news

Unusual suspect for antipsychotic-induced diabetes

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Researchers in Barcelona have done some spectacular number-crunching to come up with a potential explanation for one of the most troubling and intriguing side effects of anti-psychotic treatment. Patients on some antipsychotics put on significant amounts of weight and show an increased tendency to develop type II diabetes. The seriousness of this side effect cannot be underestimated. One of the major companies involved, Eli Lilly, recently paid out over US$690 million to settle a flood of lawsuits brought against it by lawyers representing patients who claimed that Lilly's drug, Zyprexa® (olanzapine), which they had received as treatment for schizophrenia, had left them over weight and diabetic.

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The propensity of some antipsychotics to induce diabetes in some patients was noted in the early 1960s when the phrase 'phenothiazine diabetes' was coined. The older antipsychotics also induced a range of unpleasant side effects which included severe impairment of the body's motor function, resulting in what amounted to a drug-induced Parkinson's disease-like state and various neurohormonal imbalances.

A second generation of antipsychotics began to appear in the 1990s exemplified by compounds such as olanzapine and risperidone that seemed to have less likelihood of inducing these problems but the weight gain, especially for olanzapine, remained an issue. The problem was to identify what was the mechanism by which the drug was causing patients to put on up to a kilogram a month in a year. The trouble for the drug developers was that the compounds, such as olanzapine, bind to an enormous range of receptors, which could be the cause of the weight gain and the diabetes.

Silvestre and Prous [1] have taken all of the possible receptor targets and correlated the affinity of nearly 50 antipsychotic compounds for the most likely receptor targets with the propensity to induce weight gain and diabetes. The surprise 'winner' was the muscarinic M3 receptor.

This effect is intriguing in that selective M3 muscarinic antagonists are used to treat conditions such as urinary incontinence and asthma but no evidence has yet emerged to associate these treatments with diabetes. This could suggest that schizophrenic patients might have a unique susceptibility to the 'diabetogenic' effects of these drugs. Given the fact that schizophrenic patients have a higher risk of becoming diabetic than the general population, an increased vulnerability was always suspected but the mechanism by which it might occur was not identified.

Secondly, the authors found that the likelihood of weight gain and becoming diabetic did not show as close a relationship as was imagined, especially if diabetes was believed to be a simple consequence of the weight gain.

Thirdly, although it is correct to be cautious about purely correlational data, this publication coincided closely with new experimental evidence that antipsychotic with high propensity to induce diabetes (olanzapine and clozapine) were functional antagonists of muscarinic M3 receptors in pancreatic islet cells, whereas compounds with reduced risk (riperidone and ziprasidone) were not [2].

The message from this work is simple. If you are currently developing an antipsychotic drug, have it checked for M3 antagonism.

References

1 Silvestre, J.S. and Prous J. (2005) Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. *Methods Find. Exp. Clin. Pharmacol.* 27, 289–304

2 Johnson D.E. *et al.* (2005) Inhibitory effects of antipsychotics on carbachol-enhanced insulin secretion from perifused rat islets: role of muscarinic antagonism in antipsychotic-induced diabetes and hyperglycemia. *Diabetes* 54, 1552–1558

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