Chapter 3

Orally disintegrating and standard olanzapine tablets similarly elevate the HOMA insulin resistance index and plasma triglyceride levels in healthy men

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ABSTRACT

Objective: Treatment with olanzapine is associated with obesity, diabetes mellitus and dyslipidemia. Reports have indicated that orally disintegrating tablets (ODT) cause less weight gain than standard oral tablets (OST). The aim of this study was to compare the effect of short-term treatment with these two distinct olanzapine formulations on glucose and lipid metabolism in healthy men.

Method: Twelve healthy men (age: 25.1 ± 5.5 years) received olanzapine ODT (10 mg o.d., 8days), olanzapine OST (10 mg o.d., 8days) or no intervention in a randomized cross-over design. At breakfast and dinner, glucose, insulin, FFA and TG concentration were measured at ten minutes intervals as from 30 minutes prior to until 2 h after ingestion of standard meals. Leptin and adiponectin concentrations were measured at 20 and 30 minutes intervals respectively, between 00:00-12:00 h. Physical activity was assessed with an accelerometer. Fuel oxidation was measured in fasting condition by indirect calorimetry.

Results: Treatment with olanzapine ODT and OST equally elevated the HOMA-IR (p=0.005). At breakfast, both formulations equally increased fasting and postprandial TG concentrations (p=0.013 and p=0.005, respectively) while decreasing fasting and postprandial FFA concentrations (p=0.004 and p=0.009, respectively). Body weight, body composition, physical activity or fuel oxidation did not differ between treatment modalities.

Conclusions: Eight days of treatment with both olanzapine formulations similarly increased HOMA-IR and TG concentrations and decreased FFA concentrations in response to standard meals without affecting anthropometric measures or physical activity. These data suggest that olanzapine hampers insulin action via mechanistic routes other than body adiposity or physical inactivity.
INTRODUCTION

The use of atypical antipsychotic (AP) drugs is associated with obesity (1,2), diabetes mellitus (3) and dyslipidemia (4), which limits the clinical applicability of these compounds. Olanzapine appears to carry a greater potential than other atypical AP drugs to induce these metabolic anomalies (4-8). It remains unclear if these adverse effects of AP drugs emerge in the context of (the pathophysiology of) schizophrenia only or constitute a pharmacologic feature of the drugs per se. Two types of olanzapine tablets are available for clinical use: standard (OST: oral standard tablet) and orally disintegrating (ODT: orally disintegrating tablet). Two recent trials report that treatment with ODT might be less harmful in terms of weight gain. The first paper shows that switching schizophrenia patients from olanzapine OST to ODT is accompanied by a loss of 6.6 kg of body weight (9). The second paper indicates that drug-naїve schizophrenia patients gain 3.3 kg of weight in the first 6 weeks of olanzapine ODT treatment as compared to 6.3 kg in patients treated with OST (10).

The main pharmacokinetic difference between these compounds is in the way they are handled by the gastro-intestinal tract: OST disintegrates more slowly and its absorption is delayed as compared to ODT, which dissolves instantaneously upon administration, allowing absorption through the sublingual mucosa rather than the gastrointestinal tract. The plasma concentration profiles of olanzapine attained by the use of these two compounds are very similar and differ only in the sense that the maximal concentration ($C_{max}$) is reached earlier with the ODT (11).

We have recently shown that short-term (8 days) treatment with 10 mg olanzapine o.d. hampers insulin-mediated glucose uptake during hyperinsulinemia in healthy men (Vidarsdottir, submitted for publication). These early metabolic effects are likely to presage obesity and DM after longer term use of the drug.

We hypothesized that 8 days of treatment with ODT would have less impact on lipid and carbohydrate metabolism than treatment with OST to explain its relatively modest effect on energy balance in the long run. We therefore compared the early metabolic effects of the 2 olanzapine formulations in healthy men.

SUBJECTS AND METHODS

Subjects

Twelve healthy men between 20 and 40 years were recruited through advertisements in local newspapers. The subjects were required to have a stable body mass index (BMI) between 20 and 27 kg/m² and a normal fasting plasma glucose concentration (<6.0 mmol/l). Subjects who had ever used antipsychotic medication, and subjects who were currently smoking or using medication affecting the central nervous system were excluded. All subjects provided written...
informed consent after explanation of the study procedures and possible adverse effects of the treatment. The protocol was approved by the medical ethics committee of the Leiden University Medical Center and registered by www.controlled-trials.com (ISRCTN17632637).

Drugs
All subjects received olanzapine standard tablets (OST; 10 mg o.d. for 8 days), olanzapine orally disintegrating tablets (ODT; 10 mg o.d. for 8 days) or no intervention in a randomized cross-over design. The drugs were taken at 8 AM except on day 8 when they were taken at 7 AM. The minimum plasma concentration ($C_{min}$) of olanzapine was determined on day 8 at 7 AM by high-performance liquid chromatography with UV ($\lambda = 270$ nm) detection. The detection limit of olanzapine was 5 μg/l.

Diet
To limit confounding by nutritional factors, subjects received a standard diet containing 2400 kcal/day on days 7 and 8 of each intervention period. The diet consisted of bread, fillings and drinks, prepared by the research center. The macronutrient composition of the diet was exactly the same on all occasions: 48% of energy from carbohydrates, 17% from proteins and 35% from fat. Intake of alcohol and caffeine/thein containing beverages were not allowed, the day before and during all study occasions.

Indirect calorimetry
After a 30 minute rest, fasting subjects were placed under a ventilated hood, while lying on a bed in a quiet room, for another 30 minutes. The volume of oxygen inspired ($V_{O_2}$) and the expired volume of carbon dioxide ($V_{CO_2}$) were measured every minute. Subsequently, resting energy expenditure (REE), glucose and lipid oxidation were calculated using the following equations:

\[
\text{Glucose oxidation (mg·kg}^{-1}·\text{min}^{-1}) = 4.57 V_{CO_2} - 3.23 V_{O_2} - 2.6 N \\
\text{Lipid oxidation (mg·kg}^{-1}·\text{min}^{-1}) = 1.69 V_{O_2} - 1.69 V_{CO_2} - 2.03 N \\
\text{REE (kcal/day)} = 3.91 V_{O_2} + 1.10 V_{CO_2} - 1.93 N
\]

in which protein disappearance was ignored ($N = \text{Nitrogen}$) since the error introduced in the calculation of energy expenditure is less than 2% (12).

Physical activity
Physical activity was assessed with an accelerometer (Actiband®, Cambridge Neurotechnology Ltd, Cambridge, UK) for three days (day 1-3) during each intervention. Subjects wore the accelerometer on the wrist, except whilst bathing. Activity data were sampled on a minute-by-minute basis. Activity Energy Expenditure (AEE) was calculated by Actiband Analysis Software (The Actiband Users Manual 2007, Cambridge Neurotechnology Ltd, Cambridge, UK) using the following equations: Metabolic equivalent (METs) = 1 + 0.226 * Sqrt (counts per minute). From
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this equation the energy expenditure was calculated according to the following equation: AEE = (METs – 1) * 3.5 ml O₂·kg⁻¹·min⁻¹; if METs < 3 then METs is dropped to 1.

Clinical Protocol

Subjects were studied three times in random order; without an intervention (control) and after treatment with olanzapine OST (10 mg o.d., 8 days) or ODT (10 mg o.d., 8 days). There was a time interval of at least six weeks between each study occasion. On day 7, after a 10 hour overnight fast, body fat percentage was determined by bioelectrical impedance analysis (BIA; Bodystat 1500 MDD, Bodystat ltd, Douglas Isle of Man, UK) and substrate oxidation was measured by indirect calorimetry (Oxycon β; Jaeger Toennies, Breda, The Netherlands). From this timepoint, the subjects were prescribed the standard diet described earlier. Subjects were re-admitted to the research center at 17:00 h. A cannula for blood sampling was inserted into an antecubital vein. Blood samples were collected with S-monovette (Sarstedt, Etten-Leur, The Netherlands) from a three-way stopcock that was attached to a 0.9% NaCl infusion (20 ml/h; with 100 U heparine/500ml) to keep the cannula from clotting. Blood samples were taken at 10 minute intervals as from 0.5 hour prior to until 2 hours after each meal (dinner on day 7; breakfast on day 8) for determination of insulin, glucose, free fatty acids (FFA) and triglycerides (TG) concentrations. Blood samples were taken for determination of leptin (every 20 minutes) and adiponectin (every 30 minutes) levels between 00:00 - 12:00 h. At 07:00 h the drug was taken. Dinner and breakfast were served at 18:30 h and 08:00 h, respectively. Subjects remained sedentary except for bathroom visits; at 23:00 h lights were switched off.

Assays

Each tube, except the serum tubes, was immediately chilled on ice. Samples were centrifuged at 3520 rpm at 4° C for 20 min. Subsequently, plasma/serum was divided into separate aliquots and frozen at –80° C until assays were performed. Serum insulin was measured by immunoradiometric assay (INS-IRMA; BioSource Europe S.A., Nivelles, Belgium). Plasma concentrations of FFA and TG were determined using commercially available kits (Wako Pure Chemical Industries, Osaka, Japan; Roche Diagnostics, Mannheim, Germany). Blood glucose concentrations were assessed using a blood glucose analyzer (Accu-Chek Sensor, Roche, Mannheim, Germany). Serum leptin concentrations were determined by RIA (Linco Research, St. Charles, MO); the detection limit was 0.5 μg/l. The inter-assay variation was 3.6 - 6.8%. Serum adiponectin concentrations were also measured by RIA (Linco Research, St. Charles, MO). The detection limit of the adiponectin assay was 1 μg/l, and the interassay variation was 7.0 - 9.2%.

Deconvolution analysis

Multiparameter deconvolution analysis was used to estimate various kinetic and secretory parameters of meal induced insulin secretion, calculated from insulin concentration time series. For initial waveform-independent estimates of insulin secretion Pulse 2 was used, an automated
pulse detection program. Subsequent analysis with a waveform dependent multiparameter
deconvolution method was performed as described previously, using a first component half-
life of 2.8 minutes, second component half life of 5.0 minutes and relative contribution of the
slow component to the total elimination of 0.28 (13).

HOMA model
Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated as described by
Matthews et al. (14) (HOMA-IR = fasting insulin (mU/l) x fasting plasma glucose (mmol/l)/22.5).

Statistics
Results are presented as mean ± S.E.M. Data was logarithmically transformed before analysis
when appropriate and statistically analyzed using one-tailed paired Student’s t-test, except
adipokines data which were analyzed with two-tailed paired Student’s t-test as we did not
have an a priori hypothesis in which direction serum adiponectin concentration would change
in response to olanzapine treatment. When the distribution of the data was not normal after
logarithmic transformation, they were analyzed using non-parametric Wilcoxon signed-rank
test. Significance level was set at 0.05. First, the effect of treatment with olanzapine ODT was
compared with olanzapine OST. Secondly, to evaluate the effect of treatment with olanzapine,
the mean of values in response to treatment with olanzapine OST and olanzapine ODT was cal-
culated and compared with values measured in the control group. All analyses were performed
using SPSS for Windows, version 12.0 (SPSS Inc, Chicago, Ill).

RESULTS

Subjects
Twelve men (age 25.1 ± 5.5 years) were included in the study; two of them did not show up for
the third study occasion for personal reasons. The dinner data from one subject was incomplete,
because he was nauseous and vomited on his last study occasion. None of the participants had
major side effects while they were treated with olanzapine. However, most of them felt tired
during the first days of the treatment.

Olanzapine Concentration
Minimum plasma olanzapine concentration (C_{min}) did not differ between treatment with OST
and ODT (P = 0.18).
Anthropometric variables and physical activity

Table 1 summarizes anthropometric measurements and physical activity data. There was no difference in body weight, BMI, WHR or fat percentage between treatment conditions. Olanzapine treatment did not affect physical activity as evaluated by accelerometer.

Table 1. Clinical and biochemical measurements (in fasting condition) during treatment with olanzapine OST, olanzapine ODT and without intervention (control).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Ola-OST</th>
<th>Ola-ODT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.5 ± 1.7</td>
<td>78.2 ± 2.1</td>
<td>78.0 ± 2.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6 ± 0.6</td>
<td>23.8 ± 0.6</td>
<td>23.7 ± 0.7</td>
</tr>
<tr>
<td>WHR</td>
<td>0.80 ± 0.01</td>
<td>0.81 ± 0.01</td>
<td>0.81 ± 0.01</td>
</tr>
<tr>
<td>Fat percentage (%)</td>
<td>9.6 ± 1.2</td>
<td>9.8 ± 1.3</td>
<td>10.4 ± 1.1</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71 ± 2</td>
<td>76 ± 3</td>
<td>72 ± 2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 ± 4</td>
<td>128 ± 4</td>
<td>127 ± 4</td>
</tr>
<tr>
<td>Heart rate (min)</td>
<td>63 ± 4</td>
<td>68 ± 4</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>AEE (kcal/day)</td>
<td>571 ± 67</td>
<td>511 ± 91</td>
<td>529 ± 118</td>
</tr>
<tr>
<td>HOMA IR a)</td>
<td>1.53 ± 0.19</td>
<td>2.18 ± 0.25</td>
<td>2.12 ± 0.34</td>
</tr>
<tr>
<td>Basal insulin secretion rate (mU/L/10 min)</td>
<td>0.72 ± 0.08</td>
<td>0.77 ± 0.07</td>
<td>0.72 ± 0.10</td>
</tr>
<tr>
<td>FFA concentrations (mol/l)</td>
<td>0.460 ± 0.046§</td>
<td>0.346 ± 0.020</td>
<td>0.335 ± 0.035</td>
</tr>
<tr>
<td>TG concentrations (mmol/l)</td>
<td>0.974 ± 0.106‡</td>
<td>1.327 ± 0.143</td>
<td>1.320 ±0.237</td>
</tr>
</tbody>
</table>

Data are presented as mean ± S.E.M.

Abbreviations: AEE: activity energy expenditure; BMI: body mass index; FFA: free fatty acids; HOMA: Homeostasis model assessment; TG: triglyceride; WHR: waist hip ratio.

There were no significant differences between Olanzapine OST and Olanzapine ODT.

† P = 0.005 (one tailed), Control vs. treatment
§ P = 0.004 (one tailed), Control vs. treatment
‡ P = 0.013 (one tailed), Control vs. treatment

a) Homeostasis model assessment (HOMA) was used to estimate insulin resistance from fasting insulin and glucose concentrations. The following equation was used: HOMA-IR = fasting insulin (mU/L) x fasting glucose (mmol/L)/22.5.

Metabolic profile in the fasting condition

Table 1 summarizes plasma metabolic profiles in the fasting condition. The effects of olanzapine ODT and OST on fasting plasma FFA or TG concentrations, basal insulin secretion or HOMA-IR did not differ. However, treatment with olanzapine significantly increased HOMA-IR as compared with the control group. Furthermore, treatment with olanzapine significantly increased fasting TG concentrations and decreased fasting FFA concentrations (Figure 1 and 2), while there was no difference between the effects of olanzapine ODT and olanzapine OST on these parameters.

Indirect calorimetry

For technical reasons, data from indirect calorimetry was incomplete for 1 subject (control data missing). The effects of olanzapine OST and ODT on resting energy expenditure, respiratory quotient, glucose- and lipid oxidation did not differ, where olanzapine treatment did not affect these parameters. An overview of the results is presented in Table 2.
Figure 1. FFA concentrations at breakfast.
Data are presented as mean ± S.E.M.
Olanzapine ODT and OST significantly decreased fasting and postprandial FFA concentrations at breakfast.

Figure 2. TG concentrations at breakfast.
Data are presented as mean ± S.E.M.
Olanzapine ODT and OST significantly increased fasting and postprandial TG concentrations at breakfast.
Table 2. Fuel oxidation during treatment with olanzapine OST, olanzapine ODT and without intervention (control).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Ola-OST</th>
<th>Ola-ODT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>RQ</td>
<td>0.78 ± 0.02</td>
<td>0.79 ± 0.02</td>
<td>0.79 ± 0.02</td>
</tr>
<tr>
<td>Glucose oxidation (mg·kg⁻¹·min⁻¹)</td>
<td>1.13 ± 0.35</td>
<td>1.32 ± 0.30</td>
<td>1.26 ± 0.33</td>
</tr>
<tr>
<td>Lipid oxidation (mg·kg⁻¹·min⁻¹)</td>
<td>1.31 ± 0.14</td>
<td>1.28 ± 0.10</td>
<td>1.25 ± 0.15</td>
</tr>
<tr>
<td>REE (kcal/day)</td>
<td>1285 ± 34</td>
<td>1321 ± 34</td>
<td>1291 ± 32</td>
</tr>
</tbody>
</table>

Data are presented as mean ± S.E.M.
Abbreviations: RQ: respiratory quotient; REE: resting energy expenditure.
There were no significant differences between olanzapine OST and olanzapine ODT.

Postprandial serum glucose and insulin profiles

The effects of olanzapine OST and olanzapine ODT on postprandial glucose or insulin concentrations in response to breakfast or dinner did not differ, where olanzapine treatment did not affect any of these parameters (Table 3). Insulin secretion rate was not affected either. Insulin secretion and postprandial concentration of glucose and insulin in response to dinner and breakfast could not be compared formally as the carbohydrate content differed at these meals (87 g at dinner; 103 g at breakfast). Therefore, we present postprandial data in response to breakfast only.

Table 3. Postprandial metabolic parameters at breakfast and 12 h nocturnal adipokines concentrations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Ola-OST</th>
<th>Ola-ODT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Mean glucose concentration (mmol/l)</td>
<td>5.6 ± 0.2</td>
<td>5.7 ± 0.2</td>
<td>5.3 ± 0.2</td>
</tr>
<tr>
<td>Maximal glucose increase (mmol/l)</td>
<td>2.2 ± 0.1</td>
<td>2.6 ± 0.2</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>Mean insulin concentration (mU/l)</td>
<td>56.5 ± 7.3</td>
<td>67.3 ± 10.6</td>
<td>57.6 ± 8.8</td>
</tr>
<tr>
<td>Maximal insulin response (mU/l)</td>
<td>93.3 ± 12.5</td>
<td>117.8 ± 17.1</td>
<td>96.3 ± 15.9</td>
</tr>
<tr>
<td>Meal-induced insulin secretion (mU/l/2h)</td>
<td>614 ± 81</td>
<td>694 ± 127</td>
<td>638 ± 103</td>
</tr>
<tr>
<td>Mean FFA concentration (mmol/l)</td>
<td>0.234 ± 0.014 *</td>
<td>0.189 ± 0.012</td>
<td>0.201 ± 0.027</td>
</tr>
<tr>
<td>Maximal FFA decrease (mmol/l)</td>
<td>0.347 ± 0.045 #</td>
<td>0.242 ± 0.019</td>
<td>0.229 ± 0.029</td>
</tr>
<tr>
<td>Mean TG concentration (mmol/l)</td>
<td>1.074 ± 0.116 §</td>
<td>1.505 ± 0.176</td>
<td>1.479 ± 0.246</td>
</tr>
<tr>
<td>Mean Leptin (ng/ml)</td>
<td>3.7 ± 0.9</td>
<td>3.8 ± 0.8</td>
<td>3.7 ± 0.8</td>
</tr>
<tr>
<td>Mean Adiponectin (ng/ml)</td>
<td>7.3 ± 0.6 †</td>
<td>8.4 ± 0.9</td>
<td>8.7 ± 1.0</td>
</tr>
</tbody>
</table>

Data are presented as mean ± S.E.M.
There were no significant differences between Olanzapine OST and Olanzapine ODT.
Abbreviations: FFA: Free Fatty Acids; TG: Triglycerides.
Multi parameter deconvolution analysis was used to estimate various kinetic and secretory parameters of insulin plasma concentration in response to standard meals.
* P = 0.009 (one tailed), Co vs. treatment
# P = 0.004 (one tailed), Co vs. treatment
§ P = 0.005 (one tailed), Co vs. treatment
† P = 0.034 (two tailed) Co vs. treatment
Postprandial lipid profile

Treatment with olanzapine clearly decreased the postprandial FFA concentrations and reduced the maximal postprandial FFA suppression (respectively $P = 0.009$ (one tailed) and $P = 0.004$ (one tailed)) in response to breakfast (Table 3, Figure 1). Treatment with olanzapine also increased postprandial TG concentrations in response to breakfast (Table 3, Figure 2). The effects of olanzapine ODT and OST on postprandial FFA or TG concentrations in response to breakfast did not differ (Table 3). The effect of olanzapine ODT and OST on postprandial FFA or TG concentrations in response to dinner did not differ, where olanzapine treatment did not affect these parameters (Table 4).

Table 4. Pre- and postprandial FFA and TG concentrations at dinner.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>SOT</th>
<th>ODT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Preprandial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFA concentration (mmol/l)</td>
<td>0.415 ± 0.058</td>
<td>0.335 ± 0.046</td>
<td>0.369 ± 0.063</td>
</tr>
<tr>
<td>TG concentration (mmol/l)</td>
<td>1.396 ± 0.155§</td>
<td>1.760 ± 0.279</td>
<td>1.819 ± 0.405</td>
</tr>
<tr>
<td>Postprandial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean FFA concentration (mmol/l)</td>
<td>0.344 ± 0.038</td>
<td>0.285 ± 0.028</td>
<td>0.289 ± 0.035</td>
</tr>
<tr>
<td>Maximal FFA decrease (mmol/l)</td>
<td>0.211 ± 0.062</td>
<td>0.156 ± 0.045</td>
<td>0.207 ± 0.062</td>
</tr>
<tr>
<td>Mean TG concentration (mmol/l)</td>
<td>1.493 ± 0.173</td>
<td>1.814 ± 0.293</td>
<td>1.825 ± 0.366</td>
</tr>
</tbody>
</table>

Data are presented as mean ± S.E.M.  
Abbreviations: FFA: Free Fatty Acids; TG: Triglycerides.
There were no significant differences between Olanzapine OST and Olanzapine ODT.
§ $P = 0.038$ (one tailed), Control vs. treatment

Leptin and adiponectin levels

The effects of olanzapine ODT and OST on 12 hour (nocturnal) leptin concentrations did not differ, where olanzapine treatment did not affect leptin concentrations as compared to the control group. In contrast, treatment with olanzapine significantly increased 12 hour nocturnal adiponectin concentrations, while there was no difference between the effect of olanzapine ODT and olanzapine OST (Table 3).

DISCUSSION

Here we show that 8 days of treatment with 2 distinct formulations of olanzapine, standard and orally disintegrating tablets, similarly elevate the HOMA-index of insulin resistance in the absence of measurable effects on body weight, body composition, physical activity or fuel oxidation. Also, both formulations significantly increased fasting and postprandial TG concentrations, decreased fasting and postprandial FFA concentrations and decreased the maximal postprandial suppression of FFA concentrations at breakfast. Finally, both formulations significantly increased nocturnal adiponectin, but not leptin concentrations. These data suggest that
olanzapine hampers insulin action via mechanistic routes other than body adiposity or physical inactivity. They do not explain why various papers suggest that ODT cause less weight gain than OST.

**Effects on carbohydrate metabolism**

The observation that olanzapine increased HOMA-IR is in accordance with clinical data in schizophrenia patients on long-term olanzapine treatment (3). Also, olanzapine was reported to increase fasting insulin concentrations in healthy subjects after treatment for three weeks (15). We recently showed that treatment with olanzapine (OST) for 8 days hampers insulin-mediated glucose disposal in healthy subjects (Vidarsdottir et al., JCEM in press). This finding agrees with data reported by Sacher et al., who demonstrated a decrease in whole body insulin sensitivity in healthy subjects after treatment with olanzapine for 10 days (16). Olanzapine administration also induces insulin resistance in animals (17,18). In spite of the fact that the drug clearly increased the HOMA index of insulin resistance, 8 days of olanzapine treatment did not (yet) significantly affect postprandial insulin secretion or glucose concentrations, which corroborates other data, where short-term olanzapine treatment induced fasting hyperinsulinemia without affecting the metabolic response to a mixed meal in healthy volunteers (15). This apparent discrepancy might be related to the fact that a host of factors determines the insulin and glucose response to a mixed meal: i.e. (variable) degree of absorption, gut peptide release, β-cell sensitivity, glucose disposal and suppression of endogenous glucose production, whereas the HOMA index is a mathematical reflection of whole body insulin sensitivity per se (14).

The mechanistic explanation of the effect of olanzapine on insulin sensitivity remains to be established. Long-term treatment with the drug is associated with weight gain (19), which obviously may contribute to insulin resistance in the long run. Our data suggest that olanzapine also hampers insulin action via mechanistic routes that are independent of body fat mass, physical activity and schizophrenia. Olanzapine blocks a broad range of monoamine receptors (20). Beside its relatively weak affinity for dopamine D2 receptors, olanzapine also antagonizes serotonin 5-HT2, histamine H1, α1 adrenergic, and muscarinic M3 receptors (20). Activation of all of these receptor (sub)types generally inhibits food intake, reduces body weight and/or enhances insulin secretion (21-25). Notably, various receptors blocked by olanzapine appear to be directly (i.e. independent of their effects on body weight) involved in the regulation of glucose metabolism, as has been reported for serotonin (26-28), histamine H1 (29) and α1 adrenergic receptors (30,31). Also, activation of dopamine D2 receptors with bromocriptine ameliorates insulin resistance in obese women through a mechanism that is independent of body weight (32). Thus, antagonism of either one of these receptors, alone or in combination, by olanzapine may hamper insulin action.
Effect on lipid metabolism

Short-term treatment with olanzapine significantly increased pre- and postprandial TG concentrations, decreased pre- and postprandial FFA concentrations and significantly reduced the maximal postprandial suppression of FFA concentrations at breakfast. At dinner, only preprandial TG concentrations were significantly increased. FFA concentrations and postprandial TG concentrations, however, showed the same trend as observed at breakfast (Table 4).

Hypertriglyceridemia is a frequently reported finding in schizophrenia patients on chronic olanzapine treatment (4,7,8). In a recent comprehensive evaluation of the effects of various antipsychotic drugs on plasma lipid levels in patients with schizophrenia, olanzapine affected a broad range of lipid classes. In line with our results, TG concentrations were significantly increased and FFA concentrations significantly suppressed in patients using olanzapine (33). The cause of these drug effects remains to be established. We speculate that olanzapine inhibits lipoprotein lipase (LPL) activity in muscles and impairs the stimulatory action of insulin on LPL in adipose tissue, either directly or indirectly through its neuroendocrine effects. LPL hydrolyses the triacylglycerol component of circulating lipoprotein particles, chylomicrons and very low density lipoproteins, to provide FFA for tissue utilisation. LPL activity is influenced by various hormones, including insulin, prolactin and cortisol (34). In adipose tissue, LPL activity is increased by cortisol (34) and inhibited by prolactin (35,36). Prolactin inhibits its activity both directly and indirectly by inhibiting cortisol-induced LPL activity (36). Olanzapine treatment mildly elevates plasma PRL concentrations (37) and reduces circulating cortisol (38,39), probably through serotonin (5HT2A/2C) and/or dopamine (D2) receptor antagonism. Thus, the drug may impact on lipid metabolism via these neuroendocrine ensembles. Interestingly, activation of dopamine D2 receptors by bromocriptine, which inhibits prolactin secretion, has effects on plasma lipid levels opposite to those observed here: circulating FFA concentrations rise, whereas plasma TG concentrations tend to decrease in response to 8 days of bromocriptine treatment in obese women (32). These findings suggest that dopaminergic and/or serotoninergic neurotransmission may be of considerable importance for the regulation of lipid metabolism.

Adipokines

Short-term intervention with olanzapine did not affect leptin concentrations, which agrees with previous studies showing that body adiposity is the major determinant of circulating leptin levels in patients treated with this drug (40,41). Plasma adiponectin concentrations were significantly higher during olanzapine treatment. The molecular regulation of adiponectin release by adipocytes and its subsequent clearance from the circulation is largely unknown. Plasma adiponectin concentrations are low in insulin resistant animals and humans, and adiponectin administration appears to restore insulin action in these subjects (42). Thus, up-regulation of adiponectin levels by olanzapine may counteract the deleterious effect of the drug on insulin sensitivity.
The data presented here indicate that olanzapine impacts on glucose and lipid metabolism through mechanistic routes that are independent of body adiposity or physical activity. They add to our understanding of the reason why so many schizophrenia patients treated with olanzapine are susceptible to metabolic disease (3,4). Clearly, olanzapine carries pharmacologic properties which affect metabolism not only in schizophrenia patients but also in healthy volunteers. However, our data do not explain why orally disintegrating olanzapine tablets appear to be less harmful in terms of weight gain (9,10). Also, it seems important to realize, that drug naïve schizophrenia patients (43) and their non-schizophrenia relatives (44) often are insulin resistant and glucose intolerant, which may render them more susceptible to the adverse metabolic effects of olanzapine than the healthy volunteers who were studied here.

We did not compare the effects of the drugs in terms of metabolic changes from baseline values obtained at the beginning of each individual treatment period. This design does not allow for correction of putative cross-over effects of prior treatment. However, we believe the impact of prior treatment periods on overall outcome parameters to be minor, because the treatment order was randomized and treatment periods were at least 6 weeks apart.

In conclusion, olanzapine elevates the HOMA index of insulin resistance and plasma triglyceride levels, and reduces circulating FFA concentrations in young healthy male volunteers, via a mechanistic route which is independent of body adiposity or physical (in)activity. Orally disintegrating and standard tablets similarly affect glucose and lipid metabolism.
REFERENCES

Olanzapine tablets elevate HOMA insulin resistance index and plasma triglyceride levels in healthy men


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