Danish Pharmacovigilance Update Year 4 #4
25 April 2013

Cerebral haemorrhage in association with the use of methylphenidate (Ritalin® etc.)

In February, the Danish Health and Medicines Authority (DHMA) received an adverse reaction report concerning a middle-aged patient who had been undergoing treatment with methylphenidate for ADHD since the middle of 2012. According to the report, the patient suffered a cerebral haemorrhage followed by severe aphasia. The report contained no known risk factors for cerebrovascular disease.

The patient has been discharged from the hospital and is currently in a rehabilitation programme.

The DHMA has not received other reports of cerebral haemorrhage as a potential adverse reaction from the use of methylphenidate.

As a doctor you should be aware of the following:

- Prior to prescribing methylphenidate, it is necessary to carry out a baseline evaluation of the patient's cardiovascular status, including blood pressure and heart rate.
- **Blood pressure and pulse must be checked and plotted on a percentile curve after each dosage adjustment and subsequently at least every 6 months.**
- Methylphenidate is contraindicated in patients with pre-existing cardiovascular disorders, including serious hypertension, heart failure, arterial occlusive disease, angina pectoris, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening cardiac arrhythmias and channelopathies (diseases caused by dysfunctional ion channels), and/or cerebrovascular disorders, e.g., vascular abnormalities, including vasculitis or stroke.

Cerebrovascular disorders, including cerebral haemorrhage, are described in the summary of product characteristics for methylphenidate, but the frequency cannot be estimated based on the available data.

Indication for Ritalin®
ADHD: Methylphenidate is indicated as part of a comprehensive treatment programme for ADHD (attention deficit hyperactivity disorder) in children aged 6 years or older, when remedial measures alone are insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders *[further information on the indication for methylphenidate in the treatment of ADHD is available in the summary of product characteristics]*.

Narcolepsy: The symptoms include daytime sleepiness, inconvenient sleep periods and sudden loss of muscle tone. Treatment should be given only by specialists experienced in treating narcolepsy.

Methylphenidate (Ritalin® etc.) – adverse reactions and the number of children and adults undergoing treatment during the period 2003-2012

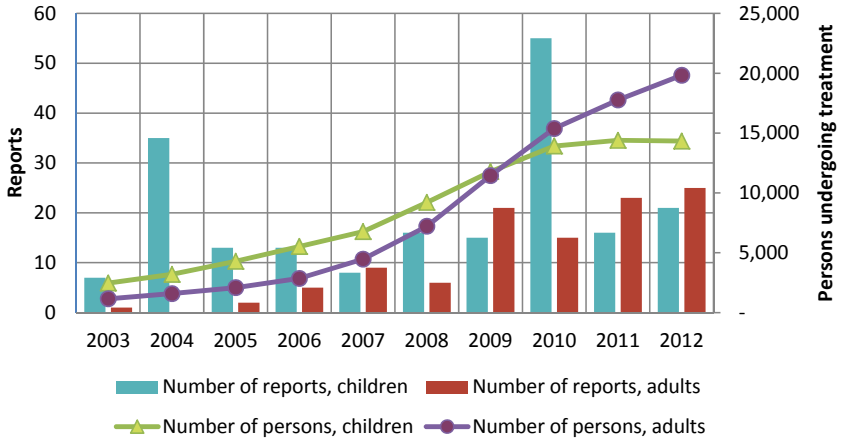
Based on the serious reports received in association with the use of methylphenidate in adults and as a follow-on to a previous report on methylphenidate[1], the Danish Health and Medicines Authority (DHMA) has reviewed the adverse reaction reports and the number of persons undergoing treatment for the period 2003-2012.

During the period 1 January 2003 to 31 December 2012, the DHMA received a total of 343 reports concerning adverse reactions following the use of drugs containing methylphenidate.

Of these reports, 199 concern adverse reactions in children (0-17 years), while 107 reports concern adverse reactions in adults (18 years and older). Furthermore, we received a total of 37 reports for which it is not possible to establish the age of the person involved.

Figure 1 shows the development in the number of reports and the number of persons undergoing treatment in the period 2003-2012 for children and adults, respectively.

Figure 1. Number of reports and persons undergoing treatment in 2003-2012



Source: The consumption figures originate from the Danish Register of Medicinal Product Statistics (SSI).

Children undergoing treatment with methylphenidate

For children undergoing treatment with methylphenidate, the number of adverse reaction reports has been fairly stable during the period 2003-2012. However, in 2010 the DHMA received an unusually high number of reports (55). The high number was primarily due to several reports from one particular paediatrician with a special focus on the issue, who reported based on a backward review of a number of medical records. During the period 2003-2012, the number of children undergoing treatment with methylphenidate has increased. It should be noted, however, that the number of users has been almost constant for the past three years. In 2003, 2,466 children were undergoing treatment with methylphenidate. In 2012, the number had increased to 14,330 children.

Adults undergoing treatment with methylphenidate

For adults undergoing treatment with methylphenidate, the number of adverse reaction reports per year has increased during the period 2003-2012. In 2003, the DHMA received 1 report. In 2012, 25 reports were received. In the same period, the number of adult users of methylphenidate has also increased – from 1,150 adults undergoing treatment in 2003 to 19,829 in 2012.

According to a review of the consumption carried out by the Danish Register of Medicinal Product Statistics (SSI) in June 2011, one out of eight adults undergoing treatment with methylphenidate have been using ADHD medicine since childhood or adolescence[2]. This means that for a number of users treatment with methylphenidate is not initiated until they are adults.
Read more about the consumption of ADHD medicine in adults on the SSI's website: *ADHD: Nu kommer de voksne også i behandling* (in Danish only).

1) Danish Pharmacovigilance Update, *Newest data on the safety of methylphenidate (Ritalin etc.) in ADHD therapy*, February 2012.

2) Health data and IT, Consumption analyses (SSI) *Surely they'll outgrow ADHD!*, (June 2011).

Possible development of narcolepsy in association with vaccination with Pandemrix®

In March and April, the Danish Health and Medicines Authority (DHMA) received the first two adverse reaction reports of possible development of narcolepsy in association with vaccination with Pandemrix®.

One of the reports concerns a child with mild mitral insufficiency, who had the first vaccination with Pandemrix® in November 2009. The patient experienced no adverse reactions after receiving the first dose. However, during spring 2010, the patient was vaccinated again and 10-14 days later changed behaviour and had difficulty staying awake. Specialists in the field diagnosed narcolepsy with cataplexy. Later, it has become evident that there is a family history of similar symptoms.

The other report also concerns a child. The patient had asthma and was vaccinated in November 2009. There is no information concerning any additional vaccination. In the early summer of 2010, the patient developed narcolepsy, fell asleep several times a day and fell from chairs etc. Also for this patient, narcolepsy was diagnosed by specialists. Following the diagnosis, the patient was started on methylphenidate.

The DHMA cannot rule out a correlation between the development of narcolepsy and the Pandemrix® vaccination in the cases reported.

Swedish registry study shows an increased risk of narcolepsy following vaccination with Pandemrix® in children and young adults

A comprehensive registry study has been conducted in Sweden in order to investigate the risk of developing narcolepsy in children and adolescents (20 years and younger) following vaccination with Pandemrix®. In the study, 3.3 million vaccinated and 2.5 million unvaccinated persons are compared regarding the risks of developing any of 50 neurological and immune related/autoimmune diseases following vaccination with Pandemrix®. The study covers the period from 1 October 2009 to 31 December 2011.

The study confirms an increased risk of narcolepsy in children and adolescents as well as an increased risk in young adults (21-30 years). The risk decreases gradually with increasing age. For a large number of other diseases studied, no significantly increased risks were found.

Three-fold increased risk of developing narcolepsy in children and adolescents

The study shows a three-fold increased risk of developing narcolepsy in children and adolescents (20 years and younger) following vaccination with Pandemrix®. The increased risk is slightly lower compared to results from an earlier registry study in Sweden. The reason could be that the number of diagnosed cases of narcolepsy has increased also in unvaccinated children and adolescents due to an increased awareness of narcolepsy. The increased risk corresponds to approximately four additional cases of narcolepsy per 100,000 vaccinated persons in the study period in question.

Two-fold increased risk of developing narcolepsy in young adults

For young adults (21-30 years), the study shows a two-fold increased risk of narcolepsy following vaccination with Pandemrix®. The increased risk decreases gradually with increasing age. The risk in the age group of 31-40 years is not significantly increased compared to the risk for unvaccinated persons. No increased risk is observed for persons aged 40 years and older.

You can read more on the Swedish Medical Products Agency's, *Läkemedelsverkets, website* (in Swedish only).

Be aware of contraindications to dabigatran (Pradaxa®)

In March, the Danish Health and Medicines Authority (DHMA) received an adverse reaction report concerning a patient treated with dabigatran for atrial fibrillation. The patient had non-alcoholic liver cirrhosis and a life-expectancy of two years. In connection with implantation of artificial heart valves, the patient's treatment was discontinued. However, it was re-initiated immediately after the operation. The patient developed bleeding and multi-organ failure and later died.

As a doctor you should be aware of the following:
Dabigatran is (e.g.) contraindicated

- in patients with hepatic impairment or liver disease expected to affect the survival time.
- in patients with prosthetic heart valves requiring anti-coagulant treatment.

The DHMA draws attention to the importance of cautious use of anticoagulants in general and recommends that the instructions in the product information be followed closely.

In January 2013, a letter was sent to doctors and other healthcare professionals to inform them about the new contraindication in patients with artificial heart valves (see the letter *here* (in Danish only)).

See the product information for Pradaxa® *here*.

Indication for Pradaxa®
Used for preventing venous thromboembolism in adult patients following knee and hip prosthesis surgery and for preventing apoplexy and systemic embolism in adult patients with atrial fibrillation.

New Danish study shows that Pradaxa® is equally effective as Marevan®

Since the marketing of the anticoagulant Pradaxa® (dabigatran) in August 2011, the Danish Health and Medicines Authority (DHMA), in cooperation with medical experts from Aalborg Hospital Science and Innovation Center in Aalborg, has followed the development in the consumption and reviewed adverse reactions reported to the DHMA's adverse reaction database.

Based on the many serious reports, almost exclusively reported by doctors, the DHMA initiated a real-life study of the Danish population to compare the safety and efficacy of Pradaxa® to the classic Marevan® treatment.
The study shows that Pradaxa® is equally effective as Marevan® – and in a number of fields more safe.

The study has just been published in *Journal of the American College of Cardiology*.

Two cases of severe cutaneous reactions (SCAR) associated with telaprevir (Incivo®) combination treatment

Following marketing of Incivo® in Japan, two cases of toxic epidermal necrolysis (TEN) have recently been reported, including one fatal case.

There are previous reports of 'drug reaction with eosinophilia and systemic symptoms' (DRESS) and Stevens-Johnson syndrome (SJS) at a rate of 0.4% and <0.1%, respectively, in association with the clinical development of the drug.

As a doctor you should be aware of the following:

- The summary of product characteristics for Incivo® includes specific guidance for monitoring and managing cutaneous reactions, which should be followed routinely. In case of serious rash, the product must be discontinued immediately and permanently.
- Since the cases of TEN were observed in association with combination treatment with Incivo®, pegylated interferon-alpha and ribavirin, the latter two drugs should also be discontinued immediately in case of rash associated with systemic symptoms.

The summary of product characteristics for Incivo® will now be updated with information about the occurrence of TEN. Furthermore, a letter of information has been sent to doctors and other healthcare professionals (see the letter *here*).

Indication for Incivo®
Used in combination with pegylated interferon-alpha and ribavirin for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease.

Rituximab (MabThera®) and severe skin reactions

Worldwide, severe skin reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have only very rarely been reported in patients with autoimmune diseases treated with rituximab. One case of TEN was fatal.

These severe skin reactions are already known in association with the haematological indication and are included in the product information. The product information will now be updated with information about these adverse reactions for the autoimmune indication – rheumatoid arthritis.

Cases reported with both first-time infusion and later infusions

The cases of TEN and SJS in patients with autoimmune diseases have been reported with both first-time infusion and later infusions. Some of the cases occurred on the day of infusion, others within a few days of infusion. In other cases, the reaction occurred several weeks or up to four months after the infusion. In several of the cases, treatments known to have been associated with TEN and SJS were given concomitantly with rituximab.

The cause of these reactions remains unknown.

If severe skin reactions occur, rituximab treatment must be immediately and permanently discontinued.

A letter of information has been sent to relevant doctors. The letter can also be seen *here*.

Indication for MabThera®

Used in adults with Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis.

Risk of other haematological primary malignancies in patients undergoing treatment with thalidomide (Thalidomide Celgene®)

A significantly increased risk of other haematological primary malignancies (acute myeloid leukaemia and myelodysplastic syndromes) has been shown in a review of an ongoing study in patients with previously untreated multiple myeloma receiving melphalan, prednisone, and thalidomide. The study compares these patients to patients undergoing treatment with lenalidomide and dexamethasone.

The study shows that the risk of developing other haematological primary malignancies due to the use of thalidomide increases over time to approximately 2% after two years and 4% after three years.

As a doctor you should be aware of the following:

- Before starting thalidomide treatment in combination with melphalan and prednisone, consider carefully both the benefits and risks of the treatment.
- Carefully evaluate patients before and during treatment using standard cancer screening and provide appropriate treatment.

The product information for Thalidomid Celgene® has been updated with information about the increased risk. Furthermore, a letter of information has been sent to doctors and other healthcare professionals (see the letter *here*).

Indication for Thalidomide Celgene®
Used in combination with melphalan and prednisone as first-line treatment of patients with untreated multiple myeloma, aged >65 years or ineligible for high dose chemotherapy.

New Danish study on valproate and the safety during pregnancy

A new Danish study has investigated whether there is a correlation between autism spectrum disorders in children and maternal use of valproate during pregnancy. Valproate is primarily used for the treatment of epilepsy, but may also be used for, e.g., mania in persons with bipolar disorder. The study has just been published in *JAMA*.

The Danish Health and Medicines Authority is aware of the new data, and the European Pharmacovigilance Risk Assessment Committee (PRAC) is currently reviewing the use of valproate during pregnancy and the risk of neurodevelopmental disorders, including an assessment of the new study.

Report of a fatal case due to severe hypocalcaemia in a paediatric clinical trial involving treatment with cinacalcet (Mimpara®)

A fatal case of severe hypocalcaemia has been reported in a paediatric clinical trial involving a patient receiving cinacalcet (Mimpara®). Therefore, the marketing authorisation holder has suspended all paediatric clinical trials on cinacalcet and is investigating the fatal case to determine if any additional actions are necessary.

As a doctor you should be aware of the following:

- Mimpara® is approved only in adults.
- The product information warns of the risk of hypocalcaemia associated with cinacalcet, and therefore patients should be carefully monitored.

Doctors and other healthcare professionals have been informed about the report in a letter (see the letter *here*).

You can find further information in the *summary of product characteristics for Mimpara®*.

Indication for Mimpara®
Treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

Mimpara may be used as part of a therapeutic regimen including phosphate binders and/or vitamin D sterols, as appropriate.

Reduction of hypercalcaemia in patients with:

- parathyroid cancer,
- primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically possible or is contraindicated.

The Danish Health and Medicines Authority's annual pharmacovigilance report 2012

The annual report 2012 has now been published on the Danish Health and Medicines Authority's website. Here you can read about the development in the number of adverse reaction reports, see the list of the most frequent drugs in adverse reaction reports and gain insight into various campaigns, focus areas and the European cooperation in the field of pharmacovigilance.

Read the entire annual report *here*.

The European Pharmacovigilance Risk Assessment Committee (PRAC) recommends restriction in the use of strontium ranelate (Protelos®)

The European Pharmacovigilance Risk Assessment Committee (PRAC) recommends restriction in the use of Protelos® which contains strontium ranelate. Protelos® is used for the treatment of osteoporosis.

Treatment with Protelos® will be investigated, since a routine assessment of safety data for the product showed a risk of cardiovascular adverse reactions, including cardiac infarction.

Read more on the Danish Health and Medicines Authority's website: *PRAC anbefaler begrænset brug af Protelos®* (PRAC recommends restriction in the use of Protelos®, in Danish only).

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