

1.1. Aripiprazole and hypothyroidism

Introduction

Aripiprazole belongs to the group of atypical antipsychotics and is indicated for *the treatment of schizophrenia in adults and in adolescents 15 years and older*. It is also indicated for *the treatment of moderate to severe manic episodes in bipolar I disorder and for the prevention of a new manic episode in patients who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment* [1]. Aripiprazole has been approved for the Dutch market since 2004 as Abilify®.

The drugs within the class of atypical antipsychotic agents show large differences considering their pharmacological profile. Other atypical antipsychotics available on the Dutch market are clozapine (Leponex®), risperidone (Risperdal®), olanzapine (Zyprexa®), paliperidon (Invega®) and quetiapine (Seroquel®).

Hypothyroidism is in most cases based on insufficient synthesis and release of thyroid hormone; in rare cases it is based on thyroid hormone resistance. Iodine deficiency is the most common cause of hypothyroidism worldwide [2]. The Netherlands Pharmacovigilance Centre received 2 reports of hypothyroidism associated with the use of aripiprazole.

Reports

On 9 November 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained 2 reports concerning hypothyroidism with the use of aripiprazole.

Specific characteristics of the reported cases:

A, 88482

This report from a pharmacist concerns a male aged 11-20 years, who experienced hypothyroidism after 7 weeks use of aripiprazole 1dd 15 mg for PDD NOS autistic disorder. The dose of aripiprazole was not changed. The patient was treated with levothyroxine for supplementation. At the time of reporting the patient had not recovered. Concomitant medication consisted of pipamperone, omeprazole and clonidine.

Aripiprazole is used off-label: it is indicated for the treatment of schizophrenia but not registered for paediatric patients younger than 15 years, in addition, the safety and efficacy of aripiprazole in children and adolescents below 18 years of age have not yet been established for irritability associated with autistic disorder [1].

B, 117637

This report from a pharmacist concerns a male aged 11-20 years, who experienced a decreased thyroid function after 1 month of aripiprazole 1dd 5mg. Concomitant medication consisted of insulin aspart, desloratadine and levothyroxine. Start date of and action taken for the levothyroxine are not reported. Follow-up on the report did not lead to further information.

Other sources of information

SmPC

Hypothyroidism is not mentioned in the SmPC for aripiprazole containing products [1].

Literature

A Medline search revealed a few publications on the possible association between aripiprazole and hypothyroidism (MeSH terms: hypothyroidism, aripiprazole) and a few publications on atypical antipsychotics and hypothyroidism (MeSH terms: hypothyroidism, atypical antipsychotics).

Church *et al.* describe a 41 year-old-male with myxedema coma, the most significant form of hypothyroidism. He had used sertraline 200 mg and aripiprazole 20 mg daily for an unknown time. He was admitted to the intensive care unit and initially treated with intravenous levothyroxine and dexamethasone. By hospital day 4, the patient was clinically stable and discharged to home. The known causes for myxedema were ruled out in this patient, which left his medication, sertraline and aripiprazole, as the likely cause [3].

The review article of Bou Khalil *et al.* on thyroid adverse effects of atypical antipsychotic drugs included a few small placebo controlled studies with amisulpride, quetiapine, and clozapine, but not studies with aripiprazole [4]. In a placebo-controlled study, 8 men were administered intravenous amisulpride and had their thyroid stimulating hormone (TSH) levels significantly elevated compared to their TSH levels after placebo administration [5]. In another randomized comparative double-blind clinical trial, a sample of 32 patients with schizophrenia were given amisulpride or flupenthixol and showed a significant elevation in thyroid-releasing hormone (TRH) stimulated TSH secretion in male patients receiving amisulpride [6]. The non-D₂ antagonist atypical antipsychotic drug clozapine shows an inverse effect. In a comparative clinical study, 13 patients treated with clozapine had their TRH-stimulated TSH significantly decreased after 1 week of treatment compared with 13 patients treated with haloperidol [7]. In a prospective double-blind study, a group of 30 schizophrenic patients taking quetiapine, risperidone, or fluphenazine showed a significant decrease in T4 levels after 6 weeks of treatment in the group receiving quetiapine, whereas other patients receiving risperidone and fluphenazine had no change in their thyroid hormones levels [8]. In conclusion, atypical antipsychotic drugs, including aripiprazole, can, according to their dopamine (ant)agonism profile, moderately interfere with TSH response to TRH without provoking major disturbances to thyroid function.

While atypical antipsychotics may decrease TRH-stimulated TSH, phenothiazines, which are typical antipsychotics, mainly alter iodine capture, complex and deactivate it, as well as decrease TSH's response to TRH. Nonphenothiazines, typical antipsychotics, can induce the formation of thyroid autoantibodies and can elevate TSH level [4].

Databases

On 9 November 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained two cases of hypothyroidism in association with aripiprazole, because of this limited number the Reporting Odds Ratio (ROR)

could not be calculated. The database did not contain any reports on myxedema and aripiprazole.

On the 5th of January 2012 the database of the Netherlands Pharmacovigilance Centre Lareb also contained cases of hypothyroidism associated with the use of other atypical antipsychotics, namely risperidone, olanzapine and quetiapine. See table 1.

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

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Hypothyroidism	Aripiprazole	2	-
Hypothyroidism	Risperidone	3	9.4 (3.4-25.9)
Hypothyroidism	Olanzapine	1	-
Hypothyroidism	Clozapine	0	-
Hypothyroidism	Quetiapine	1	-

On 9 November 2011, the WHO database of the Uppsala Monitoring Centre contained 36 reports of hypothyroidism and 6 reports of myxedema associated with the use of aripiprazole. Of the 36 reported hypothyroidism cases, 11 concerned patients younger than 18 years. The adverse drug reactions were disproportionally reported (see Table 2).

Table 2. Reports of hypothyroidism associated with aripiprazole in the WHO database

ADR (MedDRA PT)	Number of reports	ROR (95% CI)
Hypothyroidism	36	2.1 (1.5-2.9)
Hypothyroidism and myxedema	42	2.5 (1.8-3.4)

On the 5th of January 2012 the database of the Uppsala Monitoring Centre of the WHO also contained cases of hypothyroidism associated with the use of risperidone, olanzapine, clozapine and quetiapine. See table 3.

Table 3. Reports of hypothyroidism for the other atypical antipsychotics in the WHO database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Hypothyroidism	Risperidone	47	1.4 (1.1-1.8)
Hypothyroidism	Olanzapine	73	2.3 (1.8-2.4)
Hypothyroidism	Clozapine	44	0.6 (0.4-0.8)
Hypothyroidism	Quetiapine	161	4.6 (3.9-5.4)

On 17 November 2011, the Eudravigilance database contained 10 reports of hypothyroidism associated with the use of aripiprazole of which 9 were classified as 'serious'. The reports concern two females and eight males. The median age of the patients was 40 years (range 13 – 44 years). In three cases, the age was not reported.

Hypothyroidism was not reported disproportionally (ROR = 0.7, 95% CI: 0.4 – 1.4). On the 10th of January 2012 the Eudravigilance database contained several cases of hypothyroidism associated with the use of risperidone, olanzapine, clozapine and quetiapine. See table 4.

Table 4. Reports of hypothyroidism for the atypical antipsychotics in the Eudravigilance database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Hypothyroidism	Risperidone	33	0.7 (0.5-1.0)
Hypothyroidism	Olanzapine	48	1.2 (0.9-1.6)
Hypothyroidism	Clozapine	31	0.6 (0.4-0.8)
Hypothyroidism	Quetiapine	127	2.7 (2.3-3.2)

Prescription data

The number of patients using aripiprazole in the Netherlands is shown in Table 5.

Table 5. Number of patients using oral aripiprazole in the Netherlands between 2006 and 2010 [9].

Drug	2006	2007	2008	2009	2010
Aripiprazole	5,811	6,692	8,195	10,526	12,977

Mechanism

Aripiprazole is a partial D₂ agonist. Dopamine exerts its effect on the hypothalamic-pituitary-thyroid axis through the activation of dopamine D₂ receptors, but appears to have opposite effects on the hypothalamus and the pituitary thyrotrope [10]. Bou Khalil et al. stated that atypical antipsychotic drugs, due to their dopamine (ant)agonist action profile, moderately interfere with TSH response to TRH without provoking major disturbances to thyroid function. Additionally, they state that dopamine inhibits TSH secretion [11].

Class-effects

Due to the fact that there are important pharmacological differences between drugs in the class 'Atypical antipsychotics', the limited amount of cases of hypothyroidism in the Lareb database for this class and the lack of disproportionality for some drugs in the WHO and Eudravigilance database, it is not possible to conclude that hypothyroidism is a class effect.

Discussion and conclusion

Lareb received 2 reports concerning hypothyroidism with the use of aripiprazole. The young male in report A continued the aripiprazole and started with levothyroxine. The young male in report B had levothyroxine in the concomitant medication without any information on start date or dose change. Follow-up with the reporter did not lead to useful information.

Patient B has diabetes which is associated with a higher prevalence of hypothyroidism [12]. Additionally, the incidence of hypothyroidism and myxedema in the Netherlands is 0,2 per 1000 for children younger than 18 years old [13]. Protopathic bias cannot be excluded: in patients with pre-existing mental illness, drug-induced impairments in thyroid function may exacerbate their symptoms and can significantly complicate their diagnosis and management. Both

hypothyroidism and hyperthyroidism are associated with psychiatric manifestations, such as depression, anxiety, irritability and psychosis [11]. The widely described hypothyroidism associated with atypical antipsychotics and the received cases, as well as the disproportionality in the WHO database, support further investigation.

- Further investigation of the information of the marketing authorization holders is advisable

References

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This signal has been raised on February 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).