Quetiapine and paraesthesia

Introduction

Quetiapine (Seroquel®) is indicated for the treatment *of schizophrenia*. Quetiapine is also indicated for the treatment *of moderate to severe manic episodes in bipolar disorder* and for the treatment *of major depressive episodes in bipolar* disorder [1]. Quetiapine is an atypical antipsychotic. Quetiapine and the active human plasma metabolite, norquetiapine, interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for serotonin ($5HT_2$)-receptors and dopamine D1 and D2-receptors in the brain. It is precisely this combination of receptor antagonism, with a higher selectivity for $5HT_2$ relative to D2-receptors, which is supposed to contribute to the clinical antipsychotic properties and the low tendency of quetiapine to cause extrapyramidal symptoms in comparison with typical antipsychotics. In addition, norquetiapine shows a high affinity for the norepinephrine transporter. Quetiapine and norquetiapine also have a high affinity for histaminergic and adrenergic α_1-receptors, with a lower affinity for adrenergic α_2-receptors and serotonin $5HT_1$-receptors [1].
Quetiapine was granted marketing authorization in the Netherlands in 1998 [1].

Paraesthesia is a disorder in the sensory perception in which, in the absence of external stimuli (like cold, warmth of pressure), spontaneous itching or tingling is perceived. In addition, an altered sensation to temperature and touch can occur. Paraesthesia may also be an expression of neuropathy. Chronic paraesthesia can be a symptom of underlying neurological diseases or nerve damage. Paraesthesia may also occur as electrical pulses, it is then referred to as 'shock like' paraesthesia [2,3].

This observation describes the association between paraesthesia and the use of quetiapine.

Reports

From 4 April 2003 until 21 January 2014 the Netherlands Pharmacovigilance Centre Lareb received thirteen reports concerning paraesthesia with the use of quetiapine. These reports concerned twelve females and one male. The age varied from 21 to 63 years. The paraesthesias that were reported concerned mouth/nose/skin of the head, arms/fingers, legs/feet and all over the body. The latency varied from 45 minutes to 3 years; the latencies were mostly hours to days. In nine patients there was a positive dechallenge, in one case there was a positive rechallenge.
One patient started metronidazole on the same day quetiapine was started. The reaction occurred 8 days later. Both drugs were withdrawn, the metronidazole 5 days before the quetiapine. The patient recovered after an unknown period after withdrawal of these drugs. The SmPC of metronidazole [4] mentions peripheral neuropathy as an adverse reaction with an unknown frequency. It therefore might be possible that metronidazole played a role in the reaction.
In one patient azithromycin might have played a role in the reaction, paraesthesia is described in the SmPC of azithromycin [5] as an often (between 1/10 and 1/100) occurring adverse reaction. The patient experienced paraesthesia on the same day the azithromycin was started. She had been using quetiapine for about 3 years.

One of the patients (Case E, described below) used colchicine as concomitant medication. The SmPC of colchicine [6] mentions neuropathy as an adverse reaction of colchicine. In this patient the startdate of colchicine and the action taken for colchicine were unknown.

Eight of the thirteen patients experienced other symptoms besides paraesthesia as a reaction. These were for example peripheral oedema, muscle stiffness, muscle cramps and tingling of the lower legs besides other symptoms in one patient, indicating there was a wide spectrum of symptoms besides paraesthesia. Another patient experienced anxiety, sleeplessness, perspiration and tingling of the skin of the head.

Five patients experienced paraesthesia as a core symptom as a reaction. In some of these cases restless legs or symptoms resembling this, were described. These five cases are describes here:

Case A (62441) This non-serious spontaneous report from a pharmacist concerns a female aged 31-40 years, with tinglings in the legs following administration of quetiapine for sleep disorder with a latency of less than a day after start. Since the start of the quetiapine the patient sleeps very well and can only just reach her bed in time. On the other hand, 45 minutes after intake of the quetiapine the patient experiences start of tinglings. The dose of the drug has not changed. The patient outcome is unknown. Concomitant medication was desogestrel.

Case B (64622) This non-serious spontaneous report from a specialist doctor concerns a female aged 31-40 years, with tinglings and itch in arms and upper legs within a few days after administration of quetiapine for aggressiveness. The patient had to move to diminish the complaints; showering did especially help. Quetiapine was withdrawn and the patient recovered. Concomitant medication was citalopram. The citalopram was started more than a year before the reaction and was not withdrawn. The medical history indicates aplastic anaemia, borderline personality disorder.

Case C (90363) This non-serious spontaneous report from a hospital pharmacist concerns a female aged 41-50 years, with paraesthesia following administration of quetiapine with a latency of a few days after start. Dose was reduced, the patient outcome is unknown. Concomitant medication was not reported.

Case D (138980) This non-serious spontaneous report from a specialist doctor concerns a female aged 31-40 years, with paraesthesia and restless legs following administration of quetiapine for bipolar affective disorder with a latency of 55 days after start. The dose for quetiapine is not changed. The patient has not recovered. Concomitant medication was not reported. The patient has no known medical history. The patient has no known past drug therapy.

Case E (156638) This non-serious spontaneous report from a specialist doctor concerns a male aged 61-70 years, with localized tingling of the feet and hot feeling in feet following administration of quetiapine for bipolar affective disorder with a latency of 2 months after start. According to the reporter the patient described the feeling as a feeling of sandpaper. The patient woke up during the night to put ice cubes on his feet. This reduced the symptoms. The physician saw similarities with restless legs syndrome. The drug quetiapine was withdrawn. The patient recovered. Concomitant medications were ispaghula (psylla seeds), levothyroxine sodium, aripiprazole, lorazepam, colchicine and colecalciferol. The medical history indicates that the patient had a depression and also had chronic lymphatic leukaemia. The patient has no known past drug therapy.

Other sources of information

SmPC

The Dutch SmPC of quetiapine does not mention paraesthesia as an adverse drug reaction. Restless legs syndrome however is mentioned as a sometimes (between 1/100 and 1/1000) occurring adverse drug reaction [1].
Restless legs syndrome (RLS) is a disorder that is characterized by voluntary leg movements prompted by an urge to move which is often associated with unpleasant paraesthesias [7].
The US SmPC of the FDA mentions that the incidence of paraesthesia as an adverse reaction in up to 8-week placebo-controlled clinical trials with Seroquel® with doses of 300 and 600 mg/day for the treatment of bipolar depression was 3% in Seroquel® (n=698) versus 2% in placebo (n=347). The US SmPC also mentions that in and up to 3-week placebo controlled clinical trial for the treatment of bipolar mania in children and adolescent patients paraesthesia as an adverse reaction occurred in 2% in Seroquel® 400 mg (n=95), 0% in Seroquel® 600 mg (n=98) en 0% in placebo (n=90). Furthermore the US SmPC reports that in and up to 8-week placebo-controlled clinical trial for the acute therapy of bipolar depression in adult patients with Seroquel® XR 300 mg/day paraesthesia as an adverse reaction occurred in 3 % in Seroquel XR (n=137) and 2% in placebo (n=140) [8].

Literature

No further literature was found on paraesthesia associated with the use of quetiapine.

Databases

Table 1. Reports of paraesthesia associated with quetiapine in the Lareb, WHO and Eudravigilance database

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Paraesthesia	12	1.6 (0.9-2.9)
	Paraesthesia oral	1	-
WHO	Paraesthesia	228	0.4 (0.3 - 0.4)
	Paraesthesia oral	14	0.4 (0.2 - 0.6)
Eudravigilance	Paraesthesia	135	0.5 (0.5 - 0.6)
	Paraesthesia oral	8	0.3 (0.2 - 0.7)

Prescription data

Table 2. Number of patients using quetiapine in the Netherlands between 2008 and 2012 [9].

Drug	2008	2009	2010	2011	2012
Quetiapine	44,898	50,918	60,158	69,765	78,041

Mechanism

The literature does not provide a mechanism for specifically paraesthesia associated with the use of quetiapine. Some of the patients concerning the reports received by Lareb experienced symptoms that might be related to restless legs syndrome. Restless legs syndrome (RLS) is characterized by voluntary leg movements prompted by an urge to move and is often associated with unpleasant

paraesthesias [7]. On the mechanism of restless legs and quetiapine, there is literature available.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received thirteen reports of paraesthesia associated with the use of quetiapine. In the WHO database there are 228 cases present of paraesthesia and fourteen cases of paraesthesia oral associated with quetiapine. In the Lareb-, WHO- and Eudravigilance databases the association is not disproportionally present. The FDA SmPC describes two studies in which the incidence of paraesthesia as an adverse reaction was 3% in quetiapine, compared to 2% in placebo. On the other hand, the FDA SmPC also describes a study in which 2% of the patients taking a lower dose of 400 mg quetiapine experienced paraesthesia, but 0% of the patients taking the higher dose of 600 mg quetiapine did [8].
In nine cases received by Lareb there were positive dechallenges, and in one patient a positive rechallenge, which might indicate a causal relationship. Most latencies were hours to days.
Weak aspects were that many patients also experienced many other different symptoms besides paraesthesia. Three patients also used other drugs that could have played a role in the reaction.
Lareb received five cases, where paraesthesia was the core reaction. In these patients, one patient had to move to diminish the tinglings in arms and upper legs, in one patient the reported reactions were paraesthesia and restless legs, and in one patient the physician saw similarities with restless legs syndrome in the reaction. So it is possible that some of the patients experienced the reaction paraesthesia in association with restless legs syndrome. Restless legs syndrome is a known adverse reaction of quetiapine, occurring between 1/100 and 1/1000 patients [1].
The FDA SmPC shows that the background incidence of paraesthesia in the group of patients they studied was 2% in placebo in two of the three reported studies, and in one study 0% [8].
The reaction was not disproportionally present in the Lareb and WHO databases, which is also a weak aspect of the association.

Confounding by concomitant medication could not be ruled out, and in some cases the reaction may have been associated with restless legs syndrome, which is a known adverse reaction of quetiapine, and the association was not disproportionally present in both the Lareb- and WHO database. On the other hand, there were nine positive dechallenges and one positive rechallenge, and studies mentioned in the FDA SmPC showed a higher incidence of paraesthesia while using quetiapine compared to placebo [8]. For this reason, it is suggested that quetiapine might have a causative role in the occurrence of paraesthesia.

- Further investigation of the information of the marketing authorization holders and other national centers is needed to confirm the signal

References

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6. Dutch SmPC Colchicine tabletten 0,5 mg. (version date: 29 maart 2011, access date: 26-2-2014). http://db.cbg-meb.nl/IB-teksten/h21347.pdf
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8. FDA. (access date: 23-1-2014). http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020639s061,022047s034lbl.pdf
9. College for Health Insurances. GIP database. (version date: 9-6-2009, actualized 12-11-2013, access date: 27-1-2014). http://www.gipdatabank.nl/

This signal has been raised on May 2014. 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).