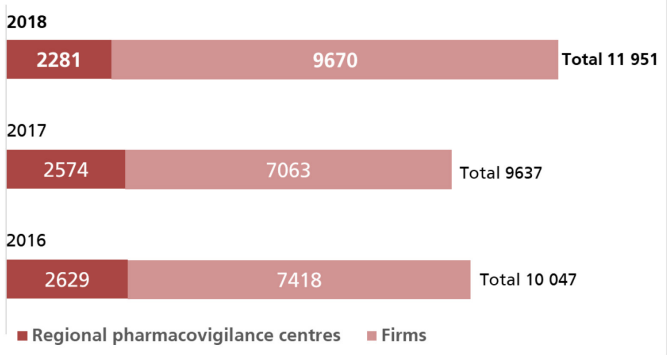
Vigilance of human medicines

Within the framework of the pharmacovigilance network, the direct reports from professionals and patients on adverse drug reactions are assessed in six regional pharmacovigilance centres (RPVC) on behalf of Swissmedic and recorded in the national database. The professionals who submit the reports receive appropriate feedback. Reports on adverse reactions from within Switzerland are also sent to Swissmedic by the pharmaceutical firms.

Activities

- A new database for recording and assessing adverse drug reactions was introduced.
- In an important step in efforts to improve efficiency and encourage paperless working, a further four authorisation holders were connected to the electronic ADR reporting gateway.
- To improve reporting quality, Swissmedic systematically evaluates the quality of the reports submitted by companies and uses the finding to help plan and conduct GVP inspections.

Adverse drug reactions, human medicinal products: number of initial reports from



Martina Schäublin, MD

Safety of Medicines division, Swissmedic

Vaccinovigilance

Complete report – link:

Adverse events following immunization – annual report 2018

Summary of adverse events following immunization reported in Switzerland during 2018

During 2018, the Safety of Medicines division at Swissmedic received 223 new case reports of suspected adverse events following immunization (AEFI) from within Switzerland. This was slightly less than the number of cases submitted during 2017 (232 reports) but higher as compared to 2016 (209 reports).

AEFI reports received during 2018 were recorded and evaluated in the new pharmacovigilance database of Swissmedic – VigilanceONE Ultimate. There are no accurate data available regarding the total number of vaccines/doses administered during 2018, so no straightforward conclusion regarding AEFI reporting rates can be drawn.

As previously, Swissmedic is encouraging high-quality, spontaneous reporting of AEFIs , to facilitate early detection of new safety signals.

Since 2010, important safety topics concerning vaccines – including potential risks – have been evaluated with participation of the Human Medicines Expert Committee (HMEC) of Swissmedic.

An increased AEFI reporting rate followed by a scientific evaluation of relevant cases can lead to risk minimisation measures in order to ensure vaccine safety, wherever necessary.

Figure 1: Number of AEFI reports by age group and gender, 2018

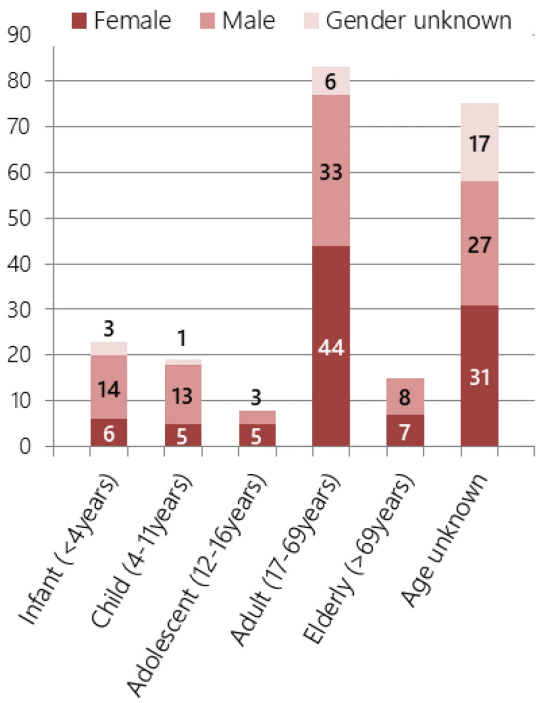


Figure 1 compares the number of reports by age group and gender. The largest number of AEFI reports involved adults (83 reports), followed by infants (23 reports), children (19 reports), elderly (15 reports) and adolescents (8 reports).

Throughout 2018, the number of reports concerning females was equal to the number of reports concerning males (98 reports in each group). In 27 AEFI reports, the gender of the persons remained unknown. In 75 case reports, the age group of the patients was not reported.

Figure 2: Number of reports by vaccine group (ATC code) and seriousness, 2018

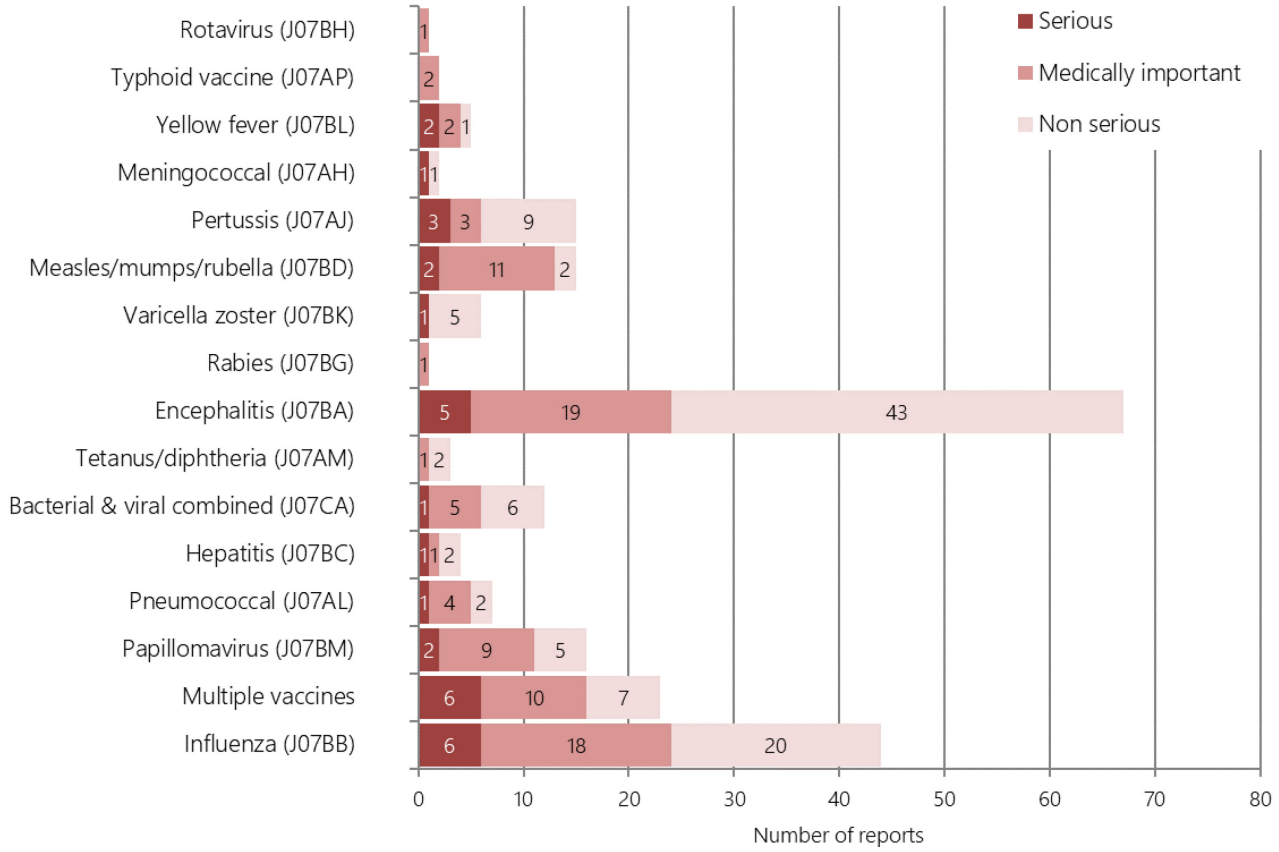


Figure 2 shows the number of spontaneous AEFI reports grouped according to vaccine group (ATC code) and seriousness. No data are available to Swissmedic regarding the number of doses administered in each particular vaccine group in 2018, so this figure does not indicate which vaccine group displayed a higher AEFI rate (number per 100,000 doses).

A safety report is generally assessed as "serious" if it involves an adverse event leading to death, hospitalisation or prolongation of an existing hospitalisation, or if it was life-threatening or resulted in a significant or persistent disability or a congenital anomaly. Furthermore, a report is assessed as "medically important" (and hence as "serious") even if it does not fulfil the criteria for "seriousness" mentioned but involves an event considered to be significant by medical judgement.

All other reports are assessed as "non serious" (e.g. self-limiting adverse events with good recovery). Of the 223 spontaneous reports received in 2018, 105 (47.1%) were non serious, 87 (39%) included medically important events and 31 (13.9%) of the reports involved AEFIs with serious consequences.

Considering all vaccines, the relative frequency (percentage) of "serious" reports (i.e. reports containing AEFIs with serious consequences) decreased overall in 2018 as compared to those recorded during the previous year (13.9% in 2018 vs. 19.4% in 2017).

Figure 3: Number of AEFI reports by reporter qualification and seriousness, 2018

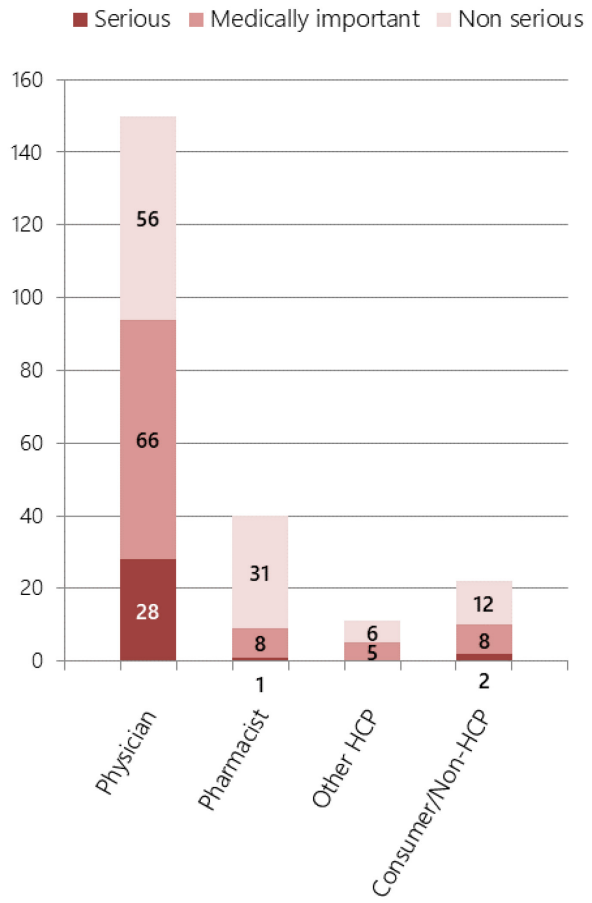


Figure 3 shows the number of Swiss AEFI reports in 2018 grouped according to primary reporter and seriousness. Health care professionals – who generally provided medically confirmed data and a good quality of individual AEFI reports – were the primary reporters in the vast majority of cases. Physicians provided the largest group of AEFI reports (150 of 223), which also included a larger number of reports assessed as serious or medically important (94 of 150 reports).

Figure 4: Number of AEFI reports by age group and seriousness, 2018

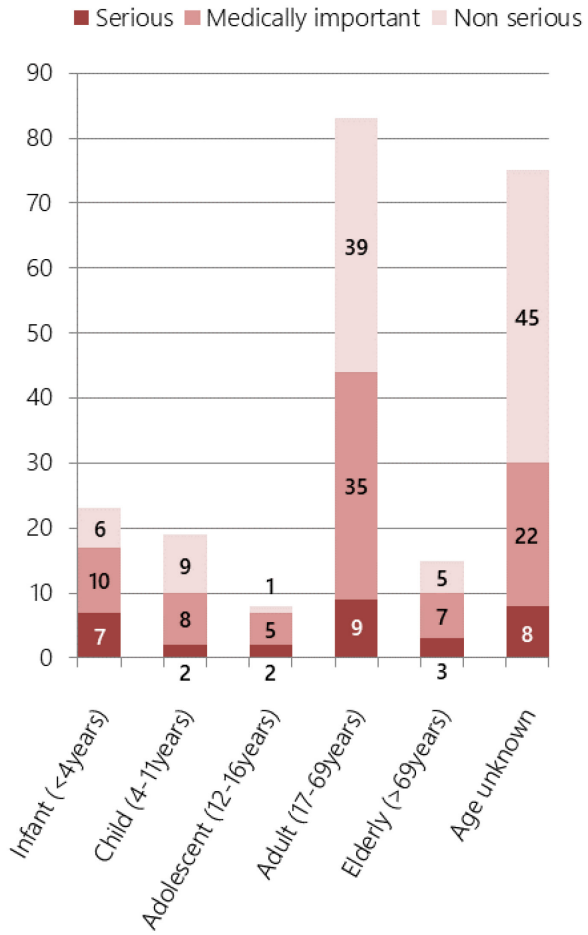


Figure 4 shows the number of spontaneous AEFI reports grouped according to age group and seriousness. It is apparent that the largest numbers of "serious" (9 reports) or "medically important" (35 reports) were recorded in the adults age group. However, during 2018, the adolescents age group showed the highest percentage of "serious" or "medically important" cases when taken together (7 of 8 reports, 87.5%) as compared with the other age groups analysed: infants (17 of 23 reports, 69.6%), adults (44 of 83 reports, 53%) and children (10 of 19 reports, 52.6%).

Valeriu Toma, MD

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Information on the Swissmedic website[1]

Healthcare Professional Communication

30.10.2019
DHPC – Umfassende Überarbeitung der ganzen Fachinformation von Haldol®
Fachinformationen für alle Darreichungsformen wurden umfassend überarbeitet

30.10.2019
DHPC – Produkte für die parenterale Ernährung
Notwendiger Lichtschutz zur Reduktion des Risikos schwerwiegender unerwünschter Wirkungen bei Frühgeborenen

24.10.2019
DHPC – Herceptin® (Trastuzumabum) 440mg, Lyophilisat, Lösung zur parenteralen Anwendung
Falsche In-Use-Haltbarkeitsangabe in der gedruckten und online verfügbaren Fachinformation

23.10.2019
DHPC – Kombinierte hormonale Kontrazeptiva (CHC) mit Dienogest
Erhöhtes Risiko venöser Thromboembolien unter CHC mit Dienogest/Ethinylestradiol (Valette, Jeanine) im Vergleich zu Levonorgestrel-haltigen CHC - begrenzte Daten zu CHC mit Dienogest/Estradiolvalerat (Qlaira)

22.10.2019
DHPC – Picato® (Ingenolmebutat)
Risiko von Hautkrebs bei Patienten mit aktinischer Keratose

17.10.2019
DHPC – Lucentis®, Injektionslösung zur intravitrealen Injektion in Fertigspritze
Schwergängigkeit des Spritzenkolbens

16.09.2019
DHPC – Gilenya® (Fingolimod)
Risiko angeborener Fehlbildungen bei Feten, die Fingolimod im Mutterleib ausgesetzt waren

30.08.2019
DHPC – Ofev® (Nintedanib)
Wichtige sicherheitsrelevante Information zu Ofev® (Nintedanib) in Bezug auf die Aktualisierung der Fachinformation entsprechend der EU-Fachinformation für Nierenversagen im Zusammenhang mit der Therapie von Patienten mit idiopathischer Lungenfibrose (IPF) mit Nintedanib

14.08.2019
DHPC – Implanon NXT® (Etonogestrel)
Aktualisierung der Instruktionen in der Arzneimittelinformation zur Einlage und Entfernung des Implantates zwecks Minimisierung des Risikos von intravaskulärer Insertion und neurovaskulärer Verletzung

07.08.2019
HPC – Aktualisierung von Warnhinweisen für die Anwendung von Methotrexat
in der Schwangerschaft sowie in Bezug auf Empfängnisverhütung und Fertilität

31.07.2019
DHPC – Lartruvo® (Olaratumab)
Widerruf der Schweizer Marktzulassung wegen fehlender therapeutischer Wirksamkeit

03.07.2019
DHPC – Verdacht auf rezidivierende thrombotische Ereignisse in Zusammenhang mit der Einnahme von direkten oralen Antikoagulantien (DOAKs) bei Patienten mit Antiphospholipid-Syndrom
Die Anwendung von DOAKs wird bei Patienten mit APS nicht empfohlen, besonders bei Hoch-Risiko-Patienten

03.07.2019
HPC – Anwendung der Vincristin-haltigen Arzneimittel
Intrathekale Verabreichung von Vincristin führt zu lebensbedrohenden Lähmungen – Anpassung der FI und Hinweis auf den Packmitteln

[1] Most of the links are available in German/French only

19.06.2019
DHPC – Actemra® (Tocilizumab)
Bei Anwendung von Actemra (Tocilizumab) sind schwerwiegende, medikamenteninduzierte Leberschädigungen, einschliesslich akutem Leberversagen, Hepatitis und Ikterus, aufgetreten, die in einigen Fällen eine Lebertransplantation erforderlich machten. Das Auftreten einer schwerwiegenden Hepatotoxizität wird als selten erachtet.

14.06.2019
DHPC – Lemtrada® (Alemtuzumab)
Einschränkung der Anwendung bei Multipler Sklerose aufgrund von Sicherheitsbedenken

06.06.2019
DHPC – Genvoya® (Elvitegravir/Cobicistat/Emtricitabin/Tenofoviralafenamid) / Stribild® (Elvitegravir/Cobicistat/Emtricitabin/Tenofovirdisoproxil) /Tybost® (Cobicistat)
Erhöhtes Risiko für Therapieversagen und für eine Mutter-Kind-Übertragung der HIV-Infektion aufgrund geringerer Elvitegravir-Exposition während des zweiten und dritten Trimenons der Schwangerschaft

04.06.2019
DHPC – Xeljanz® (Tofacitinib)
Einschränkung der 10 mg zweimal täglichen Anwendung bei Patienten mit einem erhöhten Risiko einer Lungenembolie

Announcements

29.10.2019
Adaptation of the Directory Overview of documents to be submitted HMV4
ZL000_00_006e_VZ

29.10.2019
Adaptation of the Form Variations and extensions HMV4
ZL300_00_003e_FO

29.10.2019
Adaptation of the Guidance document Formal requirements HMV4
ZL000_00_020e_WL

28.10.2019
Intensified action targeting illegally imported erectile stimulants: what they really contain
Swissmedic laboratory inspects illegal shipments of medicinal products in which tadalafil is the declared active substance

28.10.2019
UPDATE zur Sicherheitsmitteilung: COCUNE – Waschhandschuh (parfümiert/unparfümiert) der Firma Stöpler Instrumenten & Apparaten B.V. (NL)

24.10.2019
Adaptation of the Guidance document Authorisation of herbal medicinal products HMV4
ZL101_00_008e_WL

22.10.2019
New templates: product information and patient information for human medicinal products – minimum requirements as per HMV4
ZL000_00_048d_VL / ZL000_00_049d_VL

22.10.2019
Warning regarding Esillaa slimmers' tea
Swissmedic is issuing a warning regarding the slimming product Esillaa.

18.10.2019
Adaptation of the Forms Renewal of authorisation HMV4
ZL201_00_008e_FO / ZL201_00_010e_FO

08.10.2019
Anpassung der Praxis bezüglich Arzneimittelinformation
Die geltende Praxis, in welchen Fällen für ein Tierarzneimittel eine Fachinformation und eine Packungsbeilage zwingend notwendig sind, wurde vereinfacht. Die neue Praxis gilt ab sofort.

04.10.2019
Adverse events following immunization – annual Vaccinovigilance report
Summary of adverse events following immunization reported in Switzerland during 2018

03.10.2019
Swissmedic Journal
Latest edition
Swissmedic Journal September 2019

01.10.2019
Questions and answers about the revised therapeutic products legislation

30.09.2019
Fixed texts for medicinal products which are being reallocated from dispensing category C to B as of 2019
Adaptation of fixed texts for medicinal products that may continue to be dispensed by pharmacies without a medical prescription after expert advice.

27.09.2019
Training course for regulatory authorities in low- and middle-income countries
Regulatory Training Workshops – a partnership for better health

27.09.2019
Adaptation of the form New authorisation for co-marketing of medicinal product HMV4
ZL108_00_002e_FO

26.09.2019
Anti-rabies vaccines: Supply problems until at least 2020
Temporary modification of the vaccine recommendations by the FOPH

25.09.2019
Adaptation of the Guidance document Authorisation of Homeopathics, anthroposophics and other complementary medicinal products HMV4
ZL101_00_016e_WL

23.09.2019
Recall of all preparations containing ranitidine from the Swiss market
Gastric acid blocker contaminated with traces of NDMA – use available alternative treatments for this indication.

23.09.2019
Adaptation of the Guidance document Fast-track authorisation procedure HMV4 and the Guidance document Temporary authorisation for human medicinal products HMV4
ZL104_00_002e_WL / ZL109_00_001e_WL

18.09.2019
Investigation into the company Cryo-Save
Presumption of innocence principle applies to the parties concerned

09.09.2019
Adaptation of the Form Renewal of authorisation HMV4
ZL201_00_007e_FO / ZL201_00_008e_FO / ZL201_00_010e_FO

28.08.2019
Abteilung Betäubungsmittel Info & News 2019
Swissmedic Veranstaltung

27.08.2019
Swissmedic eGov services: Delegated user administration and new self-registration via CH-LOGIN from 9 September 2019
Reminder: Interruption of user administration (Swissmedic portal) and self-registration (eMessage, ElViS)

21.08.2019
Sicherheitsmitteilung: Rückruf von Unterarmgehstützen des Modells ADVANCE – Herdegen Paris, Chelles
Brechen des Handgriffs oder der Armauflagefläche

20.08.2019
SwissPAR HMV4 guidance document modified
ZL000_00_030e_WL

14.08.2019
Adaptation of the form Variations and extensions HMV4
ZL300_00_003e_FO

09.08.2019
Modification of various documents relating to authorisation
ZL000_00_006e_VZ / ZL000_00_022e_WL / ZL105_00_004e_FO

01.08.2019
Adaptation of the Guidance document Fast track authorisation procedure HMV4
ZL104_00_002e_WL

01.08.2019
Adaptation of the Guidance document Procedure with prior notification HMV4
ZL101_00_013e_WL

26.07.2019
Swissmedic laboratory publishes updated test method for nitrosamines in sartans
Safety-limit testing for the nitrosamines NDMA and NDEA using single-quadrupole GC-MS

25.07.2019
New ID and access management for Swissmedic eGov Services from mid-September 2019
Modernised user management for Swissmedic's eGovernment applications as of autumn 2019

23.07.2019
Internationale Konferenz zur Herausgabe der 10. Ausgabe der Europäischen Pharmakopöe
«EDQM and European Pharmacopoeia: State-of-the-art Science for Tomorrow's Medicines»

15.07.2019
Questions and answers on variations and extensions HMV4
Revision

15.07.2019
Medicinal products with orphan drug status
Eligibility for procedure with prior notification and modification of billing practice for fast-track authorisation procedure

12.07.2019
Information on GCP inspections

09.07.2019
Adaptation of the Guidance document Formal requirements HMV4
ZL000_00_020d_WL

08.07.2019
Renewal of authorisation for medicinal products whose authorisation expired as of 1 January 2020

08.07.2019
Update: Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents

03.07.2019
New templates for the "Information for healthcare professionals for veterinary medicinal products" and "Package leaflet for veterinary medicinal products" in Italian
ZL000_00_043i_VL | ZL000_00_044i_VL

01.07.2019
Nachtrag 9.8 der Europäischen Pharmakopöe in Kraft
Der Institutsrat hat den Nachtrag 9.8 der Europäischen Pharmakopöe auf den 1. Juli 2019 in Kraft gesetzt.

01.07.2019
Brokering of medicinal products via sales platforms
Information on broker and agent activities

01.07.2019
Supplement 11.3 zur Pharmacopoea Helvetica 11 in Kraft
Der Institutsrat hat das Supplement 11.3 zur Schweizerischen Pharmakopöe auf den 1. Juli 2019 in Kraft gesetzt.

25.06.2019
A new Drug Safety System
Gateway for the electronic exchange of individual case safety reports for companies – new version

19.06.2019
New templates for manuscripts of Information for healthcare professionals and Patient information
mandatory from 1 July 2019

14.06.2019
Revision of therapeutic products legislation: list of medicinal products reallocated from dispensing category C to dispensing category B
Monthly publication of legally approved reclassifications in accordance with Art. 45, para. 3 TPO as of June 2019

12.06.2019
New ID and access management for Swissmedic eGov Services from mid-September 2019
Advance notification: Modernised user management for Swissmedic's eGovernment applications as of autumn 2019

12.06.2019
Adaptation of the Guidance document Temporary authorisation for human medicinal products HMV4
ZL109_00_001e_WL

12.06.2019
Adaptation of the Guidance document Fast-track authorisation procedure HMV4
ZL104_00_002e_WL

03.06.2019
Neue Vertriebsform der Pharmacopoea Helvetica
ab Supplement 11.3 (1. Juli 2019)

29.05.2019
Adaptation of the Guidance document Authorisation biosimilar HMV4
ZL101_00_012e_WL

29.05.2019
Swissmedic Annual Report 2018
2018 Annual Report and annual financial statements of the Swiss Agency for Therapeutic Products (Swissmedic)

21.05.2019
Report regarding suspected illegal trading in medicinal products
As of 1 January 2019, anyone who produces, sells or distributes medicinal products is required by law to report to Swissmedic any suspicion of illegal trading in such products.

The complete list is available at the following web address www.swissmedic.ch/updates-en