Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Quetiapine and extrapyramidal effects

Introduction

Quetiapine (Seroquel®) is an atypical antipsychotic agent, indicated for *treatment of schizophrenia and treatment of moderate to severe manic episodes*. Quetiapine has affinity for both serotonergic type 2 (5-HT_2) receptors and for dopamine type 2 (D_2) receptors in the brain [1].
Extrapyramidal effects are well-known ADRs of the older generation of antipsychotics. The extrapyramidal system includes neural pathways that are responsible for the regulation of reflex movements such as balance and walk. Extrapyramidal disorders can cause a variety of symptoms such as dyskinesia, parkinsonism, akathisia, bruxism and acute dystonia.
Quetiapine, as well as other atypical antipsychotics, is believed to cause less extrapyramidal side effects compared to the older antipsychotic agents, due to the presence of a high serotonin-to-dopamine receptor blockade ratio in the brain [2].
In the SPC of quetiapine, only tardive dyskinesia is mentioned in the section special warnings (4.4). The SPC also states that the incidence of extrapyramidal effects does not differ from placebo, for therapeutic doses in clinical trials [1].

Reports

Up to December 2005, the Netherlands Pharmacovigilance Centre Lareb received, besides several reports on tardive dyskinesia, ten other reports of extrapyramidal effects in association with quetiapine (table 1).
In three cases, a contribution of concomitant medication to the symptoms cannot be excluded. Patient A also used fluoxetine since 1995, however, the causal relation with quetiapine is supported by both the latency and the positive dechallenge with this drug. Patient C started using citalopram one year prior to quetiapine, but the onset of symptoms, several weeks after starting quetiapine, makes a relation with quetiapine more plausible. Patient E also used venlafaxine since an unknown period of time as suspect medication. The dyskinesia in this patient could therefore be partly due to this drug.
The outcome was reported in eight cases. For two of these patients, cessation of quetiapine resulted in recovery. Patient E improved after biperiden treatment plus discontinuation of both suspect drugs quetiapine and venlafaxine. Three patients recovered upon treatment with biperiden despite continuation of quetiapine. The remaining two patients did not recover; for one of them the action taken with the drug was unknown, the other continued the use of quetiapine.

Table 1. reports of extrapyramidal effects associated with the use of quetiapine

Patient, sex, age	Suspect drug, dose	Concomitant medication	Adverse drug reaction	Time to onset, action taken, outcome
A M, 36	quetiapine 2dd 300 mg	lithiumcarbo-nate fluoxetine*	myoclonus, (glossitis)	the same day, patient improved after cessation
B F, 51	quetiapine 1dd 300 mg	metoprolol, acetylsalicylic acid, temazepam, clonazepam	dystonia	several weeks, medication continued, recovered after treatment with biperiden
C F, 34	quetiapine 3dd 100 mg	citalopram*	trismus, EPS	several weeks, medication continued, recovered after treatment with biperiden
D F, 36	quetiapine 2dd 100 mg	oxazepam	EPS, insomnia, dreaming abnormal	the same day, medication continued, outcome unknown
E F, 29	quetiapine 1dd 200 mg venlafaxine 1dd 100 mg	zolpidem, venlafaxine	dyskinesia	2 weeks, patient improved after biperiden treatment and cessation of both suspect drugs
F M, 44	quetiapine 700 mg dd	-	orofacial dyskinesia, dyskinesia, restlessness	several hours, action taken unknown, patient did not recover
G M, 31	quetiapine 1dd 200 mg	-	dyskinesia	3 weeks, medication continued, patient recovered after treatment with biperiden
H F, 30	quetiapine 1dd 25 mg	-	acute dyskinesia, aggression aggravated, depression aggravated	1 hour, patient recovered after cessation
I F, 31	quetiapine 1dd 75 mg	-	dyskinesia	3 months, dose increase led to aggravated symptoms, medication discontinued, outcome unknown
J F, 71	quetiapine 2dd 300 mg	-	orofacial dyskinesia	1 week, medication continued, symptoms persisted

*This concomitant drug may have contributed to the reported adverse drug reaction

Other sources of information

Databases

In the third quarter of 2005 the database of the WHO contained 3317 ADRs associated with the use of quetiapine. A total of 396 ADRs concern an extrapyramidal disorder (expressed as dyskinesia, dyskinesia tardive, dystonia, extrapyramidal disorder, hypokinesia, parkinsonism aggravated, choreoathetosis and muscle contractions involuntary).
Myoclonus and trismus are not present in the WHO database.

Extrapyramidal ADR associated with quetiapine	Number of reports	ROR (95% CI)
dyskinesia	94	11.49 (9.35-14.12)
dyskinesia tardive	104	49.10 (41.21-59.96)
dystonia	63	6.19 (4.82-7.94)
extrapyramidal disorder	59	5.05 (3.90-6.54)
hypokinesia	15	2.16 (1.30-3.60)
parkinsonism aggravated	3	9.91 (3.18-30.91)
choreoathetosis	9	7.81 (4.05-15.07)
muscle contractions involuntary	49	3.52 (2.65-4.67)

Prescription data

Table 2. total number of prescriptions of quetiapine per year since 2000 (Source: GIP College voor Zorgverzekeringen, Diemen).

	2000	2001	2002	2003	2004
Quetiapine	15,849	32,731	53,891	87,636	140,060

Literature and mechanism

The older generation of antipsychotics is associated with extrapyramidal effects, because of their dopaminergic inhibition. The blockade of nigrostriatal dopamine tracts results in a relative increase in cholinergic activity. Atypical antipsychotics, like quetiapine, have dual action by being both dopamine as well as serotonin antagonists. Their first action is to block postsynaptic D_2-receptors. The second action is blockade of presynaptic $5HT_{2A}$ receptors, which is assumed to reverse and balance out the dopamine blockade effect, resulting in few EPS [2,3]. Quetiapine has a relatively low affinity for both D_2 and $5HT_{2A}$ receptors, compared to other atypical antipsychotics. It is extensively metabolized by cytochrome P450 enzyme 3A4. Although quetiapine indeed seems to have a benign EPS profile compared to the classic antipsychotics [4-6], some case reports describe the occurrence of extrapyramidal effects in patients using quetiapine [7-11].

Elaborating on the above mechanism, a difference in EPS profile between atypical antipsychotics may arise from a different balance in the D_2 / $5HT_{2A}$ affinity between them. An increased vulnerability to antipsychotic agents in specific patients, due to polymorphism in cytochrome P450 (3A4) and / or in the DA receptor, might be an alternative explanation [11,12].

Conclusion

Lareb received 10 reports of extrapyramidal adverse drug reactions in association with quetiapine. This finding is supported by the disproportional high number of reports on EPS in association with quetiapine in the WHO database.

References

1. Dutch SPC Seroquel®. (version date 21-10-2003) http://www.cbg-meb.nl/IB-teksten/20826-20827-20828-25128-25602-25603.pdf.
2. Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. J Clin Psychiatry 2000;61 Suppl 3:16-21.
3. Stahl SM. Essential Psychopharmacology. 2nd ed. Cambridge University Press 2000; 2000.
4. Mintzer JE, Mullen JA, Sweitzer DE. A comparison of extrapyramidal symptoms in older outpatients treated with quetiapine or risperidone. Curr.Med Res Opin. 2004;20(9):1483-91.
5. Dando TM, Keating GM. Quetiapine: a review of its use in acute mania and depression associated with bipolar disorder. Drugs 2005;65(17):2533-51.
6. Weiden PJ. Switching antipsychotics: an updated review with a focus on quetiapine. J Psychopharmacol. 2005;
7. Caroff SN, Mann SC, Campbell EC, Sullivan KA. Movement disorders associated with atypical antipsychotic drugs. J Clin Psychiatry 2002;63 Suppl 4:12-9.
8. Jonnalagada JR, Norton JW. Acute dystonia with quetiapine. Clin Neuropharmacol. 2000;23(4):229-30.
9. Velayudhan L, Kirchner V. Quetiapine-induced myoclonus. Int Clin Psychopharmacol. 2005;20(2):119-20.
10. Catalano G, Grace JW, Catalano MC, Morales MJ, Cruse LM. Acute akathisia associated with quetiapine use. Psychosomatics 2005;46(4):291-301.
11. Coffey GL, Botts SR, de Leon J. High vulnerability to acute dystonic reactions: a case of antipsychotic exposure and uncontrolled seizure activity. Prog.Neuropsychopharmacol.Biol Psychiatry 2005;29(5):770-4.
12. Harten PN. Bewegingsstoornissen door antipsychotica. Uitgeverij Boom, Amsterdam; 2000.