Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Olanzapine and hyponatraemia

Introduction

Olanzapine (Zyprexa®) was approved, via a centralised procedure, in 1996. Olanzapine is indicated *for the treatment of schizophrenia*. In addition, it is also indicated for the *treatment of moderate to severe manic episode*. In *patients whose manic episode has responded to olanzapine treatment, the drug is indicated for the prevention of recurrence of bipolar disorder* [1].

Olanzapine demonstrates a broad pharmacologic profile across a number of receptor systems. In preclinical studies, olanzapine exhibited a range of receptor affinities ($K_i < 100$ nM) for serotonin 5-$HT_{2A/2C}$, 5-HT_3, 5-HT_6; dopamine D_1-D_5; cholinergic muscarinic receptors M_1-M_5; α_1-adrenergic and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5-HT, dopamine and cholinergic antagonism to be consistent with the receptor-binding profile [1].

Reports

The Netherlands Pharmacovigilance Centre Lareb received 3 reports where hyponatraemia or the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) was associated with the use of olanzapine.

Patient A is a 50 year-old-woman with a medical history of chronic psychosis, alcohol abuse, suicide attempts and an episode of malignant neuroleptic syndrome. She was using olanzapine (dose not reported) for psychosis. The patient was admitted to the hospital after a generalised tonic-clonic epileptic attack with biting of the tongue and urinary incontinence. She had suffered an additional epileptic attack earlier that day. Upon admission the patient had a sodium concentration of 118 mmol/l. The sodium concentration normalised after withdrawal of olanzapine and a restricted dietary fluid intake. Therapy with diphantoine 100 mg three times daily, thiamine 50 mg once daily, oxazepam 10 mg once daily and nandroparine 7500 IE once daily was initiated. The patient did not experience any further convulsions. The treating physician diagnosed the symptoms as ‘status epilepticus secondary to hyponatraemia’. Laboratory results revealed that the hyponatraemia was due to SIADH, induced by olanzapine use.

Patient B is a 34 year-old-female with a medical history of schizophrenia, anxiety disorder and post-traumatic stress disorder. She received flufenazine as treatment for her schizophrenia but admission to a psychiatric institution after the medication was changed to olanzapine 20 mg daily. Concomitant medication included lorazepam 2.5 mg four times daily, domperidone 10 mg twice daily and promethazine 25 mg once daily. Eight weeks after initiation of olanzapine therapy the patient experienced a generalised epileptic attack. Laboratory investigation revealed a hyponatraemia with a sodium concentration of 115 mmol/l. The hyponatraemia was treated with fluid restriction and administration of hypertonic sodiumchloride. One week later sodium concentration had normalised to 133 mmol/l. Olanzapine therapy was substituted by risperidon once the patient was discharged from the hospital.

Patient C is a 49 year-old mentally retarded and autistic (eci and familiar) woman who was using olanzapine 10 mg once daily for indication psychosis. Ten weeks after initiation of olanzapine therapy the patient was admitted to the hospital due to epileptic attacks and coma. In the hospital the patient was diagnosed with hyponatraemia. No concomitant medication had been used. Olanzapine was replaced by risperidone; the outcome of the event was not reported.

Other sources of information

Literature

A Medline search revealed no publications of olanzapine-induced hyponatraemia. A case report of hyponatraemia has been described with the use of clozapine, which is structurally closely related to olanzapine [2]. Hyponatraemia and SIADH have also been reported with the use of several other anti-psychotics such as amisulpride, chlorpromazine, fluphenazine, flupenthixol, haloperidol, trifluoperazine, thioridazine, thiothixene and risperidone [3-5].

Databases

On 20 December 2005 the Lareb database contained 259 reports on olanzapine and is disproportionally associated with hyponatraemia (ROR 5.02, 95% CI 1.58-15.88).

At the end of the 4th quarter of 2005 the WHO Collaborating Centre for International Drug Monitoring had received 99 reports of hyponatraemia associated with the use of olanzapine (ROR 2.09, 95% CI 1.71-2.55). SIADH with olanzapine was also disproportionally reported (11 cases, ROR 3.28, 95% CI 1.81-5.95).

Mechanism

The use of antipsychotics has been associated with hyponatraemia due to the syndrome of inappropriate antidiurectic hormone secretion, SIADH [5]. In a case control study in a group of psychiatric patients with 64 cases and 192 controls, logistic regression shows that hyponatraemia is often associated with factors other than psychogenic polydipsia, including psychiatric medications[6].

In animal studies the inhibitory effect of dopamine on ADH release was blocked by D_2 receptor antagonists such as haloperidol and domperidone [7,8]. Olanzapine has also affinity for D_2 receptors, and it is possible that by its antagonism of D_2 receptors, ADH release increases in analogy to haloperidol and domperidone effects. It has also been showed that the observed ADH response to a hypertonic stimulus was potentiated by D_2 antagonists [9].

On the contrary, it has also been suggested based on results in rats that dopamine could have a stimulatory effect on ADH release [10]. The mechanism of olanzapine-induced hyponatraemia therefore remains unclear.

Discussion

It is well known that patients with a psychiatric disorder can suffer from polydipsia. In studies, the prevalence of polydipsia in hospitalized psychiatric patients varies from 6.6% to 17.5%.
It has also been suggested that clozapine and olanzapine would have a beneficial effect on polydipsia in patients suffering from psychiatric diseases [11,12]. However, this could not be verified in another randomised controlled trial [13].
None of the three patients mentioned in this Lareb report used (concomitant) drugs which are known to induce hyponatreamia like SSRIs, diuretics or (ox-) carbamazepine.

Conclusion

Lareb received three cases of olanzapine-induced hyponatraemia. Hyponatraemia and SIADH are described in literature for the structurally related clozapine and other antipsychotics.

References

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