1.1. Sitagliptin and dyspnoea

Introduction

Recently an overview of possible ADRs reported to Lareb in patients using sitagliptin, was presented to the Medicines Evaluation Board (MEB) (Quarterly report 1st quarter 2011). In the overview, possible ADRs related to the respiratory tract were described in more detail, since there seemed to be a difference in types of reactions between our reports and the ADRs described in the SmPC of sitagliptin. In the present report the association between sitagliptin and dyspnoea will be described based on the fact that this reaction was reported in a substantial number of sitagliptin cases related to the respiratory tract.

Sitagliptin (Januvia®) was registered for the European market on March 21st 2007 with the Netherlands as rapporteur. It is indicated for the *treatment of type 2 diabetes mellitus. It can be used as monotherapy in patients who are inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance or as dual oral therapy in combination with metformin or a sulphonylureum derivate or a peroxisome proliferator-activated receptor gamma (PPARγ) agonist or as triple oral therapy in combination with a sulphonylurea and metformin or a PPARγ agonist and* metformin. It is also indicated *as add-on to insulin (with or without metformin)* [1].

The improvement in glycaemic control observed with sitagliptin may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells.

In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. GLP-1 does not impair the normal glucagon response to hypoglycaemia.

The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP [2].
Since its introduction in the Netherlands, sitagliptin is used by only a small proportion of the patients with diabetes mellitus [3].

Reports

On March 25, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained 6 reports concerning dyspnoea with the use of sitagliptin.

Table 1. Reports of dyspnoea associated with the use of sitagliptin

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 81243 M, 61 – 70 years	sitagliptin 100mg daily diabetes	glimepiride quinapril simvastatin	nipple thickening urticaria dyspepsia dyspnoea	several weeks discontinued recovered
B 83895 F, 51 – 60 years	sitagliptin/metformin 50mg/1000mg daily diabetes	metformin pravastatin	oedema dizziness fatigue myalgia dyspnoea renal insufficiency	2 months discontinued recovered
C 86616 M, 61 – 70 years	sitagliptin 100mg daily type II diabetes mellitus	sotalol cabergoline acetylsalicylic acid hydrocortisone simvastatin metformin losartan levothyroxine	dyspepsia dyspnoea	2 weeks discontinued recovered
D 102368 F, 51 – 60 years	sitagliptin/metformin 50mg/ 850mg daily diabetes mellitus	amlodipine glimepiride salbutamol hydroquinine simvastatin irbesartan	arthralgia dyspnoea	2 days discontinued recovering
E 108686 M, 41 – 50 years	sitagliptin 100mg daily diabetes mellitus non-insulin-dependent	metformin gliclazide simvastatin perindopril	oedema epigastric pain dyspnoea	6 weeks discontinued recovered
F 110243 F, 61 – 70 years	sitagliptin 100mg daily diabetes		upper respiratory tract infection dyspnoea suffocation feeling	3 years discontinued recovering

Details of the above mentioned reports are discussed below.

Patient A is a male aged 61-70 years with dyspnoea following administration of sitagliptin 100 mg daily for diabetes mellitus with a latency of several weeks. In addition to dyspnoea the patient experienced persisting urticaria on legs and trunk (treated with betamethasone cream), nipple thickening and dyspepsia that was increasing in severity (treated with omeprazole). Prior to the start of sitagliptin, the patient used rosiglitazone which was withdrawn due to the increased risk of cardiovascular complications. The patient recovered after withdrawal of sitagliptin. Concomitant medications were glimepiride, quinapril and simvastatin.

Patient B, a female aged 51-60 years, experienced dyspnoea following administration of sitagliptin 50 mg / metformin 1000 mg daily for diabetes mellitus with a latency of two months. The patient also experienced oedema and myalgia, dizziness, fatigue, and renal insufficiency (severity not reported). After sitagliptin / metformin had been withdrawn the patient recovered in five days. Concomitant medications were metformin and pravastatin.

Patient C is a male aged 61-70 years with a history hypertension, angina pectoris, coronary artery bypass graft, albuminuria and prolactinoma. Two weeks after starting sitagliptin 100 mg daily for diabetes mellitus, the patient experienced dyspnoea and dyspepsia. After withdrawal of sitagliptin, the patient recovered.

Concomitant medications were levothyroxine, simvastatin, sotalol, cabergoline, losartan, acetylsalicylic acid, hydrocortisone and metformin.

Patient D is a female aged 51-60 years with dyspnoea and arthralgia following administration of sitagliptin 50 mg / metformin 850 mg daily for diabetes mellitus with a latency of two days. After unsuccessful treatment with antibiotic therapy, and after performing a chest X-ray that showed no abnormalities, the patient was started on salbutamol for his dyspnoea. In addition, sitagliptin / metformin was withdrawn and the patient recovered. Concomitant medications were hydroquinine, irbesartan, salbutamol, simvastatin, glimepiride and amlodipine.

Patient E, a male aged 41-50 years with a history of hypertension experienced dyspnoea, epigatric pain and oedema following administration of sitagliptin 100 mg daily for diabetes mellitus with a latency of six weeks. According to the reporting physician, the complaints could not be explained by a cardiac or pulmonary cause. After withdrawal of sitagliptin, the patient fully recovered in three weeks. Concomitant medications were gliclazide, perindopril, metformin and simvastatin.

Patient F is a female aged 61-70 years with dyspnoea, an upper respiratory tract infection and feelings of suffocation following administration of sitagliptin 100 mg daily for diabetes mellitus with a latency of three years. After withdrawal of sitagliptin the patient recovered. No concomitant medications were reported.

Other sources of information

SmPC

Dyspnoea is not mentioned in the SmPC for sitagliptin containing products [1]. The SmPC does describe upper respiratory tract infections as a reaction that was reported in more than 5% of patients, no matter the causality [1].

Literature

A Medline search revealed one publication describing dyspnoea in diabetes patients using sitagliptin. The investigators describe fifteen intolerant sitagliptin patients who developed several respiratory complaints, including wheezing / dyspnoea, after treatment with sitagliptin. Latencies varied from 1- 8 weeks and patients recovered within one week after withdrawal of the drug. All intolerant patients had seasonal or perennial allergic rhinitis treated with intermittent antihistamines and nasal steroid sprays. They authors propose that "*…..underlying inflammatory changes in DPP IV activity combined with further drug-mediated DPP-IV inhibition leads to decreased inactivation of neuropeptides and/or cytokines that are glandular secretagogues. This plus similar mechanism(s) in the brain may be responsible for the rhinorrhea, cough and fatigue we associated with sitagliptin treatment*" [4].

Databases

On March 28, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained six cases of dyspnoea in association with sitagliptin containing products, which was reported disproportionally (ROR = 5.8, 95% CI: 2.5 – 13.7).

On March 28, 2011, the WHO database of the Uppsala Monitoring Centre contained 190 reports of dyspnoea, concerning 114 females and 58 males. In 18 cases the sex was not reported. The median age of the patients was 64 years (range 35 - 90). The association was disproportionally present (ROR = 0.7, 95%

CI: 0.6 – 0.8) in the database. In 109 cases a positive dechallenge was reported and in eight of these there was also a positive rechallenge.

On March 28, 2011, the Eudravigilance database contained 87 reports of dyspnoea associated with the use of sitagliptin which was reported disproportionally (ROR = 0.7, 95% CI: 0.6 – 0.9). It concerns 56 females and 28 males. In 3 cases, the sex of the patient involved was not reported. The median age of the patients was 64 years (range 38 - 87). A total of 80 reports were classified as serious.

The data in the WHO and Eudravigilance database show that dyspnoea was disproportionally less present in sitagliptin reports than in reports of other drugs. A possible explanation could be the fact that there is a large number of sitagliptin reports in the WHO database describing ADRs representing lack of efficacy, such as “blood glucose increased”, “drug ineffective”, glycosylated haemoglobin increased” and “wrong technique in drug usage process”. These ADRs comprise about 20% of the total number of ADRs reported with sitagliptin, possibly masking the dyspnoea signal.

Prescription data

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

Table 2. Number of patients using sitagliptin in the Netherlands between 2007 and 2009 [3].

Drug	2007	2008	2009
Sitagliptin	1,292	5,376	7,471
Sitagliptin / metformin	-	440	1,367

Mechanism

The mechanism through which sitagliptin may induce dyspnea remains unknown. As described above, sitagliptin is a DPP-4 inhibitor and its mechanism of action is based on the prevention of hydrolysis and inactivation of GLP-1 and GIP, thereby increasing the plasma concentrations of the active forms of both hormones, resulting in an increase of insulin synthesis and release from pancreatic beta cells.

However, DPP-4 is also known as CD26, a multifunctional type II trans-membrane glycoprotein, functioning as a proteolytic enzyme, receptor, co-stimulatory protein, and involved in adhesion and apoptosis [5,6]. Expression of CD26 occurs in several tissues including alveolar pneumocytes and serosal submucosal glands of the bronchus [7].

Discussion

Although dyspnoea is a symptom that can be caused by several causes, and no clear underlying pathologies were reported in the individual cases, it should still be considered to mention dyspnoea in the SmPC as a separate symptom and not as upper respiratory tract infection. An important consideration for this suggestion is the fact that there was a positive dechallenge in all of the Lareb cases and in 57% of the cases in the WHO database, suggesting a causal relationship between sitagliptin use and dyspnoea. In addition, latencies were consistent with those mentioned in the article by Baraniuk *et al*. [4] in five of six Lareb cases.

Since the Eudravigilance database mainly contains serious cases, whereas only a few countries, among which the Netherlands, report also non serious cases, the results of the disproportionality analysis in the Eudravigilance database should be interpreted with caution.
Another point of concern is the relative long time to onset in our cases. The majority of reports of dyspnoea in a SRS database will be reported when the time to onset is relatively short. Given the long time of onset in our cases, it is possible that dyspnoea will not be recognized as an ADR in daily practice so pronounced underreporting may be present. This may cause a reduction of disproportionality.

Conclusion

These cases suggest a signal of dyspnoea occurring with sitagliptin containing products.

- Signal of possible association of dyspnoea associated with the use of sitagliptin

References
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This signal has been raised on July 2011. 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).