Orally Disintegrating and Oral Standard Olanzapine Tablets Similarly Elevate the Homeostasis Model Assessment of Insulin Resistance Index and Plasma Triglyceride Levels in 12 Healthy Men: A Randomized Crossover Study

Solrun Vidarsdottir, MD, PhD; Pauline Vlug, MD; Ferdinand Roelfsema, MD, PhD; Marijke Frölich, PhD; and Hanno Pijl, MD, PhD

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Corresponding author: *Hanno Pijl, MD, PhD, Department of Endocrinology and Metabolism, Leiden University Medical Center, Leiden, The Netherlands, (h.pijl@lumc.nl).*

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 oral standard tablets (OST). The aim of this study was to compare the effect of short-term treatment with these 2 distinct olanzapine formulations on glucose and lipid metabolism in healthy men.

Method: Twelve healthy men (mean ± SEM age: 25.1 ± 5.5 years) received olanzapine ODT (10 mg od, 8 days), olanzapine OST (10 mg od, 8 days), or no intervention in a randomized crossover design. At breakfast and dinner, glucose, insulin, free fatty acids (FFA), and triglyceride concentrations were measured at 10-minute intervals from 30 minutes prior to 2 hours after ingestion of standard meals. Leptin and adiponectin concentrations were measured at 20- and 30-minute intervals, respectively, between 0000h–1200h. Physical activity was assessed with an accelerometer. Fuel oxidation was measured in fasting condition by indirect calorimetry. The study was conducted from April 2006 through September 2006.

Results: Treatment with olanzapine ODT and OST equally elevated the homeostasis model assessment of insulin resistance (HOMA-IR) ($P = .005$). At breakfast, both formulations equally increased fasting and postprandial triglyceride concentrations ($P = .013$ and $P = .005$, respectively) while decreasing fasting and postprandial FFA concentrations ($P = .004$ and $P = .009$, 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 triglyceride concentrations and decreased FFA concentrations in response to standard meals without affecting anthropometrics or physical activity. These data suggest that olanzapine hampers insulin action via mechanistic routes other than body adiposity or physical inactivity.

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The use of atypical antipsychotic drugs is associated with obesity,[1,2] diabetes mellitus,[3] and dyslipidemia,[4] which limit the clinical applicability of these compounds. Olanzapine appears to carry a greater potential than other atypical antipsychotic drugs to induce these metabolic anomalies.[4–8] It remains unclear if these adverse effects of atypical antipsychotic 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 (oral standard tablets [OST]) and orally disintegrating (orally disintegrating tablets [ODT]). Two recent trials report that treatment with ODT might be less harmful in terms of weight gain. The first article 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 article indicates that drug-naive 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 gastrointestinal tract: OST disintegrate more slowly and their absorption is delayed as compared to ODT, which dissolve 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 2 compounds are very similar and differ only in the sense that the maximal concentration is reached earlier with the ODT.[11]

We have recently shown that short-term (8 days) treatment with 10 mg olanzapine od hampers insulin-mediated glucose uptake during hyperinsulinemia in healthy men.[12] These early metabolic effects are likely to presage obesity and diabetes mellitus 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.

METHOD

Subjects

Twelve healthy men between ages 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/m^2 and a normal fasting plasma glucose concentration (< 6.0 mmol/L). Subjects who had ever used antipsychotic medication, and subjects who where 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. The study was conducted from April 2006 through September 2006.

Drugs

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

Diet

To limit confounding by nutritional factors, subjects received a standard diet containing 2,400 kcal/d 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-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 (VO_2) and the expired volume of carbon dioxide (VCO_2) were measured every minute. Subsequently, resting energy expenditure (REE) and glucose and lipid oxidation were calculated using the following equations:

$$\text{Glucose oxidation } (\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}) = (4.57\times VCO_2) - (3.23\times VO_2) - (2.6\times N),$$

$$\text{Lipid oxidation } (\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}) = (1.69\times VO_2) - (1.69\times VCO_2) - (2.03\times N), \text{ and}$$

$$\text{REE (kcal/d)} = (3.91\times VO_2) - (1.10\times VCO_2) - (1.93\times N),$$

in which protein disappearance was ignored (N = nitrogen) since the error introduced in the calculation of energy expenditure is less than 2%.[13]

Physical Activity

Physical activity was assessed with an accelerometer (Actiband, Cambridge Neurotechnology Ltd, Cambridge, United Kingdom) for 3 days (days 1–3) during each intervention. Subjects wore the accelerometer on the wrist, except while 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, United Kingdom) using the following equations: metabolic equivalent (METs) $= 1 + 0.226\cdot\sqrt{}$ (counts per minute). From this equation the energy expenditure was calculated according to the following equation: AEE = $(\text{METs} - 1)\cdot 3.5$ mL $O_2\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; if METs < 3, then METs is dropped to 1.

Clinical Protocol

Subjects were studied 3 times in random order: without an intervention (control) and after treatment with olanzapine OST (10 mg od, 8 days) or ODT (10 mg od, 8 days). There was a time interval of at least 6 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, United Kingdom), and substrate oxidation was measured by indirect calorimetry (Oxycon β; Jaeger Toennies, Breda, The Netherlands). From this time point, the subjects were prescribed the standard diet described earlier. Subjects were readmitted to the research center at 1700h. 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 3-way stopcock that was attached to a 0.9% sodium chloride infusion (20 mL/h; with 100 U heparine/500ml) to keep the cannula from clotting. Blood samples were taken at 10-minute intervals from 0.5 hour prior to 2 hours after each meal (dinner on day 7; breakfast on day 8) for determination of insulin, glucose, free fatty acids (FFA), and triglyceride concentrations. Blood samples were taken for determination of leptin (every 20 minutes) and adiponectin (every 30 minutes) levels between 0000h–1200h. At 0700h the drug was taken. Dinner and breakfast were served at 1830h and 0800h, respectively. Subjects remained sedentary except for bathroom visits; at 2300h, lights were switched off.

Assays

Each tube, except the serum tubes, was immediately chilled on ice. Samples were centrifuged at 3,520 rpm at 4°C for 20 minutes. 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 triglycerides 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, Missouri); the detection limit was 0.5 μg/L. The interassay variation was 3.6%–6.8%. Serum adiponectin concentrations were also measured by RIA (Linco Research, St. Charles, Missouri). 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, we used Pulse 2, 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.[14]

Homeostasis Model Assessment

Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated as described by Matthews et al.[15] (HOMA-IR = fasting insulin [mU/L] × fasting glucose [mmol/L]/22.5).

Statistics

Results are presented as mean ± SEM. Data were logarithmically transformed before analysis when appropriate and statistically analyzed using 1-tailed paired Student *t* test, except adipokines data, which were analyzed with 2-tailed paired Student *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 nonparametric Wilcoxon signed rank test. Statistical significance level was set at .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 calculated and compared with values measured in the control group. All analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Subjects

Twelve men (age 25.1 ± 5.5 years) were included in the study; 2 of them did not show up for the third study occasion for personal reasons. The dinner data from 1 subject were 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 did not differ between treatment with OST and ODT ($P = .18$).

Anthropometric Variables and Physical Activity

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

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 triglyceride 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 triglyceride concentrations and decreased fasting FFA concentrations (Figures 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 were incomplete for 1 subject (control data missing). The effects of olanzapine OST and ODT on resting energy expenditure, respiratory quotient, and 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.

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. 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 Lipid Profile

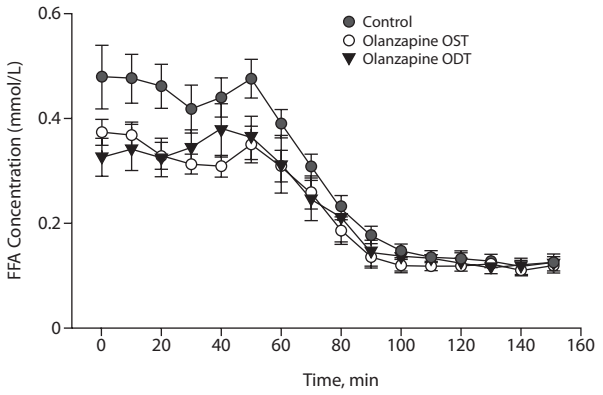
The effect of olanzapine ODT and OST on postprandial FFA or triglyceride concentrations in response to dinner did not differ, where olanzapine treatment did not affect these parameters (Table 4). The effects of olanzapine ODT and OST on postprandial FFA or triglyceride concentrations in response to breakfast did not differ (Table 3). However, olanzapine treatment clearly decreased the postprandial FFA concentrations and significantly reduced the maximal postprandial FFA suppression (respectively, $P = .009$ [1-tailed] and $P = .004$ [1-tailed]) in response to breakfast (Table 3, Figure 1). Also, treatment with olanzapine significantly

Table 1. Clinical and Biochemical Measurements (in fasting condition) During Treatment With Olanzapine OST, Olanzapine ODT and Without Intervention (control)[a,b]

Parameter	Control (n = 12)	Olanzapine OST (n = 11)	Olanzapine ODT (n = 11)
Weight, kg	77.5 ± 1.7	78.2 ± 2.1	78.0 ± 2.3
BMI, kg/m^2	23.6 ± 0.6	23.8 ± 0.6	23.7 ± 0.7
Waist-hip ratio	0.80 ± 0.01	0.81 ± 0.01	0.81 ± 0.01
Fat, %	9.6 ± 1.2	9.8 ± 1.3	10.4 ± 1.1
Diastolic blood pressure, mm Hg	71 ± 2	76 ± 3	72 ± 2
Systolic blood pressure, mm Hg	131 ± 4	128 ± 4	127 ± 4
Heart rate, beats/min	63 ± 4	68 ± 4	68 ± 4
Activity energy expenditure, kcal/d	571 ± 67	511 ± 91	529 ± 118
HOMA-IR[c]	1.53 ± 0.19†	2.18 ± 0.25	2.12 ± 0.34
Basal insulin secretion rate, mU/L/10 min	0.72 ± 0.08	0.77 ± 0.07	0.72 ± 0.10
FFA concentrations, mmol/L	0.460 ± 0.046§	0.346 ± 0.020	0.335 ± 0.035
Triglyceride concentrations, mmol/L	0.974 ± 0.106‡	1.327 ± 0.143	1.320 ± 0.237

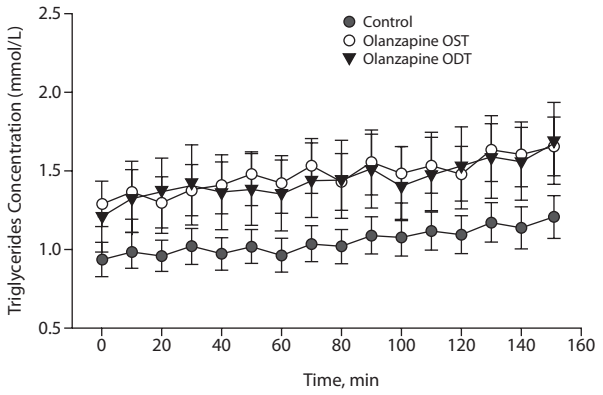
[a]Data are presented as mean ± SEM.
[b]There were no statistically significant differences between olanzapine OST and olanzapine ODT.
[c]Homeostasis model assessment (HOMA) was used to estimate insulin resistance from fasting insulin and glucose concentrations. The following equation was used: HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5.
†P = .005 (1-tailed), control vs treatment.
§P = .004 (1-tailed), control vs treatment.
‡P = .013 (1-tailed), control vs treatment.
Abbreviations: BMI = body mass index, FFA = free fatty acids, HOMA-IR = homeostasis model assessment of insulin resistance, ODT = orally disintegrating tablets, OST = oral standard tablets.

Figure 1. Free Fatty Acids (FFA) Concentrations at Breakfast[a,b]



[a]Data are presented as mean ± SEM.
[b]Olanzapine ODT and OST significantly decreased fasting and postprandial FFA concentrations at breakfast.
Abbreviations: ODT = orally disintegrating tablet, OST = oral standard tablet.

Figure 2. Triglyceride Concentrations at Breakfast[a,b]



[a]Data are presented as mean ± SEM.
[b]Olanzapine ODT and OST significantly increased fasting and postprandial triglyceride concentrations at breakfast.
Abbreviations: ODT = orally disintegrating tablet, OST = oral standard tablet.

increased postprandial triglyceride concentrations in response to breakfast (Table 3, Figure 2).

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, OST and ODT, similarly elevate the homeostasis model assessment (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 triglyceride 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 articles 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

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Table 2. Fuel Oxidation During Treatment With Olanzapine OST, Olanzapine ODT, and Without Intervention (Control)[a,b]

Parameter	Control (n=11)	Olanzapine OST (n=11)	Olanzapine ODT (n=11)
Respiratory quotient	0.78 ± 0.02	0.79 ± 0.02	0.79 ± 0.02
Glucose oxidation, $mg \cdot kg^{-1} \cdot min^{-1}$	1.13 ± 0.35	1.32 ± 0.30	1.26 ± 0.33
Lipid oxidation, $mg \cdot kg^{-1} \cdot min^{-1}$	1.31 ± 0.14	1.28 ± 0.10	1.25 ± 0.15
REE, kcal/d	1,285 ± 34	1,321 ± 34	1,291 ± 32

[a]Data are presented as mean ± SEM.
[b]There were no statistically significant differences between olanzapine OST and olanzapine ODT.
Abbreviations: ODT = orally disintegrating tablets, OST = oral standard tablets, REE = resting energy expenditure.

Table 3. Postprandial Metabolic Parameters at Breakfast and 12 Hours Nocturnal Adipokines Concentrations[a,b]

Parameter[c]	Control (n=12)	Olanzapine OST (n=11)	Olanzapine ODT (n=11)
Glucose concentration, mmol/L	5.6 ± 0.2	5.7 ± 0.2	5.3 ± 0.2
Maximal glucose increase, mmol/L	2.2 ± 0.1	2.6 ± 0.2	2.3 ± 0.3
Insulin concentration, mU/L	56.5 ± 7.3	67.3 ± 10.6	57.6 ± 8.8
Maximal insulin response, mU/L	93.3 ± 12.5	117.8 ± 17.1	96.3 ± 15.9
Meal-induced insulin secretion, mU/L/2 h	614 ± 81	694 ± 127	638 ± 103
FFA concentration, mmol/L	0.234 ± 0.014*	0.189 ± 0.012	0.201 ± 0.027
Maximal FFA decrease, mmol/L	0.347 ± 0.045#	0.242 ± 0.019	0.229 ± 0.029
Triglyceride concentration, mmol/L	1.074 ± 0.116§	1.505 ± 0.176	1.479 ± 0.246
Leptin, ng/mL	3.7 ± 0.9	3.8 ± 0.8	3.7 ± 0.8
Adiponectin, ng/mL	7.3 ± 0.6†	8.4 ± 0.9	8.7 ± 1.0

[a]Data are presented as mean ± SEM.
[b]There were no statistically significant differences between olanzapine OST and olanzapine ODT.
[c]Multiparameter deconvolution analysis was used to estimate various kinetic and secretory parameters of insulin plasma concentration in response to standard meals.
*P = .009 (1-tailed), control vs treatment.
#P = .004 (1-tailed), control vs treatment.
§P = .005 (1-tailed), control vs treatment.
†P = .034 (2-tailed), control vs treatment.
Abbreviations: FFA = free fatty acids, ODT = orally disintegrating tablets, OST = oral standard tablets.

Table 4. Preprandial and Postprandial Free Fatty Acids (FFA) and Triglyceride Concentrations at Dinner[a,b]

Parameter	Control (n = 12)	OST (n = 11)	ODT (n = 11)
Preprandial			
FFA concentration, mmol/L	0.415 ± 0.058	0.335 ± 0.046	0.369 ± 0.063
Triglyceride concentrations, mmol/L	1.396 ± 0.155§	1.760 ± 0.279	1.819 ± 0.405
Postprandial			
FFA concentration, mmol/L	0.344 ± 0.038	0.285 ± 0.028	0.289 ± 0.035
Maximal FFA decrease, mmol/L	0.211 ± 0.062	0.156 ± 0.045	0.207 ± 0.062
Triglyceride concentration, mmol/L	1.493 ± 0.173	1.814 ± 0.293	1.825 ± 0.366

[a]Data are presented as mean ± SEM.
[b]There were no statistically significant differences between olanzapine OST and olanzapine ODT.
§P = .038 (1-tailed), control vs treatment.
Abbreviations: ODT = orally disintegrating tablets, OST = oral standard tablets.

reported to increase fasting insulin concentrations in healthy subjects after treatment for 3 weeks.[16] We recently showed that treatment with olanzapine (OST) for 8 days hampers insulin-mediated glucose disposal in healthy subjects.[12] This finding agrees with data reported by Sacher et al,[17] who demonstrated a decrease in whole body insulin sensitivity in healthy subjects after treatment with olanzapine for 10 days. Olanzapine administration also induces insulin resistance in animals.[18,19] 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.[16] This apparent discrepancy might be related to the fact that a host of factors determines the insulin and glucose response to a mixed meal: ie, (variable) degree of absorption, gut peptide release, β-cell sensitivity, glucose disposal, and suppression of endogenous glucose production, whereas the HOMA index of insulin resistance is a mathematical reflection of whole body insulin sensitivity per se.[15]

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,[20] 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.[21] Besides its relatively weak affinity for dopamine D_2 receptors, olanzapine also antagonizes serotonin 5-HT_2, histamine H_1, and

α_1 adrenergic and muscarinic M_3 receptors.[21] Activation of all of these receptor (sub)types generally inhibits food intake, reduces body weight, and/or enhances insulin secretion.[22–26] Notably, various receptors blocked by olanzapine appear to be directly (ie, independent of their effects on body weight) involved in the regulation of glucose metabolism, as has been reported for serotonin,[27–29] histamine H_1,[30] and α_1-adrenergic receptors.[31,32] Also, activation of dopamine D_2 receptors with bromocriptine ameliorates insulin resistance in obese women through a mechanism that is independent of body weight.[33] Thus, antagonism of either 1 of these receptors, alone or in combination, by olanzapine may hamper insulin action.

Effect on Lipid Metabolism

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

Hypertriglyceridemia is a frequently reported finding in patients with schizophrenia who are on chronic treatment with olanzapine.[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, triglyceride concentrations were significantly increased and FFA concentrations significantly suppressed in patients using olanzapine.[34] 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 utilization. LPL activity is influenced by various hormones, including insulin, prolactin, and cortisol.[35] In adipose tissue, LPL activity is increased by cortisol[34] and inhibited by prolactin.[36,37] Prolactin inhibits its activity both directly and indirectly by inhibiting cortisol-induced LPL activity.[37] Olanzapine treatment mildly elevates plasma prolactin concentrations[38] and reduces circulating cortisol,[39–40] probably through serotonin ($5\text{-}HT_{2A/2C}$) and/or dopamine (D_2) receptor antagonism. Thus, the drug may impact on lipid metabolism via these neuroendocrine ensembles. Interestingly, activation of dopamine D_2 receptors by bromocriptine, which inhibits prolactin secretion, has effects on plasma lipid levels opposite to those observed here: circulating FFA concentrations rise, whereas plasma triglyceride concentrations tend to decrease in response to 8 days of bromocriptine treatment in obese women.[33] 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.[41,42] 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.[43] 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 that 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-naive schizophrenia patients[44] and their nonschizophrenia relatives[45] 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 crossover 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 that is independent of body adiposity or physical (in)activity. Orally disintegrating and standard tablets similarly affect glucose and lipid metabolism.

Drug names: bromocriptine (Parlodel, Cycloset, and others), insulin (Novolog), olanzapine (Zyprexa).

Author affiliations: Department of Endocrinology and Metabolism, Leiden University Medical Center, The Netherlands.

Potential conflicts of interest: None reported.

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