Acarbose in obese patients with polycystic ovarian syndrome: a double-blind, randomized, placebo-controlled study

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BACKGROUND: The present study assessed the effects of low-dose acarbose on obese patients with polycystic ovarian syndrome (PCOS). METHODS: A double-blind placebo-controlled study was conducted on 30 obese hyperinsulinaemic women with PCOS treated with 150 mg/day acarbose or placebo for 6 months. The women were evaluated for hirsutism, menstrual regularity, body mass index (BMI), insulin resistance and glucose tolerance, sex hormone-binding globulin (SHBG), LH, FSH, testosterone and androstenedione, and side-effects. RESULTS: The patients in the acarbose group showed a reduction in BMI (35.87 ± 2.60 versus 33.10 ± 2.94 kg/m²) and in the Ferriman–Gallwey index (8.85 ± 2.31 versus 8 ± 1.82), and an increased chance of menstrual regularity (rate = 2.67). SHBG concentration increased (21.01 ± 7.9 versus 23.85 ± 7.77 nmol/l) and the free androgen index was reduced (14.81 ± 9.06 versus 11.48 ± 6.18). None of these parameters were modified in the placebo group. Mild side-effects occurred in 84% of the patients in the acarbose group and disappeared after the first 3 months. CONCLUSION: A low dose of acarbose administered to obese patients with PCOS promotes a reduction in free androgen index and BMI and an increase in SHBG, with improvement of hirsutism and of the menstrual pattern, and is well tolerated by patients.

Key words: acarbose/hypoglycaemic drugs/hyperinsulinaemia/polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is characterized by menstrual irregularity, hyperandrogenism, chronic anovulation and enlarged ovaries with more than eight peripherally located, follicles <10 mm (Franks, 1995). In ~25–60% of cases, patients with PCOS present glucose intolerance with consequent compensatory hyperinsulinaemia, and 30–40% of these cases are overweight or obese, with a body mass index (BMI) of >25 kg/m² (Dunaif et al., 1987). Insulin resistance may lead to hyperandrogenism by various mechanisms such as a central action (pituitary), a direct ovarian stimulus, or by a hepatic action with a reduced production of steroid hormone-binding globulin (SHBG) and insulin-like growth factor binding protein-1 (IGFBP-1) (Ehrmann et al., 1992).

Drugs that improve insulin sensitivity have been used for the treatment of patients with PCOS, with metformin being the drug most extensively studied (Leo et al., 2003; Lord et al., 2003). Although effective, metformin has important side-effects which often limit its use. In this respect, studies have been conducted to determine the action of other agents that act on insulin sensitivity.

α-Glucosidase inhibitors such as acarbose act by reducing and slowing down the intestinal absorption of glucose, with a reduction of the postprandial wave and a consequent reduction of insulin secretion (Laube, 2002). The use of these drugs by type II diabetic patients reduces the serum levels of glycosylated haemoglobin and increases insulin sensitivity (Lindström et al., 2000). The most common side-effects of acarbose are abdominal distention, flatulence and meteorism, with the latter being dose dependent (Coniff et al., 1996). The lowest dose of acarbose with a positive impact on glycaemia of diabetic patients was 150 mg/day (Rodier et al., 1998; Santusandio et al., 1993; Scheen, 1998).

Geisthovel et al. (1996) first studied the use of acarbose in non-diabetic patients. When they evaluated hyperandrogenic patients during the perimenopausal period they demonstrated that a dose of 300 mg/day reduced hyperandrogenism and improved insulin sensitivity in these patients. Ciotta et al. (2001) were the first to administer the same dose of acarbose for 3 months to hyperinsulinaemic non-obese patients with PCOS, obtaining a reduction of androgenic activity and regularity of the menstrual cycle. However, all treated patients presented gastrointestinal side-effects possibly due to the high dose used. Only one study compared the use of metformin to the use of acarbose in patients with PCOS and reported similar results (Hanjalic-Beck et al., 2004).
Although the insulin resistance present in PCOS does not depend on body weight, obesity is known to worsen the situation (Reis et al., 1995). The concentration of insulin receptors per adipocyte is reduced in obese patients (Kahn et al., 1993) and ~44% of women with PCOS may be obese (Carmina and Lobo, 1999).

On the basis of these facts, the objective of the present study was to assess the endocrine, metabolic and clinical effects of acarbose in obese patients with PCOS. In view of possible side-effects that might limit the treatment with oral hypoglycaemic agents, a low-dose scheme was used.

**Materials and methods**

A prospective randomized double-blind study was conducted on 30 obese patients with PCOS and insulin resistance, who were treated with 150 mg/day acarbose or placebo for 6 months. The patients were selected from June 2002 to May 2003 at the Gynecology Institute of the Federal University of Rio de Janeiro. All patients signed an informed consent form after receiving an explanation about the study and the project was approved by the Research Ethics Committee of the Gynecology Institute of the Federal University of Rio de Janeiro.

The inclusion criteria were: menstrual disorders (<6 menstruations/12 months), clinical (Ferriman–Gallwey index ≥8; Ferriman and Gallwey, 1961) or laboratory (testosterone >80 ng/dl and/or androstenedione >190 ng/dl) hyperandrogenism (Zawadski and Dunai, 1992), BMI (weight/height²) of 30–40 kg/m² (National Institute of Health, 2000), and insulin resistance (area under the insulin curve after the glucose tolerance test (GTT) >6000 mIU/ml; Reis et al., 1995).

The exclusion criteria (threshold values) were: alterations of hepatic function aspartate aminotransferase (GOT), 31 IU/l and alanine aminotransferase (GTP), 36 IU/l, alterations of renal function (creatinine, 1.3 mg/dl and urea, 40 mg/dl), alterations of thyroid function [thyroid-stimulating hormone (TSH), 5.50 mIU/ml and free thyroxin, 1.76 ng/dl], presence of hyperprolactinaemia (20 ng/ml), presence of congenital adrenal hyperplasia [dehydroepiandrosterone sulphate (DHEA-S), 350 mg/dl and 17-hydroxyprogesterone (17-OHP), 180 ng/ml], presence of diabetes (fasting glycaemia of 126 mg/dl), and the use of hormonal medications or medications that might interfere with carbohydrate metabolism over the last 6 months.

**Treatment**

The patients were assigned by computed randomization (GraphPad StatMate, San Diego, CA, USA) to two groups of 15 patients each respectively taking 50 mg acarbose or 50 mg placebo three times a day for 6 months. The medications were prepared and coded by the Industrial Pharmacy of the University Hospital of Ribeirão Preto using Glucobay (Bayer, Rio de Janeiro, RJ, Brazil) or flour and identified by codes (double-blind). The patients were submitted to clinical, metabolic and laboratory evaluation before and after 6 months of treatment.

**Clinical evaluation**

The patients were submitted to clinical (number of menstrual cycles, Ferriman–Gallwey index) and anthropometric (weight, height, BMI) evaluation before and after treatment.

**Laboratory tests**

Between the 2nd and 7th days of the menstrual cycle (or on any day in amenorrheic patients), the following basal measurements were performed: LH, FSH, prolactin, testosterone, androstenedione, DHEA-S, 17α-OHP, steroid hormone-binding globulin (SHBG), urinary cortisol, free thyroxin, TSH, urea, creatinine, GOT and GTP. A GTT was performed 3 days after a diet containing 300 mg carbohydrate, with ingestion of glucose (75 g Dextrose; Vita, Rio de Janeiro, RJ, Brazil) and venipuncture at 0, 30, 60, 90 and 120 min and analysis of the areas under the insulin and glucose curves (Reis et al., 1995). The insulinaemic index was calculated from the ratio between serum glucose concentration at 30 min and insulin concentration at the same time point (Wareham et al., 1995). According to Kosaka et al. (1996), there is a strong correlation between insulinaemic index and insulin resistance.

The evaluation of diabetes mellitus was performed according to the norms of the Expert Committee on the Diagnosis of Diabetes Mellitus (1999): fasting glycaemia (8 h) ≥126 mg/dl or glycaemia ≥200 mg/dl after 120 min during the 75 g GTT.

All blood samples were obtained by venipuncture in the forearm using a number 21 butterfly catheter, centrifuged and stored at −20°C. The hormone determinations were carried out at the University Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo. Glycaemia was determined by the enzymatic colorimetric glucose oxidase test (Merck-Biortol, São Paulo, SP, Brazil). Insulinaemia was determined by radioimmunoassay (Coat-a-Count; DPC, Los Angeles, CA, USA) with intra- and inter-assay coefficients of variation (CV) of 5.1 and 7.2% respectively. FSH, LH, SHBG and prolactin were determined by chemoluminescence (Inmulite 2000, DPC), with intra- and inter-assay coefficients of variation of 4.2 and 9.9% for LH, 5.1 and 12.5% for FSH, 5.3 and 6.6% for SHBG, and 3.6 and 7.4% for prolactin respectively. Testosterone, androstenedione and DHEA-S were determined by radioimmunoassay (Goldlab, São Paulo, SP, Brazil) and the intra- and inter-assay CV were 7.9 and 11.3% for testosterone, 8.5 and 12.3% for androstenedione, and 6.1 and 10.5% for DHEA-S. 17-oOHP was determined by radioimmunoassay (Treck, Santa Monica, CA, USA) with intra- and inter-assay CV of 5.3 and 5.9% respectively. TSH, free thyroxin and urinary cortisol were determined by chemiluminescence (ACS:180, Bayer, Rio de Janeiro, RJ, Brazil) with intra- and inter-assay CV of 3.98 and 3.96% for TSH, 3.44 and 3.96% for free thyroxin, and 4.5 and 6.4% for cortisol respectively. The free androgen index was calculated by the equation proposed by Siteri and Simberg (1986) using the value of 0.03467 for the conversion of the measurement of total testosterone (Young, 1968).

**Statistical analysis**

In view of the need to determine simultaneously the within- and between-group variations and considering the borderline size of the samples and the high variability of the data, Bayesian methodology using non-informative Priors and the Winbug software, version 1.3 (MRC Biostatistic Unit, Cambridge, UK) were used for statistical analysis.

**Results**

During the study, among the 30 patients selected, we excluded two patients from the acarbose group (one for abandonment of treatment and the other because of pregnancy) and one from the placebo group (abandonment), with no case of treatment intolerance. Four patients (28%) in the placebo groups and 11 (84%) in the acarbose group presented mild abdominal distention and flatulence, and all the patients in the acarbose group reported a reduction of side-effects after...
the first 3 months. No patient showed laboratory changes regarding liver or renal function during treatment.

Before treatment, the groups did not show any difference regarding any of the clinical or laboratory parameters (Table I). Compared to pretreatment values, the acarbose group presented a reduction in BMI, an improved menstrual pattern (especially in the last 2 months of treatment), increased serum SHBG concentration, and increased free androgen index, while the placebo group did not show any difference between the pretreatment and post-treatment values for any parameter analysed (Table I and Figures 1 and 2). The probability of a patient in the acarbose group to menstruate in the last 2 months was 3.34-fold higher (95% CI 1.08–12.55) than in the second 2 months and 2.67-fold higher (95% CI 1.00–8.98) than in the placebo group in the last 2 months. About 85% of the patients in the acarbose group menstruated in the last 2 months versus 50% in the placebo group.

Regarding hirsutism, although the acarbose group did not present a significant reduction compared to pretreatment indices, statistical comparison adjusted for pretreatment values between the acarbose and placebo groups showed a significant reduction after treatment in the acarbose group (8.00 ± 1.82 versus 10.36 ± 3.84 for placebo) (Figure 3). After treatment, there was a difference between the acarbose and placebo groups regarding BMI, free androgen index and Ferriman–Gallwey index.

Discussion

Several studies have demonstrated the association between PCOS and insulin resistance (Burghen et al., 1980; Taylor et al., 1982; Barbieri et al., 1983; Flier et al., 1985; Dunaif et al., 1987; Stuart et al., 1987), with the estimate that, among the various causes of PCOS, insulin resistance may be present in 38% of cases (Legro et al., 1999). Insulin resistance represents a condition whereby the ‘normal’ insulin concentration does not produce an adequate biological effect (Kahn et al., 1976). In this situation, pancreatic β-cells can elevate synthesis to compensate for resistance to the peripheral utilization of insulin. In addition, there is a reduction of hepatic clearance that culminates in hyperinsulinaemia (Barbieri and Hornstein, 1988). The lack of a biological effect of insulin in PCOS is a matter of debate, being attributed to molecular changes such as mutations of post-transduction errors of the insulin receptor (Dunaif et al., 2001; Kido et al., 2001).

Insulin regulates androgen metabolism not only by controlling their synthesis and secretion, but also indirectly by modulating the hepatic production of SHBG and IGFBP-1 (Leo et al., 2003) and by increasing the activity of cytochrome P450 17α in ovarian stroma and theca cells (Nestler and Jakubowicz, 1996). In obese patients with PCOS, in addition to all the mechanisms described, there is worsening of hyperandrogenism due to the synergism of obesity with insulin resistance, with a lower hepatic production of SHBG, an increase in the activity of cytochrome P450 17α both in the ovary and in the adrenal gland, and a greater conversion of estrone by aromatase in peripheral adipose tissue, with a direct action on LH and an indirect action on thecal cells (Leo et al., 2003). About 30–40% of patients with PCOS are obese (BMI ≥ 30 kg/m²) (Dunaif et al., 1987) and in these patients the degree of insulin resistance is higher than in patients who are only obese (Rajkhowa et al., 1994; Reis et al., 1995).

Since the aetiology of PCOS is linked to insulin resistance and may be complicated by obesity, it is plausible that medications which reduce glucose absorption with a consequent improvement of an exaggerated insulin response are ideal for treatment. Many drugs have been used for this purpose, the main ones being metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol, and acarbose. Among them, metformin is the drug for which the greatest accumulation of beneficial evidence regarding the physiopathology of PCOS has been obtained (Lord et al., 2003), with actions leading to increased ovulation rates and reduction of arterial

### Table I

Clinical, endocrine and metabolic parameters of the patients with polycystic ovarian syndrome before and after treatment with acarbose for 6 months (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Acarbose</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre (n = 15)</td>
<td>Post (n = 14)</td>
<td>Pre (n = 15)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25.93 ± 1.83</td>
<td>26.69 ± 1.46</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>35.04 ± 2.84</td>
<td>35.87 ± 2.06</td>
</tr>
<tr>
<td>Ferriman–Gallwey index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre (n = 15)</td>
<td>Post (n = 14)</td>
<td>Pre (n = 15)</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>10.29 ± 4.70</td>
<td>10.36 ± 3.84</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>5.46 ± 2.45</td>
<td>6.14 ± 3.00</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre (n = 15)</td>
<td>Post (n = 14)</td>
<td>Pre (n = 15)</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>70.64 ± 29.70</td>
<td>73.85 ± 34.34</td>
</tr>
<tr>
<td>Androstenedione (ng/dl)</td>
<td>133.95 ± 96.13</td>
<td>138.25 ± 45.79</td>
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<tr>
<td>Free androgen index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre (n = 15)</td>
<td>Post (n = 14)</td>
<td>Pre (n = 15)</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>13.99 ± 10.08</td>
<td>15.05 ± 12.20</td>
</tr>
<tr>
<td>Area under the glucose curve after the GTT (mg/dl)</td>
<td>16.057 ± 3472</td>
<td>15.377 ± 3045</td>
</tr>
<tr>
<td>Area under the insulin curve after the GTT (μIU/ml)</td>
<td>16.909 ± 8167</td>
<td>15.692 ± 5252</td>
</tr>
<tr>
<td>Insulin resistance index</td>
<td>0.95 ± 0.27</td>
<td>0.97 ± 0.36</td>
</tr>
</tbody>
</table>

Reference values for the determinations: LH = 1.1–11.6 IU/l; FSH = 2.8–11.3 IU/l; testosterone = 20–81 ng/dl; androstenedione = 0.4–2.7 ng/dl; SHBG = 18–114 nmol/l.

*aStatistically significant difference between groups after treatment.

*bStatistically significant difference within the acarbose group.

Analysis by the Bayesian method.
pressure, insulinaemia and low-density-lipoprotein cholesterol levels. However, the drug is not always well tolerated or may be inefficient (Lord et al., 2003). Thus, new modalities of treatment are welcome.

Acarbose is a pseudo-tetrasaccharide produced from the culture of a natural microorganism called *Actinoplanes strain* SE 50. An unsaturated cyclitol with an important contribution to the inhibitory effect on α-glucosidase exists in its molecule (Müller, 1985). In the small intestine, the drug forms a reversible and dose-dependent bond with the oligosaccharide site of α-glucosidase. This reduces the hydrolysis of oligo- and disaccharides in the middle third of the duodenum, leading to reduction and later interruption of monosaccharide absorption and transport into the circulation. The drug has been used for the treatment of type II diabetes and has been found to be highly effective (Mertes, 2001).

Regarding carbohydrate metabolism, acarbose leads to a 20% reduction of the postprandial peak of glycaemia. This effect may last for as much as 5 h, with an increase in the time of glucose absorption that prevents glucidic toxicity and the consequent hyperinsulinaemia (Hanefeld et al., 1991). The reduced glucose absorption leads to an indirect increase in glucagon 1-like peptide (GLP-1) which acts on the satiety centre of the brain, reducing appetite and facilitating weight reduction (Gutzwiller, 1997). Through the action of GLP-1, acarbose produces a reduction of appetite with a consequent reduction of BMI (Calle-Pascual et al., 1996). Other studies have reported reduction of the final weight of patients with type II diabetes mellitus after the use of acarbose (Wolever et al., 1998).

The lowest dose of acarbose with clinical effects is 150 mg/day, with doses >300 mg/day already exceeding the saturation of the α-glucosidase receptor and causing no increase in the effect of the drug (Rodier et al., 1988; Santeusanio et al., 1993). These are important aspects of treatment since side-effects such as flatulence, meteorism and abdominal distention are dose dependent. With a daily dose of 300 mg there is a 100% rate of side-effects, which is reduced to 47% within 2 months (Laube, 2002). In the present study there were fewer side-effects (84%) with a 100% reduction within 3 months.

Because of its mechanism of action, acarbose represents a good therapeutic option for patients with PCOS and insulin resistance. The first report of the use of this drug by non-diabetic patients was published by Geisthovel et al. (1996), who detected a reduction of ovarian hyperandrogenism associated with attenuation of the postprandial glucose peak and with insulin sensitivity in hyperinsulinaemic and hyperandrogenic postmenopausal patients (Geisthovel et al., 1996). The first study that administered acarbose to patients with PCOS during menacme showed favourable effects on the Ferriman–Gallwey score and on acne/seborrhoea, with improvement in insulin sensitivity, increased SHBG, and reduced LH and hyperandrogenism (Ciotta et al., 2001). However, with the posology studied in both investigations (300 mg/day) there was a 100% frequency of gastrointestinal side-effects. Recently, the use of acarbose (300 mg/day) was compared to the use of metformin (1.5 g/day) in patients with PCOS regardless of body weight and the results were similar both regarding clinical, endocrine and metabolic parameters and the cases of treatment discontinuation (Hanjalic-Beck et al., 2004; Sönmez et al., 2005).

Although a long list of benefits regarding clinical, metabolic and reproductive measures has been attributed to...
metformin, a careful inspection of controlled studies shows that the results are modest (Harbone et al., 2003), opening perspectives for the combination of drugs with different mechanisms. These data support the need for a better knowledge of new therapeutic options for patients with PCOS since the incidence of side-effects may be the limiting factor responsible for the decision about the treatment to be chosen. The present study points in this direction since it showed the clinical efficacy of acarbose used at the lowest biologically active dose (Rodier et al., 1988; Santeusanio et al., 1993).

Without changing the insulinaemic response after glucose stimulation, acarbose was able to reduce the body weight and androgen activity of patients with PCOS, with less pronounced side-effects than obtained with standard posology. In contrast to the data reported by Ciotta et al. (2001), who detected a response of insulinaemia, our data indicate that the action of acarbose occurred mainly in terms of a reduction of body weight in obese patients. These differences can be explained by the weight of the patients, since all our patients were obese, in contrast to the normal weight of the patients of Ciotta et al. (2001).

The treatment of obese women with PCOS involves some additional difficulties due to the particularities of the synergism of physiopathological conditions, with higher rates of failure regarding the ovulatory response and the improvement of insulin resistance. Metformin induces a lower therapeutic response in obese patients with PCOS compared to obese patients without PCOS, especially regarding the level of improvement of insulin sensitivity (Maciel et al., 2004; Metwally, 2004). In this respect, acarbose seems to be a good option for this subgroup of obese patients with PCOS since it has an effective action on body weight, with favourable clinical repercussions. However, acarbose had no effect on insulinaemic metabolism, although a comparative study showed no difference between acarbose and metformin (Hanjalic-Beck et al., 2004). These observations open perspectives for studies using a combination of the two medications.

BMI was reduced only in the acarbose group, corroborating the results obtained by Calle-Pascual et al. (1996) and Wolever et al. (1998) who reported a reduction in BMI in type II diabetic and obese patients. The reduction in BMI was a determinant of the results of the present study and may explain in part the increase in SHBG, since there is an inverse relationship between obesity and serum SHBG concentration (Rajesh et al., 1982; Hergenc et al., 1999; Garault et al., 2002; Lukanova et al., 2004). The reduction in BMI favours the use of acarbose in obese patients, since metformin does not have the same action on body weight (Lord et al., 2003). However, there are studies showing a decrease in weight or in abdominal adiposity (Morin-Papunen et al., 2000; Pasquali et al., 2000).

Regarding the menstrual pattern, the present study demonstrated that the patients taking acarbose tended to have regular menses, with a 2.67-fold higher chance of the occurrence of this event during the last 2 months of treatment compared to the placebo group. Ciotta et al. (2001) also reported regularity of menstrual cycles in 60% of the patients in the acarbose group but in their study they did not assess the chance of occurrence of this event, an important feature that provides the real dimension of the action of the drug on menstruation. This tendency to regular menstruations seems to be related to weight reduction, which favours increased SHBG production, reduction of the fraction of free androgens, a lower peripheral estrone conversion, and a lower action on ovarian androgens. Regarding hirsutism, a treatment of 6 months is rather short to investigate the effect on this characteristic, and the placebo group was already more hirsute (not significantly) before treatment, so the difference was not necessarily due to the effect of acarbose.

No improvement in insulin resistance or in the area under the insulin curve was observed, in contrast to the data reported by Chiasson et al. (1996), Geisthovel et al. (1996) and Ciotta et al. (2001), who obtained the inverse result with double the dose used in the present study. Rodier et al. (1988) and Santeusanio et al. (1993) reported a reduction in glycosylated haemoglobin levels with the use of 150 mg/day acarbose and Rachamani et al. (2004) reported a reduction in insulin resistance with the low dose. However, the present study was the only one conducted exclusively on obese patients and the results agree with those reported on the effects of metformin on very obese women, suggesting a synergism of physiopathological conditions (obesity and insulin resistance) (Maciel et al., 2004).

The present study, a pioneering investigation of the effects of acarbose on obese patients with PCOS, suggests that this drug could be used in a safe manner by patients with PCOS and hyperinsulinaemia and that low and well-tolerated doses of the drug have an action on body weight and hyperandro- genism in these patients. The study opens perspectives for future investigation combining drugs with different mechanisms of action in patients with PCOS, especially obese ones for whom standard treatments are less effective.

References
Acarbose and polycystic ovary syndrome


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