A pilot study of the long-term effects of acipimox in polycystic ovarian syndrome

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BACKGROUND: To evaluate the effects of long-term acipimox administration on glucose-induced insulin secretion and peripheral insulin sensitivity in polycystic ovarian syndrome (PCOS), 20 PCOS subjects (eight lean and 12 obese) and 14 body mass index-matched controls (seven lean and seven obese) were investigated. METHODS: Fasting blood samples were collected for basal hormone and lipoprotein assays, after which patients underwent an oral glucose tolerance test (OGTT). The following day a euglycaemic–hyperinsulinaemic clamp was performed. After 4–6 weeks of treatment with acipimox at a dose of 250 mg given orally three times a day, the patients repeated the study protocol. RESULTS: No significant differences were found in the glucose, insulin or C-peptide responses to OGTT before and after anti-lipolytic drug administration in any group, nor was there any effect on insulin sensitivity. Concerning the lipid profile, acipimox administration led to a significant decrease of cholesterol and low-density lipoprotein levels in obese PCOS patients as well as in obese and lean controls. Lower triglycerides were found after the drug administration in both obese groups. Post-treatment free fatty acid levels were not significantly different when compared with basal values. CONCLUSIONS: Acipimox does not appear to be an effective insulin-lowering drug in PCOS, even if it can be used in obese women with PCOS as an additional therapeutic agent to ameliorate the atherogenic lipid profile of the syndrome.

Key words: acipimox/free fatty acids/insulin/lipids/polycystic ovarian syndrome

Introduction

Women with polycystic ovarian syndrome (PCOS) are characterized by an increased prevalence of metabolic disturbances; indeed obesity is present in ~40–50% of PCOS patients (Ciampelli and Lanzone, 1998). Furthermore, hyperandrogenism, which represents another classical feature of the syndrome, leads to a typical body fat distribution generally known as central or upper body obesity (Evans et al., 1983) and is closely related to the degree of peripheral insulin resistance (Holte et al., 1994a,b). A key mechanism in this relationship is thought to be an enhanced mobilization of free fatty acids (FFA) (Bjorntorp, 1991), since an increase in plasma FFA would contribute to insulin resistance and glucose intolerance (Ferranini et al., 1983; Golay et al., 1986; Reaven and Chen, 1988). This hypothesis seems to be supported by the presence of a significant link between FFA plasma levels and insulin sensitivity index in PCOS subjects (Holte et al., 1994b).

However, whereas there is substantial evidence to show that increased FFA availability is associated with a reduction in glucose uptake, there are few data available to show the opposite, that lowering FFA is associated with enhanced glucose uptake.

With the introduction of the anti-lipolytic nicotinic acid analogue acipimox, which significantly decreases plasma FFA levels, several studies have been published about the use of this compound in order to ameliorate glucose tolerance in normal and diabetic subjects; while there is general accordance about the improved insulin-mediated glucose uptake after acute acipimox administration (Fulcher et al., 1992a,b; Kruszynska et al., 1997; Santomauro et al., 1999), conflicting data have been reported in a similar evaluation after long-term acipimox treatment, with improved (Fulcher et al., 1992c) or unchanged (Vaag and Beck-Nielsen, 1992) insulin sensitivity.

One study (Kumar et al., 1994) reported on the use of a slow-release acipimox formulation to treat a patient affected by type-A insulin resistance syndrome (acanthosis nigricans, polycystic ovaries, hirsutism and androgenization). After an 8 week treatment period the authors observed a 4-fold increase in peripheral insulin sensitivity, thus suggesting the usefulness of this kind of therapy in hyperandrogenic insulin-resistant women.

The aim of the present study was to evaluate the metabolic effects of long-term acipimox administration in PCOS subjects.

Materials and methods

Subjects and study design
We studied 20 consecutive Caucasian (native Italians) patients with PCOS (age range 19–33 years) attending our divisional outpatients’
services. All the women had spontaneous onset of puberty and normal sexual development, and all had oligomenorrhea with chronic anovulation since puberty. All the women were euthyroid and none had taken medications known to affect plasma sex steroid levels for at least 3 months before the study.

PCOS was diagnosed on the basis of clinical findings (the presence of amenorrhea or oligomenorrhea and hirsutism), plasma androgen levels at the upper limit of, or above, the normal range (androstenedione 2.0–6.98 nmol/l; testosterone 0.6–2.0 nmol/l), and the presence of bilaterally normal or enlarged ovaries containing at least 7–10 microcysts (<5 mm in diameter) on ultrasonography. In ~50% of cases, the diagnosis was also confirmed by laparoscopy. A normal LH/FSH ratio was not considered an exclusion criterion (Lanzone et al., 1996). The presence of a late-onset adrenal enzyme defect was excluded by an adrenocorticotrophic hormone test (250 μg i.v., Synacthen; Ciba-Geigy, Basel, Switzerland) according to published criteria (New et al., 1983). Obesity was defined as a body mass index of >25 kg/m² (normal range 19–25). Waist circumference was obtained as the minimum value between the iliac crest and the lateral costal margin, whereas hip circumference was determined as the maximum value over the buttocks.

Seven lean and seven obese normo-ovulatory volunteers served as controls; the mean (± SD) length of the menstrual cycle in these subjects was 28.9 ± 2.2 days. Ovulatory cycles had been confirmed previously by mid-luteal plasma progesterone levels of ≥25 nmol/l for three consecutive cycles.

Informed consent was obtained from each patient, and the study protocol was approved by our Institutional Review Board. Studies were conducted in the regularly cycling control subjects during the early follicular phase of their menstrual cycles (days 2–6) and in the women with PCOS on random days. In no case had recent ovulation occurred in the women with PCOS as evidenced by retrospective measurement of serum progesterone levels on the days of the study.

The patients were hospitalized and, after following a standard carbohydrate diet (300 g/day) for 3 days and fasting overnight for 10–12 h, blood samples were collected for basal hormone and lipoprotein assay. Patients then underwent an oral glucose tolerance test (OGTT). The following day, after another overnight fasting, a euglycaemic–hyperinsulinaemic clamp was performed.

The patients then left the hospital and had 4–6 weeks of treatment with acipimox (Obetam; Pharmacia Upjohn, Milan, Italy) at a dose of 250 mg given orally in connection with breakfast, at lunch-time and at bed-time (22:00). Five patients (two PCOS and three controls) had transient upper-body flushing as a side-effect of acipimox administration.

Patients were recommended to not modify their usual diet. The presence of an ovulatory cycle was excluded during therapy by weekly assays of progesterone serum levels. Anovulatory patients returned to hospital at a time that was irrespective of the cycle phase, whereas ovulatory subjects returned in the early follicular phase of the subsequent menstrual cycle.

The compliance with treatment was checked with a questionnaire about the side-effects and a subjective evaluation of the tolerability of the administered drug; the patients were also asked about incidental missed administrations, but all reported to have correctly followed the scheduled treatment.

Without interrupting the therapy, the patients repeated the OGTT, the hormonal and lipoprotein assay and the clamp study. The morning acipimox administration was performed at least 2 h before the tests.

Plasma levels of growth hormone (GH), testosterone, dehydroepiandrosterone sulphate, androstenedione, 17-hydroxyprogesterone, FSH, LH, sex hormone-binding globulin (SHBG), triglycerides, high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), low-density lipoprotein cholesterol (LDL), cholesterol and FFA were determined in basal conditions.

The OGTT was performed as follows: at 09:00 after overnight fasting, an indwelling catheter was inserted into the antecubital vein of one arm. Blood samples were collected basally and, after ingestion of 75 g glucose in 150 ml water within 5 min, at 30, 60, 90, 120, 180 and 240 min. Insulin, glucose and C-peptide were assayed in all samples.

Samples for hormone assay were promptly centrifuged and the plasma was stored at ~20°C until assay, whereas samples for biochemical assay were assayed immediately.

The euglycaemic–hyperinsulinaemic clamp was performed as follows. A retrograde i.v. catheter was inserted into a hand or forearm vein for blood sampling and kept in a warming device at >60°C to arterialized the venous blood samples. Another indwelling catheter was inserted into a contralateral forearm vein for the infusions. Insulin (Actrapid HM; Novo Nordisk, Copenhagen, Denmark) was administered at a dosage of 40 mIU/m² × min (De Fronzo et al., 1979). After reaching the steady-state velocity for the insulin infusion within 10 min in order to achieve steady-state insulin levels of ~717 pmol/l during the clamp (range 574–897), a variable infusion of 20% glucose was begun via a separate infusion pump and the rate was adjusted according to plasma glucose determinations every 5 min to maintain plasma glucose between 4.4 and 4.99 mmol/l. The plasma glucose level was determined by the glucose oxidase technique with a glucose analyser ( Beckman Instruments, Palo Alto, CA, USA). Total body glucose utilization (M) was determined between 90 and 150 min of the glucose clamp and expressed as mg/kg body wt/min (mg/kg/min). We preferred the use of this index as the measure of insulin sensitivity because the M/I ratio fails to narrow the range of individual sensitivity values (Bergman et al., 1985).

All hormones were determined by commercial radioimmunooassay kits (Radium, Pomezia, Italy). Gonadotrophins and insulin were assayed by the dextran–charcoal separation technique. The intra- and inter-assay coefficients of variation (CV) were <8 and <15% respectively, for all determinations. The kit for GH assay had a sensitivity of 0.04 μg/l while intra- and inter-assay CV were 2.5 and 5.8% respectively.

For each determination, all samples from the same patient were assayed simultaneously.

Total cholesterol and triglyceride concentrations were determined by an enzymatic assay (Bristol, Paris, France). HDL concentrations were determined after precipitation of chylomicrons, vLDL and LDL (Boehringer, Mannheim, Germany). vLDL was separated (as the supernatant) from LDL and HDL by lipoprotein ultracentrifugation. A magnesium chloride/phosphotungstic acid technique was used to precipitate LDL from the bottom fraction after ultracentrifugation. FFA were determined by an acyl-coenzyme A oxidase-based colorimetric method. All lipids assay were performed according to our standard laboratory procedures as previously reported (Ciampelli et al., 1999).

A normal glycaemic response to OGTT was defined according to the criteria of the American Diabetes Association (ADA) (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997).

**Statistical analysis**

All results are expressed as mean ± SD. Insulin, glucose and C-peptide plasma concentrations are also expressed as the area under the curve (AUC) after glucose ingestion, calculated by the trapezoidal rule.

Non-normally distributed variables were logarithmically transformed. Student’s two-tailed t-tests for paired data were used to
compare the effects of acipimox within each group of subjects. Comparisons between the groups were made by one-way analysis of variance (ANOVA), and any significant difference identified using the Bonferroni correction for multiple comparisons. Values of $P < 0.05$ were considered significant.

The power of the study was evaluated using the Statistics for Biomedical Sciences, version 4.02 by Stanton A. Glantz [Windows version by R. Goldstein and R. Solomon (1997), McGraw-Hill, Milan, Italy]. Since the main evaluation concerns the peripheral insulin resistance variation after acipimox administration, the study was set to identify an acipimox mediated change of $\approx 25\%$ in the insulin sensitivity ($M$ value) in the group of obese PCOS patients; considering an $\alpha = 0.05$ the power calculation was 0.883.

## Results

Based on their body mass index (BMI; kg/m$^2$), patients were divided into four groups: lean PCOS (eight patients), lean controls (seven patients), obese PCOS (12 patients) and obese controls (seven patients). No subject showed impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus (NIDDM).

Table I shows the clinical and endocrine features of the studied groups. PCOS subjects showed higher waist:hip ratio (WHR) and androgen levels when compared with BMI-matched controls. Within PCOS and control women, no differences were found between lean and obese groups except for SHBG levels, which were lower in obese groups. Any significant change was observed for all variables within each investigated group after acipimox administration.

Table II shows the metabolic parameters and lipidic patterns of the studied groups. Basally obese PCOS subjects showed lower GH plasma levels when compared with lean PCOS ($P < 0.01$). Significantly higher triglycerides were found in the obese groups when compared with lean counterparts. No significant difference was found in basal conditions for any of the other investigated variables; also FFA levels did not significantly differ between groups, even if obese PCOS women showed slightly higher levels with respect to the other three groups.

Long-term acipimox treatment led to a significant decrease of cholesterol and LDL levels in obese PCOS subjects as well as in lean and obese controls. Furthermore, lower triglyceride levels were found after drug administration in both obese groups. No other significant differences were found after treatment in each investigated group; also, FFA levels were not significantly different when compared with basal values, although a slight trend toward higher FFA plasma levels after treatment was observed.

Figure 1 shows glucose, insulin and C-peptide response to oral glucose load, expressed as AUC before and after acipimox administration in the four analysed groups. No significant differences were found in basal conditions between the lean as well as the obese groups, except for the insulin AUC which was higher in obese groups compared with lean ones. No significant variations were found after acipimox administration.

Insulin-dependent glucose utilization ($M$) in the study population is shown in Figure 2. Basally obese groups showed significantly lower $M$ values when compared with lean counter-parts, whereas superimposable results were found within obese or lean groups in comparing PCOS with control women. No changes were found in $M$ value after the nicotinic acid analogue administration.

In considering the entire group of PCOS (20 patients) and controls (14 patients), no significant variations were found in the insulin-mediated glucose-uptake after acipimox administration (PCOS: $5.33 \pm 2.81$ versus post $4.67 \pm 1.92$ mg/kg/min, not significant; controls: $5.25 \pm 2.53$ versus post $5.31 \pm 2.17$ mg/kg/min, not significant), nor in the other considered variables.

## Discussion

In 1963 Randle and co-workers postulated the operation of a glucose/fatty acid cycle, based upon experiments on perfused rat heart and hemi-diaphragm (Randle et al., 1963). They found that by increasing the availability, and thereby the oxidation, of FFA, the oxidation of glucose was decreased, thus suggesting the presence of a competition between lipids and glucose as a source of energy in the muscle cells. In human in-vivo experiments, FFA have been shown to impair glucose uptake by both cardiac and skeletal muscle (Nuutila et al., 1992).

Holte and co-workers reported that obese women with PCOS had markedly increased plasma FFA concentrations (Holte et al., 1994b). This may be due to the increased truncal–abdominal fat mass, with a high lipolytic activity (Martin and Jensen, 1991), and a generally impaired insulin suppression of FFA release from adipose tissue in the insulin-resistant state (Coppack et al., 1992). Furthermore, the observed effect of testosterone in facilitating FFA release from abdominal fat tissue (Rebuffe-Scrive et al., 1991) could be of importance in determining the metabolic alterations found in PCOS.

Another recent report found a tendency towards higher FFA concentrations and defective suppression of rate of lipid oxidation in obese PCOS subjects during the hyperinsulinaemic clamp (Morin-Papunen et al., 2000), thus strengthening the hypothesis of FFA as an important factor in determining hyperinsulinaemia and insulin resistance in PCOS.

In our series, we did not find significant differences between the four investigated groups as to plasma FFA levels; only obese PCOS women showed a slight, but not significant, increase in plasma FFA concentrations. These data are not in keeping with those reported by Holte’s group (Holte et al., 1994b) concerning higher FFA levels in PCOS patients; it is possible that factors other than PCOS status might influence the FFA plasma levels, such as environmental or dietary factors.

Nevertheless the possibility that small variations in the FFA levels as well as different sensitivity to circulating FFA concentrations might be able to influence insulin metabolism cannot be excluded.

Acipimox, an analogue of nicotinic acid, is a powerful inhibitor of lipolysis that significantly decreases plasma FFA levels (Fucella et al., 1980); thus it represents a good tool in understanding the role of FFA depression on metabolic disturbances of PCOS. Our data show that the long-term administration of this compound was not able to modify the
### Table I. Clinical and endocrine features of the studied groups before and after acipimox treatment

<table>
<thead>
<tr>
<th></th>
<th>Lean PCOS (n = 8)</th>
<th>Lean controls (n = 7)</th>
<th>Obese PCOS (n = 12)</th>
<th>Obese controls (n = 7)</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>After</td>
<td>Basal</td>
<td>After</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.49 ± 2.16</td>
<td>22.61 ± 2.09</td>
<td>22.13 ± 2.31</td>
<td>22.31 ± 2.01</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.82 ± 0.02</td>
<td>0.82 ± 0.03</td>
<td>0.74 ± 0.06d</td>
<td>0.73 ± 0.05</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>2.18 ± 0.62</td>
<td>2.25 ± 0.59</td>
<td>1.28 ± 0.45c</td>
<td>1.51 ± 0.53</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>7.50 ± 2.06</td>
<td>10.22 ± 3.66</td>
<td>3.91 ± 1.93d</td>
<td>4.79 ± 2.31</td>
</tr>
<tr>
<td>DHEAS (µmol/l)</td>
<td>4.53 ± 1.76</td>
<td>4.91 ± 2.50</td>
<td>3.76 ± 0.97</td>
<td>4.47 ± 1.69</td>
</tr>
<tr>
<td>17-OHP (nmol/l)</td>
<td>2.39 ± 0.76</td>
<td>2.45 ± 0.88</td>
<td>1.28 ± 0.54d</td>
<td>1.67 ± 0.91</td>
</tr>
<tr>
<td>SHBG (mmol/l)</td>
<td>45.18 ± 16.95</td>
<td>41.23 ± 17.61</td>
<td>43.51 ± 13.67</td>
<td>42.70 ± 15.95</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>9.23 ± 6.62</td>
<td>11.66 ± 5.99</td>
<td>6.75 ± 2.39</td>
<td>5.77 ± 3.81</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>4.65 ± 1.70</td>
<td>5.50 ± 2.11</td>
<td>6.51 ± 2.99</td>
<td>5.25 ± 1.14</td>
</tr>
</tbody>
</table>

SD. Statistical analysis between groups is not reported after acipimox treatment.

*a* < 0.05 versus lean and obese groups.

*p < 0.01 between lean and obese groups.

*p < 0.05 versus PCOS counterparts.

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PCOS = polycystic ovarian syndrome; DHEAS = dehydroepiandrosterone sulphate; 17-OHP = 17-hydroxyprogesterone; SHBG = sex hormone-binding globulin.

### Table II. Metabolic parameters and lipidic patterns of the studied groups before and after acipimox administration

<table>
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<tr>
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<th>Lean PCOS (n = 8)</th>
<th>Lean controls (n = 7)</th>
<th>Obese PCOS (n = 12)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>After</td>
<td>Basal</td>
<td>After</td>
</tr>
<tr>
<td>Fasting glucose (nmol/l)</td>
<td>4.21 ± 0.46</td>
<td>4.25 ± 0.43</td>
<td>4.49 ± 0.61</td>
<td>4.31 ± 0.67</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>63.00 ± 25.26</td>
<td>70.39 ± 23.39</td>
<td>57.43 ± 20.03</td>
<td>64.03 ± 29.17</td>
</tr>
<tr>
<td>Fasting C-peptide (pmol/l)</td>
<td>479.95 ± 225.08</td>
<td>516.36 ± 238.32</td>
<td>482.77 ± 205.19</td>
<td>573.45 ± 243.91</td>
</tr>
<tr>
<td>Growth hormone (µg/l)</td>
<td>2.31 ± 1.06</td>
<td>2.64 ± 1.58</td>
<td>2.31 ± 1.07</td>
<td>2.18 ± 1.36</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.11 ± 0.31</td>
<td>4.22 ± 0.42</td>
<td>4.06 ± 0.58</td>
<td>3.41 ± 0.35</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>92.14 ± 8.45</td>
<td>95.00 ± 13.22</td>
<td>85.31 ± 12.23</td>
<td>57.90 ± 11.54</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>57.71 ± 9.53</td>
<td>58.00 ± 9.78</td>
<td>65.17 ± 22.54</td>
<td>66.13 ± 22.17</td>
</tr>
<tr>
<td>vLDL (mg/dl)</td>
<td>12.38 ± 4.72</td>
<td>11.75 ± 3.41</td>
<td>11.81 ± 6.71</td>
<td>11.34 ± 2.73</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.68 ± 0.26</td>
<td>0.60 ± 0.27</td>
<td>0.69 ± 0.14</td>
<td>0.65 ± 0.17</td>
</tr>
<tr>
<td>FFA (mEq/l)</td>
<td>0.51 ± 0.41</td>
<td>0.63 ± 0.19</td>
<td>0.51 ± 0.26</td>
<td>0.62 ± 0.34</td>
</tr>
</tbody>
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n = number of patients. Data are expressed as mean ± SD. Statistical analysis between groups is not reported after acipimox treatment.

*p < 0.01 between lean and obese groups.

*p < 0.05 versus lean and obese groups.

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PCOS = polycystic ovarian syndrome; LDL = low-density lipoprotein; HDL = high-density lipoprotein; vLDL = very-low-density lipoprotein; FFA = free fatty acids.
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Figure 1. Glucose, insulin and C-peptide response to oral glucose load, expressed as area under the curve in the four studied groups before (□) and after (■) acipimox administration. All data are expressed as mean ± SD. Significance: a P < 0.01 versus lean polycystic ovarian syndrome (PCOS); b P < 0.05 versus lean controls.

Figure 2. Insulin-dependent glucose utilization (M) in the four studied groups before (□) and after (■) acipimox administration. All data are expressed as mean ± SD. Significance: a P < 0.05 versus lean counterparts; b P < 0.01 versus lean PCOS; c P < 0.02 versus lean controls.

administration of acipimox in any of the investigated groups. Thus it could be argued that the lack of effects on insulin is due to an inadequate dose of the anti-lipolytic compound.

Actually acipimox is effective in the suppression of lipolysis at a plasma concentration of 10^{-5} mol/l (Stirling et al., 1985) and it has been shown that oral administration of a single dose of 250 mg acipimox to humans produces a plasma concentration of acipimox of >10^{-5} mol/l for 6–8 h (Musatti et al., 1981). Therefore the chosen administration dose of 250 mg three times a day (every 8 h) should allow effective acipimox plasma levels during the greater part of the day. On the other hand, our data are in line with previous reports that showed unchanged (Saloranta et al., 1993a; Nam et al., 1996; Shih et al., 1997) or increased (Vaag and Beck-Nielsen, 1992; Saloranta et al., 1993b) fasting FFA levels after long-term treatment by acipimox.

Since FFA is the major energy source of the body, it can be speculated that, during FFA suppression, the body attempts to maintain energy production at a constant level by allowing FFA levels to increase. Thus the rebound rise in FFA concentrations (or the absence of any variation) could be theoretically due to a change in the sensitivity of the adipocyte to factors inhibiting lipolysis, as suggested by the finding of different sensitivity to the anti-lipolytic effect of acipimox during the insulin-dependent glucose utilization or the insulin response to oral glucose load in PCOS as well as in control subjects.

The basal FFA levels did not decrease after long-term administration of acipimox in any of the investigated groups. Thus it could be argued that the lack of effects on insulin is due to an inadequate dose of the anti-lipolytic compound.

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course of the day (Saloranta et al., 1993a). Alternatively, the fall in FFA could trigger the output of lipolytic hormones, such as glucagon, cortisol and GH, aimed at maintaining the FFA concentration unchanged. This last hypothesis is supported by the findings of increased levels of counter-regulatory hormones during long-term acipimox treatment (Fulcher et al., 1992c; Saloranta et al., 1993a).

In our series we evaluated GH levels, which remained unchanged after acipimox administration, thus arguing against a role of GH in explaining the lack of FFA fall after acipimox. However, one study (Saloranta et al., 1993a) showed increased GH levels after chronic acipimox administration at 03:00 and 06:00, whereas the same hormone levels were unchanged if evaluated at 08:00. It is possible that the time of blood sampling may have influenced our results, hiding a GH modification.

Our data are in line with previous reports, which similarly were not able to show modifications in the peripheral insulin resistance in NIDDM patients after long-term anti-lipolytic treatment (Vaaq and Beck-Nielsen 1992; Saloranta et al., 1993a,b). We are not aware of possible explanations in order to justify the different results shown in NIDDM subjects by other authors (Fulcher et al., 1992c; Paolisso et al., 1998), who reported a significant improvement in insulin action after a similar treatment. It is also possible that our ‘negative’ results could be due to an inadequacy in the sample size; indeed, the obtained 88% power calculation was a retrospective and not prospective measurement.

In our series, triglyceride, LDL and cholesterol levels were significantly reduced in the obese groups, irrespective of PCOS status, after the anti-lipolytic drug administration. Furthermore, a decrease in LDL and cholesterol levels was also found in lean controls after treatment. These data suggest an effect of acipimox on lipid profile, which is more pronounced in obese groups, while a clear difference between PCOS and control women was not highlighted.

Although fasting plasma FFA levels did not change from baseline levels after treatment, the modification of serum lipids suggests that FFA levels will have been lower at several times during the day; although this is probably not enough to effect insulin-mediated glucose disposal. Furthermore, we cannot exclude the possibility that acipimox not only influenced the appearance of FFA by inhibiting lipolysis, but also had an effect on FFA disappearance (oxidation and re-esterification) (Saloranta et al., 1993a), leading to modifications in the lipid metabolism at the hepatic level. Finally, the possibility of a direct effect of acipimox on lipids other than FFA should be considered.

In conclusion, our study indicated that acipimox therapy improves the lipoprotein profile, without changing insulin sensitivity, mainly in obese subjects, without clear differences between PCOS or control women. The use of this compound as an insulin-lowering drug does not seem to be supported in PCOS, even if it could be used in obese PCOS women as an additional therapeutic agent in order to ameliorate the atherogenic lipid profile of the syndrome.

References


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