

Olanzapine and amenorrhea

Introduction

In 1996, olanzapine (Zyprexa®) was approved by a centralised procedure. 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].

Reports

Until 27 April 2006, the Netherlands Pharmacovigilance Centre Lareb received 7 reports of amenorrhea associated with the use of olanzapine. The time to onset varies from a few weeks to 10 months. The outcome was reported in 3 cases. One patient recovered after drug withdrawal and two patients did not recover; in one patient there was a dose increase to 15 mg once daily.

In case D, hyperprolactinaemia (1150 mU/L, range 50-629 mU/L) was also reported. Benzodiazepine was used as concomitant medication in 4 of the 7 patients.

Table 1. reports of amenorrhea associated with the use of olanzapine

Patient, Sex, age	Dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A F, 27	10 mg od psychosis	clorazepic acid, flurazepam	amenorrhea	1 month, dose increased, not recovered
B F, 30	10 mg od psychosis	not reported	amenorrhea	a few weeks, not recovered
C F, 41	10 mg od	promethazine, valproic acid, lorazepam, zolpidem, mirtazapine	secondary amenorrhea	not reported
D F, 26	10 mg td	valproic acid, levopromazine, temazepam	amenorrhea, hyperprolactinaemia	17 weeks, not reported
E F, 36	3 month 10 mg od, 2 month 15 mg od	diazepam	amenorrhea	3 months after start 10 mg od, soon after start 15 mg od, drug withdrawn, outcome not reported
F F, 29	20 mg od	cyproterone/ ethinylestradiol	Amenorrhea	a few weeks, drug withdrawn, recovered
G F, 22	5 mg od	clonazepam, venlafaxine, zopiclon, oestrogen/ levonorgestrel	amenorhea	10 months, drug continued, not recovered

Other sources of information

SPC

Amenorrhea in relation with olanzapine has not been described in the SPC, but hyperprolactinaemia has been described with an incidence of >10%. However, associated clinical manifestations such as gynaecomastia, galactorrhoea and breast enlargement are rare. In most patients, levels returned to normal without cessation of treatment [1].

Literature

In a review in *Drugs*, it was suggested that olanzapine is generally regarded as prolactin sparing, but hyperprolactinaemia can occur with higher doses of olanzapine. Several studies do not pay attention to the clinical manifestations of hyperprolactinaemia. The duration of the trials is too short to identify amenorrhea because amenorrhea is usually defined as occurring over a period of at least 3 months. In female schizophrenic patients, an illness-related under-function of the hypothalamic-pituitary-gonadal axis may also contribute to menstrual irregularities [2].

In a double-blind, olanzapine, placebo and haloperidol controlled trial, prolactin elevations with olanzapine were lower than with haloperidol, but was statistically relevant (doses of 10 ± 2.5 mg/day and 15 ± 2.5 mg/day) compared with placebo. In the olanzapine group an early increase in serum prolactin was seen which was dose-related and temporary. Therefore, olanzapine was not associated with persistent elevations of prolactin [3]. Temporary elevated prolactin levels were also found in a study where olanzapine (12.2 ± 3.1 mg/day) was compared to other anti-psychotics. It is also stated that other factors could contribute to acute endocrine symptomatology, like illness itself, stress factors, concomitant medication or other patient's conditions [4].

A correspondence letter mentioned a case report of a 33-year old woman with elevated serum prolactin levels after receiving olanzapine. Olanzapine was started at 5 mg/day and increased to 20 mg/day in 4 weeks. During the 5th week of olanzapine therapy, she was missing her menstrual period. Serum prolactin level was 146.6 ng/mL (with a normal range of 1.5-19.0 ng/mL). Olanzapine was withdrawn and replaced with quetiapine. Serum prolactin levels began to decrease to 74.5 ng/mL and 17.3 ng/mL in the second and eighth week, respectively [5].

Databases

On 27 April 2006, the Lareb database contained 7 reports on olanzapine and amenorrhea, which is disproportional (ROR 25.7, 95% CI 12.2- 54.0).

On 27 April 2006, the WHO Collaborating Centre had received 40 reports of olanzapine and is disproportional present in association with amenorrhea (ROR 1.6, 95% CI 1.2- 2.2). These 40 reports also include the Lareb reports.

Mechanism

Olanzapine has affinity for the dopamine receptor and is a D₂ receptor antagonist. Olanzapine selectively reduces dopamine firing of mesolimbic dopaminergic neurons [1].

Dopamine is a prolactin-inhibiting factor [2]. Therefore, D₂-antagonism by blocking dopamine receptors leads to hyperprolactinaemia. Hyperprolactinaemia can lead to menstrual irregularities like amenorrhea [2-4]. Amenorrhea is due to secondary hypogonadism; an indirect effect on the normal functioning of the hypothalamic-pituitary-gonadal axis [2].

Conclusion

Lareb received 6 reports of amenorrhea in association with olanzapine. This association is supported by the disproportional high number of reports in the WHO database. Literature confirms that antipsychotic-induced hyperprolactinaemia could lead to amenorrhea.

References

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