Olanzapine

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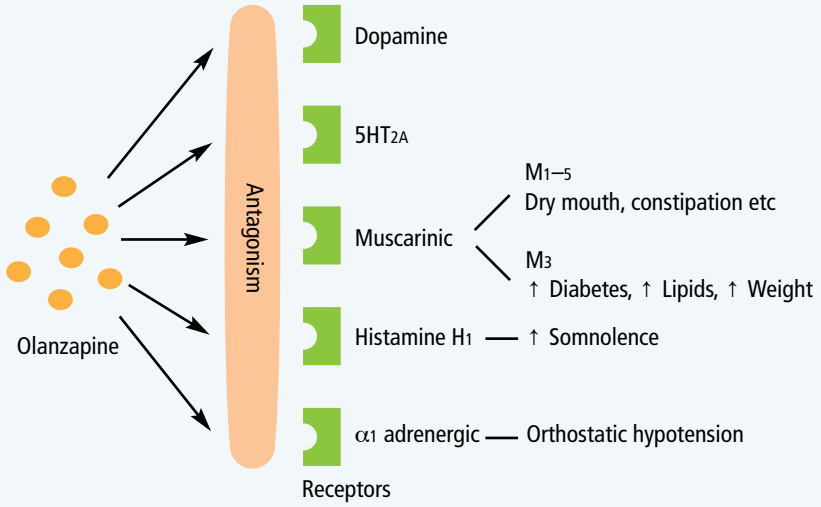

NOTES. Olanzapine is an antagonist that binds with high affinity to serotonin (5HT2A/2C, 5HT6), dopamine (D1–4), histamine (H1), and adrenergic (α1) receptors. It is an antagonist with moderate affinity binding for serotonin (5HT3) and muscarinic M1–5 receptors. The therapeutic effects are likely mediated through antagonism at dopamine and 5HT2A receptors with antagonism at other receptors resulting in side effects, especially the muscarinic M3 receptor that has been implicated in the increased risk of diabetes.

Figure 1. The pharmacological action of olanzapine

Introduction

The prevalence of diabetes in patients with schizophrenia has been found to be higher than in the general population prior to the introduction of second-generation or 'atypical' antipsychotics, with many reports of insulin resistance and abnormalities of glucose homeostasis in patients with schizophrenia. The underlying mechanism for this is not fully known and it could be explained as an intrinsic association with schizophrenia itself or as a result of lifestyle choices in patients with schizophrenia.

Olanzapine is a commonly used 'atypical' antipsychotic with efficacy in the treatment of schizophrenia and a range of other psychiatric illnesses. Compared with first generation or 'typical' antipsychotics, olanzapine presents lower risks of extrapyramidal side effects and tardive dyskinesia, but higher rates of weight gain and metabolic side effects such as the development of glucose intolerance, diabetes and dyslipidaemia, thereby increasing the likelihood of cardiovascular disease.

Pharmacology

The precise mechanism of action of olanzapine is unknown but it exhibits a wide array of receptor affinities that may explain the clinical and adverse effects (Figure 1). Efficacy in schizophrenia may be by a combination of dopamine D_2 and serotonin $5HT_{2A}$ receptor antagonism in the mesolimbic pathway. Olanzapine shows higher affinity for serotonin $5HT_{2A}$ receptors than dopamine D_2 receptors with selectivity for dopamine receptor sub-types in the mesolimbic and mesocortical systems over the nigrostriatal and tuberboinfundibular systems, perhaps the reason for reduced risk of extrapyramidal side effects and hyperprolactinaemia. Antagonism at muscarinic, histaminic and alpha-adrenergic receptors leads to side effects, such as dry mouth, micturition difficulty, constipation, weight gain, somnolence, dizziness and hypotension. Weight gain, dyslipidaemia and hyperglycaemia are more common with olanzapine than other second-generation antipsychotics, particularly in adolescent populations with evidence that

the effect may be mediated by profound antagonism of muscarinic M_3 receptors.

Olanzapine is well absorbed when taken orally with 80% bioavailability although undergoing first pass metabolism, and reaches peak plasma concentrations after 6 hours. It has linear kinetics with an elimination half-life of 21–54 hours reaching steady state concentration after one week. Olanzapine is metabolised by direct glucuronidation and cytochrome P450 (CYP) system isoenzymes 1A2 and 2D6. Smoking may induce 1A2 leading to the possibility of loss of efficacy for those who begin or resume smoking after a period of cessation. The presence of multiple elimination pathways means that patients with renal or heptic impairment may still be managed with olanzapine without the need for a dose reduction.

Trials of safety and efficacy

There is extensive clinical experience of the use of olanzapine in adults with schizophrenia with numerous meta-analysis and large-scale studies comparing the effectiveness of olanzapine with other second-generation antipsychotics. Improvement in the symptoms of schizophrenia with antipsychotic drugs is normally seen within one week. Most patients experience a reduction in symptoms rather than remission, with many patients remaining on the medication indefinitely. A recent Cochrane Review examined the effects of olanzapine compared to other second-generation antipsychotic drugs for schizophrenia.[1] The review compared olanzapine to other second-generation antipsychotic drugs. Olanzapine was more effective in treating symptoms of schizophrenia, but caused more weight gain than other comparators except for clozapine. Associated problems such as glucose and cholesterol increase were also more frequent in the olanzapine group. These findings were confirmed by a recent meta-analysis comparing metabolic side effects.[2] Olanzapine has been found to cause more weight gain and glucose increase than all other drugs except for clozapine. Olanzapine also caused more cholesterol increase than some other drugs. A subsequent meta-analysis compared the comparative efficacy, risk of all-cause discontinuation, and major side effects of the two first first-generation (haloperidol and chlorpromazine) and 13 second-generation antipsychotic drugs (including olanzapine) in patients with schizophrenia.[3] The differences in side effects were considerable. Apart from haloperidol, ziprasidone and lurasidone, all drugs produced more weight gain than placebo, and olanzapine produced significantly more weight gain than most other drugs.

Specific evidence in relation to diabetes

The prevalence of diabetes mellitus is higher in patients with schizophrenia compared with the general population. The relationship between schizophrenia and diabetes is complex and poorly understood. Second-generation antipsychotics have been associated with metabolic effects such as hyperglycaemia, diabetes mellitus, weight gain and dyslipidaemia. Such metabolic effects raise significant concern over increasing cardiovascular risk in a population who experience earlier mortality due to cardiovascular disease and other causes. Evidence suggests that hyperglycaemia can occur independently or secondary to weight gain whereas dyslipidaemia rises in association with body weight.

The mechanisms by which olanzapine causes the metabolic effects have not been defined. A study in healthy volunteers found that olanzapine reduces insulin sensitivity in association with significant elevations in postprandial insulin, glucagon-like peptide 1 and glucagon in the absence of weight gain, increases in food intake and hunger or psychiatric disease.[4] A number of mechanisms to explain the metabolic liability of olanzapine have been postulated, including involvement of a variety of receptors. A prime mechanistic target is the acetylcholine muscarinic M_3 receptor (M_3R).[5] Previous work has shown that binding affinity to the M_3R is a predictor of diabetes risk. Indeed, drugs with the greatest rates of metabolic effects, such as olanzapine and clozapine, are very high affinity M_3R antagonists. Olanzapine has also been shown to block acetylcholine binding to the pancreatic islet M_3R *in vitro*, thereby inhibiting glucose-stimulated insulin release from the beta cells, while genetic modification of M_3R in mice has significant effects on glucose tolerance and insulin secretion.

Key points

- Olanzapine is an 'atypical' antipsychotic used in the treatment schizophrenia
- The prevalence of diabetes is higher in patients with schizophrenia
- Olanzapine causes glucose intolerance, diabetes and dyslipidaemia but the mechanism is not well defined
- All patients with schizophrenia require routine metabolic monitoring
- Metabolic dysfunction is an important source of cardiovascular risk for schizophrenia patients

Discussion

Olanzapine is a commonly used 'atypical' antipsychotic with efficacy in the treatment of schizophrenia and a range of other psychiatric illnesses. Olanzapine causes substantially more metabolic side effects than many other second-generation antipsychotics. Before choosing olanzapine it is important to weigh up the potential efficacy and individual patient characteristics with the potential of secondary diseases and increased cardiovascular risk. All patients with schizophrenia require metabolic monitoring. Metabolic side effects can be managed by switching to an antipsychotic with more limited metabolic liability, lifestyle modifications, the pharmacological management of cardiovascular risk factors and the use of drugs that improve insulin sensitivity, such as metformin.

Declaration of interests

There are no conflicts of interest declared.

References

References are available in *Practical Diabetes* online at www.practicaldiabetes.com.

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