An overview of reports on dabigatran

Introduction

Dabigatran (Pradaxa®) was registered for the European market on March 18th 2008 and is currently available as capsules containing 75mg, 110mg or 150mg of the active substance. The approved indications are *primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery* (75mg and 110mg) and *prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors* (110mg and 150mg) [1].

The introduction of dabigatran added a new therapy to the arsenal of anticoagulants. For its indications, low molecular weight heparins (LMWH) and vitamin K antagonists (VKA) are the preferred prophylactic treatments for patients undergoing knee or hip surgery and patients with atrial fibrillation respectively. Since Pradaxa® has obtained a market authorization from EMA, there has been discussion regarding its risk-benefit profile compared to the older types of anticoagulants. The number of dabigatran users in The Netherlands is shown in table 1 [2].

Table 1. Number of dabigatran users in the Netherlands between 2008 and 2011

Drug	2008	2009	2010	2011
Dabigatran	29	1,026	1,048	2,056

Dabigatran is a competitive, reversible, direct thrombin inhibitor, which inhibits the conversion from fibrinogen to fibrin, resulting in the prevention of thrombus formation. The SmPC mentions that, in general, routine anticoagulant monitoring is not required when using dabigatran. However, according to the SmPC, the measurement of dabigatran related anticoagulation, using diluted thrombin time (dTT), ecarin clotting time (ECT) or activated partial thromboplastin time (aPTT) testing, may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors [1].

Since the group of novel oral anticoagulants represents a group of new chemical entities, the ADR profile of these drugs is not completely known at the moment. ADRs occurring in the overall population are likely to differ from those that occurred in the clinical trials that led to registration of the drugs. Therefore, the safety of these drugs should be closely monitored. In this overview the reports on this new drug received by Lareb through the spontaneous reporting system and through the Lareb Intensive Monitoring System (LIM) will be discussed. An overview will be provided in the next quarterly reports in order to monitor the safety of this new class of drugs.

Reports of ADRs

On January 11, 2013 the Netherlands Pharmacovigilance Centre Lareb had received 106 reports of adverse drug reactions, from the spontaneous reporting system and from LIM, related to the use of dabigatran. These reports contained a total of 180 possible adverse drug reactions. Of these 106 reports, 54 were reported as serious according to the CIOMS criteria. In seven reports a fatal

outcome was reported. An overview of the most frequently reported ADRs is presented in table 2.

Table 2. Reported adverse drug reactions on dabigatran, grouped by system organ class received through spontaneous reporting and Lareb Intensive Monitoring (only the System Organ Classes containing ADRs are displayed).

System Organ Class	ADRs Lareb	ADRs LIM	≥ 2 reports in Lareb database and/or in LIM	common and very common adverse drug reactions according to SPC
Blood and lymphatic system disorders	6	0	anaemia (3), thrombocytopenia (3)	anaemia, haemoglobin decreased
Cardiac disorders	7	3	arrhythmia (3), myocardial infarction (2)	-
Eye disorders	1	1		-
Gastrointestinal disorders	40	15	diarrhoea (11), dyspepsia (6), dysphagia (3), gastric disorder (2), gastrointestinal disorder (3), gastrointestinal haemorrhage (9), lower abdominal pain (2), nausea (5), upper abdominal pain (2), vomiting (3)	gastrointestinal haemorrhage, abdominal pain, diarrhea, dyspepsia, nausea
General disorders and administration site conditions	8	2	death* (2), fatigue (4), feeling cold (2)	-
Infections and infestations	1	1		-
Injury, poisoning and procedural complications	5	0	prescription error (2)	-
Investigations	4	0		-
Metabolism and nutrition disorders	10	0	decreased appetite (5)	-
Musculoskeletal and connective tissue disorders	1	2		-
Neoplasms, benign, malignant and unspecified	5	0	malignant neoplasm (5)	-
Nervous system disorders	19	2	cerebrovascular accident (6), headache (4), hypoaesthesia (2), ischaemic stroke (4)	-
Psychiatric disorders	4	0		-
Renal and urinary disorders	6	1	pollakiuria (2)	-
Reproductive system and breast disorders	1	0		-
Respiratory, thoracic and mediastinal disorders	4	3	dyspnoea (5)	epistaxis
Skin and subcutaneous tissue disorders	4	1	rash (2)	-
Surgical and	2	0		-

System Organ Class	ADRs Lareb	ADRs LIM	≥ 2 reports in Lareb database and/or in LIM	common and very common adverse drug reactions according to SPC
medical procedures				
Vascular disorders	18	3	cerebral haemorrhage (2), cerebral infarction (2), haemorrhage (2), pallor (3), peripheral coldness (2), transient ischaemic attack (6)	-

* In two cases death was reported as a suspected ADR. In five other cases, suspected ADRs with a fatal outcome were reported.

When comparing the adverse drug reactions most frequently reported via the spontaneous reporting system and LIM, to those mentioned as common or very common in the SmPC of dabigatran, there are differences that require further analysis. Cases that are considered to be of particular interest are those with a fatal outcome, bleedings, and malignant neoplasms. These cases will be described below.

Events with fatal outcome associated with dabigatran use

A total of seven cases with fatal outcome were reported via the spontaneous reporting system. The details of these reports are described below.

Cases

Patient A is a male aged 71 years or older with a history of COPD, hypertension, severe diabetes mellitus, atrial fibrillation, congestive heart failure and hypercholesterolaemia. The patient participated in a trial comparing two doses of dabigatran in patients with non-valvular atrial fibrillation. Two years after starting dabigatran the patient experienced a severe dyspnoe increase which led to hospitalisation. After four days, he developed acute renal dysfunction and moderate hypoglycaemia for which he was treated with furosemide, fluid and sodium restriction, and withdrawal of insulin and glimepiride. After recovery from these events the patient was discharged. Five weeks later he was re-hospitalised due to a severe gastroenteritis, and in the following 5 days the patient developed a severely dysregulated diabetes mellitus, severe hyperkalaemia, severe acute renal insufficiency and a minor gastrointestinal bleeding. The patient died four days later due to the acute renal insufficiency. According to the reporter (cardiologist), glimepiride and insulin were suspect drugs for the hypoglycaemia, and spironolactone and bumetanide were suspect for the acute renal insufficiency. The reporter indicated that there was no reasonable relationship between the events and the use of dabigatran.

Patient B is a female aged 71 years or older with a history of hypercholesterolaemia, hemistrumectomy, uterus extirpation, cataract ODS and gonarthrosis, who experienced thrombocytopenia following administration of prophylactic dabigatran after knee surgery (150mg daily), with a latency of eleven days. Dabigatran was withdrawn and treatment with low molecular weight heparin was initiated. Two days later, the patient was hospitalised with a large cerebrovascular accident, which transformed into a haemorrhagic stroke. She died four days later. An autopsy was performed, but results have not been reported to Lareb. Concomitant medications were pantoprazole, simvastatin, diclofenac and

ferrous fumarate. Since pantoprazole and diclofenac canalso cause thrombocytopenia, an additive effect of dabigatran cannot be ruled out.

Patient C is patient of unknown sex aged 61 – 70 years, who experienced a cerebral haemorrhage following administration of dabigatran (110mg twice daily) with an unknown latency. It is not reported if dabigatran was continued or withdrawn. The patient died approximately 6 weeks after starting dabigatran. According to the reporter, the patient participated in a trial investigating the use of the anticoagulant apixaban (direct factor Xa inhibitor) in the past. The reporter (cardiologist) did not report a possible relationship between the event and the use of dabigatran. Concomitant medication was not reported. No additional information could be obtained.

Patient D is a male aged 61 – 70 years with a history of diabetes mellitus, severe obesity, large alcohol consumption, heavy smoking, cardiovascular disease, enlarged heart, myocardial infarction and back complaints. The patient started dabigatran (150mg twice daily) for the treatment of paroxysmal atrial fibrillation. Within four days he developed a cardiac arrhythmia, myocardial re-infarction, saddle embolus of the aorta and a cardiac aneurysm that was probably ruptured. The patient was provided with acenocoumarol but refused this, as well as the use of a statin and medication to treat his diabetes mellitus. The patient died four days after starting dabigatran. Due to this short latency, it is the opinion of the reporting physician that the events were not related to dabigatran.

Patient E is a male of unknown age who experienced ischemic stroke after starting dabigatran (daily dose unknown) for atrial fibrillation, with an unknown latency. The patient died on an unspecified date. According to the reporter (cardiologist), there was no possible causal relationship between the events and the use of dabigatran. The patient used dabigatran previously without any complaints.

Patient F is a female of unknown age who developed an unspecified type of cancer with fatal outcome after starting dabigatran for an unknown indication, with an unknown latency. According to the reporter (consumer), there was no possible causal relationship between the event and the use of dabigatran.

Patient G is a male aged 71 years or older with a history of coronary disease and a pacemaker insertion. The patient suddenly died two weeks after starting dabigatran (110mg twice daily) for an unknown indication. The cause of death was not reported, but according to the reporter (general physician) it was probably due to an acute cardiac problem. The causal relationship with dabigatran is unclear. It is unknown if an autopsy was performed.

Conclusion
Most of the above described cases of events with fatal outcome do not appear to be directly caused by the use of dabigatran. In five cases the reporters state that there is no causal relationship with the use of dabigatran. It should be noted however, that case F is a poorly documented consumer report, that cannot be assessed accurately.
In the two remaining cases a causal relationship is possible or probable. In case B the use of dabigatran could hypothetically have led to a thrombocytopenia associated cerebrovascular infarction and in case G there was an unexplained sudden death, in which the causal relationship with dabigatran remains unclear.

Malignant neoplasms associated with dabigatran use

Due to their seriousness and medical relevance, the reports concerning malignant neoplasms in patients using dabigatran are described below.

Patient A is a male of unknown age with a history of acute coronary syndrome, arterial stenosis, COPD and herniated nucleus pulposus. He was diagnosed with small cell lung cancer 8 months after starting dabigatran for atrial fibrillation. Dabigatran was continued and the patient was treated with chemotherapy (not further specified). The patient outcome was not known at the time of reporting.

Patient B is a male of unknown age (date of birth 12-nov-1934) with a history of atrial flutter, and asymptomatic chronic atrial fibrillation, for which he was treated with acenocoumarol. On the patients request, he switched to dabigatran. On an unspecified moment after starting dabigatran he was diagnosed with an unspecified type of cancer and experienced rectal blood loss, after which dabigatran was withdrawn. The patient outcome was not known at the time of reporting. According to the reporting specialist doctor, there was no causal relationship between the rectal blood loss and the use of dabigatran. He did not report a possible relationship between the cancer and dabigatran use.

Patient C is a female aged 71 years or older who experienced a gastrointestinal bleeding (location not reported) after starting dabigatran for atrial fibrillation, with a latency of 2 days. Dabigatran was withdrawn and the patient recovered. On an unspecified moment she was diagnosed with a mildly differentiated carcinoma of the colon. The outcome of this event was not known at the time of reporting. According to the reporting specialist doctor, there was a possible causal relationship between dabigatran use and the GI bleeding. The reporter did not comment on the relationship between dabigatran and the colon carcinoma.

Patient D is a female of unknown age who developed an unspecified type of cancer with fatal outcome after starting dabigatran for an unknown indication, with an unknown latency. According to the reporter (consumer), there was no possible causal relationship between the event and the use of dabigatran.
NOTE: This report is identical to case F described in the section concerning events with fatal outcome

Patient E is a person of unknown sex and age who experienced a gastrointestinal bleeding and developed an unspecified type of cancer after starting dabigatran for the treatment of atrial fibrillation. The latency and outcome for both events, and the action taken with dabigatran are not reported. The reporter did not comment on the relationship between dabigatran and the colon carcinoma.

Other sources of information regarding malignant neoplasms associated with dabigatran use

SmPC
The SPC of dabigatran does not contain any information regarding malignant neoplasms as possible ADRs. The use of dabigatran is contraindicated in patients with malignant neoplasms at high risk of bleeding.

Literature

No cases of neoplasms (benign or malignant) associated with the use of dabigatran, or a possible pharmacological mechanism, could be found in the literature.

Databases
Since the Lareb database has a limited number of reports, and the reported cases of malignant neoplasms are diverse in nature, the WHO database of the Uppsala Monitoring Centre was accessed. This database contains several malignant neoplasms that are present disproportionately. It should be noted however that the majority of them concern neoplasms of the gastrointestinal tract (see table 3). In these cases selection bias cannot be ruled out, if the neoplasms were already present and at high risk of bleeding prior to starting dabigatran.

Table 3. Reports of disproportionately present neoplasms associated with the use of dabigatran in the WHO database.

Drug	ADR	Number of reports	ROR (95% CI)
Dabigatran	Colon cancer	29	4.8 (3.3- 6.9)
	Gastrointestinal carcinoma	9	6.3 (3.3 – 12.2)
	Colon adenoma	6	8.5 (3.8 – 19.0)
	Colon neoplasm	4	11.9 (4.4 – 22.1)
	Rectal cancer	6	4.8 (2.1 – 10.7)
	Cerebral haemangioma	3	69.6 (20.5 – 236.2)

Conclusion
Most of the cases of malignant neoplasms associated to the use of dabigatran are poorly documented, with missing latencies in the majority of them. In addition, it cannot be ruled out that cases C and E concern the same patient and could therefore be duplicate reports. In terms of statistical analyses, the WHO database shows a statistically significant disproportionality for several gastrointestinal malignancies. However, as described above, the possibility of selection bias cannot be ruled out. In the literature, no cases of new malignancies associated with the use of dabigatran could be found. Based on the available data, the causality between the use of dabigatran and the development of malignant neoplasms cannot be assessed.

Bleedings associated with dabigatran use
Bleedings are the most commonly reported ADRs according to the SmPC and occur in 14% of patients, with major bleedings occurring in less than 2%. Since the occurrence of bleedings is an important issue with the new oral anticoagulants since them have no antidote, reports concerning bleedings are compared with the information present in the SPC.

Lareb received a total of 22 reports of bleedings associated with the use of dabigatran. The most common types of bleedings are gastrointestinal bleedings and central nervous system bleedings (CVA, cerebral haemorrhage). In one of the reports the outcome was fatal. This case is also present in the section describing the events with fatal outcome (case C).

The types of bleedings reported to Lareb seem similar to those present in the SmPC, which mentions gastrointestinal bleedings (common), intracranial bleedings

(uncommon), skin bleedings (uncommon) and several types of bleedings due to medical procedures or trauma.

Discussion and conclusion

The aim of this report was to give an overview of the ADRs associated with the use of dabigatran, using information from the spontaneous reporting system and the LIM system. The overall safety profile presented in this report is in general consistent with the information provided in the SmPC of dabigatran. Based on their medical significance, cases with fatal outcome and cases of new malignant neoplasms were reviewed in detail, and cases of bleedings were summarised. For events with fatal outcome, a causal relationship with dabigatran does not seem likely in most cases based on the information available.

For cases of malignant neoplasms, causality could not properly be assessed due to the lack of relevant information. We suggest a review of the PSUR by the Marketing Authorization Holder for signals of malignant neoplasms.

The cases of bleedings seem consistent with those reported in the SPC of dabigatran in terms of location of the bleedings. Since frequencies of occurrence cannot accurately be calculated using spontaneous reporting, the quantitative aspects should not be compared with data present in the SmPC.

- Further investigation of the information of the marketing authorization holder regarding signals of malignant neoplasms is advisable

References

1. European SPC Pradaxa® (dabigatran). (version date: 23-8-2011, access date: 6-2-2012) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf.
2. College voor Zorgverzekeringen. GIP Databank. College voor Zorgverzekeringen. GIP Databank. (version date: 22-3-2011, access date: http://www.gipdatabank.nl/.

This report has been published on May 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).

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