Quetiapine and sleep apnoea syndrome

Introduction

Quetiapine (Seroquel®, Seroquel XR®) belongs to the group of atypical antipsychotics and is indicated for the treatment of *schizophrenia.* It is also indicated for *the acute treatment of manic and depressive episodes associated with bipolar disorder and the maintenance treatment of bipolar disorder*. Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain: serotonin 5HT1A and 5HT2, dopamine D1 and D2, histamine H1, and adrenergic α1 and α2 receptors. The efficacy of quetiapine in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. Quetiapine has been approved for the Dutch market since April 1998 [1].

The group of atypical antipsychotics contains drugs with a diverse pharmacological profile. Other atypical antipsychotics available on the Dutch market are clozapine (Leponex®), olanzapine (Zyprexa®), paliperidon (Invega®), risperidone (Risperdal®) and aripiprazole (Abilify®).

Sleep apnoea is a sleep disorder characterized by abnormal pauses in breathing or instances of abnormally low breathing, during sleep. Snoring and daytime sleepiness are the most common presenting complaints. Additional symptoms include restless sleep, fatigue and poor concentration [2].

Reports

On March 26th 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports of sleep apnoea in patients using quetiapine.

A, 73632
This industry report concerns a male aged 41-50 years, who experienced severe sleep apnoea after one year of quetiapine use (500 mg/day). Due to heavy snoring the patient was referred to a pulmonary disease specialist who diagnosed serious sleep apnoea with hypotension and tachycardia. According to the information of the marketing authorization holder the patient “was given extra oxygen during the night”. The dose of quetiapine was tapered and finally withdrawn after which the sleep apnoea resolved. Concomitant medication was valproic acid, bromazepam and lithium. He had a BMI of 27 kg/m^2.

B, 128364
This report from a specialist doctor concerns a male aged 41-50 years, with sleep apnoea following administration of quetiapine (50 mg a.n.) for post-traumatic stress disorder with a latency of 3 days after start. His wife noticed abnormal pauses in breathing during his sleep. Quetiapine was withdrawn and the patient recovered. The patient did not use any concomitant medication. He had a normal posture and was a smoker.

Other sources of information

SmPC

Sleep apnoea is not mentioned in the SmPC of quetiapine [1].

Literature

There are a few publications on the possible association between quetiapine and sleep apnoea syndrome.

Freudenmann et al. describe moderate to severe respiratory dysfunction after normal oral doses of quetiapine in two obese patients. In the first case, acute respiratory failure and coma occurred after a single dose of quetiapine in combination with lorazepam in a 59 year old female with previously unknown sleep apnoea syndrome. Intensive care treatment and mechanical ventilation led to full recovery. The second case was a 59 year old male with an operated obstructive sleep apnoea syndrome in which quetiapine was associated with nocturnal respiratory dysfunction and confusion. After stopping quetiapine the patient recovered [3].

Shirani et al. performed a retrospective study in which they studied the impact of atypical antipsychotic use on obstructive sleep apnoea. They found that use of atypical antipsychotics was associated with a significantly increased risk (odds ratio 4.53) of obstructive sleep apnoea in patients diagnosed with depression and high pre-test likelihood of obstructive sleep apnoea after adjusting for the effect of depression and several common medical/pharmalogical confounders [4].

Rishi et al. studied the effects of atypical antipsychotics on obstructive sleep apnoea by retrospectively analyzing medical intake data and polysomnographic studies of patients referred to a community hospital sleep disorders center. When adjusted for body mass index, sex and use of benzodiazepines and sleeping aids, the odds ratio of severe obstructive sleep apnoea in patients using atypical antipsychotics (n=46) was 1.9 compared to non- atypical antipsychotic users (95% confidence interval, 1.1-3.3). They concluded that atypical antipsychotic medication use may increase the risk of more severe obstructive sleep apnoea independent of weight and neck circumference [5].

Databases

On March 26th 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports of sleep apnoea associated with the use of quetiapine. Because of this limited number the Reporting Odds Ratio (ROR) could not be calculated for quetiapine. On the 26th of March 2012, the database of the Netherlands Pharmacovigilance Centre also contained cases of sleep apnoea associated with the use of other atypical antipsychotics. See table 1. Sleep apnoea is reported disproportionally for the group of atypical antipsychotics (ROR = 19.0, 95% CI: 7.1-50.8)

Table 1. Reports of sleep apnoea for the atypical antipsychotics in the Lareb database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Sleep apnoea	Quetiapine	2	-
Sleep apnoea	Clozapine	2	-
Sleep apnoea	Risperidone	1	-

On the 26th of March 2012 the WHO database of the Uppsala Monitoring Centre contained 155 reports of sleep apnoea associated with the use of quetiapine. This was reported disproportionally. The WHO database also contained cases of sleep apnoea associated with the other atypical antipsychotics. See table 2. Sleep apnoea is reported disproportionally for the group of atypical antipsychotics (ROR = 4.2, 95% CI: 3.7-4.7)

Table 2. Reports of sleep apnoea for the atypical antipsychotics in the WHO database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Sleep apnoea	Quetiapine	155	9.6 (8.2-11.3)
Sleep apnoea	Olanzapine	54	4.1 (3.1-5.4)
Sleep apnoea	Clozapine	76	2.5 (2.0-3.1)
Sleep apnoea	Aripiprazole	18	2.5 (1.6-4.0)
Sleep apnoea	Risperidone	23	1.6 (1.1-2.4)
Sleep apnoea	Paliperidone	1	-

On August 18th, the Eudravigilance database contained 110 reports of sleep apnoea in association with the use of quetiapine, which was reported disproportionally. The Eudravigilance database also contained cases of sleep apnoea associated with the other atypical antipsychotics. See table 3.

Table 3. Reports of sleep apnoea for the atypical antipsychotics in the Eudravigilance database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Sleep apnoea	Quetiapine	110	4.0 (3.3-4.9)
Sleep apnoea	Olanzapine	79	3.6 (2.9-4.5)
Sleep apnoea	Clozapine	66	2.1 (1.6-2.6)
Sleep apnoea	Aripiprazole	4	0.5 (0.2-1.2)
Sleep apnoea	Risperidone	27	1.0 (0.7-1.5)
Sleep apnoea	Paliperidone	2	-

Prescription data

The number of patients using atypical antipsychotics in the Netherlands is shown in Table 4 [6].

Table 4. Number of patients using atypical antipsychotics in the Netherlands between 2007 and 2011.

Drug	2007	2008	2009	2010	2011
Quetiapine	36,049	44,898	50,918	60,158	70,725
Olanzapine	41,832	41,924	40,875	41,524	41,966
Clozapine	8,194	8,619	8,959	9,526	9,912
Aripiprazole	6,692	8,195	10,526	12,916	14,867
Risperidone	54,367	54,138	51,758	51,806	50,418
Paliperidone	186	840	673	782	1,411

Mechanism

The exact mechanism by which quetiapine causes sleep apnoea is not clearly understood. A potential mechanism proposed by Rishi et al. concerns an imbalance between collapsing and expanding forces of airway muscles which results in airway obstruction and sleep apnoea. Obstructive sleep apnoea may, at least in part, be due to a differential decrease of genioglossal activity relative to diaphragmatic activity during inspiration. A balance between these muscle activities is necessary for airway patency. Atypical antipsychotics have tranquilizing properties that may impact upper airway tone potentiating obstructive sleep apnoea [5].

Class-effects

Despite the fact that there are important pharmacological differences between drugs in the class of atypical antipsychotics, it seems that sleep apnoea is probably a class effect. There are quite a lot of cases for the different atypical antipsychotic agents in the WHO database that are reported disproportionally. In Eurdravigilance sleep apnoea was reported disproportionally for quetiapine, clozapine and olanzapine. In the Lareb database sleep apnoea is also reported disproportionally for the class of atypical antipsychotics but the number of cases per individual drug is limited. In the literature sleep apnoea has also been associated with the group of atypical antipsychotics [4,5]. However, sleep apnoea is only mentioned in the SmPC of risperidone and paliperidone.

Discussion and conclusion

Obstructive sleep apnoea afflicts 2-4% of the middle-aged adult population [7]. Major risk factors are obesity, craniofacial abnormalities and upper airway soft tissue abnormalities. Potential risk factors include heredity, smoking, nasal congestion and diabetes [2]. Compared to the general population, mentally ill patients exhibit greater rates of obesity, smoking and impaired glucose tolerance and carry a higher risk of obstructive sleep apnoea [4]. Despite these confounding effects obstructive sleep apnoea has independently been associated with the use of atypical antipsychotics [5].

Lareb received two reports of sleep apnoea associated with the use of quetiapine. Patient A was overweight and also used bromazepam which together with the use of antipsychotics increases the chance of sleep apnoea [5]. Patient B is a smoker which is a potential risk factor. Therefore the role of possible confounding factors cannot be excluded, however both patients had a positive dechallenge.

The obstructive sleep apnoea associated with atypical antipsychotics described in the literature and the reported cases by Lareb, as well as the disproportionality in the WHO- and Eudravigilance database support further investigation.

- Signal of sleep apnoea associated with quetiapine
- Further investigation of the information of the marketing authorization holders is advisable

References

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The Marketing Authorization Holder of quetiapine has informed Lareb of the following:
Quetiapine is used off-label for sleep disorders, which is not encouraged by the Marketing Authorization Holder of quetiapine. Off-label use could possibly be a contributing factor to this signal.*

** Tak, L.M. et al, geen quetiapine bij slaapstoornissen, Ned Tijdschr Geneeskd. 2013;157:A5740*

This signal has been raised on November 2012. 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).