TIAPRIDE-INDUCED CHRONIC HYPERPROLACTINAEMIA: INTERFERENCE WITH THE HUMAN MENSTRUAL CYCLE

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ABSTRACT

Four regularly menstruating volunteers were submitted to an oral treatment, for 3 consecutive cycles and starting on the first day of a cycle, with tiapride at daily doses ranging from 1 \times \text{100 mg} to 2 \times \text{100 mg}. The first and the last cycle under treatment, as well as a prior control cycle, were thoroughly studied by means of daily measurements of blood concentrations of LH, FSH, prolactin (PRL), oestradiol and progesterone. Tiapride, a benzamide derivative with dopaminergic blocking activity at the level of the lactotrophes, increased mean PRL secretion in each subject but a permanent hyperprolactinaemia above 700 \text{U/ml} was attained only in one subject.

Despite these widely fluctuating PRL levels in most subjects, the resulting overall hyperprolactinaemia induced in all cases a progressive deterioration of the function of the corpus luteum: 5 cycles showed luteal phases reduced by 2–5 days, one cycle was characterized by some slight luteinisation but questionable ovulation and the 2 remaining cycles were anovulatory. The interruption of drug intake one week after the onset of menses led thereafter to a cycle with a likely inadequate luteal phase but of normal length. It is concluded that even a non-permanent hyperprolactinaemia can impair the normal function of the hypothalamo-pituitary-ovarian axis, as well as exhibit some effects in a cycle consecutive to the normalization of PRL.

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Part of this work has been presented in 1976 at the 6th International Seminar on Reproductive Physiology and Sexual Endocrinology (L’Hermite et al. 1977).}
With the exception of the impaired luteal progesterone secretion, the pooled hormonal data from the short luteal phase cycles under tiapride-induced hyperprolactinaemia exhibit very little significant differences, as compared to the corresponding values in the control cycles. Some delay in the onset of follicular maturation, however, should be assumed since the follicular phase had been lengthened by 1 to 31 days in 5 of the 6 cycles with luteinisation during treatment. The present results are compatible with a double impact – both at the ovarian and the hypothalamo-pituitary levels – of hyperprolactinaemia in its mechanisms of impaired function of the hypothalamo-pituitary ovarian axis.

Numerous psychotropic drugs which stimulate prolactin (PRL) secretion are capable of interfering with reproductive processes (De Wied 1967; L’Hermite et al. 1978c). Earlier experiments conducted by giving orally sulpiride to normal female volunteers indicated that this drug, probably through the resulting hyperprolactinaemia, might induce some deterioration of the human corpus luteum function (Delvoye et al. 1974; Robyn et al. 1976).

Tiapride, a substituted benzamide drug related to sulpiride, has been shown previously (L’Hermite et al. 1978c) to promote systemically long-lasting elevations of PRL concentrations without affecting acutely LH and FSH levels, similarly to sulpiride (L’Hermite et al. 1978b) but in opposition to pimozide (Collu et al. 1975). Although all three compounds block the dopaminergic receptors located on the pituitary lactotrophes, resulting in increased PRL release (MacLeod & Robyn 1977; L’Hermite et al. 1978c; Debeljuk et al. 1978), they are not similar with respect to their activity on the other dopaminergic systems of the brain (Puech et al. 1978); it appeared also that substituted benzamide drugs, in opposition to classical neuroleptics, act on cerebral dopaminergic receptors which are independent of adenylyl cyclase activity (Jenner et al. 1978). The inhibition of the midcycle gonadotrophins peak in women treated with pimozide, as reported by Leppäluoto et al. (1976), cannot be attributed to hyperprolactinaemia since pimozide itself significantly inhibits in vitro the gonadotrophins response to LRH of cultured dispersed rat anterior pituitary cells (Debeljuk et al. 1978); on the contrary, the benzamide compound, sulpiride, exhibited no such effect on both basal and LRH-stimulated levels (Debeljuk et al. 1978). Since substituted benzamides (especially tiapride and sulpiride) seem to exert their activity upon the hypothalamus via increased prolactin concentrations (Portaleone et al. 1978a, b), their use appears to provide the investigator an ideal model of drug-induced hyperprolactinaemia.

In the present study, the endocrine perturbations induced by tiapride administration, resulting in varying degree of hyperprolactinaemia, were investigated in four previously regularly menstruating women orally treated for 3 consecutive cycles with daily doses of 100–200 mg of tiapride.
METHODS

Four regularly menstruating women (20-40 years old) volunteered for an oral treatment with tiapride (Tiapridal®; Delagrange, Paris) during 3 cycles, starting on the first day of a cycle. Subjects No. 1 and 3 took 2 x 100 mg per day, subject No. 2 took only 100 mg once in the evening while subject No. 4 received 3 x 50 mg daily.

Blood samples were collected daily between 10.00 and 16.00 during the first and the third cycle under treatment, as well as during a control menstrual cycle, which was immediately preceding the experiment in 2 of the 4 cases. In one volunteer, in whom the second cycle under treatment lasted much longer than normally, drug intake was interrupted after a period of time equivalent to 3 cycles; blood samples were therefore still collected until the next menstruation.

All samples were assayed for their LH, FSH, PRL, oestradiol and progesterone concentrations by specific radioimmunoassays under non-equilibrium double-antibody conditions, as previously described (L’Hermite & Midgley 1971; Robyn et al. 1971).

Gonadotrophins results were expressed by reference to the 2nd I.R.P. of hMG; PRL results were given in terms of µU per ml of the research standard 71/222 distributed by the M.R.C. (Division of Biological Standards and Control, Holly Hill, London, England). For the PRL RIA, anti-human PRL serum V.L.S. No. 3 (distributed by the N.I.A.M.D.D., N.I.H.H, Bethesda, Md., USA) and highly purified human pituitary PRL 207-38-1 (generously given by Dr. U. J. Lewis, La Jolla, Ca., USA) for labelling were used; a pool of sera collected from women in the immediate post-partum period served as a laboratory standard in each assay. According to the experimental conditions utilized, 1.0 mg of the V.L.S. No. 2 human pituitary PRL was found to be equivalent to 22 µU of the 71/222 standard.

Steroids RIAs, after prior ether extraction, used specific antisera (anti-oestradiol no 3341 and anti-progesterone no 3865, obtained from Roussel, UCLAf, France) in combination with tritiated labelled steroids ([6,7-3H(N)] oestradiol-17β and [1,2-3H(N)] progesterone, both purchased from N.E.N., Boston, Mass., USA).

All statistical analysis were conducted after logarithmic transformation of the data; Student’s t-test or variance analysis were used as appropriate.

RESULTS

The individual hormonal patterns of each subject are depicted in Figs. 1-4: furthermore, Table 1 gives several major parameters of the control as well as of the experiment cycles. It should be noted that subject No. 2, though menstruating quite regularly, exhibited a short luteal phase (as calculated from the LH peak to the onset of the next menstrual period) already in her control cycle.

Tiapride administration resulted in each case in more or less marked elevations of serum PRL levels: mean PRL levels during treatment were always significantly (see Table 1) greater than during the corresponding control cycle; mean PRL levels were 5.1 and 5.3 times control levels in the 2 subjects receiving 2 x 100 mg of tiapride, 3.2 times control level in subject No. 4 taking 3 x 50 mg of tiapride, and only 1.4 times control level in subject No. 2 who took only 100 mg once a day. As was planned in the protocol, no hormonal data
### Table 1.
Analysis of several major parameters of the control and treatment cycles.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Duration of cycle (duration of luteal phase) Days</th>
<th>Mean PRL levels μU 71/222 per ml</th>
<th>Peak(^2) oestradiol level in the follicular phase pg/ml</th>
<th>Peak progesterone level in the luteal phase ng/ml</th>
<th>Schedule of daily drug intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>27</td>
<td>28</td>
<td>53</td>
<td>8 + 28(^1)</td>
<td>404</td>
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<tr>
<td>2</td>
<td>26</td>
<td>29</td>
<td>25</td>
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<tr>
<td>4</td>
<td>28</td>
<td>25</td>
<td>30</td>
<td>22</td>
<td>276</td>
</tr>
</tbody>
</table>

C = control cycle; T = treatment period; 1, 2 and 3 indicate the experimental cycles and their order.

? means that no data were available because blood sampling had not been performed.

1\(^1\) after interruption of tiapride administration.

2\(^2\) peak value may have been missed due to the less frequent sampling schedule.

3\(^3\) peak level considered as the maximal oestradiol value, provided that it is followed by a gonadotrophin peak within the next few days.

\(* = P < 0.01 \text{ and } *** = P < 0.001, \text{ as compared by } t\)-test to control values.

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were available during the second treatment cycle, except for subject No. 2 in whom this second cycle lasted for 53 days. There was no significant difference with respect to mean PRL levels between the first and the third treatment cycle of each of the subjects No. 2-4; however, mean PRL levels of subject No. 1 were significantly \( t = 3.63; P < 0.001 \) lower during the first treatment cycle than during the remaining period of treatment. As can be seen from Figs. 1-4, individual PRL levels fluctuated more or less from day to day and a permanent hyperprolactinaemia – i.e. PRL levels regularly above 700 µU/ml – was reached during tiapride administration only in subject No. 1. On the other hand, most PRL values were still below this upper limit of the normal range in subject No. 2, who received only 100 mg of tiapride once a day. After treatment interruption, PRL levels went back towards normal values within 48 h (subject No. 1, Fig. 1).

Tiapride treatment resulted in all cases in some perturbation of the menstrual cycle, which became more profound with the continuation of treatment (Table 1). Thus, the luteal phase was reduced by 2-4 days in all cases during the first treatment cycle; the luteal phases lasted only 7 to 11 days and the maximal

![Fig. 1](https://example.com/figure1.png)

Development of LH, FSH, PRL, oestradiol (OE) and progesterone (P) levels during a control cycle as well as during and after a period of oral administration of tiapride \( (2 \times 100 \text{ mg daily}) \) in subject No. 1. The onset of each menstruation is indicated by a vertical interrupted line. The number of the case appears in a square box at the upper left. The period of drug administration is delineated by a horizontal black bar. The numbers of the x axis mark the number of days, starting at the onset of the control cycle.
Fig. 2.
Development of LH, FSH, PRL, oestradiol (OE) and progesterone (P) levels during a control cycle (not immediately preceding the experiment) as well as during 3 consecutive cycles under oral administration of tiapride (1 x 100 mg daily) in subject No. 2. The numbers at the x axis mark the number of days, starting at the onset of, respectively, the control and the experiment cycles. For explanation of other symbols, see legend to Fig. 1.

progesterone levels were reduced more or less considerably. The length of the follicular phase was unchanged in subject No. 4 but became on the contrary longer than in the corresponding control cycle in the other subjects. Nevertheless, there was no systematic impairment of the oestradiol peak, which was even greater than in the control cycle for 3 out of the 4 cases.

After this first treatment cycle, the second cycle lasted longer (30 to 53 days) than the control cycle in subjects No. 1, 3 and 4. An evaluation of the corpus luteum function was only available for subject No. 1, in whom a luteal phase of 9 days with a maximal progesterone production of only 6.3 ng/ml was observed at the end of a long 53-day cycle.

A third cycle under tiapride administration has been studied in 3 subjects In one of them (No. 2), some luteinisation (with a maximal progesterone level of only 1.5 ng/ml!) still occurred during 6 days after a delayed gonadotrophin peak. In the 2 other subjects (No. 3 and 4), a gonadotrophin peak can hardly be seen (Figs. 3 and 4), progesterone levels remained very low and only little oestradiol (< 100 pg/ml) was produced throughout these cycles, which have thus to be considered as anovulatory.

In subject No. 1 in whom drug administration had been withdrawn 8 days after the end of the second treatment cycle, follicular maturation, as evidenced by increased oestradiol production, began apparently only after the interruption
Development of LH, FSH, PRL, oestradiol (OE) and progesterone (P) levels during a control cycle followed by 3 consecutive cycles under oral administration of tiapride (2 \times 100 \text{ mg daily}) in subject No. 3. The numbers at the x axis mark the number of days, starting at the onset of the control cycle. For explanation of other symbols, see legend to Fig. 1.

of treatment, resulting in a 28-day cycle with a luteal phase of only 10 days, instead of the 14-day luteal phase regularly observed in control cycles of this subject. The less frequent blood sampling schedule makes it hazardous to assess that the oestradiol peak in the follicular phase as well as the peak progesterone in the luteal phase were of lower amplitude (Table 1).

The average hormonal pattern of four short luteal phase (SLP) cycles (less than 11 days of luteal phase), as combined from the day of the LH peak, is depicted in Fig. 5; it should be noted that neither the likely inadequate luteal phase cycle occurring in subject No. 1 after treatment nor the last cycle with very poor luteinisation (and perhaps no ovulation) in subject No. 2 have been taken in consideration in establishing this mean pattern. As can be seen in Fig. 5, there are very few mean values that are significantly different in the SLP cycles than in the corresponding control cycles; it should, however, be recalled that all these values were combined according to the day of the LH peak, which occurred 1–31 days later on in 3 of these 4 SLP cycles.

The reduction of the overall mean progesterone secretion during the luteal phase is quite obvious (Fig. 5). Mean values on days 6 (t = 3.14; P < 0.02), 7 (t = 3.61; P < 0.02) and 8 (t = 2.59; P < 0.05) are indeed significantly lower than the corresponding control values. It might also be noted that the first significantly increase in progesterone concentrations occurred on day –1 (F =
8.89; \( P < 0.01 \)) in the SLP cycles but only on day + 1 (\( F = 5.34; P < 0.05 \)) in the control cycles.

Mean oestradiol levels were not significantly different in the SLP cycles than the corresponding values in the control cycles. The peak oestradiol level occurred in both cases on day – 1 and was of comparable amplitude; although it is not statistically significant, this oestradiol peak appeared sharper in the SLP than in the control cycles. Similarly, mean oestradiol levels appeared somewhat lower during the luteal phase of the SLP than of the control cycles.

Although none of the mean LH values were significantly different in the SLP than in the control cycles, a tendency to greater LH secretion in the follicular phase can be observed (Fig. 5) and is reflected by significantly greater (\( t = 4.39; P < 0.01 \)) mean LH values on days – 10, – 9 and – 8 in the SLP than in the control cycles. Although their amplitudes are comparable, the mean LH peak appeared to last only 3 days in the SLP cycles instead of 4 days in the control cycles. After this peak, mean FSH levels declined more rapidly in the SLP cycles. On the contrary, there was in the control cycles a tendency to show a secondary rise of mean LH levels in the luteal phase, a tendency which was absent in the SLP cycles (Fig. 5): mean LH levels were almost significantly (\( F = 3.34; P > 0.05 \)) greater on day + 6 than on day + 4, and significantly greater (\( F = 4.78; P < 0.05 \)) on day + 6 than on day + 7 in the control cycles.

Development of LH, FSH, PRL, oestradiol (OE) and progesterone (P) levels during a control cycle (not immediately preceding the experiment) as well as during 3 consecutive cycles under oral administration of tiapride (3 × 50 mg daily) in subject No. 4. The numbers at the x axis mark the number of days, starting at the onset of, respectively, the control and the experiment cycles. For explanation of other symbols, see legend to Fig. 1.
Mean (± SEM) serum levels of LH, FSH, oestradiol (OE) and progesterone (P) as well as mean (± SEM) FSH/LH ratios in the control cycles (on the left) as well as in 4 short luteal phase cycles (on the right) observed during tiapride administration. The asterisks point out to the mean values that are significantly (P < 0.05) different in the short luteal phase cycles than the corresponding control values; it should be noted that all cycles were combined according to the day of the LH peak and that the length of the follicular phase was thus longer by 1–31 days in 3 of the 4 short luteal phase cycles.

In the 2 anovulatory cycles observed in subjects No. 3 and 4, the hormonal patterns observed differed from one subject to the other. In subject No. 3, a progressive rise in LH and FSH levels is thereafter followed by irregular and asynchronous bursts of gonadotrophins without induction of a true ovulatory peak; oestradiol levels fluctuated to some extent but remained always below 60 pg/ml. In subject No. 4, a first rise in both gonadotrophins apparently induced some oestradiol production but without any continuation; afterwards, there might be aborting oestradiol and gonadotrophin peaks not followed by any luteinisation.
DISCUSSION

Tiapride administration resulted in all subjects in increased PRL concentrations but "true" hyperprolactinaemia (above 700 μU/ml) was not reached permanently, except in one subject: this is somewhat different from what has been observed with sulpiride, when administered at an oral daily dose of 3 x 50 mg (Delvoye et al. 1974; Robyn et al. 1976). This difference in the persistence of hyperprolactinaemia is probably attributable to the schedule of drug administration (once or twice a day instead of three times) and partly to the dose; thus, subject No. 2, taking tiapride only once a day, experienced a much lower hyperprolactinaemia than the other subjects. According to the earlier results of acute administration of sulpiride (L'Hermite et al. 1978b) and tiapride (L'Hermite et al. 1978c), there is apparently no difference between the two drugs with respect to the duration of their PRL stimulation. Our results, also, do not suggest that the stimulatory effect of tiapride on PRL secretion might decline with continued drug administration.

Nevertheless and despite the less persistent hyperprolactinaemia observed in the present study, tiapride administration induced in all cases a progressive deterioration of the function of the corpus luteum: the length of the luteal phase was reduced by 2 to 4 days during the first treatment cycle and by 3 to 5 days in the following cycles. In the third treatment cycle, questionable ovulation with slight luteinisation occurred in one subject while the 2 others experienced anovulatory cycles. These perturbations of the menstrual cycle are comparable to those observed during sulpiride-induced hyperprolactinaemia (L'Hermite et al. 1975; Aono et al. 1978a), with the exception that amenorrhoea had not been observed throughout the present study. It is also comparable to the finding of a decreased progesterone production in 3 out of 5 women orally treated with TRH, resulting in transient PRL elevations (Jewelewicz et al. 1974). Short luteal phase cycles have also been described in association with moderate hyperprolactinaemia in some infertile patients (Corenblum et al. 1976; del Pozo et al. 1976; Mühlstedt et al. 1978; Seppälä et al. 1976).

Some deterioration of the corpus luteum function can apparently also take place in a cycle with hyperprolactinaemia during the first week only, as indicated by the likely inadequate luteal phase observed after drug withdrawal in the last cycle of one subject.

When hormonal data in SLP cycles under tiapride were combined according to the day of the LH peak, the mean LH, FSH and oestadiol as well as the mean FSH/LH showed very little difference in comparison to the corresponding mean values of the control cycles. It must, however, be recalled that the length of the follicular phases had increased by 1–31 days (except in subject No. 4, in whom it remained the same), indicating a definite delay in the cycling process of the hypothalamo-pituitary-ovarian axis. A change in the FSH/LH ratio,
although not significant in the present study but suggested by the greater LH concentrations on days 10 to 8, might explain this delay; an interference, at the ovarian level, of hyperprolactinaemia with the action of FSH cannot, however, be excluded. In the SLP cycles under tiapride, the FSH/LH ratios tended indeed to be lower – at least until the onset of the LH peak – than in the control cycles, as reported by Strott et al. (1970) in 7 cycles with short luteal phase but unknown PRL levels.

Although it had been previously postulated that hyperprolactinaemia would block the stimulatory effect of gonadotrophins on steroidogenesis by the Graafian follicles (Besser & Thorner 1975), recent experiments documented conclusively that oestradiol production by these follicles in response to either exogenous or even endogenous gonadotrophins was not impaired in women with pathological hyperprolactinaemia (Archer & Josimovich 1976; Fraser et al. 1978; Kemmann et al. 1977; Lachelin et al. 1977; McGarrigle et al. 1978; Pepperell et al. 1977). The present data further support the latter thesis in women with tiapride-induced hyperprolactinaemia, as recently reported by Aono et al. (1978b) during short term sulpiride administration.

An impairment of the positive feedback effect of oestrogens on gonadotrophins has been reported in hyperprolactinaemic patients (Aono et al. 1976; Glass et al. 1975), as well as during sulpiride-induced hyperprolactinaemia (L’Hermite et al. 1978a). In the present study, there was little evidence for such a phenomenon, except the shorter duration of the mean LH peak, the more rapid decline of mean FSH levels after the peak and perhaps the absence of a secondary rise in LH levels in the early luteal phase of the SLP cycles.

The amplificatory effect of progesterone on the positive effect of oestrogens upon gonadotrophins has been found to remain present in hyperprolactinaemic patients (Glass et al. 1976). Since the first rise in progesterone concentrations occurred two days earlier (on day −2) in the SLP than in the control cycles, one might question whether this increased progesterone secretion had not been necessary to produce a comparable gonadotrophin ovulatory peak despite the alteration of the positive feedback effect of oestrogens. A restoration of this positive feedback effect can indeed be obtained with progesterone supplementation in hyperprolactinaemic patients (Faglia et al. 1978). The earlier rise in progesterone might itself be explained in the light of the in vitro results of McNatty et al. (1974), indicating that some prolactin is required for progesterone production by human maturing granulosa cells while hyperprolactinaemia would impair it.

Prolactin can selectively increase the dopamine turnover in the median eminence (Hökfelt & Fuxe 1972; Annunziato & Moore 1978); there is anatomical and experimental evidence, even in the human, for retrograde transport of PRL to the hypothalamus (Oliver et al. 1977; Bergland & Page 1978; Assies et al. 1978) and a close correlation between dopaminergic and LRH-containing
structures has been evidenced in the rat hypothalamus (McNeill & Sladek 1978; Alonso et al. 1978). Furthermore, the administration of prolactin or of sulpiride induced in animals an accumulation of LRH immunoreactive material in hypothalamic neurones (Léonardelli et al. 1973; Léonardelli 1977) while the hypothalamic activity of benzonates appeared to be mediated via PRL secretion (Portaleone et al. 1978a, b). Since dopamine has been reported to inhibit to some extent in the human the secretion of LH (Leblanc et al. 1976), it is conceivable to hypothesize that tiapride might interfere with the hypothalamo-pituitary-ovarian axis via hyperprolactinaemia, itself modulating the hypothalamic secretion of endogenous LRH through an increased dopamine turnover.

The mechanisms by which hyperprolactinaemia can be responsible for reductions in the length of the luteal phase and in the luteal progesterone production remain unclear. The presence of specific PRL receptors in human ovaries (Saito & Saxena 1975) does not necessarily mean that PRL is luteotrophic in the human: further work is required to localize and characterize these receptors. One level of impact of hyperprolactinaemia might be a direct impairment of the progesterone secretion of the corpus luteum, in accordance with the in vitro data of McNatty et al. (1974). Alternately this effect might be mediated through reduced gonadotrophin secretion during the luteal phase; the luteotrophic activity of LH is indeed well demonstrated (LeMaire et al. 1971). Both effects could also combine or, on the contrary, the function of the corpus luteum could depend only on the previous hormonal events. Our data do not permit to clarify this point.

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