Vigilance - News

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I: Editorial

Safety of medicines – quality of information and communication

Dear Reader,

Catchwords such as “quality”, “balance” and/or “transparency” are appearing more and more often in today’s media. For communications on the safety of medicines, these requirements are of paramount importance because our task is to rapidly identify the potential risks of a therapeutic product and to take the appropriate measures, particularly to issue the necessary information.

Many suspected cases of adverse drug reactions (ADRs) are only registered and analysed by our spontaneous reporting system once the products have been authorised. When assessing an individual spontaneous report, the comprehensiveness of the information and the quality of the data play a major role. Potential causal associations can be better understood, for example, when the patient’s medical history and concomitant medications are known.

The more information that is available for a product, the more comprehensive the risk-benefit analysis of the therapeutic product’s complete life cycle can be. This process is a constant one and if appropriate, suitable formal measures must be taken to monitor and minimise the risk of ADRs. The spectrum of such measures ranges from informing health professionals and the public to withdrawing the product from the market. We have selected some examples to illustrate the complex questions which we often face in our daily work.

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A well-functioning, spontaneous reporting system relies on collaboration between the authorities and various partners. These partners include health professionals such as physicians, pharmacists and nursing staff but also the patients themselves, who complete and send in the Swissmedic ADR reporting form to one of the six regional pharmacovigilance centres located in Basel, Bern, Geneva, Lausanne, Lugano or Zurich. The centres evaluate the reports and forward them to Swissmedic in an anonymised format:
http://www.swissmedic.ch/marktueberwachung/00091/00136/00146/index.html?lang=en

Cooperation with other national health authorities, e.g. with the US Food and Drug Administration (FDA) or the Australian Therapeutic Goods Administration (TGA), enables comparison of international signals with the current information in Switzerland and timely responses (see Chapter IV. Information on the safety of medicines, published on the Swissmedic website).

The pharmaceutical industry has also developed an increased interest in early identification of ADRs, particularly those which are less known and severe. The rapid exchange of information and transparent communication among all concerned is therefore essential. For this reason, the last special conference on the Safety in Medicines intended for the industry focused on the topic of communication, while current and future developments regarding patient safety was the key topic at the third Swiss Haemovigilance Conference. For those who could not take part at these and other events, we are devoting a chapter which includes an overview.

We hope that this edition of the PV Newsletter will make our decision-making processes a little more transparent for readers, and we look forward to your feedback at vigilance@swissmedic.ch.

The Editors

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II: Flash: Signals relating to the safety of medicines from the Swiss database of the Vigilance Unit

Ongoing evaluation of the safety of medicines and communication to the public

At present, regular reminders are issued on the importance of ongoing evaluation of the safety of medicines and the need for rapid, transparent communication based on rigorous analysis of the data available - data which are often provisional and incomplete. In a context where scientific studies are widely covered by the media, it falls upon the regulatory authorities to inform the public and health professionals, putting the elements of knowledge that are available into perspective. The data should therefore be released at the appropriate moment and in clear terms, stating the significance, the limits and the practical consequences of the information available. This task is particularly delicate when the uncertainties and questions are more numerous than the details for a response.

In a context of uncertainty, patient safety must be at the heart of the communication strategy, and orient the message. Faced with a continuous stream of information whose interest is at the time relative and of unequal importance, a systematic approach is needed. Criteria have therefore been defined in order to answer the central question: "Is the information pertinent for patient safety?" These criteria are mentioned briefly below and respond to the following questions:

Is the potential or proven risk associated with the treatment:

- Unexpected (not foreseeable, and therefore not likely to be recognised and associated with the treatment)?
- Serious (adverse reaction leading to death or hospitalisation)?
- Frequent (incidence or prevalence among treated cases)?
- Avoidable by applying appropriate measures (patient selection, preliminary examinations, clinical or biological monitoring, therapeutic alternatives)?

Are sufficient data available?

- Is the level of proof of a suspected risk high or low (quality of the trials, causality criteria)?

What is the importance of the medicinal product in the treatment of a health problem?

- Utility of the medicinal product (essential treatment, comfort treatment, efficacy, etc)?
- Is there a therapeutic alternative (other treatments available, efficacy and safety of the alternatives, etc)?

All 7 criteria are subjected to scientific evaluation. An additional criterion can be of critical importance for patient safety although escaping scientific consideration, but still requiring intervention and communication even if no risk has been identified: media interest in a given subject.

Examples abound, in fact, where allegations of a risk that is nonexistent but receives wide media coverage, leads to genuine public health concerns because of an abrupt rejection of using an effective, safe treatment or a vaccination. Controversies surrounding autism and vaccination against measles, mumps and rubella (MMR) led, for example, to a significant reduction in vaccination coverage in England and to a recurrence of measles and mumps epidemics, although numerous subsequent studies showed no evidence for a causal link between vaccination and autism. In this case, the principle incriminating article was withdrawn by the editor 12 years after its publication, because of serious ethical and methodological shortcomings in the conduct of the study [1].

Conversely, media attention may also at times make it possible to identify rapidly an unrecognised problem, to stimulate corrective

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measures and, above all, to disseminate important information widely to the public. Media attention, however, reinforces the random nature of defining priorities in terms of public health. In addition the gap, which is at times considerable, between the perceived and the real risk no doubt complicates communication efforts and offers a challenge to the measure of complexity of our societies.

In this constantly changing environment, marked by the demand for instant and continuous information, transparent communication is an absolute necessity. It implies, however resisting the temptation to react immediately and instead providing time for analysis and reflection while exposing issues openly, the remaining open questions, the ongoing efforts in response, and the concrete measures to be taken based on the information available at that time. Once again, these measures must answer the question: "What can or must I do as a patient or health professional, when faced with a potential or proven risk associated with a medication?". The answers can cover a large range of possibilities, and range from stopping treatment in consultation with one's physician to a re-evaluation of the indication, adjustment of the dose, or the monitoring of clinical or laboratory parameters, to provide a few examples.

This approach will be illustrated briefly using two recent examples published on the Swissmedic website (available in German and French) [2].

Angiotensin receptor blockade and risk of cancer

In July 2010, an article in The Lancet Oncology [3] reported a possible association between cancer and the use of angiotensin II receptor blockers (ARBs), also known as sartans, which is a class of medicines that constitutes one of the five pillars for treating hypertension (the others are angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers and beta blockers).

Analysis of this publication and of other available data revealed numerous methodological issues which raised serious doubts about the validity of the results obtained. The very low increase in the risk, although statistically significant, is in fact based on a selection of trials which represent a fraction of studies carried out with sartans. Those included in the meta-analysis were mostly conducted with a single sartan: telmisartan. In addition, the main increase in risk in one of the studies was influenced by the arm with telmisartan and rampiril (an angiotensin-converting enzyme inhibitor) compared with rampiril alone, whereas direct comparison of telmisartan alone and rampiril alone did not reveal an increased risk [4]. These studies were not designed with the intention of evaluating the risk of cancer. The data concerning cancer may therefore not have been collected in a uniform, standardised manner. The impossibility of gaining access to individual data has also not permitted determination of the time between starting treatment and the onset of a cancer, or to determine the patient's risk factors (age, sex, tobacco consumption). Finally, the biological plausibility is also the subject of controversy. Although experimental trials show that the renin-angiotensin system plays a role in regulating cell proliferation, tumour growth, angiogenesis and metastasis, several clinical and experimental trials seem to suggest that the blockade by angiotensin II type 1 receptor blockers would rather have the effect of inhibiting the growth of various tumours. A pro-tumour effect by ARBs thus appears to have low biological plausibility.

Although the data are still incomplete at this stage, it is important to convey a clear message to the numerous users of this class of drugs and to their physicians. Using the criteria mentioned above, it is clear that the potential risk was unexpected and potentially serious, but the possible increased risk is extremely low. The data are also unconvincing given the current state of knowledge and presents a low level of evidence. The incriminated drug moreover belongs to a major class of medicines used to treat hypertension; its abandonment could seriously compromise adequate blood pressure control in many patients, despite the existence of other therapeutic alternatives. Indeed, most cases of hypertension can only be controlled by combining various therapeutic principles.

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Dissemination of information that suggests the risk of cancer is associated to a treatment can generate a great deal of anxiety or at least uncertainty among patients receiving this treatment. Abrupt cessation of treatment could lead to serious complications in the short or longer term. It is therefore essential to put the information back into context rapidly and to provide clear, precise information. For the present case, it was important to state that the data did not provide evidence of an increased risk of cancer, and that the treatment should under no circumstances be interrupted or modified without first consulting the attending physician.

Cardiovascular risk and treatment of Parkinson's disease associated with the combination of entacapone and levodopa/ carbidopa

Within the framework of its communication policy on ongoing evaluations of the safety of medicines, the FDA issued a statement in August 2010 regarding a possible increased cardiovascular risk when receiving treatments combining entacapone with levodopa/ carbidopa for Parkinson's disease [5]. In this present case, preliminary data had already led to an adaptation of the Product Information for Health Professionals to be required in Switzerland and in Europe, which mentioned the possible increased cardiovascular risk under the section on adverse effects.

The data had been completed in the meantime by a meta-analysis conducted by the FDA. This last study confirmed a statistically significant increase in cardiovascular incidents in the group treated with entacapone combined with levodopa/carbidopa, compared with the group treated with levodopa/carbidopa without entacapone. The results, however, were modified by the inclusion or exclusion of a single study among the 15 included in the meta-analysis. In the presence of other methodological problems, it was not possible in the end to conclude that there was an increased cardiovascular risk, or even less to refute it.

After analysing the situation according to the criteria mentioned above, Swissmedic decided to publish a short message on its website with a link to more in-depth information on the available data and difficulties surrounding their interpretation [5]. The purpose of this message was mainly to draw the attention of practitioners to the modification of the Product Information for Health Professionals and to encourage a reassessment of risk and closer monitoring when prescribing combination treatment with entacapone in the presence of risk factors or cardiovascular diseases.

Conclusion

In both examples, regardless of the level of evidence, it is essential to continue research and data analyses to determine clearly whether the alleged risk can be definitively ruled out or whether the suspicion, even if improbable, of a slightly increased risk is later confirmed. In all cases, continuous re-evaluation of risks associated with a treatment and regular updating of information are essential elements for the safety of medicines, for as long as they are on the market.

References:

1. *Dyer, C., Wakefield was dishonest and irresponsible over MMR research, says GMC, in BMJ 2010. S. c593.*
2. *Swissmedic. Angiotensin-Rezeptor-Blocker (ARB) und Publikation in Lancet-Oncology zu möglicher Krebsentstehung. 2010, available from: http://www.swissmedic.ch/marktueberwachung/00091/00092/01359/index.html?lang=de*
   http://www.swissmedic.ch/marktueberwachung/00091/00092/01359/index.html?lang=fr
3. *Sipahi, I., et al., Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol, 2010. **11**(7): S. 627-36.*
4. *Ärzteschaft, A.d.d. AT1-Antagonisten (Sartane) und Krebsrisiko. 2010, available from: http://www.akdae.de/Stellungnahmen/Weitere/index.html*
5. *Swissmedic. Mögliches kardiovaskuläres Risiko von Entacapon in Kombination mit Levodopa/Carbidopa zur Behandlung der Parkinson-Krankheit wird überprüft. 2010, available from: http://www.swissmedic.ch/marktueberwachung/00091/00092/01423/index.html?lang=de*
   http://www.swissmedic.ch/marktueberwachung/00091/00092/01423/index.html?lang=fr

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Adverse Drug Reaction as a result of imaging? – Nephrogenic Systemic Fibrosis (NSF) and contrast media

Generally known, but often forgotten, is the link between the potential development of nephrogenic systemic fibrosis (NSF) after the use of a contrast medium containing gadolinium during magnetic resonance imaging (MRI). Because it occurs rarely, the latency period is several weeks, and various contrast media are used, there should be reminder of this issue.

Background

In 2000, The Lancet published 15 cases of the disease which at the time was called "nephrogenic fibrosing dermopathy" [1]. Once systemic involvement became clear, it was renamed "nephrogenic systemic fibrosis (NSF)".

At a nephrology centre in Denmark, 13 cases of NSF were recorded among candidates for a kidney transplant who had undergone magnetic resonance angiography with gadodiamide[2].

In January 2006, a marked association between the use of contrast media containing gadolinium and the occurrence of NSF was demonstrated in Austria. In March 2007, the manufacturer (GE Healthcare) issued a Healthcare Professional Communication (HPC) regarding its product (Omniscan®) and NSF. In July 2007, Swissmedic published an HPC on Magnevist® and NSF. In November 2009, a press release by the EMA was issued throughout Europe. The classification of the products containing gadolinium, which specifies three risk classes (high, medium, low), does not appear to cover all aspects and is not universally used. For instance the classification has not been adopted by the American College of Radiology (see also under Pathogenesis).

Classification of contrast media

The Swiss Drug Compendium lists 16 products for MRI: Artirem®, Dotarem®, Endorem®, Gadovist®, Magnegita®, Magnevist®, Magnevist® 2 mmol/l, Magnograf®, MR-Lux®, MultiHance®, Omniscan®, Primovist®, ProHance® perforable ampoules, ProHance® pre-filled hypodermic syringes, Resovist®, Teslascan®. With the exception of Artirem® and Magnevist® 2 mmol/l, which are only used locally (intra-articular administration), all contrast media are intended for parental use.

Contrast media containing gadolinium are summarised in the substance class "paramagnetic contrast media", with the ATC code V08CA. In the Compendium, these include:

- Gadodiamide = Omniscan®
- Gadobutrol = Gadovist®
- Gadobenic acid = MultiHance®
- Gadoteridol = ProHance®
- Gadoteric acid = Artirem®, Dotarem®
- Gadoxetic acid = Primovist®
- Gadopentetic acid / gadopentetate dimeglumine = Magnegita®, Magnevist®, Magnevist® 2 mmol/l, Magnograf®, MR-Lux®

Clinical picture

With a latency period of 2 – 4 weeks after the MRI, the skin swells, becomes less elastic and hardens. The initial thickening of the skin can develop first on the lower limbs before reaching the upper limbs and the torso. It progresses to the development of fibromatous tissue around the joints and internal organs. This process can be so marked that it can impede mobility and cause contractures. Around 5% of the published cases indicated rapid progression leading to the death of the patients.

Kidney function as a determinant

NSF has been almost exclusively diagnosed in patients requiring dialysis. As far as it is known, no cases of NSF in stages 1 to 3 of renal failure have been described to date.

Diagnosis

The medical history and clinical examination provide the clues, supported by a skin biopsy as a gold standard for the diagnosis.

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Typical histological signs of NSF are spindle cells that are positive for the surface markers CD34 and Procollagen 1, and also clumped collagen bundles, increased interstitial mucin deposits and the absence of inflammation.

Progression

Given the low number of published cases, experience remains limited. An improvement or recovery of renal function is of no doubt great benefit for the general health status. By various procedures, at least the progression is prevented and subjective relief is achieved.

Reports of adverse reactions in Switzerland

For ATC class V08CA = paramagnetic contrast media, the following have been recorded:

- 154 reports (including 4 deaths)
- 50 % concerned the organ class skin and skin appendages,
- 37 % concerned the organ class gastrointestinal tract,
- 21 % concerned the organ class respiratory system.

Even with ongoing exposure, there are some fluctuations from year to year in reporting frequency. This applies to both the total number of reports and the individual organ classes or symptoms. A certain fluctuation in NSF has been noted in recent years but this does not indicate either a decrease or increase in reports. In early 2008, an article reviewing 20 cases of NSF was published [3]. The last case reported occurred in 2006, so it would appear that the safety measures have been taking effect in recent years.

Pathogenesis

To date, it would appear that three products stand out from the others in terms of frequency: Gadodiomide, Gadopentetate dimeglumine and Gadoversetamide (authorised in the USA but not in Switzerland). As so-called linear, non-ionic chelates they are less stable at a chemical level, which means that the gadolinium is released earlier. In vivo, however, the "ionic" or "non-ionic" charge plays only a lesser role. What is relevant in this situation is the differing chemical structure: "linear" or "macrocyclic".

From pharmacokinetic studies it is known that the filtration of gadolinium-containing contrast media is primarily glomerular and then eliminated. With reduced renal function, the half-life is extended to over 30 hours, and the gadolinium remains in the body for a considerably longer time. Under unfavourable conditions, the half-life can be undoubtedly considerably longer. Local and systemic factors (blood vessels, infection, metabolic acidosis, etc.) can explain this, which is why NSF only affects a minority of patients with severe renal failure.

Recommendations

The decision to administer gadolinium-containing contrast media in patients with severe renal failure should be very carefully reviewed.

Metabolic acidosis should be compensated for prior to carrying out the MRI. For patients needing dialysis, the MRI should ideally be performed shortly before the dialysis.

Warnings and contraindications

The Swiss Product Information for Health Professionals covers the issue well by means of warnings and contraindications. In the USA, this was not the case, and thus the US FDA published a safety warning on 9 September 2010 and tightened the wording of the “labelling”. All patients should have their renal function checked before a gadolinium-containing contrast medium is used. Of the 7 products which are authorised in the USA, 3 are now contraindicated for patients with acute kidney injury or chronic, severe renal failure, i.e. Magnevist® / Gadopentetate dimeglumine, Omniscan® / Gadodiamide, und Optimark® / Gadoversetamide (the last is not authorised in Switzerland).

Treatment

To date there is no curative therapy and no reliable, effective strategy. In Switzerland, the "Swiss Study Group of NSF" is studying this complication, led by the Institute for Diagnos-

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tic Radiology at the Zurich University Hospital.

Conclusion

Since the introduction of gadolinium-containing contrast media in MRI imaging, over 100 million examinations of patients with healthy kidneys have been performed without NSF occurring. There are, however, some NSF patients in Switzerland, and over 200 patients worldwide. The occurrence of further cases may be prevented by strict compliance with the Product Information for Health Professionals prior to use.

Literature:

1. *Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE: Scleromyxoedema-like cutaneous disease in renal-dialysis patients. Lancet 2000; 356:1000-1001*
2. *Marckmann P, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG, Thomsen HS: Nephrogenic Systemic Fibrosis: Suspected Causative Role of Gadodiamide Used for Contrast-Enhanced Magnetic Resonance Imaging. J Am Soc Nephrol 2006;17: 2359-2362*
3. *Bongartz G, Weishaupt D, Mayr M: Schweiz Med Forum 2008; 8: 116-123*

Oral isotretinoin for the treatment of acne: a pharmacovigilance update

Swissmedic presents an updated overview of oral isotretinoin with regard to its indication, use and adverse effects: particularly for psychiatric disorders and rare, serious skin reactions.

1. Indication / Use

Isotretinoin [3] is authorised for the treatment of severe forms of acne (such as nodular acne, acne conglobata or acne with the risk of permanent scarring) and in cases of resistance to appropriate standard therapy cycles with systemic antibiotics and topical therapies.

Isotretinoin is contraindicated for women of childbearing age [2].

Dispensing category: **A**, i.e. dispensed on non-renewable medical prescription.

2. Psychiatric disorders

Since the founding of the official pharmacovigilance centre in 1990 and until September 2010, Swissmedic has received over 40,000 reports of suspected adverse reactions to medicinal products. In recent years, it has received an average of 4,000 reports of suspected adverse reactions per year.

By September 2010, Swissmedic had received 501 reports (see Chart A) on 1,025 cases of adverse reactions to oral isotretinoin. It should be noted that on average, two adverse reactions per report were received.

Chart A shows that most of the adverse reactions from the 501 reports fall in the following "top 5" organ classes (SOC / WHO Adverse Reaction Terminology):

- Psychiatric disorders
- Skin and appendages disorders
- Foetal disorders
- Gastrointestinal tract disorders
- Body as a whole – general disorders

The adverse reactions under the group of "other" adverse effects are not specified further.

Since the last publication regarding oral isotretinoin, which was published on the Swissmedic website in 2008 [1], a total of 42 reports of suspected adverse reactions have been received. Six of these concerned psychiatric symptoms, of which four were for depression and one was for depression with suicidal tendencies. None of these reports between 2008 and 2010 concerned suicide or attempted suicide.

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Chart A:

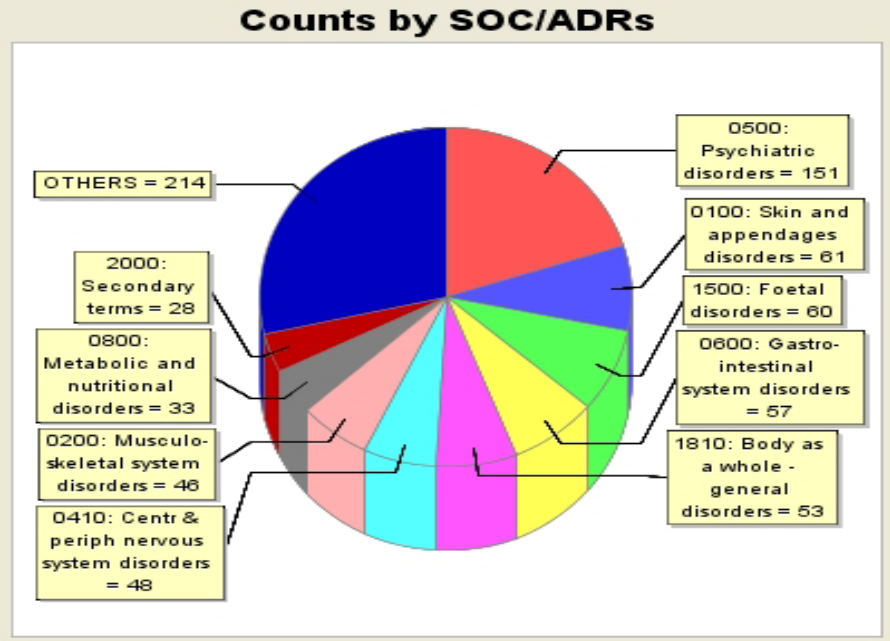
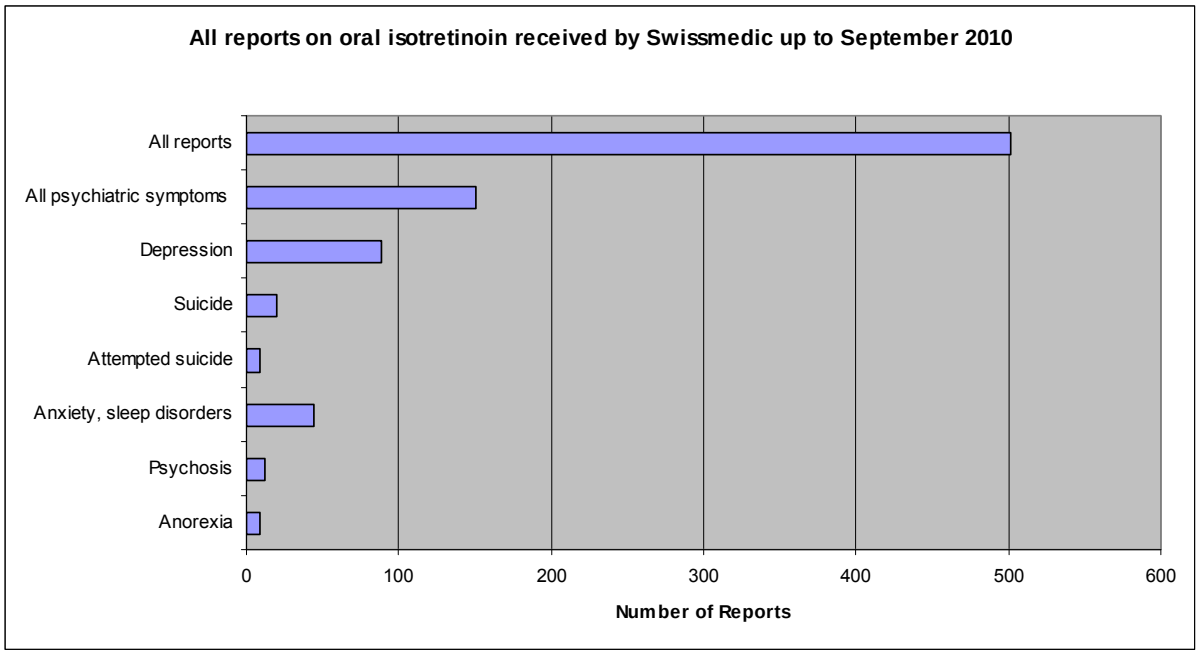


Chart B:



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Of the total 501 reports, 151 cases concerned psychiatric symptoms: depression, anxiety and sleep disorders in 133 cases, attempted suicide in 9 cases, and suicide in 20 cases (Chart B). In half of these 20 reports, the causal link between taking isotretinoin was taken into consideration because of the timing, and in the others it appears unlikely.

From the total number of spontaneous reports (Chart B), it is possible to determine neither the frequency of adverse psychiatric events nor indicate a definite causal link between the psychiatric symptoms and a treatment with isotretinoin. Such reports nevertheless constitute a considerable proportion of spontaneous reports regarding isotretinoin. When evaluating the reports, numerous factors must be taken into account such as the age of the patient for whom this treatment was prescribed (young adults and adolescents), the reason for the therapy, its duration, the dosage and the results.

On an epidemiological level, no link between psychiatric disorders and isotretinoin could be established.

3. Rare, serious skin reactions

Within the framework of post-marketing surveillance activities on an international level, rare cases of serious skin reactions have been reported in connection with products containing oral isotretinoin, such as exudative erythema multiforme (EEM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (Lyell syndrome). These events can be severe and lead to hospitalisation, disability, life-threatening conditions or death.

Such serious skin reactions often occur within the first 4 weeks following the start of treatment and are often accompanied with prodromes such as high fever, sore throat, general malaise and adverse effects on the mucous membranes. Initial skin symptoms are frequently uncharacteristic and can take the form of reddening with pain on palpation, which can progress to blistering within hours. In the first four weeks of treatment, patients should be made particularly aware of such early symptoms. When appropriate, they should stop taking the oral isotretinoin product.

A corresponding warning has been included in the updated Product Information for Health Professionals [2] on oral isotretinoin products (under the Sections regarding Precautions and Adverse Reactions). Health professionals were informed by means of a Healthcare Professional Communication (HPC) issued by the original manufacturer [3]. In addition, Swissmedic required that an announcement with the same content, with regard to both original and generic preparations, be placed in official publications for physicians and pharmacists in Switzerland.

4. Conclusion

Swissmedic issues a reminder that oral isotretinoin products must only be prescribed by physicians who are familiar with the use of systemic retinoids in the treatment of severe acne and who have in-depth knowledge of the risks of therapy with isotretinoin and the necessary monitoring, or those under the supervision of such specialists.

It is, and remains, important for prescribing physicians to monitor patients carefully for any signs of depression and/or similar symptoms in order to identify them at an early stage; particularly those who have already suffered from psychiatric disorders. If appropriate, a suitable treatment for depression should be started. It is possible that halting the treatment with isotretinoin is not sufficient to relieve the symptoms, and that psychiatric or psychological therapy will be needed [2].

For more detailed information on warnings, precautions (teratogenicity) and adverse reactions, Swissmedic refers readers to the Product Information for Health Professionals on oral isotretinoin products [2, 3].

Oral isotretinoin products remain under careful surveillance. Information on the reports received related to suspected adverse reactions are published periodically.

References:

1. http://www.swissmedic.ch/marktueberwachung/00091/00092/00690/index.html?lang=en

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2. *Swiss Pharmacopoeia: http://www.kompendium.ch/Search.aspx*
3. *Oral isotretinoin products authorised in Switzerland:*
   - *Curakne® 5 mg/10 mg/20 mg/40 mg / Pierre Fabre (Suisse) SA*
   - *Isotretinoin-Mepha® 10/20/40 / Mepha Pharma AG*
   - *Liderma® / Teva Pharma AG*
   - *Roaccutan® capsules / Roche Pharma (Schweiz) AG (see also "Healthcare Professional Communication" by the company Roche, February 2010 http://www.swissmedic.ch/marktueberwachung/00091/00092/01209/index.html?lang=en)*
   - *Tretinac® / Spirig Pharma AG*

Clusters and quality problems encountered on an everyday basis

Detecting signals – adverse drug reactions (ADRs) which are unexpected in their nature, frequency, or seriousness – may be particularly difficult to identify when the list of known ADRs of a drug is already long. This is an important consideration in the context of the observational approach within pharmacovigilance, which involves observing the drug tolerability in real-life situations, under the conditions in which it is used by patients.

Clusters are two or more linked cases reported in a close temporal relationship or in the same geographical area. These include mother-child pairs both presenting with a reaction, siblings with identical exposure, several reports concerning the same patient, or several reports from the same source. Any unexplained incidence of an ADR calls for careful investigations to be conducted without delay in order to detect a potential quality problem with the drug, and to take preventive measures as early as possible. Cluster analysis can also be used to evaluate groups of patients with a moderate increase in well-known risks. This point is of particular importance for the identification of signals concerning antineoplastic medicines, which may generally elicit numerous ADRs with varying degrees of severity.

Here, we are presenting two series of cases which are associated with the prescription of antineoplastics and immunoglobulins.

Fluorouracil (5FU)

The toxicity of 5FU is well known, depending on the dose, the route of administration (injection or infusion) and the general condition of the patient. The most frequent side effects are gastrointestinal (nausea, vomiting, diarrhoea, mucositis, stomatitis, anorexia), cutaneous (alopecia, palmar-plantar erythema) and in the bone marrow (pancytopenia, aplasia).

Nearly one in three patients presents with side effects requiring a reduction of the dose administered. It has recently been shown that side effects are more marked with genetic predisposition [1] (variants in dihydropyrimidine dehydrogenase and/or thymidilate synthase activity) and can affect up to 37% of patients receiving radio-chemotherapy [2].

We describe here briefly cases, which were reported over a few days and concern four patients who unexpectedly developed marked signs of toxicity (involving the skin and mucous membranes of the digestive tract) after the administration of 5FU in a standard radio-chemotherapy protocol, and which led to hospitalisation for two patients. The four cases were reported by the same specialised hospital over the same period and for the same pathology: rectal adenocarcinoma (stage T3N1M0). The following controls were carried out:

- The doses administered complied with recommended norms (1000mg/m2/day of 5FU for 4 days) as was the radiation dosimetry (45Gy)
- The protocol for the manufacturing of the product and certificate of analysis were checked
- The storage and transport methods (by constant monitoring of the temperature) showed no anomalies
- Elements of the quality control for the batch involved were examined (with parallel analysis of samples used and those pre-

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served in the serum bank, including analysis to detect fluoracetaldehyde)

Possible sun exposure of the irradiated area (photosensitivity is a known side effect) in patients was ruled out. Finally, the absence of any side effects in 20 to 25 other patients treated with the same protocol, with the same batch of the product, was noted, as well as the fact that no other reports from third parties were received.

A problem with the stability of the product was suspected but not confirmed. To date, the problem still remains unexplained.

In practical terms, the delivered units from the batch involved were recalled, and the remainder was blocked until results from the controls were obtained.

Human immunoglobulin

Here, the problem was only partially discovered by a cluster in the narrower sense as described above. For plasma products, thromboembolic events (TEE) are the most frequent adverse reaction, with an increase in blood viscosity being the presumed underlying mechanism. These ADRs are rare but relatively severe, including cardiac infarction, stroke and pulmonary embolism.

When calculating the incidence rate from worldwide spontaneous reports in relation to the quantity of the product sold, there was an approximately threefold increase in the TEE incidence in 2008 compared with the largely constant rates for 2005 – 2007, followed by a further threefold increase in 2010. Because of the many unknown influencing factors, calculations of incidence based on spontaneous reports are generally questionable, and particularly in such cases with a rare ADR and a high background incidence.

A small "genuine" cluster of cases reported internationally strengthened the signal in August 2010. This triggered further investigations of the quality of the product, because small amounts of proteins with influence on the coagulation cascade in the end product could also have been responsible for the increased TEE incidence. In this case, factor XI was particularly suspected, but to date, this has not been possible to prove. Since various batches from different sites were linked to varying TEE incidence, the manufacturing process and recent modifications, partially related to new production sites, equipment and procedures, were particularly suspected. The focus was on fractionation and purification. Here, a process with a lower yield but higher purity was replaced with a process having a higher yield. It is worth noting that the specifications of the European Pharmacopoeia, which contains a monograph for human immunoglobulin, were fully met in each case.

Since the root cause and the procoagulation factor involved could not be identified rapidly or conclusively enough despite various investigations, all batches of the product were finally recalled to the patient level as a precautionary measure in September 2010, including in Switzerland. Throughout the entire period concerned, no ADRs regarding TEE were received in Switzerland.

The second example shows the rather rare situation that even the reporting rates from spontaneous reports can provide very important indications of a not-yet discovered problem, despite the many unknown influencing factors within the spontaneous reporting system and the resulting high level of scepticism regarding all estimations of incidence. A requirement for this, however, and as was the case in the previous example, is that historical reporting rates are relatively stable and not distorted by early media exposure.

The increasing complexity of manufacturing processes, scattered over various sites for a single product, often renders the search for the root cause extremely difficult. The problem is particularly marked in rapidly growing companies or those under acquisitions and mergers.

Finally, this story indicates there is a need for action regarding release specifications. The existing monograph in the European Pharmacopoeia is clearly insufficient. No decision has yet been taken on a possible update to the monograph or other measures

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related to the product specifications. As we have noted, the precise cause has not been clarified conclusively.

Conclusion

It should be emphasised that any abrupt, unexplained increase (localised or not) in the number of ADRs reported for a given medicinal product should be suspected as a potential quality problem and that it is necessary to conduct a detailed analysis. This also means Swissmedic takes all necessary measures to protect patients as rapidly as possible, ranging from simply informing health professionals to the blocking or recalling of all batches involved.

References:

1. *Morel A., Boisdron-Celle M., Fey L. et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluoro-uracil tolerance in Mol. Cancer Ther. 2006 ; 5 : 2895 – 2904*
2. *Rödel C., Fietkau R., Keilholz L. et al. Akuttoxizität der simultanen Radiochemotherapie des Rektumkarzinoms in Strahlenther. Onkol. 1997; 173: 415 - 421*

Current discussion and state of scientific knowledge on the use of psychostimulants such as methylphenidate (Ritalin®) in children, adolescents and adults for the treatment of attention deficit disorders

Background

The use of psychostimulants such as Ritalin® has been discussed in the scientific and lay press for many years, and has been a controversial and, at times, polemical issue. In the foreground are factors such as the determination of the indication – the "fashionable diagnosis" of attention deficit hyperactivity disorder (ADHD), its use to enhance performance or to sedate healthy children, and the risks involved, including their addictive potential and questionable influence on suicidal tendencies. To a certain degree, questions have arisen with regard to the basic scientific concepts of psychiatry and pharmacotherapy of physical disorders on whose basis ("current state of science and technology") psychiatric drugs are used in Switzerland and internationally. The growing use of these drugs is equated with misuse. A similar discussion is also taking place in Switzerland's neighbouring countries, and efforts are being made to monitor the use of Ritalin® more closely.

What is methylphenidate?

The first product containing the active substance methylphenidate was authorised in Switzerland under the name of *Ritalin*® in 1954. Other related products followed after 2005. Afterwards, dexmethylphenidate was also identified: it has a virtually identical chemical and pharmacological molecular form to methylphenidate.

The main area of use is the treatment of ADHD in children. In chemical terms, methylphenidate is linked to the central nervous system stimulant amphetamine, which has a significant potential for misuse including for doping purposes. In addition to ADHD there are other, less frequent indications for central nervous system stimulants. Because of the risks of dependency and addiction, methylphenidate falls under the law on narcotics, which particularly applies to intravenous administration or very high doses. For ADHD patients requiring a far lower dose, however, an increase of cases of dependency or misuse as an intoxicant has not been observed. Misuse appears mostly to concern adolescents and adults who also are taking other substances. The incidence of cases of misuse is not known.

How is methylphenidate prescribed in Switzerland for its intended purpose?

- Indicated only in accordance with recognised, well-established and validated diagnostic criteria. Diagnosis is established by physicians with special training in the relevant disorders

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- As part of a comprehensive, concomitant treatment programme that usually also includes psychological, educational and behavioural therapies
- Not prescribed for all children with ADHD, and in particular not for those with secondary causes due to environmental factors or those with other underlying psychiatric disorders
- Not for the treatment of normal fatigue
- Therapy-free periods (e.g. during school holidays); a renewed confirmation for indication following a therapy-free period
- Some children who were diagnosed as having ADHD also present with symptoms in adulthood. For adults, the symptoms should thus have begun during childhood if a treatment is to be started.

What is *Swissmedic's* role?

- Swissmedic granted the *market authorisation* based on internationally accepted standards.
- The *Product Information for Health Professionals and Patients* regarding products containing methylphenidate are continually updated (most recently in 2010). Swissmedic imposes stringent requirements. The 2009 EU harmonisation measures were also implemented in Switzerland. Swissmedic is carefully monitoring the scientific literature on the subject.
- *Market surveillance:* As is required for new medicinal products, the pharmaceutical company must submit *Annual Safety Reports* to Swissmedic. The spectrum of *national, spontaneous reports* on suspected adverse reactions corresponds to the information contained in the comprehensive Product Information for Health Professionals. As expected, reactions relating to the psychiatric and the central nervous system are those most frequently reported, while more severe reactions, such as those requiring hospitalisation, are rare. The Market Authorisation Holder must also provide details in the annual report of the quantities dispensed.
- *Information measures:* Swissmedic has regularly issued reminders regarding the correct use of the product, including on its website. In August 2010, Swissmedic published a collection of "*Questions and answers regarding the correct use of methylphenidate"* (available in German and French):
  http://www.swissmedic.ch/marktueberwachung/00091/00092/01375/index.html?lang=de

  http://www.swissmedic.ch/marktueberwachung/00091/00092/01375/index.html?lang=fr
- *Illegal import or export*: Any such products which are found are seized and destroyed by the customs authorities, as instructed by Swissmedic.

Hypersensitivity reactions to intravenous iron: drug safety monitoring data and literature review *

Introduction

Iron deficiency treatment

- Recent iv iron formulations have been advertised as safer than older compounds.
- There is an increased focus of the media on iron deficiency disorders.
- This may urge practitioners into more frequent use of intravenous iron.

Aim of the study

To review the safety data of both intravenous preparations currently marketed in Switzerland, iron sucrose (Venofer®) and ferric carboxymaltose (Ferinject®).

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Methods

Study design

1. Systematic literature review 2000 - 2010: trials addressing iron safety or including such data.
2. Descriptive analysis of Swissmedic pharmacovigilance data (1990 - Feb 2010) on serious anaphylactoid reactions, i.e. life-threatening or leading to hospitalization.

Results

Literature review

- 30 trials (7,248 patients) were identified, among which 6 specifically addressed safety.
- The most frequent indication was chronic renal failure (14 trials).
- In 21 trials (5,366 patients), no serious hypersensitivity reactions were observed.
- In 9 trials (1,882 patients), the incidence of serious hypersensitivity reactions was <1% of administered doses.
- No fatality was reported.
- One study noted a marked dose effect on the incidence of serious hypersensitivity reactions.

Swiss pharmacovigilance data (Swissmedic)

- **Venofer®**: 34 serious anaphylactoid reactions over 20 years (among 66 anaphylactic reactions, for a total of 235 reported adverse effects).
- **Ferinject®**: 19 serious anaphylactoid reactions over 2 years and 3 months (among 114 anaphylactic reactions, for a total of 257 reported adverse effects).
- With both drugs, >85% of serious anaphylactoid reactions occurred in women with a mean age of 35 - 40 years.
- No fatality was reported.

Conclusions

1. Although the overall incidence of serious hypersensitivity reactions seems to be low, adequately designed studies are lacking. Safety remains an issue if population exposure is large.
2. The larger number of pharmacovigilance reports on ferric carboxymaltose (Ferinject®) might indicate a higher incidence of serious anaphylactoid reactions. This trend should be interpreted with caution given the notoriously heterogeneous reporting. Pharmacovigilance data since February 2010 will give us more insight into this phenomenon.

Implications for Practice

1. Oral treatment should remain the first - line therapy, with the exception of patients receiving erythropoietin treatment or with inflammatory bowel disease.
2. If definitive indication for intravenous iron:
   - minimize dosage
   - maximize infusion time
   - let a sufficient amount of time elapse between serial administrations
   - ensure proximity of life support measures, first of all adrenaline.

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III: Conferences

Periodic review of vaccine pharmacovigilance issues by Swissmedic's Human Medicine Experts Committee (HMEC)

The HMEC is Swissmedic's scientific and clinical expert advisory body for therapeutic products. This year, Swissmedic established that vaccine experts in HMEC shall convene on a regular and as-needed basis to provide reviews on current vaccine pharmacovigilance issues in Switzerland.

In July 2010, Swissmedic published the "Final Report: Analysis of the PaniFlow® database on suspected adverse events following pandemic influenza (H1N1) 2009". The report was based on over 500 case reports registered in PaniFlow®.

The HMEC vaccine experts met on 6 July 2010 to review the Final Report and to provide confidential second opinions on the causality assessments for cases reporting serious or unexpected adverse reactions of special interest. HMEC issued a statement which concluded that no new safety concerns were identified based on current available data. Swissmedic welcomes follow-up information on reports already registered (e.g. for the final outcome) and new reports. There is no time limit to report a suspected adverse reaction to a medication.

The Final Report and the HMEC statement are found here:
http://www.swissmedic.ch/marktueberwachung/01315/index.html?lang=en

3rd Swiss Haemovigilance Seminar with over 100 participants

The 3rd Swiss Haemovigilance Seminar was held at the BEA Expo complex in Bern on 26 August 2010.

Target audience for this event organised by Swissmedic were mainly the haemovigilance officers in hospitals administering transfusions. Other key individuals were representatives of all professions involved in the transfusion chain (including laboratory and nursing staff). Over 100 participants attended. Swiss and international speakers gave presentations on current and future developments in haemovigilance, preventive measures and selected aspects of transfusion safety.

Professor René de Vries, President of the International Haemovigilance Network (IHN), opened the event with an overview of international developments in haemovigilance.

Bacterial contamination of platelet concentrates is currently a main national topic. As shown by both Swiss and international haemovigilance data, this is the greatest remaining risk of transfusion. Since the end of 2009, a process for pathogen inactivation of platelet concentrates is available in Switzerland and is currently being implemented nationwide. User experiences with the process have been successful, and as of January 2011, the first blood transfusion services will start producing pathogen-inactivated platelet concentrates in their routine setting.

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Other hot topics presented included:

- Screening methods for the prevention of transfusion-related viral infections
- An update on TRALI (transfusion-related acute lung injury), a frequently life-threatening transfusion reaction. Haemovigilance data contributed towards implementing a specific preventive measure in Switzerland in 2007 (the "male-donor-plasma-only strategy" [1])
- The employment of various types of transfusion committees (in hospitals, on a regional basis) and their tasks
- A report on the experience of introducing the bedside test [2] in a hospital
- The role of nursing staff in haemovigilance
- Prospect of new emerging dangers that could influence the blood supply and/or blood safety, with the example of Chagas disease

The conference closed with an outlook on future challenges for haemovigilance in the presentation "Indicators for safety and appropriate use of blood components".

All presentations plus several photos and the annual haemovigilance report for 2009 are now available on our website for downloading:
Haemovigilance Seminar 26.08.2010:
http://www.swissmedic.ch/marktueberwachung/00159/00160/00438/index.html?lang=en
Annual Haemovigilance Report for 2009:
http://www.swissmedic.ch/marktueberwachung/00159/00160/00437/index.html?lang=en

1. *See Annual Haemovigilance Reports for 2007 and 2008*
2. *Short explanation of the bedside test: The bedside test is a pre-transfusion examination that is performed immediately prior to transfusion at the site of administration, i.e. the patient's bedside. It serves to confirm/check the ABO blood group of the recipient, and is the last possibility to avoid an ABO-incompatible transfusion, e.g. due to confusion of patients or blood components. In Switzerland, this test is not legally required but it is carried out in many Swiss hospitals on a voluntary basis.*

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26th International Conference on Pharmacoepidemiology & Therapeutic Risk Management,- Brighton, UK, 19-22 August 2010

The numerous presentations and workshops were varied, grouped by topic, and were highly suitable even for non-epidemiologists. Every day, 6 -7 concurrent sessions were held on a number of different topics.

The following core subjects merit a detailed account:

- H1N1 pandemic / vaccines
- Risk management and communication
- Signal detection
- Oral contraceptives
- Quality of pharmacoepidemiological studies

1. H1N1 Pandemic

Pandemic influenza (H1N1) 2009 was not only the subject of many presentations but also this year's "hot topic". The following study results should be mentioned:

In Taiwan, following mass vaccination (15 million vaccine doses), the incidence of facial nerve paralysis (Bell's palsy) and severe anaphylaxis was higher than in other countries. An in-depth analysis of the background incidence rate revealed that in Taiwan, both facial nerve paralysis and severe anaphylaxis are generally more frequent in comparison with other countries.

This example illustrates once more the need for caution when interpreting study results and above all when comparing data from different sources (*32).

Based on a GPRD study, the immunisation campaign in the UK was described as successful. In the first 7 weeks, individuals belonging to certain risk groups were vaccinated with priority. The probability of being vaccinated against pandemic influenza (H1N1) 2009 rose drastically with the number of chronic illnesses from which an individual suffered: 2.5 times higher for patients with 2 risk factors and 5.5 times higher for those with 4 risk factors, compared with patients presenting with only a single risk factor (*31).

A surveillance project in the USA (Early Access Data) revealed that the side effect profile of the H1N1 vaccines used was comparable to that of usual influenza vaccines, in particular for severe reactions (*33).

The following observations were made in connection with the "hot topic":

- The pandemic was moderate: it reached Europe during the summer and resulted in fewer deaths than expected.
- One third of deaths were in younger patients without concomitant diseases.
- Fatalities resulting from pandemic influenza (H1N1) 2009 were higher among the Asian and Afro-American populations. The reasons have yet to be established.
- Schools were the most frequent site for transmission.
- For the first time, preparations were made for a pandemic, and vaccines were available.
- The authorities acted in part too hastily or too late.
- The media frequently spread panic and played on the population's fears.
- Better, more objective information was called for, for example publications in good, specialised journals.
- Conflict of interest was discussed intensively that many people, particularly from the WHO (clinical scientists and scientists from industry), with potential interest in the use of the vaccines, were involved in the decisions / guidelines.

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2. Risk management and communication

The effect of DHPCs (Direct Healthcare Professional Communications) and Dear Doctor Letters was discussed.

Studies revealed that in the UK and the Netherlands, only one third of all physicians questioned stated that they took measures following a Dear Doctor Letter, such as changing their prescription habits, discussing the issue with patients, or possibly stopping the use of the medicinal product in question.

The fact that DHPCs influence the prescribing behaviour of doctors only with regard to frequently prescribed medications was revealed by a Dutch study. No more than one quarter of the DHPCs led to changes in the administration of the product. Repeated DHPCs relating to restrictions in the use of a medicinal product were shown to have only a very short-term effect (*24).

It was also demonstrated that the media had a greater effect on the use of medicines than communications from authorities (*312).

3. Signal recognition

Signal recognition is an issue of long-standing debate. A speaker from EMA illustrated that a more precise method for signal recognition than the one in present use would be possible, but not with the limited resources currently available (Keynote address: Thomas Lönngren).

Analysis within the AERS (Adverse Event Reporting System of the FDA) revealed that excluding mild adverse reactions increased the probability of a signal being recognised, and that signal recognition methods must be revised (*528).

4. Oral contraceptives (OC)

A prospective, controlled long-term study in 7 European countries (59,510 participants) revealed that users of drospirenone/ ethinylestradiol less frequently began treatment with antihypertensive medications than women using other contraceptives (*548). The reasons for this will need to be established by means of further studies.

A prospective, controlled cohort study carried out in the USA and various European countries (65,000 participants) came to the conclusion that European and American OC users varied very little in terms of their demographic characteristics. One striking finding, however, is the fact that far more American women take other medicinal products, above all psychotropic drugs (mostly SSRIs), than European women (24.9% vs. 12.0%), and that entails an increased potential for interactions (*569).

5. Quality of pharmacoepidemiological studies

Very lively discussion took place on whether the numerous pharmacoepidemiological studies were more harm than benefit for authorities in terms of decision-making processes. The call was unmistakeable for better quality studies, more transparency, reproducible methods and reduced quantity. However, most of those present were not of the opinion that more stringent requirements should be imposed on publications.

** Abstract number from Pharmacoepidemiology & Drug Safety Volume 19, Supplement 1, August 2010*

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Special conference for the pharmaceutical industry: medicinal products and communication

In June 2010, Swissmedic organised a special conference for the pharmaceutical industry, focusing on effective information exchange and cooperation between authorisation holders and Swissmedic regarding the safety of medicines.

Four themes were selected:

1. Key general regulatory issues

Swissmedic experts explained the legal and scientific bases of Periodic Safety Update Reports (PSURs), Pharmacovigilance Plans (PVPs) and Healthcare Professional Communications (HPCs). It was noted, for example regarding PSURs, that although time and administrative requirements were often met, at times inadequate quality of the submitted documentation complicated the evaluation.

For international signals, the internal collaboration among the authorities in certain countries or different departments was presented. The role of the authorisation holder, which must provide the appropriate data analysis and/or the revised Product Information, was emphasised: scientifically justified and openly formulated documentation that is specific to the signal facilitates the decisions by authorities regarding the necessary measures to be taken.

Prof. Dr. Karin Fattinger, Chief Physician at the Department of Internal Medicine at Bern's Inselspital (Island Hospital), addressed ways of improving the safety of medicines in medical practices and hospitals. Important indicators within hospitals, such as the frequency of ADRs, frequency of medication errors, medicinal products with high ADR risks, etc., should be recorded and evaluated within the "Drug Event Monitoring" project.

2. Risk communication and the media

Dr. Ragnar Lofstedt, a world-renowned risk management expert, gave an entertaining presentation on the current increasing interest in risk evaluations. The probability of a risk occurring with possible consequences and the individual experience are weighed against each other. The correct choice of communication (verbal expressions, selected medium, communicating partners, neutrality and knowledge of the issue from experts) has a decisive effect on the extent to which a risk is perceived and how urgent the reaction will be.

As a current example of risk assessment among the general public and the media, the concern regarding pulmonary embolism when taking the contraceptive pill led to incertitude throughout Switzerland in 2009.

3. Communication regarding the safety of medicines from the pharmaceutical industry's point of view

A further presentation was on the duty of the pharmaceutical industry to protect patients by documenting the possible risks related to their medicinal products in a timely and comprehensive way. Full transparency of information exchanged between the authorisation holder, the authorities, with experts and with patients is required. It was emphasised that the Product Information for Patients included in a medicinal product should be both legally binding but also easily understood by patients.

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4. Communication of risks related to vaccines

As questions were frequently raised on the risks related to vaccinations both during and following the influenza pandemic, the safety of vaccines was addressed. Since vaccines are usually administered to healthy individuals and above all to children, the benefit-risk assessment is of particular importance here. Causality assessments regarding unexpected reactions to vaccines are often more difficult because of a lack of definitions, imprecise information on temporality, and misinterpreted statements. For these reasons, data quality and the open exchange of the data are very important.

An open round table discussion then closed this interesting symposium.

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IV: Information on the safety of medicines - published on the Swissmedic website

HPC Quixil®: Zusätzliche Vorsichtsmassnahmen zur Vermeidung von Gasembolien bei der Anwendung von per Druckgas versprühten Fibrinklebern *
01.12.2010

HPC Tisseel®: Zusätzliche Vorsichtsmassnahmen zur Vermeidung von Gasembolien bei der Anwendung von per Druckgas versprühten Fibrinklebern *
01.12.2010

Pandemrix® – Narkolepsie *
25.11.2010

Swissmedic expands international network
08.11.2010

Verwaltungsverordnung Anleitung Anforderung an die Arzneimittelinformation von Humanarzneimitteln, Merkblatt Erläuterungen Fachinformation und Merkblatt Erläuterungen Patienteninformation *
02.11.2010

Mögliches kardiovaskuläres Risiko von Entacapon in Kombination mit Levodopa/Carbidopa zur Behandlung der Parkinson-Krankheit wird überprüft *
28.10.2010

Abschaffung der ALAT-Testung *
20.10.2010

Worldwide operations to combat illegal online supply of medicines
14.10.2010

Warnung vor dem sog. Wundermittel "Miracle Mineral Supplements (MMS)“ *
13.10.2010

Cubicin® (Daptomycin) – Aktualisierung der Sicherheitsinformation nach Berichten über eosinophile Pneumonien *
12.10.2010

Pharmacovigilance der Impfung gegen humane Papillomaviren - Rückblick 4 Jahre nach Marktzulassung *
06.10.2010

HPC Diabetes-Medikamente mit dem Wirkstoff Rosiglitazon - Sistierung der Zulassung, Avandia® und Avandamet® in der Schweiz ab 1. Dezember 2010 nicht mehr erhältlich *
05.10.2010

Erhöhtes Risiko für Fieberkrämpfe bei Kleinkindern in Australien im Zusammenhang mit einem saisonalen Grippeimpfstoff *
05.10.2010

Rotavirus vaccine Rotarix® and intussusception : interim results of a post-marketing study
23.09.2010

Octagam 5 % resp. 10%, Lösung zur intravenösen Anwendung *
21.09.2010

Dangerous potency products obtained over the Internet
20.09.2010

Fragen und Antworten zum richtigen Gebrauch von Präparaten mit Methylphenidat bei der Behandlung der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) *
09.09.2010

HPC Tygacil (Wirkstoff Tigecyclin) – erhöhte Mortalität in vergleichenden klinischen Studien *
09.09.2010

Less antibiotics sold in 2009 than in previous years
07.09.2010

HPC: Parfenac Salbe/Créme (Bufexamac) *
07.09.2010

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Pandemrix® - EMA Investigation
27.08.2010

Angiotensin-Rezeptor-Blocker (ARB) und Publikation in Lancet-Oncology zu möglicher Krebsentstehung *
27.08.2010

Warnung vor HIV-Tests zur Eigenanwendung *
12.08.2010

Once again, increasing imports of illegal medicinal products – dangerous slimming products
28.07.2010

Ketoprofen-Gel und Photoallergie - Swissmedic erinnert an die korrekte Anwendung *
23.07.2010

Uterine perforation with the use of Mirena® – Swissmedic issues a reminder regarding essential precautions
28.06.2010

Swissmedic warnt vor Risiken bei unsachgemässer Anwendung topischer Lokalanästhetika *
25.06.2010

Please find the complete list at the following web address:
http://www.swissmedic.ch/aktuell/00003/index.html?lang=en

**** in German and/or French only***

Report of a suspected adverse drug reaction (ADR)

► The ADR reporting form can be filled in electronically:

MU101_20_001d_FO Meldung einer vermuteten unerwünschten Arzneimittelwirkung (UAW) [in German]
MU101_20_001f_FO Annonce d'effets indésirables suspectés d'un médicament (EI) [in French]

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