EFFECT OF METFORMIN HCl VERSUS CLOMIPHENE CITRATE ON CARBOHYDRATE METABOLISM IN POLYCYSTIC OVARIAN SYNDROME (PCOS)

MEMON Z, KARIM N, AHMED SP.* AND ANSARI MA.**

Department of Pharmacology, SMC, DUHS, Karachi
*Department of Pharmacology, Faculty of Pharmacy, University of Karachi
**Liaquat University of Medicine and Health Sciences, Jamshoro

ABSTRACT

Metformin HCl and clomiphene citrate are the two main drugs used for treating polycystic ovary syndrome (PCOS). To evaluate the effects of each of these two on the basic pathogenesis that is carbohydrate metabolism in PCOS a clinical trial was carried out on one hundred infertile PCOS patients with ages between 18-30 years. They were enrolled from the department of Gynaecology and Obstetrics Unit-III, Dow University of Health Sciences (DUHS), Karachi. Fifty patients were given tablet metformin HCl 500 mg thrice daily for four months (group I) while the other fifty patients were given tablet clomiphene citrate 50 mg-100 mg/day for 5 days following spontaneous or medroxyprogesterone acetate induced menstrual cycle (group II). Fasting serum glucose and fasting serum insulin was done at day-0 and day-120. In group I significant reduction was found in both these parameters. Fasting serum glucose reduced from 104.6±13.4 mg/dl at day-0 to 96.2±11.7 mg/dl at day-120. Fasting serum insulin reduced from 22.1±11.3 µU/ml at day-0 to 10.3±7.1µU/ml at day-120. In group II Fasting serum glucose showed a non-significant increase and fasting serum insulin showed non-significant decrease. In conclusion metformin HCl has exerted beneficial effects on the carbohydrate metabolism in comparison to clomiphene citrate.

Keywords: Metformin, Clomiphene citrate, polycystic ovary syndrome, carbohydrate metabolism, fasting serum glucose, fasting serum insulin.

INTRODUCTION

Polycystic ovary syndrome, also known clinically as stein leventhal syndrome, is an endocrine disorder that affects approximately 10% of all women (Gallagher, 2007). It occurs amongst all races and nationalities, is the most common hormonal disorder among women of reproductive age and is a leading cause of infertility (Goldenberg, 2008; Boomsma, 2008). The principal features are weight problems, lack of regular ovulation and or menstruation and excessive amounts or effects of androgenic hormones. Abnormality of insulin secretion and action has been implicated in the pathophysiology of PCOS women with PCOS having the constellation of symptoms, insulin resistance, obesity, hypertension and dyslipidemia, defining so called syndrome X (Hansen, 1999).

Insulin resistance has been defined as a state of a cell, tissue or organism in which a greater than normal amount of insulin is required to elicit a quantitatively normal response (Mantzoros et al., 1995). It leads to increase insulin secretion by β-cells and compensatory hyperinsulinemia. If β-cells compensatory response declines, relative or absolute insulin insufficiency develops. Both obese and nonobese women with PCOS seem to be more insulin resistant and hyper-insulinemic than age and weight matched normal women. Therefore women with PCOS have high risk for abnormalities of carbohydrate metabolism such as impaired
Effect of Metformin HCl versus Clomiphen Citrate

Effect of Metformin HCl versus Clomiphen Citrate 2 glucose tolerance (IGT) and NIDDM (Non-insulin dependent diabetes mellitus) (Ehrmann et al., 1999).

Metformin HCl is a biguanide anti-hyperglycemic agent which improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. It decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity. It does not produces hypoglycemia in either diabetic or non-diabetic subjects and does not cause hyperinsulinemia (Karim, 2005).

Clomiphen citrate is an orally active antiestrogenic substance that promotes the release of follicle stimulating hormone from the pituitary gland thus stimulating the development of ovarian follicles and ovulation (Clark, 1981).

MATERIALS AND METHODS

100 infertile females having PCOS were selected from the Gynaecology and Obstetrics Unit-III Dow University of Health Sciences (DUHS), Karachi. These were women of reproductive age group with ages between 18-30 years having infertility, oligomenorrhoea, obesity, hirsutism, fasting hyperinsulinemia. Consent of all patients were obtained and their preliminary data, follow up visits, laboratory investigations were recorded on a specially designed proforma.

Study Design

This study was a clinical trial done for a period of four months on each patient. Tablet metformin HCl 500 mg thrice daily was given for four months. It was started initially once a day for a week and increased gradually to twice a week and then finally to thrice a week in the third week. First two weeks are not included in the study period. Tablet clomiphen citrate 50 mg to 100 mg was given once per day for 5 day following spontaneous or medroxyprogesterone acetate induced menstrual cycle. Those who ovulated were kept on the same dose for next three cycles (total period 4 months). Those who did not ovulated were subjected to increase in dose 100 mg/day (two tablets per day) for the next 2 cycles (total period 4 months). For assessing effect on carbohydrate metabolism, fasting serum glucose and insulin were done at day-0 and day-120.

Analytical methods

a) Fasting serum glucose

Plasma glucose was determined by using Kit No.12194 Merck-Germany. It is based on the principle, that, glucose dehydrogenase catalyzes the oxidation of glucose as follows:

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\text{B-D-Glucose} \rightarrow \text{D. Gluconolactone} + \text{NADH + H}^{-}
\]

The quantity of NADH formed is proportional to glucose concentration.

Reagents:

- Enzyme mixture (Powder form) is dissolved in 250 ml of diluent provided with the kit. It is stable at +20°C to +8°C up to expiry date, after reconstitution.
- Diluent is deionized water, ready to use.

Procedure

- The sample tray of Selectra analyzer was loaded with the samples to be analyzed.
- Reconstituted reagent was placed in the reagent tray.
- The sample and reagent probes take the sample and reagent from respective trays and deliver in the reaction rotor.
- Results were displaced on the digital screen of the selectra monitor within 10 minutes.

b) Insulin assay

The serum insulin levels were measured by using IMX insulin reagent No. 2A 10-20 Abbott USA. The insulin assay is based on Microparticle Enzyme Immunoassay (MEIA) technology. IMX insulin reagent and sample is added to the reaction cell in the following sequence:
• The probe delivers the sample, anti-insulin coated microparticles and assay buffer to the incubation well of the reaction cell forming an antibody-insulin complex.
• An aliquot of the reaction mixture containing insulin bound to the anti-insulin antibodies is transferred to the glass fiber matrix.
• The matrix is washed to remove unbound material.
• The anti-insulin alkaline phosphate conjugate is dispersed on the matrix and binds to the antibody antigen complex.
• The matrix washed again to remove unbound material.
• The substrate, 4-methyl umbelliferyl phosphate is added to the matrix and MEIA optical assembly of IMX system measures fluorescent product.

**RESULTS**

In metformin treated group I both the parameters of carbohydrate metabolism fasting serum glucose and fasting serum insulin showed a significant decrease. Fasting serum glucose decreased from 104.6±13.4 mg/dl at day-0 to 96.2±11.7 mg/dl at day-120 while fasting serum insulin reduced from 22.1±11.3 𝜇U/ml at day-0 to 10.3±7.1 𝜇U/ml at day-120 (Table 1).

In clomiphene citrate treated group II fasting serum glucose increased from 109.4±13.9 mg/dl to 115.7±14.1 mg/dl at day-120. Fasting serum insulin showed a decrease from 21.7±11.1 𝜇U/ml at day-0 to 21.3±10.9 𝜇U/ml at day-120. Both results were non-significant on statistical evaluation (Table 2).

When comparing group I to group II the baseline day-0 values were almost similar to each other but at day-120 group I showed significant reduction while group II showed non-significant increase in fasting serum glucose level (Table 3).

As regards the comparison of fasting serum insulin between the two groups significant reduction was seen in group I whereas group II also showed reduction but this was found to be non-significant statistically (Table 4).

**DISCUSSION**

Polycystic ovary syndrome is one of the most common endocrinopathy of women of childbearing age (Goldenberg et al., 2005). Insulin resistance of the polycystic ovary syndrome appears to impart an increased risk of glucose intolerance, diabetes and lipid abnormalities and may enhance the development of macrovascular disease Ehrmann (2005). The cause of polycystic ovary syndrome is poorly understood and both the diagnosis and treatment of the disorder are controversial Zarwadski (1992); Rotterdam (2004) but insulin resistance and accompanying compensatory hyperinsulinemia are the key factors Dunaif (1989). It is typically characterized by irregular menses, androgen excess and polycystic appearing ovaries. The condition is associated with insulin resistance and obesity. Insulin resistance leads to hyperinsulinemia as pancreatic insulin rises to maintain normoglycaemia. This in turn alters carbohydrate, lipoprotein and cholesterol metabolism and steroid hormone metabolism Ibanez et al. (2001).

In our study fasting serum glucose level reduced significantly from 104.6±13.4 mg/dl to 96.2 mg/dl in group I. This is coinciding with the study of Morin-Papunen et al. (2000). In his study fasting serum glucose level reduced significantly from 5.2±0.1 mmol/L to 4.9±0.1 mmol/L after 3 months of metformin therapy. Kolodziejczyk (2000) found non-significant reduction in fasting serum glucose level after 12 weeks of metformin therapy which is not coinciding with our study. Fasting serum insulin level in group I also showed a significant reduction from 22.1±11.3 𝜇U/ml at day-0 to 10.3±7.1 𝜇U/ml at day-120.
This is coinciding with the studies of Nestler (1996) and Kolodziejczyk (2000).

As regards the fasting serum glucose and fasting serum insulin levels in group II clomiphene citrate treated group non significant results were found. This is probably because clomiphene citrate is basically an antiestrogen which has effect on follicle growth. It does not address the underlying abnormalities in the polycystic ovary syndrome including hyperinsulinemia and hyperandrogenism Guzick (2007).

**CONCLUSION**

Our study has clearly shown that insulin sensitizing agent metformin HCl has exerted beneficial effects on the carbohydrate metabolism in comparison to clomiphene citrate.

**REFERENCES**


