Olanzapine and Cerebrovascular Accident

Introduction

Olanzapine (Zyprexa®, Zeprexa Velotab® and Zypadhera®), is a thienobenzodiazepine and belongs to the atypical antipsychotic (AP) drugs. Olanzapine (Zyprexa®) was registered in the Netherlands in 1996. Olanzapine is available as coated tablets, orodispersible tablets and as a powder and solvent for prolonged release suspension for injection (Zypadhera®). [1-3] It is indicated for *the treatment of schizophrenia, moderate to severe manic episodes. In patients whose manic episode has responded to olanzapine treatment, olanzapine is also indicated for the prevention of recurrence in patients with bipolar disorder* [1,2].

Olanzapine's antipsychotic effect is mediated by its strong antagonism for serotonin 5-HT2A/2C receptors, and dopamine D1-D4 (especially D2) receptors. for serotonin Olanzapine also has a high affinity for histamine H1 and alpha 1-adrenergic receptors [1-3].

Olanzapine is not approved for the treatment of psychosis and behavioural symptoms in patients with dementia. Clinical trials have shown an increased risk of cerebrovascular accident (CVA) in elderly with vascular/mixed type dementia [1-3].

The incidence and prevalence of cerebrovascular disease increases with age. The prevalence of CVA in people >65years ranges from 46-72 per 1000 person years [4]. Evidence from studies have shown distinct risk factors for stroke: older age, cognitive impairment, dementia, anticoagulant use, hypertension, a history of a previous CVA, atrial fibrillation, and schizophrenia [5,6].

The current observation describes the association between olanzapine and CVA in patients who were not diagnosed with dementia.

Reports

On July 12th, 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained six reports of CVA in patients for whom dementia was not reported. including five under the age of 75 years, associated with the use of olanzapine. These reports are listed in Table 1.

Table 1. Reports of cerebrovascular accident (CVA) in association with the use of olanzapine.

Patient, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 137253 M, 21-30 years Specialist doctor to MAH	olanzapine, 5mg schizophrenia	Not reported	CVA, basal ganglia infarction weight gain	4 years discontinued recovered
B 65161 M,41-50 years general practitioner	olanzapine, 5mg paranoid schizophrenia	folic acid lactulose, lorazepam methyltestosteron carbasalate calcium	CVA	3 months no change not yet recovered

Patient, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
C 45776 M, 61-70 years physician	olanzapine 20mg bipolar affective disorder	rivotril, lithium, salbutamol	CVA	10 months no change not yet recovered
D 147588 F, 61-70 years Specialist doctor	olanzapine 10mg psychosis	not reported	CVA	23 days discontinued unknown
E 50180 F, 71 years and older general practitioner	olanzapine 10mg bipolar affective disorder	not reported	CVA	2 years discontinued fatal
F 59175 M, age not reported physician	olanzapine 2.5mg	not reported	CVA	Not reported unknown unknown

Patient A had used olanzapine in different strengths (no specific dosages were reported). Patient B is a male who developed three CVAs within a time period of 5 months, the first CVA 3 months after start of olanzapine. Patient D was diagnosed with hypertension 6 months before start of olanzapine and 23 days after start of olanzapine she had a hemorrhagic CVA. Patient E suffered from pre-terminal renal insufficiency. In only one case the patient recovered after discontinuation of olanzapine and one case was fatal. The age range for five of the patients (in case F, the age is unknown) is 21-30 years to 70 years and older years (mean age 54 years). The latency period varied from 23 days to 4 years. Patient C did not have dementia and in the other cases dementia was not reported in the medical history. Patients A, B and C had smoking, and patients C and D had hypertension as the most important known risk factors for a CVA.
In two of the cases olanzapine had not been withdrawn and the patients had not recovered at the time of reporting. In the other two cases the outcome is unknown.

Lareb also received a total of 6 reports of CVA in association with other atypical antipsychotic drugs (aripiprazole, risperidone and quetiapine) in patients in which dementia was not reported in the anamneses or medical history.

Other Sources of Information

SmPC

In placebo-controlled clinical trials of elderly patients (mean age 78 years) treated for dementia-related psychosis, there was a 3 times higher risk of CVAs in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively), including fatalities [1-3].

Literature

Sacchetti et al. [5] showed from observational cohort studies that the risk for CVA is not only increased for patients with dementia, but also includes other elderly patients with other neurological illnesses treated with both typical and atypical AP. Furthermore, there has been an increase in CVA deaths in patients with schizophrenia who were treated with conventional AP, thus the risk of CVA is not

limited for treatment with atypical AP. The risk of a CVA is probably greater in the first weeks of treatment and is dose-independent [5].

In 2013, Yanagawa, et al. [7] presented a case report of a 33-year-old male with schizophrenia who developed multiple cerebral infarctions possibly caused by hypoperfusion due to hemorrhagic shock and potential thromboembolism by olanzapine. In another case report, a 52 year old man with a schizophrenia-like psychosis which was treated with olanzapine, developed speech and language disorders due to a CVA [8].

Douglas et al. [9] reported in 2008 that all AP are associated with an increased risk in CVA. This risk is higher for atypical AP than for typical AP. Treatment with any AP was associated with a rate ratio for CVA of 1.73 (95% confidence interval 1.60 - 1.87): 1.69 (1.55 - 1.84) for typical AP and 2.32 (1.73 - 3.10) for atypical AP. In patients receiving any AP, the rate ratios were 3.50 (2.97 - 4.12) for those with dementia and 1.41 (1.29 - 1.55) for those without dementia [9].

Databases

On July 12th, 2013 the Lareb database contained six reports of CVA associated with the use of olanzapine. The reporting odds ratio (ROR) for the association was 5.8 (95% CI 2.6 - 13.2). The database of the Uppsala Monitoring Centre of the WHO contained 353 reports of olanzapine with cerebrovascular accident (ROR = 1.7 (95%CI 1.5 - 1.8)). On August 14, 2013, the Eudravigilance database of the EMA contained a total of 239 reports of CVA associated with the use of olanzapine with an ROR of 0.9 (95%CI 0.8 - 1.0).

Table 2. Reports of CVA associated with olanzapine in the Lareb, WHO and EMA database.

Database	Preferred Term	Number of reports	ROR (95% CI)
Lareb	Cerebrovascular accident	6	5.8 (2.6-13.2)
WHO	Cerebrovascular accident	353	1.7 (1.5-1.8)
EMA	Cerebrovascular accident	239	0.9 (0.8-1.0)

An age stratification (from the WHO database) for CVA in association with olanzapine is shown in table 3. The ROR for all age ranges is significantly disproportional.

Table 3. WHO database and Age stratification of CVA with the use of olanzapine

Age Range (years)	Number of reports of CVA	ROR (95% CI)
0-44	58	2.17 (1.7-2.8)
45-64	85	1.54 (1.3-1.9)
65- ≥75	79	2.4 (1.9-3.0)
Unknown	131	

Prescription Data

The number of patients using olanzapine in the Netherlands is shown in table 4 [10].

Table 4. Number of patients using olanzapine in the Netherlands between 2008 and 2012 [10]

Drug	2008	2009	2010	2011	2012
Olanzapine	41,924	40,875	41,524	41,427	41,357

Mechanism

Potential hypothetic mechanisms which may lead to a CVA in antipsychotic drugs include thrombosis, orthostatic hypotension, and hyperprolactinaemia [4]. Thrombosis is caused by antipsychotic drug ADRs: sedation, obesity and increased platelet aggregation. Antagonism on alpha-1 receptors leads to orthostatic hypotension which can cause cerebral hypoperfusion. Hyperprolactinemia increases platelet aggregation, decreases insulin sensitivity and damages endothelial function which may increase the risk for atherosclerosis [4]. During a CVA there is an increased level of interleukin-6. This cytokine is also abnormal in people with dementia and schizophrenia which may make them more susceptible to develop a CVA [5].
However, there are no studies that confirm all these hypotheses.

Class effects
It is probable that there is a class effect of atypical antipsychotics and the association CVA. The product information of risperidone describes CVA, cerebral ischemia and TIA as possible drug adverse reactions. CVA is not described in the SmPC of seroquel and risperidone. Lareb received 6 reports of CVA in association with other atypical antipsychotics:

Report 50544
This case concerns a female aged 84 years with a fatal CVA (with hemiparalysis right and dysarthria) two months following administration of aripiprazole 15mg for psychosis. The patient had a medical history of chronic pain and cataracts. She had no medical history of memory loss nor dementia. Concomitant medication was amlodipine, clonazepam, azetazolamide, rimexolon eyedrops and lantoprost/timolol eyedrops.

Report 52866
This case concerns a 34-year old female who was treated with aripiprazole 15mg once daily for schizophrenia and had a CVA (with hemiparesis left) with a latency of 6 weeks after start. The patient recovered. Concomitant medication were oral contraceptives (OAC). Use of OAC is also a risk factor for CVA

Report 69577
A 29-year old female treated with seroquel 100mg twice daily for borderline personality disorder had a transient ischemic attack (with hemiparesis right and aphasia) 23 months after start. The patient recovered. Seroquel was continued. Concomitant medication was not reported.

Report 69563
A 41-year old female had a CVA (with hemiparalysis) following treatment with seroquel 25mg once daily for an unknown indication and with unknown latency period. The outcome is unknown.
Report 82513
A 13-year old male received treatment with risperidone 0.25 mg twice daily for anxiety and behavioral disorder and had an ischemic CVA 40 days after start. Risperidone was discontinued and the patient recovered.

Report 148256
This report concerns a 15-year old male with a CVA (hemiparesis left, dysarthria, and aphasia) following treatment with risperidone for Asperger's Syndome with a latency of 6 years after start. Eight months previously the drug dose had been increased from 1.5 mg once daily to 2 mg once daily. The risperidone was discontinued. The patient is recovering. No other etiologies were found for the CVA. The patient has migraine with aura in his medical history.

Discussion and Conclusion

Lareb received six reports of CVA associated with the use of olanzapine. One patient had hypertension and another patient had renal insufficiency and this may increase the risk for a CVA. Two patients were > 65 years, and two patients had schizophrenia, increasing their risk for a CVA.
The association between olanzapine and CVA is disproportionally present in the Lareb and WHO databases but not in the Eudravigilance database. In the WHO database, olanzapine was associated with 40% of patients <65 years and 22% of patients ≥ 65 years of age. Also, the association CVA and treatment with olanzapine was disproportional in all age ranges.
In the literature, CVA is described as an ADR in the elderly without dementia using typical and atypical AP. Two case reports of CVA in adults aged 33 and 52 years old being treated with olanzapine have been described.
In conclusion, the elderly, especially elderly with an illness, people with dementia and schizophrenia have a higher risk of developing a CVA, however, olanzapine use and CVA occur across all age ranges. The mechanism is still unclear. This quarterly report focuses on olanzapine but the other atypical AP have also been associated with strokes.

- CVA should be mentioned in the SmPC of olanzapine for all patients

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