Update overview of reports of cardiac adverse drug reactions and reactions with fatal outcomes from all causes associated with domperidone

Introduction

In Quarterly Report 2013-3, Lareb gave an overview of reports of cardiac adverse drug reactions (ADRs) associated with domperidone [1]. Since July 2014 the status of domperidone has changed to prescription only [2]. This update overview describes the cardiac adverse drug reactions, supplemented with the reactions with fatal outcome from all causes, associated with domperidone.

As reported in Quarterly Report 2013-3, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) decided to start a safety review of domperidone containing products at its 4-7 March 2013 meeting. The review was triggered by the Federal Agency for Medicines and Health Products (FAMHP) in Belgium, who had concerns about domperidone's cardiac effects [3]. On 23 April 2014, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed the recommendations to restrict the use of domperidone-containing medicines, followed by restriction of the indications, restrictions concerning dose and duration of therapy, and sharpening of the contra-indications [4]. The recommendation was accepted by the European Committee on July 14, 2014 [5].

In the Netherlands, domperidone was granted marketing authorization in 1979. Domperidone (Motilium®) is indicated *for the relieve of the symptoms of nausea and vomiting*. Domperidone is available as tablets, suppositories and as suspension [6].

Due to media attention in the Netherlands on the association between domperidone and cardiac adverse drug reactions, there was an increase in the reporting of this association since March 2013.

Reports

On April 15 2015 the database of the Netherlands Pharmacovigilance Centre Lareb contained reports of 58 patients with 69 cardiac ADRs, or ADR Death or Sudden death. It is important to note that one patient can suffer from several ADRs. These reports are listed in table 1. In 19 patients (with 20 ADRs) the outcome was fatal.

Table 1. Reported cardiac ADRs and ADR Death and Sudden death associated with domperidone

Suspected adverse drug reaction (MedDRA PT)	Number of times reported	Number of times fatal outcome
Arrhythmia	6	0
Atrial fibrillation	1	0
Bradycardia	1	0
Cardiac arrest	9	8
Cardiac failure	1	1
Cyanosis	1	0
Myocardial infarction	3	2
Palpitations	14	0
Sinus tachycardia	1	0
Tachycardia	5	0
Torsade de pointes	2	1
Chest discomfort	2	0
Death	4	4
Sudden cardiac death	3	3
Sudden death	1	1

Suspected adverse drug reaction (MedDRA PT)	Number of times reported	Number of times fatal outcome
Electrocardiogram abnormal	1	0
Electrocardiogram QT interval prolonged	3	0
Electrocardiogram ST segment depression	1	0
Heart rate increased	8	0
Heart rate irregular	2	0

It is important to note that one patient can suffer from multiple ADRs

In addition to the 19 patients with cardiac ADRs with fatal outcome and the ADRs death and sudden death, the Netherlands Pharmacovigilance Centre Lareb contained 2 reports with fatal outcome from other causes, that is 1 report of anaphylaxis, and 1 of acute tubular necrosis.

Description of the reports received by Lareb with fatal outcome from all causes associated with domperidone

Of the total of 21 reports with fatal outcome from all causes, 6 reports concerned males, 14 concerned females, and in 1 report the gender was not reported. The latencies varied between minutes to 8 months, the median latency was 2 days, and in 3 reports the latencies were unknown. The mean and median ages were 53 years. In three patients the ages were unknown.

5 reports with fatal outcome concerned children. These reports concerned 1 patient in the age group 0-2 years with the ADR sudden death with the indication nausea, where the probable cause of death was myocarditis. The medical history of this patient indicated premature birth and multiple congenital disorders including intraventricular haematoma with tetraventriculair hydrocephalia, and non-congenital pulmonary cytomegalovirus infection. There were 2 reports of patients in the age group 2-4 years. The indications were gastroenteritis with vomiting, diarrhoea and haematemesis in one patient, where the ADR was death caused by aspiration. Obduction showed an arteria lusoria. The other patient is this age group had the indication gastroenteritis and the ADR was unknown cause of death. The medical history of this patient indicated Prader-Willi syndrome. There were 2 patients in the age group 11-20 years. One of these patient had the indication vomiting post chemotherapy in osteosarcoma, with the ADR cardiac failure, and concomitant medication including ondansetron, amphotericin b and an unspecified anthracycline. In the other report the indication was vomiting, and the ADR cardiac arrest. This patient was also treated for pneumonia with amoxicillin.

In the cases concerning adults or where the ages were unknown, in 11 of the 16 cases other factors were described which might have caused or aggravated the reaction: coronary disease, non-specified antipsychotics and non-specified cardiovascular drugs, Henoch Schönlein vasculitis, possible underlying cardiac or non-cardiac disease (eating poorly and vomiting for months in one patient, and not feeling well for days before starting domeridone with nausea, dyspepsia and diarrhoea), a cerebrovascular accident prior to start of domeridone with gradually increasing problems of not eating anymore and vomiting, breast cancer in the medical history, intestinal infection and obstructed kidneys, hypokalaemia and in the medical history atrial fibrillation, concomitant medication indicating hypertension, and in the patient with acute tubular necrosis, dehydration and the use of lithium and acute on chronic renal failure as part of the medical history.

19 of the 21 of the cases with fatal outcome from all causes were received before July 2014. There were 2 reports received after July 2014, of which in one case the reaction happened after July 2014. This report concerned a female in the age group 70 years or older with the ADR death, who had not been feeling well for days before the start of domperidone, with nausea, dyspepsia and diarrhea, where the reporter mentioned that several causes might have led to the reaction.

Other sources of information

SmPC

The SmPC of domperidone mentions the following [6]:
Among the warnings and precautions for use (section 4.4):
"Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. In these reports patients were included in whom there were confounding risk factors, electrolyte abnormalities and concomitant treatment which may have played a role (referring to section 4.8).
Epidemiological studies have shown that domperidone has been associated with a higher risk of serious ventricular arrhythmias or sudden cardiac death (referring to section 4.8). A higher risk was observed in patients older than 60 years, patients who received a daily dose of more than 30 mg and patients receiving concomitant QT prolonging drugs or inhibitors of CYP3A4.
The lowest effective dose of domperidone is to be used in adults and children. Domperidone is contraindicated in patients with a known, existing extension of the cardiac conduction intervals, particularly QTc, and in patients with significant electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesemia) or bradycardia or in patients with underlying heart conditions such as congestive heart failure due to an increased risk of ventricular arrhythmia (referring to section 4.3). It is known that electrolyte disorders (hypokalemia, hyperkalemia, hypomagnesemia) and bradycardia increase the risk of proarrhythmia.
Treatment with domperidone should be stopped if signs or symptoms appear that may be associated with cardiac arrhythmia."
Among the contraindication (section 4.3) are patients with a known, existing prolongation of the cardiac conduction interval especially QTc, and patients with significant electrolyte disturbances or underlying heart diseases such as congestive heart failure, and patients with moderate or severe hepatic impairment.
Section 4.8 (adverse drug reactions) of the SmPC refers to section 4.4 and mentions the following cardiac adverse drug reactions: ventricle arrhythmia, prolongation of the QTc-interval, torsade de pointes and sudden cardiac death.

Prescription data

The number of patients using domperidone in the Netherlands is shown in table 2.*

Table 2. Number of patients using domperidone in the Netherlands between 2009 and 2013 [7].

Drug	2009	2010	2011	2012	2013
Domperidone (Motilium®)	81,634	85,546	86,007	73,466	50,944

* The GIP database only gives information about resources outpatients (i.e. outside institutions such as hospitals and nursing homes) have been provided and reimbursed under the Health Insurance Act. Over-the-Counter drug use is not included.

Discussion and conclusion

On April 15 2015 the database of The Netherlands Pharmacovigilance Centre Lareb contained 21 reports with fatal outcomes from all causes with the use of domperidone.
Many of these cases occurred before July 2014, when the indications, dose and duration of therapy were restricted, contra-indications were sharpened [4,5], and when the OTC status was changed to prescription only [2]. There were 2 reports received after July 2014, of which in one case the reaction happened after July 2014.
The reports with a fatal outcome are heterogeneous, and in most reports underlying pathology cannot be excluded as cause of cardiac arrest and/or death.
Due to the media attention for the association between the use of domperidone and the occurrence of cardiac disorders, Lareb received most of these reports since March 2013. Some of the reports describe cases that occurred years ago, therefore recall bias cannot completely excluded.
Although cardiac adverse drug reactions like ventricle arrhythmia, torsades des points, sudden cardiac death, and prolongation of the QTc-interval are described in the SmPC of domperidone [6], in many of the cases there were other factors besides the domperidone, that might have contributed to the reactions or might have been confounding factors, which makes it difficult to establish a clear connection between the use of the drug domperidone and the reactions based on the reports Lareb received.

References

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