INHIBITION OF OVULATION WITH DOPAMIN-ANTAGONISTS

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Abstract

Analysing the results of the Motilium treatment of women in reproductive age different internal medical diseases, the authors discuss the possibility of a new kind of nonhormonal ovulation-inhibitory anticonception. Domperidon preparation have been used as antiemetic and for induction of lactation. This agent increases the seruM prolactin level in early pregnancy, in puerperas and menopause. The results of endocrinologic study of the 3 women treated for gastrointestinal complaints with 3 x 10 mg domperidon are discussed. The analysis of the protein and steroid hormon values determined during treatment, as well as the basal temperature curves indicated anovulatory menstruation. In the authors opinion treatment with dopamine antagonists with subsequent elevation of prolactin level makes the ovulation-inhibitory oral contraceptives unnecessary. They expect that dopamine antagonists will substitute hormonal contraceptives and eliminate the undesirable side-effects of the latter. Cessation of treatment quickly reverses the effect, indicating the reversible character of the increase of prolactin level. The authors also assume that dopamine antagonists will substitute high-dose progesterone presently used for postcoital contraception. Precoital treatment with dopamine antagonists abolishes or postpones ovulation.

Key words: prolactin, dopamine antagonists, hormonal inhibition of ovulation.

Introduction

Combined oral contraceptive tablets introduced more than three decades ago were supposed to solve the problem of birth regulation. However the agents with high level of active substances damaged not only the reproductive system, but also the whole organism.

The use of hormonal contraceptive tablets frequently elicited infertility or damages of the cycle by affecting the endometrial structures or inducing hyperprolactinemia (BROUWERS et al., 1980).

Taking oral contraceptive tablets is a serious risk factor in family planning. Furthermore these tablets also lead to the developement of vascular diseases (COBRIN et al., 1985).

Several new aspects of contraception providing better family planning in future came up.

The Motilium preparation produced by the Richter Pharmacological Works contains 10 mg domperidon and is used as antiemetic and lactation-inducing drug. This drug was found to elevate the serum prolactin level in pregnants, puerperas and women in menopause (FARKAS, 1989; FARKAS et al., 1989).

Can domperidon as a dopamin inhibitor which elevates the serum prolactin level inhibit the ovulation in the physiological cycle?

If the answer is positive, then taking the dopamine inhibitors makes oral contraceptives unnecessary and even deleterious. The wide use of these drugs is expected in neurology and internal medicine.

Pharmacological and biological effects of domperidon

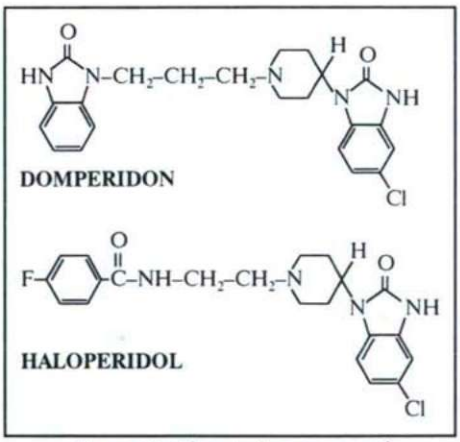

Figure 1. Chemical structure of domperidon and haloperidol.

Chemical structure of domperidon is similar to that of neuroleptics (Fig. 1.). It also elevates the serum prolactin level but does not penetrate via the blood brain barrier. In rare cases this agent induces mastodynia or galactorrhea.

Cessation of treatment with this substance normalizes the serum prolactin level.

Domperidon is a new antidopamine preparation. It stimulates prolactin secretion in hypophysis independently of the applied dose. The domperidon-induced prolactin secretion is higher in luteal than in follicular phase of a normal cycle. It can interfer with the menstrual cycle, but does not affect the fertility in males.

Metoclopramid inhibits both the periferal and the central dopaminreceptors. Following treatment with both agents, there was a 10-fold increase in serum prolactin level. Long-time metoclopramid treatment further elevates the prolactin values (a 25-fold increase), while long-term taking of omperidon decrease the serum

prolactin level below the normal values (a 6-fold decrease) (BROUWERS et al., 1980.).

Dopamine itself is a prolactin-inhibiting factor (PIF). Special very short tubero-infundibular dopaminergic neurons (TIDA) have been found in the vicinity of eminentia mediana (FUXE, 1964).

Somatropine and prolactin have a definite rhythm. The question arises whether it is a real endogenous rhythm?

There is a close relationship between the secretion of these hormones and periods of sleep. Somatotropin secretion is elevated in the early phase of sleep (during the first two hours) and is followed by a marked increase of its serum concentration. By the third hour the concentration of this hormon decreases to 0.

The prolactin rhythm differs from that of somatotropin, for the prolactin level reaches its maximal values by the end of the sleeping period. The oscillation amplitude for somatotropin is about 5 units and for prolactin 1 unit (WISSER and BREUER, 1981).

Materials and methods

We have treated three women of reproductive age for gastrointestinal symptoms (emesis, nausea) and disturbances of gastric motility with daily 3 tables of domperidon (3 x 10 mg). Their first mentsruation occured at the age of 13–14. All the patients were 20–37 years old. They menstruated every 28 days for 4–5 days. One patient have already had 2 children, the rest have not yet been pregnant, but had stable cycle. Thus their fertility can also be considered as a proved. Neither patient took contraceptive drugs, all of them used biological methods.

Fasted venous blood samples have been taken on the day 6 before-, and days 9, 14 and 22 during treatment. Following centrifugation, the serum was stored at -20C°.

Prolactin, FSH, LH and 17-beta-oestradiol levels were determined with RIA (IZINTA MTA KITT).

During the period of treatment all the patients had normal sexual life and did not use contraceptive drugs. During the cycle they measured their basal temperature and plotted temperature curves.

We compared the results of domperidon treatment to those following treatment with three-phasic TRI-REGOL tablets, because the new substance contains less oestrogen.

Results

Compared to the controls, the serum prolactin values on the 22nd day of the cycle were elevated in all three patients. In 2 cases these values exceeded 500 mIU/l (Fig. 2.).

In one case the FSH level increased from 5,3 IU/l to 14,7 IU/l by the 22nd day of the cycle. In two other cases its values remained around 10 IU/l both in the follicular and luteal phases (Fig. 3.).

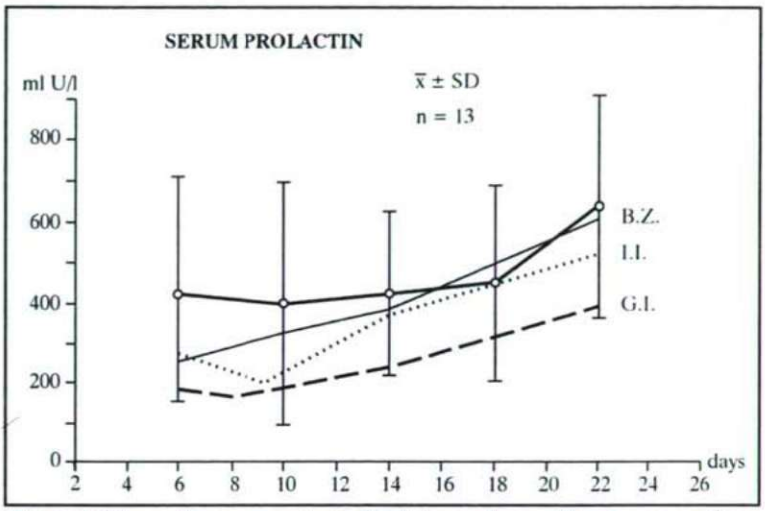

Figure 2. Change in serum prolactin level due to domperidon treatment from day 6 until day 22 of the cycle (n=3). (Before TRI-REGOL treatment x +/-SD, n=13)

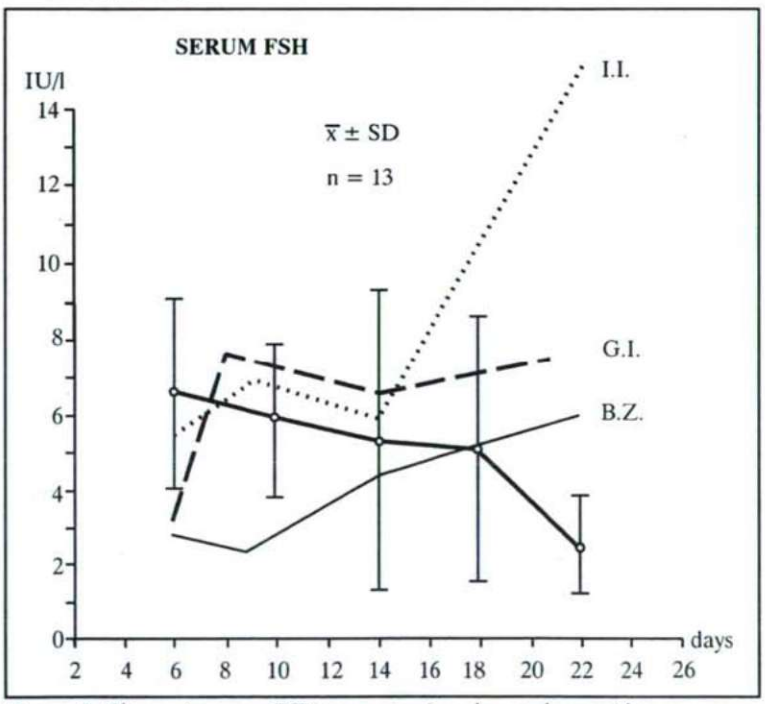

Figure 3. Change in serum FSH concentration due to domperidon treatment from day 6 until day 22 of the cycle. (n=3) (Before TRI-REGOL treatment x +/-SD, n=13)

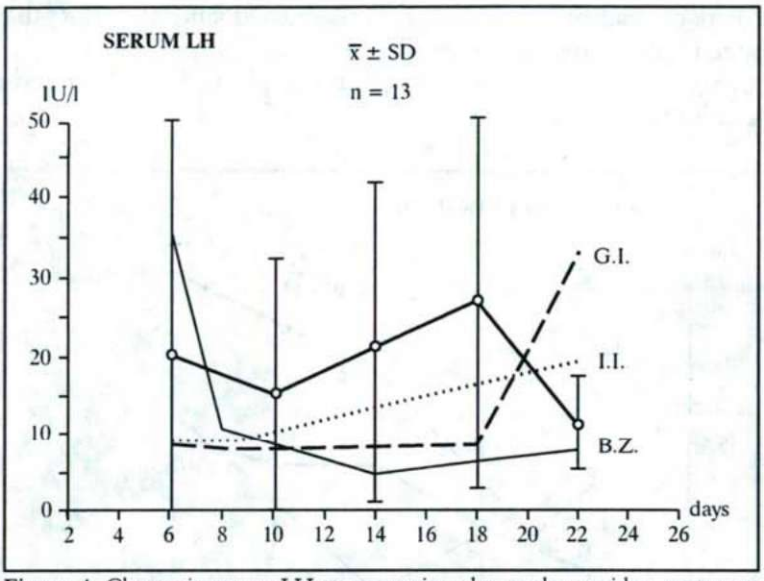

Figure 4. Change in serum LH concentration due to domperidon treatment from day 6 until day 22 of the cycle. (n=3). (Before TRI-REGOL treatment x +/-SD, n=13)

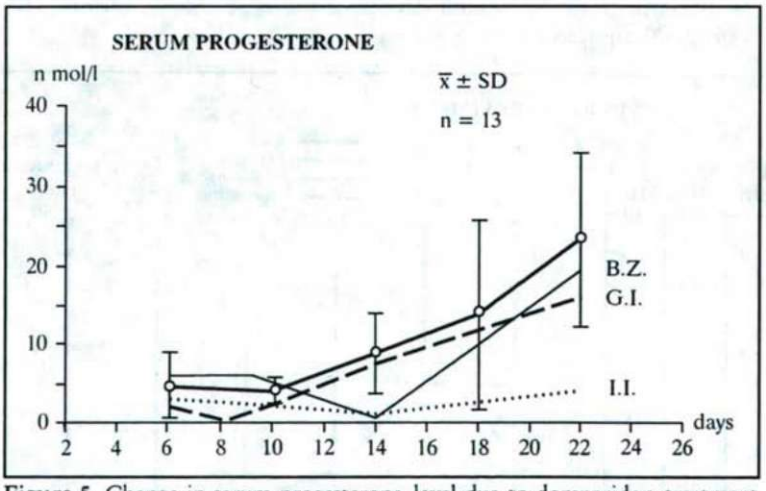

Figure 5. Change in serum progesterone level due to domperidon treatment from day 6 until day 22 of the cycle. (n=3). (Before TRI-REGOL treatment x +/-SD, n=13)

There was a lack of LH-peakat on the 14th day, however in 2 patients its concentration by the 22nd day exceeded the levels detected before treatment (Fig. 4.).

The 17-beta-oestradiol level markedly decreased and did not show typical „double-peaked" physiological curve (Fig. 5.).

Serum progesteron level remained within the physiological range both in the follicular and luteal period (Fig. 6.)

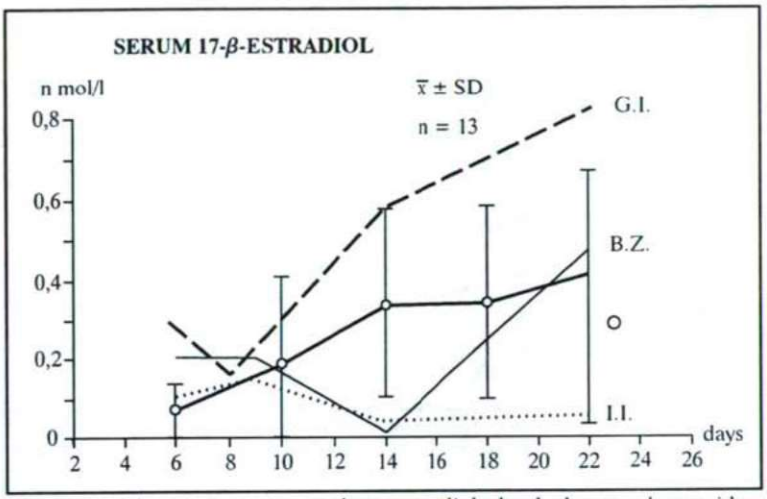

Figure 6. Change in serum 17-beta-oestradiol level due to domperidon treatment from day 6 until day 22 of the cycle. (n=3). (Before TRI-REGOL treatment x +/-SD, n=13)

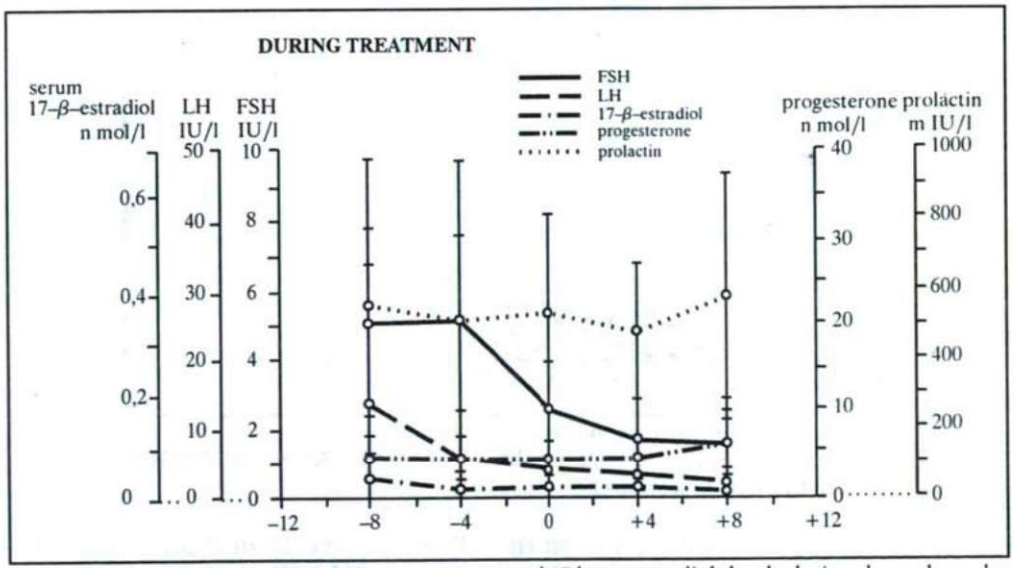

Figure 7. Serum prolactin, FSH, LH, progesterone and 17-beta-oestradiol levels during the cycle under TRI-REGOL treatment (x+/- SD, n=13).

Serum prolactin, FSH, LH, progesterone and 17-beta-oestradiol levels during the cycle under TRI-REGOL treatment (x +/-SD, n=13) (Fig. 7.).

The basic temperature curve of the patients was monophasic, typical of unovulatory cycles. Pregnancy occured in none of the cases and the menstruation cycle was restored.

Discussion

Female hypothalamic-hypophyseal regulation occurs at two levels. The lower level is regulated by the releasing factors and is known in literature as a tonic mechanism (FLERKO, 1962). Neural cyclic regulation is considered as an upper level. Szontágh (1976) found that lower progesteron levels affect the cyclic mechanism by inhibiting the releasing factor thus leading to a transient infertility.

Prolactin release is inhibited by hypothalamic dopamine. Some literary data indicate that prolactin regulates its release not only at the hypothalamic, but also at the hypohyseal level. That means that prolactin inhibits the hormon secreting activitiy of the hypophyseal lactotropic cells (HERBERT et al., 1979).

Domperidon as a dopamin inhibitor enhances prolactin secretion. The serum prolactin values become higher at the luteal phase of the ovulation cycle, compared to the follicular stage. Treatment with biphasic contraceptive tablets (Anteovin) fails to show such difference between the stages of the cycle, however the mean prolactin values were significantly lower, than in control cycles (FARKAS, 1988; FARKAS et al., 1986). Sas (SAS and FARKAS, 1979) showed that the luteal progesteron release is markedly lower, if plasma prolactin level is inhibited by bromocryptin to the values below 3 ng/ml (1 ng/ml = 32.5 IU/l). It seems that under physiological conditions prolactin plays no important role in ovulation. However if prolactin concentration is increased by domperidon or lowered below a certain level by bromocryptin, anovulation occurs. A further increase of concentration of the active substance not elevate the prolactin level. The effect will quickly reverse after cessation of treatment, indicating the reversibility of the increased prolactin level (FARKAS et al., 1989).

Treatment started from the 6th day of the cycle with 30 mg/day domperidon would abolish the LH peak typical of the ovulation. Pregnancy did not occur. Our patients had regular menstruation in regular time.

Despite the fact that our study has been performed only on 3 patients, we could clearly indicate that domperidon treatment elevates the serum prolactin level, abolishes the LH-peak and induces anovulatory menstruation. To clarify the anovulatory mechanisms elicited by dopamin inhibitor, further collection of data, wider clinical and laboratory studies are necessary.

Our data indicate that in women of reproductive age treated for gastrointestinal complaints with domperidon, oral anticonception becomes unnecessary. We expect that introduction of dopamine antagonists instead of hormonal anticonceptives woul overcome the pathological side-effects elicited by the latter on the reproductive system and the whole organism. Other dopamine antagonists substances could possibly solve the problem of postcoital anticonception, substituting the high doses of progesteron. Our results in this field will be published later.

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