

1.1. Atomoxetine and tics

Introduction

The presumed mechanism of action of atomoxetine (Strattera[®]) is the highly selective and potent inhibition of the presynaptic norepinephrine transporter, without directly affecting the serotonin or dopamine transporters. In 2002, the drug was registered in the USA and in December 2004 registration in the Netherlands was approved [1,2]. Since registration, the number of patients on atomoxetine has slowly increased over the years (Table 1). 75% of the users are under 18 years old [3].

Table 1. Number of patients on atomoxetine in the Netherlands [3].

Year	Number of patients
2005	1091
2006	3463
2007	5167

Atomoxetine is indicated for the treatment of “attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older and in adolescents as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD. Diagnoses should be made according to DSM-IV criteria or the guidelines in ICD-10 [1].

Tics are defined as “sudden repetitive movements, gestures, or utterances that typically occur in bouts and mimic some aspect of a normal behavioral repertoire” [4]. Tic symptoms are often accompanied by attentional deficits such as ADHD [4]. Tics could be mediated by increased dopaminergic activity [4]. The role of the noradrenergic and serotonergic system in tics has not yet been established [4].

The SmPC states that atomoxetine does not worsen tics in patients with ADHD and comorbid chronic motor tics or Gilles de la Tourette Syndrome (GTS) [1].

Reports

On November 13, 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained five reports (Table 2) concerning tics during the use of atomoxetine; two of them originated from a paediatric psychiatrist, one from a paediatrician, one from a pharmacist and one from a consumer.

Table 2. Reports of tics associated with the use of atomoxetine.

Patient, Sex, Age, Relevant medical history	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 63430 M, 17 no tics in medical history	atomoxetine 60mg/day; increased to 85mg/day; increased to 100mg/day ADHD	methylphenidate	tics	not reported; tics developed after dose increase (twice), continued spontaneous full recovery after first dose increase and the patient is recovering after second dose increase
B 69501 M, 9	atomoxetine 18mg/day,		behaviour disorder,	not reported; tics developed after dose

GTS	increased to 25mg/day, increased to 40mg/day, increased to 60mg/day, decreased to 40mg/day		tics	increase, discontinued, partly recovered
C 54131 M, 10 GTS	atomoxetine 18mg ADHD	risperidone	tics	1 day, discontinued, recovered with sequel (severity sequel symptoms unknown)
D 74264 M, 6 tics on dexamphetamine	atomoxetine 10mg ADHD		tics	14 day, discontinued, recovered
E 81981 M, 7 no tics in medical history	atomoxetine 18mg		dry eyes, psychotic, tics	day, no change, recovered

One patient (C) recovered after discontinuation of atomoxetine and increasing the risperidone dose, one patient (E) recovered spontaneously while continuing atomoxetine, three patients recovered (partly) after withdrawal of the drug. One patient (A) used a concomitant drug which is known to be associated with tics (methylphenidate). Another patient (B) was switched from methylphenidate to atomoxetine. Two reports (patients A and B) show a possible dose-relation in this association. Patient A was initially treated with atomoxetine 60 mg OD which did not cause tics. He developed tics after a dose increase to 85 mg per day, from which he recovered spontaneously. The tics reoccurred after dose increased to 100 mg per day and the patient was slowly recovering when the case was reported. Patient B started with atomoxetine 18 mg OD, which was increased to 25 mg OD. Both doses did not cause tics. The patient experienced severe tics after dose increase to 40 mg OD, which remained severe after dose increase to 60 mg OD and after decrease to 40 mg OD. The patient partly recovered after discontinuation of therapy. In none of the patients additional physical examination to the occurrence of the tics was reported.

Other sources of information

SmPC

The Dutch SmPC states that atomoxetine does not worsen tics in patients with ADHD and comorbid chronic motor tics or GTS [1].

Literature

Since the registration of atomoxetine five case reports have been published about the occurrence of tics during the use of this drug. In 2004, Lee et al reported the occurrence or exacerbation of tics during the use of atomoxetine for ADHD in four paediatric patients [5]. The latency was between five and 30 days after start. Three patients had experienced tics on stimulants before and one patient was known with GTS. Discontinuation of atomoxetine led to improvement or recovery of the symptoms in all patients [5]. In 2005, Ledbetter reviewed a case study in which the onset of a motor tic was associated with a trial of atomoxetine [6]. In 2007, Párraga wrote about two patients who developed (exacerbation of) tics on atomoxetine in relatively low doses. One child, an eight-year-old boy, had a history of stimulant-induced tics. The patient's tic control was adequate prior to atomoxetine treatment. While on atomoxetine the patient promptly experienced tic exacerbation. The second boy was six years old and had no history of tics. He was initiated with atomoxetine for the treatment of ADHD and after a mild dose increase he

presented tic precipitation. Both patients had a decrease in tic activity when the atomoxetine was discontinued [7]. In 2008, Sears et al described a patient, without any prior history of a movement disorder, who developed tics following a single dose of atomoxetine that did not improve until interventional therapy with clonazepam was initiated. No structural, infectious, endocrine or genetic conditions that can cause tics were found [8]. In September 2008, Párraga described another patient who developed tics on atomoxetine. A 6 year old boy was treated with atomoxetine for ADHD. In the past he experienced transient facial tics during periods of stress. A couple of days after start the boy developed abdominal tics with a frequency up to 4/minute. Withdrawal of atomoxetine led to a significant decrease in frequency, but no full recovery [9]. A randomized, double-blind, placebo-controlled study sponsored by the manufacturer of atomoxetine examined the changes in severity of tics and ADHD during atomoxetine treatment in patients with GTS. They included 117 patients between 7-17 years old and used an atomoxetine dose of 0.5-1.5 mg/kg/day. A reduction in tic severity was found in the atomoxetine group [10]. In conclusion: the case reports and the information from this controlled study show conflicting information. However this study only included patients with ADHD and GTS and no patients with no history of tic disorders. In the case reports two patients with no history of tics were described [7,8].

Databases

In November 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained five reports of tics in association with the use of atomoxetine. The reporting odds ratio (ROR) is statistically disproportional (ROR=275, 95%CI: 96-785).

The database of the World Health Organization contained 385 reports of involuntary muscle contractions (which is one type of tics). The ROR is statistically disproportional: 6.1 (95%CI: 5.5-6.7).

On December 8, 2008, the Eudravigilance database contained 29 reports of tics associated with atomoxetine use. 23 reports concerned male patients, four female patients and sex was not specified in two cases. Two patients were older than 16 and six patients were younger than eight. In four cases the tics were reported as isolated events. In the remaining reports tics were reported beside behavioral or somatic symptoms. The reaction was rated serious in 27 cases. In two patients the reaction was disabling of nature, in ten cases hospitalization was reported to be required. Other causes led to the qualification of a serious reaction in 15 reports.

Mechanism

The exact mechanism of tics is not yet known. It is thought that an increased dopaminergic activity, especially in the subcortical areas, plays an important role [4,11]. Atomoxetine is brought onto the market as the drug with a low potential to produce tics, because it does not increase the dopamine transmission in the subcortical areas [11]. Bymaster et al. found that selective inhibition of the norepinephrine transporter (NET) causes an increase in the norepinephrine and dopamine level [12]. The mechanism held responsible for this effect is the reuptake of norepinephrine and dopamine by NET [12]. It is thought that atomoxetine only inhibits NET in the prefrontal cortex [12-14]. It is not yet known if atomoxetine causes this effect in other parts of the brain; the drug might have broader effects on neuromodulators than is currently known [8].

Discussion

Tics and GTS have been associated with ADHD. It has been noted that 7-10% of ADHD patients develop a tic disorder, which often presents in the first two years after diagnoses. Simple tics are followed by the development of more complex tics in many cases and the course of a tic disorder can be unpredictable [8]. Another confounder could be that atomoxetine was brought onto the market with the message that it would cause less tics than methylphenidate. This could have led to channeling; the prescribing of atomoxetine in patients who are more susceptible to develop tic disorders or have already been diagnosed with tics or GTS. All these factors complicate the determination of a causal relationship between atomoxetine and tics.

However as mentioned before, since atomoxetine has been registered several case reports of tics associated with atomoxetine use have been published. The reports Lareb received were well

documented and especially the dose-dependent relationship which was suggested in two of the five reports, is an indication for the existence of a causal relationship. The ROR's of both the Lareb and WHO database support this.

Conclusion

Lareb received five reports of tics associated with atomoxetine. Three patients (partly) recovered after withdrawal of the drug. A dose-dependent relationship was noted in two reports. Disproportionality in both the Lareb and WHO database supports this association as well as publications in the literature.

References

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This signal has been raised on February 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).