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Effect of Rimonabant and Metformin on GIP and GLP-1 in Obese Women with Polycystic Ovary Syndrome.

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Effect of Rimonabant and Metformin on GIP and GLP-1 in Obese Women with Polycystic Ovary Syndrome.

Running title: Rimonabant and Metformin effects on Incretin Hormones in PCOS

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Rimonabant, a canabonoid receptor-1 blocker, has been shown to reduce weight, free androgen index (FAI) and insulin resistance in obese patients with polycystic ovary syndrome (PCOS) compared to metformin during a 12 week period 1. Subsequent treatment with metformin in these subjects for another three months maintained their weight loss with further improvement of the metabolic and biochemical parameters, compared to six months of metformin treatment alone2. Metformin's actions appear to be mediated by activation of AMP kinase activity protein kinase.

The incretin hormones, glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) have been reported to play an important role in not only insulin sensitivity, but also energy balance. Recently, exenatide, which shares similar glucoregulatory properties to GLP-1 has been reported to improve both FAI and insulin sensitivity in women with PCOS, through weight PCOS3. Therefore, we have aimed to determine whether rimonabant may potentially have an effect on the incretin system thereby augmenting its weight reduction effect.

Subjects and methods

A randomized open labelled parallel study of metformin and rimonabant for 12 weeks in 20 patients with PCOS with a body mass index (BMI) ≥30kg/m2 was undertaken followed by an extension arm with the addition of metformin for another 12 weeks2. All the patients who were on rimonabant were changed over to metformin 500mg three times daily for 3 months, whereas all the patients who were on metformin were continued on metformin for another 3 months.

The diagnosis of PCOS was based on all three diagnostic criteria of the Rotterdam consensus, namely clinical and biochemical evidence of

hyperandrogenemia (Ferriman-Gallwey score >8; free androgen index >8 respectively), oligomenorrhoea or amenorrhea and polycystic ovaries on transvaginal ultrasound.5 Subjects had no concurrent illness, were not on any medication for the preceding 6 months and were not planning to conceive. None of the patients had successful pregnancy or miscarriage at least 5 year prior to the study entry. Subjects were advised not to change their lifestyle including physical activity or dietary habits during the study period. Non-classical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease and androgen-secreting tumours were excluded by appropriate tests. All patients gave informed consent. The study was approved by the Hull and East Riding Local Research Ethics committee.

Clinical and biochemical assessments were performed at baseline, 12 weeks and 24 weeks. Blood samples were processed and analysed. GIP and GLP-1 were measured using ELISA methods (Linco Research, Missouri, USA) with an intra-assay CV of 7.3% at 4.2 pmol/L and 7% at 28 pmol/L respectively. Data are reported as mean ± SEM.

Statistical analyses were carried out using the paired t test. The biochemical data was normally distributed when tested using the Kolmogorov-Smirnov test. For all analysis, a two-tailed $P \leq 0.05$ was considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows NT, version 14.0 (SPSS Inc., Chicago, IL).

Results

All the 20 subjects completed the study. The compliance was 98% in both groups.

There was a significant increase in GIP levels after rimonabant treatment for 3 months (7.78±0.38 vs. 21.62±1.96 pmol/L p value–0.04) that decreased when changed over to metformin (21.62±1.96 vs. 8.94±0.4 pmol/L p value–0.08). There were no significant changes in GIP levels either at 3 months (6.88±0.28 vs. 6.08±0.2 pmol/L p value –0.23) or at 6 months (6.08±0.2 vs. 6.22±0.34 pmol/L p value–0.89) with metformin (Figure 1).

There were no significant changes in GLP-1 levels after rimonabant treatment for 3 months (18.6±0.9 vs. 21.4±1.2 pmol/L p value–0.42) and 6 months (21.4±1.2 vs. 21.6±0.9 pmol/L p value–0.92) or after metformin treatment at 3 months (22.2±1.5 vs. 21.0±1.4 pmol/L p value–0.72) and 6 months (21.0±1.4 vs. 19.6±1.8 pmol/L p value–0.54). There was no significant correlation between the increase in GIP and weight loss with rimonabant (r=0.12; p=0.89).

Discussion

This study showed a significant (and reversible) increase in GIP levels after 3 months of rimonabant treatment. There were no changes in either GLP-1 or GIP levels with metformin.

The increase in GIP levels could be due to rimonabant stimulating incretin hormones rather than secondary to weight loss since there was no correlation between weight loss and increase in GIP levels. However, this latter finding may simply be a consequence of the number of study participants.

Curiously, this study demonstrates that rimonabant affects GIP levels but not GLP – 1 in this group of obese patients with PCOS. GLP-1 is produced by L cells located mainly in the ileum and colon, and to a lesser extent by L cells in the duodenum and jejunum, whereas GIP is produced by K cells in the proximal gut4.

CB1 receptors are also present in the duodenum and jejunum and activation of CB1 receptors depresses gastro-intestinal motility by inhibiting contractile transmitter release. Moreover, CB1 receptor activation/agonists inhibit gastric emptying and intestinal transit, delays gastric emptying in humans and rodents and also inhibit gastric acid secretion5, functions that precisely mirror those of GIP. In conclusion therefore, it is likely that the increase in GIP by rimonabant in patients with PCOS may contribute to the metabolic changes found with the drug, but that the rise may simply be a compensatory response to maintain gastro-intestinal homeostasis.

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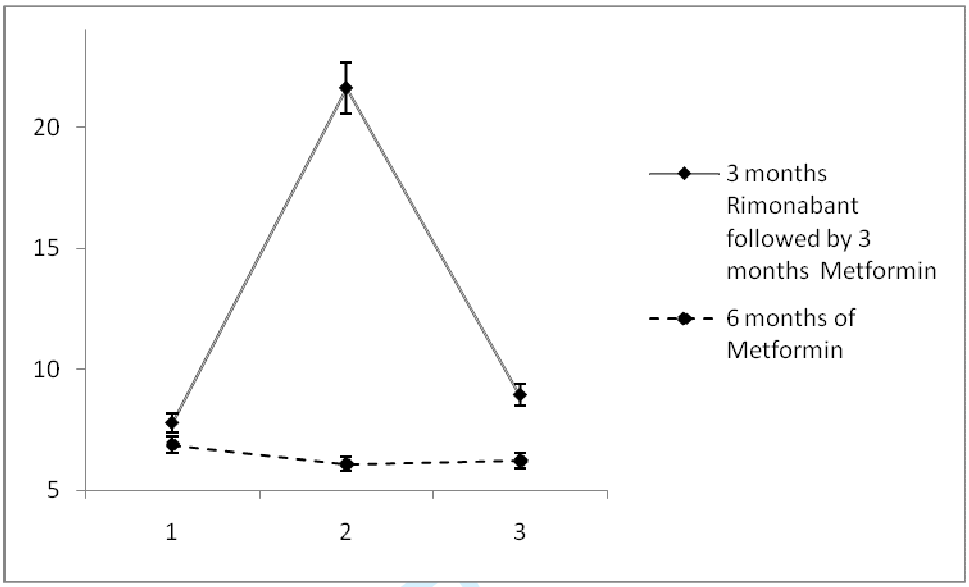
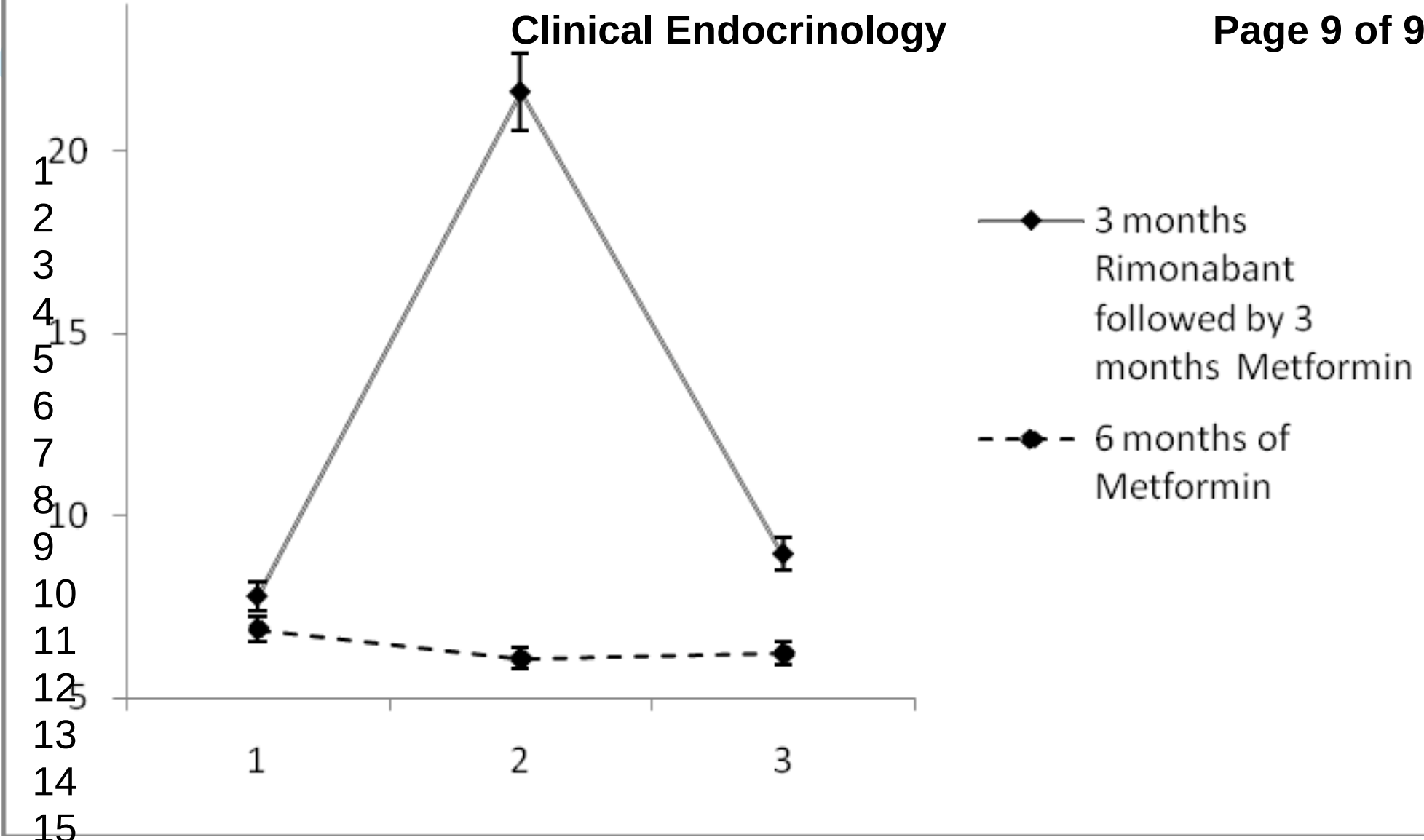
Figure 1

Glucose-dependent insulinotropic polypeptide (GIP) levels after 3 months of Rimonabant followed by 3 months of Metformin and after 3, 6 months of Metformin



X axis – visit 1, visit 2, visit 3

Y-axis – Glucose-dependent insulinotropic polypeptide in pmol/L


20
15
10
5
1
2
3
3 months Rimonabant followed by 3 months Metformin
6 months of Metformin