COMMENTS AND RESPONSES

Acute Insulin Response and β-Cell Compensation in Normal Subjects Treated With Olanzapine or Risperidone for 2 Weeks

Response to Jindal

We recently reported that short-term treatment with olanzapine or risperidone did not impair acute insulin response or β-cell compensation in healthy subjects (1). Dr. Jindal (2) has cited some possible inconsistencies between our study and other reports, which we would like to address.

First, Dr. Jindal notes that our conclusions contrast with those of Ader et al. (3) and points to differences in antipsychotic doses as one possible reason. However, the final olanzapine dose in our study (10 mg/day) is consistent with the package insert's target dose for patients with schizophrenia and also appears to be consistent with common prescribing practices for the treatment of schizophrenia at the time our study began (March 2000), since two analyses of large prescription databases in that time frame reported mean olanzapine doses of 11.0–11.5 mg/day (4,5). On the other hand, the rationale behind dose selection in the Ader study is not entirely clear to us. They state that the 15 mg olanzapine dose was "based on those used in typical treatment of patients," but they did not adjust for the much smaller body mass of the dogs used in their study.

A second point relates to differences in diet between our study and the Ader report. As Dr. Jindal points out, we attempted to restrict human subjects to an isocaloric diet, while dogs were fed ad libitum in the Ader study. It is worth noting that diet composition and caloric intake were not closely monitored during outpatient phases of our study (up to 9 days), and mean weight increased significantly (~3 kg) in both the olanzapine and risperidone cohorts (6). Nonetheless, our effort to limit weight gain was based on a desire to glean whether there may be direct pharmacodynamic effects of these drugs on insulin secretion. This was felt to be a valid objective given the oft-cited reports of new-onset diabetes and diabetic ketoacidosis with these drugs in the absence of weight gain (7). Providing free access to food is also a valid approach, depending on the hypothesis being tested. We would like to point out, however, that the fat-fed control group in the Ader study appears to have been chosen post hoc and that the provided diet was one of the ways that the treatment and control groups differed. As stated in our paper, Ader et al. did not observe a significant change in β-cell compensation in the olanzapine-treated animals compared with their own pretreatment baseline.

Finally, Dr. Jindal claims that our results are at odds with a recent study by Chiu et al. (8). We do not feel that these results necessarily conflict with our own. Our analysis focused on the acute insulin response and on the disposition index as a measure of β-cell compensation. Chiu et al. found a decrease in the total area under the curve for insulin after the intravenous glucose tolerance test in olanzapine-treated patients, but they did not report a disposition index or the area under the curve for glucose. Given that the glucose disappearance rate did not change in those patients, it is not clear to us that insulin secretion was inappropriate or impaired after olanzapine treatment, and we do not believe the results support the authors' conclusion that "olanzapine has an acute and direct effect to decrease insulin secretion."

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