# SERUM PROLACTIN LEVELS DURING INHIBITION OF LACTATION BY CYCLOFENIL

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SUMMARY

Inhibition of lactation is now usually achieved by the use of dopaminergic or antiserotoninergic drugs. An interesting, alternative approach, however, is represented by the use of antiestrogenic agents, though their mechanism of action is still uncertain. We have given cyclofenil at daily doses of 1200, 800 and 600 mg to a total of 100 post-partum women who required not to lactate. The clinical results were excellent or good in 83 women, fair in 9 and poor in 8. After 3, 5, and 7 davs of treatment serum prolactin levels of treated women, if compared with those of control group, showed a decrease ranging from 25 to 27%, from 42 to 44%, and from 60 to 64% respectively. Blood coagulation, as judged by several laboratory parameters, did not show abnormal changes in any subject treated with cyclofenil.

Inhibition of puerperal lactation can now be effectively achieved by means of dopaminergic ([1, 2]) or antiserotoninergic ([3, 4]) drugs, which apparently act through a reduction of serum levels of prolactin. Exogenous estrogens, which have been used for many years in this indication, and act directly on the mammary gland without interfering with prolactin levels, are being gradually abandoned because of their inconsistent effects, the drawback of withdrawal uterine bleedings and mainly the thromboembolic risks associated with their administration. An alternative approach to inhibition of lactation has been provided by Zuckerman ([5]) and Shaaban ([6]), who have successfully used antiestrogenic agents such as clomiphene and tamoxifen. Masala ([7]) has observed that tamoxifen administration reduces prolactin level in puerperal women. Canales ([8]) reports no effect on prolactin plasmatic levels in puerperal lactation by clomiphene, which, nevertheless, induces a marked inhibition of lactation. The mechanism of action of these substances, however, has not been elucidated; antiestrogens might exert their action either at a peripheral level, like estrogens, or centrally, i.e. by lowering serum prolactin concentrations ([9]). We deemed it of interest, therefore, to assess the lactation preventing effect of another antiestrogen, cyclofenil, and to explore at the same time its influence on serum prolactin levels.

## MATERIAL AND METHODS

A total of 100 consenting puerperal women, who were unable or unwilling to breast feed, were given orally cyclofenil at three different daily doses, in a duble blind trial, as follows:

Group A (50 women): 400 mg t.i.d. (1200 mg daily)

Group B (40 women): 400 mg b.i.d. (800 mg daily)

Group C (10 women): 200 mg t.i.d. (600 mg daily)

Ten further women, who received inert tablets, served as controls. The treatments started within 36 hours from delivery and lasted 7 days.

Table 1. — *Comparative clinical efficacy of different daily dosages of cyclofenil in the inhibition of lactation.*

| Treatment group | N. of women | Index of clinical efficacy | | | |
|---|---|---|---|---|---|
| | | 0 excellent | 1 good | 2 fair | 3-4 poor |
| A (1200 mg/day) . . . . . | 50 | 26 | 15 | 6 | 3 |
| B (800 mg/day) . . . . . | 40 | 24 | 10 | 2 | 4 |
| C (600 mg/day) . . . . . | 10 | 4 | 4 | 1 | 1 |
| Control . . . . . | 10 | — | — | 2 | 8 |

Clinical response was measured by scoring both milk secretion and breast engorgement according to the following scale: 0 = none, 1 = moderate, 2 = marked. The two scores of each patient were then summed up to give an index of clinical efficacy, ranging from 0 (excellent) to 4 (poor).

Serum prolactin levels were determined in all subjects before and 3, 5 and 7 days after the beginning of treatment. Prolactin was measured by radioimmunoassay ([10]) using a Biodata Kit (Serono); the standard was calibrated against international standard WHO 71/222. The sensitivity is of 1.5 ng/ml. The following parameters of blood coagulation were also measured at baseline and at the seventh day of treatment: Quick test, plasma prothrombin, thromboelastogram, platelet aggregation.

## RESULTS

The clinical responses of treated and control patients, as measured by summed scores of milk secretion and breast engorgement, are shown in Table 1. As can be seen, excellent or good results were achieved in 83 women out of 100 treated with cyclofenil; there was a trend toward a better outcome in the higher dosage groups (800 and 1200 mg daily).

Serum prolactin levels are reported in Table 2. Statistical analysis by Student's test failed to show significant differences between the basal values of each treated group and control women. Treatment with cyclofenil (at all daily doses) was associated with a progressive decrease in prolactin levels. A decrease was also apparent in control group, though of a lesser degree. If compared with the appropriate values of the control group, those observed in group A on the 3rd, 5th and 7th day were reduced by 26.5%, 43% and 60% respectively. The corresponding decreases in group B were of 27.4%, 43.7% and 64%, and those in group C of 25%, 42% and 62%. The differences from control group were always statistically significant ($P < 0.001$) while there were no significant differences among the treated group at any time.

As far as blood coagulation is concerned, the variables explored did not differ

Table 2. — *Mean serum levels of prolactin ± S.D. (ng/ml).*

| Treatment group | Baseline | Day 3 | Day 5 | Day 7 |
|---|---|---|---|---|
| A | 141±26 | 86±13* | 54±14* | 34±10* |
| B | 149±29 | 85±15* | 53±14* | 30±12* |
| C | 138±23 | 88±16* | 55±13* | 32±9* |
| Control | 150±12 | 117±18 | 94±17 | 84±23 |

* $p < 0.001$ versus correspondent values of control group.

in cyclofenil-treated women in respect of control women, and in no case abnormal values were found.

## DISCUSSION

The present findings show that cyclofenil can inhibit milk secretion and breast engorgement in a high proportion of women. There were only eight failures in a total of 100 patients. Inhibition of lactation, however, was eventually achieved also in these eight subjects by continuing the treatment for a further week. Besides being effective, cyclofenil appeared also to be safe inasmuch as no adverse reactions were observed.

Ciclophenil induces a good inhibition of lactation and the clinical result is similar to that obtained with clomiphene and tamoxifen. Conflicting results are reported on action of antiestrogens on PRL secretion ([5, 6, 7, 8]). Kaiser ([11]) and Dewhurst ([12]) have reported that clomiphene decrease PRL secretion in Chiari-Frommel syndrome, while according to Zuckermann ([5]), Weinstein ([13]) and Casale ([8]), clomiphene does not modify PRL plasma level. Willis ([14]) and Jordan ([15]) have evidenced that in women with breast cancer tamoxifen reduces prolactin levels and inhibits PRL release after TRH stimulation.

Masala ([7]) has observed that tamoxifen considerally reduces PRL level in puerperal women and reduces the response to TRH stimulation.

We observed a reduction of PRL level on 3rd - 5th - 7th day of treatment: comparing these results to the values obtained on the same days in controls, it seems likely that cyclofenil acts directly on PRL.

It is worthwhile to underline that there is not a statistically significant difference in PRL plasmatic reductions and in clinical response obtained in the groups treated with the lowest and the highest dose of cyclofenil.

These results support the hypothesis that cyclofenil can act by decreasing PRL secretion.

Recently Gorin observed that stimulation with TRH in males treated with tamoxifen gives a reduction of PRL release. Masala ([7, 16]) supports that tamoxifen and clomiphene act by inhibiting lactogenic action of PRL but this does not justify the decrease of PRL level observed on 5th day of treatments. This reduction is concordant with the results we have observed on 3rd - 5th - 7th day of treatment with cyclofenil.

The mechanism of action of cyclofenil in inhibiting lactation is unclear. We may presume, however, as suggested by Shaaban ([6]) for tamoxifen, that a mode of action other than a peripheral mechanism is involved. Indeed, the significantly greater decrease in prolactin levels observed in cyclofenil-treated women than in control women indicates that this agent might act upon prolactin release. Cyclofenil might exert its action at the hypothalamic hypophyseal level by blocking the specific estrogen receptors and inducing by this way a partial inhibition of prolactin secretion ([9]). To prove or disprove this hypothesis, however, further and more in-depth studies will be necessary.

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