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Impact of short-term treatment with benzodiazepines and imidazopyridines on glucose metabolism in healthy subjects

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Abstract

Aim: In the last years there has been a progressive reduction of the average duration of sleep and an increase in the incidence of sleep disturbances. At the same time, an increase of the incidence of the metabolic syndrome has been described, partly attributable to the progressive worsening of dietary habits and the increase in sedentary lifestyle. Recent studies suggest that adequate sleep is essential to maintain good glucose metabolism and sleep disturbances may contribute to the manifestation of the metabolic syndrome. Benzodiazepines (BZ), such as brotizolam, and imidazopyridines, such as zolpidem, are frequently used as hypnotics but their potential impact on glucose metabolism has never been evaluated so far.

Methods: In 12 healthy volunteers [age (mean ± SEM) 38.3 ± 8.1 years; body mass index (BMI) 21.9 ± 0.8 kg/m2] we studied glucose and insulin responses to oral glucose tolerance test (OGTT, 75 g) before and after 15 days treatment with brotizolam 0.25 mg/day or zolpidem 10 mg/day.

Results: Brotizolam increased glucose delta area under curve response to the OGTT by 122 % ($p < 0.01$) and zolpidem by 86 % ($p < 0.01$) without significant variations of insulin levels, suggesting an impact on insulin sensitivity and/or insulin secretion.

Conclusions: This study suggests that BZ and imidazopyridines have a rapid glucometabolic effect that is detectable as early as after 15 days treatment.

Introduction

In the last years there has been a progressive reduction of the average duration of sleep and an increase in the incidence of sleep disturbances (both general impairment of sleep quality and increase of specific disorders like obstructive sleep apnea syndrome) [1, 2].

At the same time there has been an increase of incidence of metabolic syndrome due to the coexistence of alterations in glucose metabolism, lipid metabolism and hypertension that act simultaneously in increasing cardiovascular risk [3].

Although the most important cause of increase of metabolic syndrome is lifestyle change, epidemiological and experimental studies suggest that sleep plays an important role in modulating glucose metabolism, the neuroendocrine control of food intake and blood pressure. As a consequence, sleep disturbances may contribute to the manifestation of the metabolic syndrome [3]. The discovery of the association between sleep disturbances and the different components of metabolic syndrome offers important insights into the treatment of sleep disturbances for the prevention of cardiovascular risks [1].

It is well known that benzodiazepines (BZ), molecules that bind γ-aminobutyric acid A (GABA A) receptor in the central nervous system, are largely used as anxiolytics and hypnotics, and produce an increase in sleep length but also significant alterations in sleep structure [4, 5]. BZ reduce sleep latency, the number of awakenings, the wakefulness state and the length of stage 1, 3, and 4 while they increase that of stage 2 and modify the latency and length of rapid eyes movements (REM) sleep [4, 5]. These alterations seem not to be caused by imidazopyridines, new molecules used as hypnotics able to bind GABA A receptor with a specific selectivity for the BZ 1/omega one subtype [6–8]. These molecules reduce sleep latency and extend total sleep time but have little effects on sleep structure [6–8].

At present, despite their frequent use in clinical practice, the impact of these molecules on glucose metabolism has never been evaluated so far.

Based on this background, the aim of our study was to investigate in vivo in humans, the effects of a short-term modulation of GABA system, known to be involved in the control of insulin secretion [9–15], through the administration of brotizolam, a benzodiazepine, and zolpidem, an imidazopyridine, on the insulin and the glucose response to an oral glucose tolerance test (OGTT) in healthy subjects.

Materials and methods

Twelve healthy volunteers [4 men and 8 women; age (mean ± SEM) 38.3 ± 8.1 years; BMI 21.9 ± 0.8 kg/m2] were studied. None of them had a personal or family history of diabetes mellitus or a personal history of sleep disorders according to the Pittsburgh sleep quality index (PSQI). All the subjects gave their written informed consent to participate in the study, which had been approved by the Ethical Committee of the University of Turin. All subjects underwent the two following testing sessions in random order at least 1 month apart:

(a) 15 days treatment with brotizolam 0.25 mg/day at 2200 hours.

(b) 15 days treatment with zolpidem 10 mg/day at 2200 hours.

Diet and physical exercise were standardized for at least 15 days before and during all the sessions tests.

On day 0 and on day 16 of each session, all the subjects underwent an oral glucose tolerance test (OGTT; glucose 75 g p.o.). After overnight fasting, OGTT was performed in the morning at 08:30–09:00 a.m., 30 min later an indwelling catheter had been placed into an antecubital vein of the forearm kept patent by slow infusion of isotonic saline solution.

Blood samples were collected every 15 min from time −15 min up to +120 min. Glucose and insulin levels were assayed at each time point in all the sessions.

Plasma glucose levels (mmol/l) were measured by the glucose oxidase colorimetric method (Glucofix; Menarini Diagnostics, Florence, Italy).

Serum insulin levels (pmol/l) were measured in duplicate by immunoradiometric assay (INSIK-5; SORIN Biomedica, Saluggia, Italy). Sensitivity of the assay: 17.36 ± 2.08 pmol/l. Inter- and intra-assay coefficients of variation (CV): 6.2–10.8 and 5.5–10.6 %.

Glucose and insulin levels are expressed as mean ± SEM absolute levels or delta area under curve (ΔAUC) calculated by trapezoidal integration. Matsuda index was calculated as in [16]. The statistical analysis was carried out using non-parametric Mann–Whitney test, as appropriate.

Results

As expected, in all the experimental conditions, OGTT induced a significant increase ($p < 0.01$) of both glucose and insulin levels. Glucose and insulin responses to OGTT performed on day 0 were similar (p n.s.) between the two sessions (Fig. 1). Notably, 15 days treatment with brotizolam increased glucose ΔAUC response to OGTT by 122 % (166.63 ± 31.72 mmol/l min on day 16 vs. 89.67 ± 33.08 mmol/l min on day 0; $p < 0.01$) while zolpidem by 86 % (182.96 ± 29.44 mmol/l min on day 16 vs. 126.04 ± 32.11 mmol/l min on day 0; $p < 0.01$), whereas no statistical differences were observed in terms of insulin responses both after brotizolam (28673.13 ± 4311.59 pmol/l min on day 16 vs. 23637.31 ± 3653.76 pmol/l min on day 0) and after zolpidem (40019.17 ± 9027.81 pmol/l min on day 16 vs. 40915.77 ± 9096.56 pmol/l min on day 0) (Fig. 2). Based on the OGTT data, insulin sensitivity calculated by Matsuda index decreased by 12 % after brotizolam (4.8 ± 0.4 on day 16 vs. 5.6 ± 0.5 on day 0) and by 4 % after zolpidem (5.2 ± 0.6 on day 16 vs. 5.2 ± 0.7 on day 0), although both these variations did not attain statistical difference.

Discussion

Our paper describes for the first time that a benzodiazepine (i.e., brotizolam) and an imidazopyridine (i.e., zolpidem) affect glucose metabolism as early as after 15 days treatment.

These effects include an elevation of AUC glucose during OGTT, without significant variations in insulin secretion, consistent with alteration in insulin sensitivity and/or insulin secretion.

The pathophysiological mechanisms underlying these effects are at present unknown, but an indirect effect due to an alteration of sleep structure seems unlikely, as the increase in glucose response to OGTT was present even after zolpidem treatment that is known not to impair sleep architecture [6–8].

The hypothesis of a direct influence of brotizolam and zolpidem on insulin sensitivity is suggestive, though there are no data in the literature describing a direct effect of GABA on this parameter. A double-blind placebo-controlled study showed that administration of clonazepam during a frequently sampled intravenous glucose tolerance test reduced the acute insulin response in a concentration-dependent manner. The authors speculated that insulin sensitivity and glucose disposal could be influenced by the muscle relaxing action of this drug, but this hypothesis has never been definitely proved so far [16]. Similarly, the variations on Matsuda index we observed should be interpreted cautiously, though the lack of statistical significance could be related to the small number of subjects studied [17, 18].

Similarly, a potential GABA-mediated activation of counter-regulatory responses has theoretically to be excluded as BZ that have been demonstrated to inhibit the activity of the autonomous nervous system, glucagon and growth hormone secretion, lipolysis and glycogenolysis [19].

A potential impact of GABA activation on insulin secretion should be taken into account carefully. In fact, GABA has been reported to affect insulin secretion though both inhibitory and stimulatory effects have been reported in different experimental models [9–15]. Actually, the apparent absence of a compensatory increase of insulin secretion to the enhanced glucose ΔAUC could support the hypothesis of a partial inhibition of beta-cell responsiveness to glucose load after brotizolam or zolpidem pretreatment. Nevertheless, we have to take into account that in this study the absence of statistical differences in terms of insulin response in both test sessions could be related to the small number of subjects included in our protocol.

Notably, in none of our healthy subjects, neither brotizolam nor zolpidem led the glucose response to OGTT to the range of impaired glucose tolerance (IGT). Though many studies suggest that acute

administration of these drugs determines glycemic disregulation, there are no data in the literature on the long-term effect of BZ as a risk factor for diabetes. Further research is then needed to investigate the metabolic effect of a long-term treatment with the aforementioned drugs in subjects with a high personal risk to develop diabetes.

In conclusion, this study shows that BZ and imidazopyridines have a rapid glucometabolic effect in healthy human volunteers that is detectable as early as after 15 days treatment. These results, though preliminary, may suggest the need for screening for the risk of developing diabetes mellitus before starting a long-term treatment with these drugs and a periodic metabolic follow up during the treatment.

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Conflict of interest

The authors E. Gramaglia, V. Ramella Gigliardi, I. Olivetti, M. Tomelini, S. Belcastro, E. Calvi, A. Dotta, E. Ghigo, A. Benso, and F. Broglio declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figures

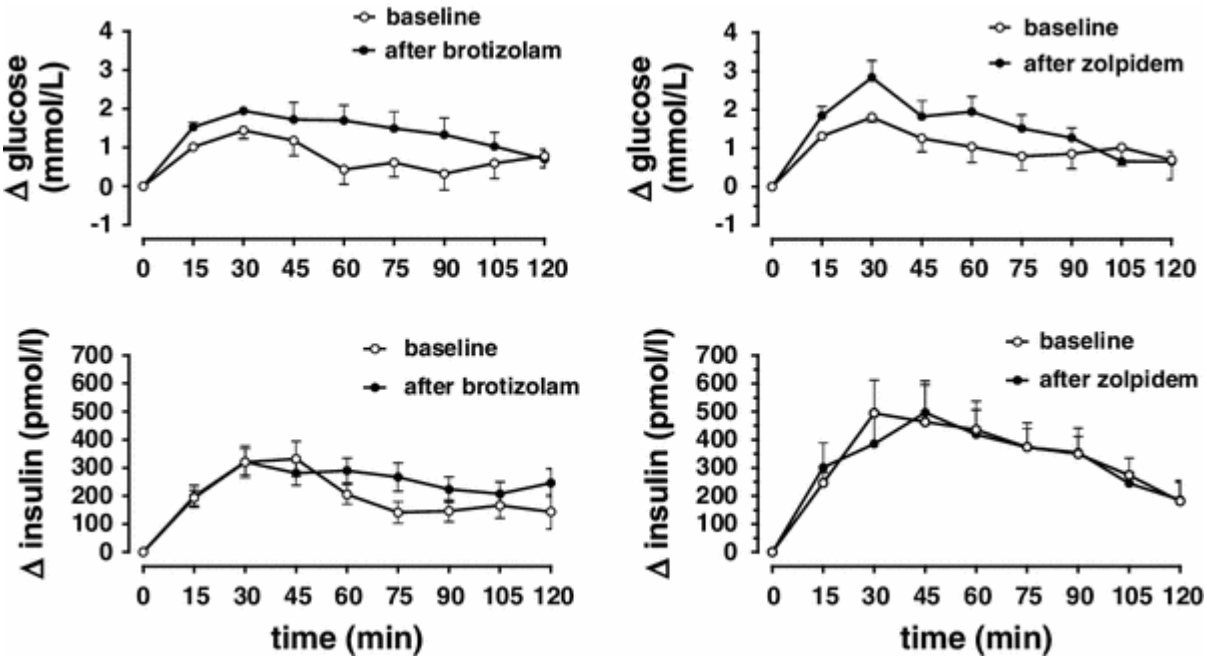

Fig. 1 Mean (±SEM) glucose and insulin responses to OGTT performed before and after 15 days treatment with brotizolam (0.25 mg/day) or zolpidem (10 mg/day)

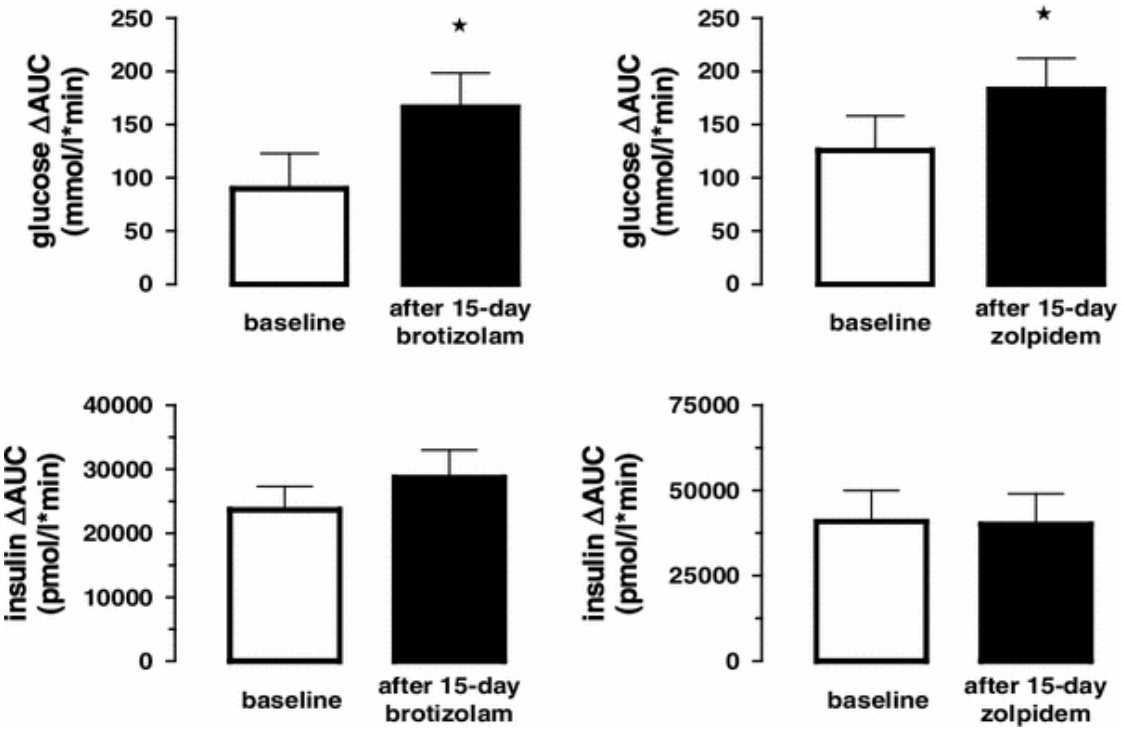

Fig. 2 Mean (±SEM) ΔAUC glucose and insulin responses to OGTT before and after 15 days treatment with brotizolam (0.25 mg/day) or zolpidem (10 mg/day) (five pointed star) = $p < 0.01$