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Hyperprolactinaemia—A Clinical Study With Special Reference to Long-term Follow-up, Treatment with Dopamine Agonists, and Pregnancy

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Although our present knowledge of hyperprolactinaemia as a cause of galactorrhoea and menstrual irregularities has its origin in the early 1970s, observations dating back to the mid-19th century pointed to these associations, as mentioned by Blackwell (8). Classically, three clinical entities involving galactorrhoea and amenorrhoea have been identified: the Chiari-Frommel syndrome, with persistence of postpartum amenorrhoea and galactorrhoea for more than one year after delivery without any evidence of a pituitary tumour; the Ahumada-del Castillo syndrome, the spontaneous onset of amenorrhoea and galactorrhoea without any obvious pituitary tumour; and the Forbes-Albright syndrome, which is comparable to the above but with roentgenological evidence of a pituitary adenoma. Since the development of a specific radioimmunoassay for measurement of human prolactin (PRL) (36), it has been shown that in all of these three syndroms the serum PRL concentration is elevated.

The hormone PRL was discovered in 1928 by Stricker and Grueter, who first described its lactogenic actions in mammals (cited by Rillema et al. (68)). It is only in the last two decades that the importance of this hormone in human reproductive disorders has been recognized. The discovery of lactogenic activity in highly purified human growth hormone (47) initiated a ten-year controversy concerning the existence of a separate human PRL. It was long assumed that pituitary PRL activity was an intrinsic property of growth hormone. However, in 1970 a human PRL molecule was identified (29) and was soon also isolated from the pituitary gland (37, 46).

The PRL molecule is a single polypeptide containing 198 amino acids (74). The PRL molecule in man has been shown to be heterogeneous (78) and to have different distinct forms, Little, Big and Big-Big, with decreasing bioactivity and increasing

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molecular weight, in that order (91). The most common molecular weight is that of Little PRL (22000), which is believed to be the bioactive form of the hormone. These heterogeneous forms of PRL have been found in both normal and hyperprolactinaemic states. This matter is further complicated by the finding of functional heterogeneity within the population of the lactotrophs in the pituitary gland as illustrated by major differences in both synthetic rates and thyreotropin releasing hormone (TRH) responsiveness (86).

Although the role of prolactin-inhibiting factors in the control of PRL secretion is now well established, there is substantial evidence to suggest that stimulatory factors (prolactin-releasing factor) may also play an important part. Hypothalamic control of PRL secretion seems to be mediated by at least two different prolactin-inhibiting factors, which are synthesized by tubero-hypophyseal neurons (91). The role of hypothalamic dopamine as a major prolactin-inhibitory factor is clearly documented. Dopamine is secreted directly into the hypophyseal portal blood system and binds, within the pituitary gland, to receptors on the cell membrane of the lactotrophs through which a direct inhibitory effect is exerted (17, 44). Evidence suggest that gamma-aminobutyric acid (GABA), in addition to dopamine, functions as a prolactin inhibitor. However, it seems that the PRL inhibitory activity of dopamine is far greater than that of GABA (91). One special feature of the synthesis and release of dopamine is the inhibitory action of PRL via a short-loop feedback mechanism (34). Production of dopamine by the posterior lobe of the pituitary gland has also been demonstrated (65).

For many years it was believed that the action of inhibitory factors was the only mechanism for regulating PRL secretion, but there is now considerable evidence to suggest that stimulatory factors also play an important role. Experimental observations in several species, including humans, indicate that TRH, vasoactive intestinal peptide, cholecystokinin and angiotensin II may be involved in the control of PRL secretion (91). Thus, PRL secretion seems to be under the control of a complex dual regulatory system which involves both inhibitory and stimulatory factors.

In 1676 the physician Dodart (22) described ergot-related cessation of lactation. This was the first medical correlation between an ergot alkaloid and endocrine function. A search for an ergot derivative that could suppress lactation in humans with minimal or no ergotoxic effects was initiated in the 1960s. Several ergot alkaloids were

shown to inhibit PRL secretion and suppress lactation in animals, but could not be used in humans because of their severe side effects.

Bromocriptine (BRCR) (2-bromo-alpha-ergocryptine mesylate), a semi-synthetic ergot alkaloid which stimulates dopamine receptors and inhibits PRL secretion, was introduced in the early 'seventies (25) and proved to be a highly effective and well tolerated drug in reducing serum PRL levels in patients with hyperprolactinaemia.

It is generally accepted today that BRCR therapy is the treatment of choice for most infertile women with hyperprolactinaemia and amenorrhoea (63). The treatment results in rapid normalization of serum PRL levels and restoration of ovulatory function and fertility in more than 90% of hyperprolactinaemic women (5). It is still unclear, however, whether the suppressive effect of BRCR on prolactin hypersecretion is permanent (28), or whether the hyperprolactinaemia may return after discontinuation of the drug as has been found in some studies (7, 51, 77).

The major risk associated with pregnancy in women harbouring a pituitary adenoma is expansion of the tumour, resulting in compression of the surrounding neural structures. Bergh et al. (3), however, found that the risk of pregnancy-related tumour growth in hyperprolactinaemic women treated with bromocriptine was low. In a review Nillius et al. (61) noted that clinical complications due to growth of a prolactinoma occurred in only 2% of 488 pregnancies in women with hyperprolactinaemia who were given primary BRCR therapy. However, there are only few reports on the long-term effects of pregnancy on PRL hypersecretion or on the effect of multiple pregnancies in hyperprolactinaemic women treated with BRCR.

The aetiology and natural history of prolactinomas are largely unknown. It is not clear which or how many of the small prolactinomas which enlarge and become macroprolactinomas or invasive lesions (8). Long-term studies have indicated that the frequency of further enlargement of the tumour among patients with microprolactinomas is low (48, 59, 76, 89). It has been reported that BRCR effectively reduces the size of prolactinomas (53, 80). However, re-expansion of large pituitary adenomas has occurred soon after withdrawal of BRCR treatment (82). In such cases sellar changes indicating intra-pituitary adenomas have been observed by plain radiography and multidirectional tomography. A disadvantage of these examinations is that the change in the size of an adenoma is assessed indirectly. Modern radiological technology, such as computed tomography, is superior, as it provides information not only about the sella turcica but also about the pituitary

gland itself.

During evaluation of the radiographs of the sella turcica calcific deposits in pituitary adenomas have, although rarely, been observed (43). From radiological studies an incidence of granular calcification within pituitary adenomas of 0.3 to 14% has been reported (13). However, it is not known whether these calcifications represent regression or progression of a pituitary tumour.

The dopamine agonist BRCR is the most commonly used drug in the treatment of hyperprolactinaemia (84). Adverse reactions are often a problem at the beginning of the treatment and sometimes persist during chronic treatment. Moreover, the drug usually has to be taken several times a day to maintain the therapeutic effect, although some patients can be effectively treated with a once-daily dose (14). For this reason efforts have been made to find dopamine agonists with a more favourable profile of adverse effects and a longer duration of action. Other ergot derivates such as lisuride, metergoline, and pergolide mesylate have been used, but these have essentially the same action as BRCR and cause similar adverse reactions (75, 58). CV 205-502 is a new long-acting, non-ergot dopamine agonist which effectively inhibits PRL secretion in healthy volunteers (30). We have performed the first clinical trials with this new drug in hyperprolactinaemic women.

Evaluations of hyperprolactinaemic women have revealed a wide range of variations in clinical symptoms. Further knowledge of such variations is of importance when decisions have to be taken as to how to treat and follow up patients with hyperprolactinaemia.

AIMS OF THE INVESTIGATION

This investigation was undertaken

1. to determine whether long-term treatment with BRCR in hyperprolactinaemic women could result in permanent suppression of the PRL hypersecretion after discontinuation of the therapy;

2. to study the long-term effects of pregnancy on PRL hypersecretion and the effects of multiple pregnancies on hyperprolactinaemic women;

3. to examine the changes (regression/progression) of the sella turcica during long-term follow-up in hyperprolactinaemic women and to evaluate the risk of serious tumour enlargement in women with a PRL-secreting adenoma;

4. to investigate how often clinical investigations are necessary for a safe follow-up of women with hyperprolactinaemia; and

5. to investigate the duration of action, efficacy and side effects of a new non-ergot dopamine agonist, CV 205-502, in the treatment of women with hyperprolactinaemia.

RESULTS

A: The effects of long-term bromocriptine treatment and pregnancy in women with hyperprolactinaemia

The principal aim of these studies was to determine whether long-term treatment with BRCR can cause permanent suppression of PRL levels in serum even after withdrawal of the drug. Further aims were to evaluate the long-term effect of pregnancy on PRL hypersecretion and to examine the radiological changes of the sella turcica during long-term follow-up in hyperprolactinaemic women

Prolactin secretion and menstrual function after long-term bromocriptine treatment

Seventy-five women, 16 to 40 years of age, with long-standing amenorrhoea and hyperprolactinaemia were followed up after discontinuation of long-term BRCR treatment. The PRL concentration before treatment ranged between 25 and 1470 ug/l (mean 135 ug/l). Forty-nine of the women had pretreatment serum PRL concentrations below 100 ug/l, and 26 women had levels above 100 ug/l. BRCR had been given in daily doses of between 2.5 and 50 mg for up to 65 months (median 24 months). Twenty-two women had previously had a BRCR-induced term pregnancy and six women had had two term pregnancies.

Treatment with BRCR was not restarted in 33 women (44%). The PRL levels in the serum in this group had decreased by 55 % after 6 months' follow-up as compared

with the pretreatment values. Three of these 33 women had become normoprolactinaemic. Regular menstruation occurred for at least 12 months in 19 of the 33 women after discontinuation of the treatment. Most of the women with menstruation had PRL levels of less than 100 ug/l before treatment. When the group of 33 patients was subdivided into those with PRL concentrations above and below 100 ug/l, it was found that the women with PRL levels above 100 ug/l showed a more marked decrease in their PRL secretion than those with only moderate hyperprolactinaemia. There was no correlation in the 33 women between the pretreatment PRL levels and the levels recorded after BRCR withdrawal. Ten women in the group of 33 were followed up for a number of years after discontinuation of treatment. After 5 years the mean PRL value had decreased by 54 % compared with those before therapy. Seven women had regular menstrual bleeding, and two patients were normoprolactinaemic.

Treatment was reinstituted in 42 of the 75 women (56%) within 3 months after discontinuation of therapy, mainly because of increasing PRL levels in the serum. In 18 of these 42 women, treatment was discontinued a second time. Six of these patients had regular menstrual bleeding after 6 months' follow-up and three of them were normoprolactinaemic.

Return of menstruation and normalization of prolactin in hyperprolactinaemic women with bromocriptine-induced pregnancy

Fifty-eight hyperprolactinaemic women, 22 to 36 years of age, were followed up for 13 to 108 months after a total of 73 bromocriptine-induced term pregnancies to investigate whether pregnancy had any adverse long-term effects on the hyperprolactinaemic state. Fifteen of these women had had two term pregnancies, 13 of which were induced by BRCR. The pretreatment PRL concentrations ranged from 24 to 1470 ug/l (mean 92 ug/l). The treatment had been given in daily doses of between 2.5 and 30 mg for 1 to 48 months before conception occurred. None of the women showed evidence of extrasellar extension of a presumptive prolactinoma or of an empty sella at the radiological examination. Pituitary tumour complications during pregnancy occurred in two women, who developed visual field defects in the third trimester. These defects improved when BRCR was reinstituted

A marked decrease in serum PRL concentrations, i.e. a decrease of 50% or more of

the pretreatment value, occurred in 20 of the women (34%) after pregnancy, lactation and weaning. Seven of them regained regular uterine bleeding and four had normal PRL levels in serum after completion of breast-feeding. No decrease in serum PRL was found in 36 women (62%), of whom five regained regular menstrual function. Higher serum PRL levels after pregnancy were found in two women, neither of whom displayed any change in the radiological appearance of the sella turcica or any symptoms of tumour growth.

Spontaneous uterine bleedings returned in 16 of the 58 women after pregnancy (27%). Twelve of the women regained regular uterine bleedings and four had oligomenorrhoea. With only two exceptions, the women in whom spontaneous uterine bleedings returned had PRL levels in their serum below 100 ug/l before treatment and pregnancy. This group of women was followed up for 6 years without any evidence of a further increase in the PRL levels being found.

Fifteen women had two term pregnancies of which 13 were induced by bromocriptine. There was no difference between the mean serum PRL level before treatment and that after the first pregnancy, but after the second pregnancy the mean PRL level in serum had decreased compared with the level after the first pregnancy.

Long-term radiographic follow-up of the sella turcica in hyperprolactinaemic women and microcalcification in prolactin-secreting pituitary adenomas

In this study 73 hyperprolactinaemic women, 17 to 56 years of age, were followed up for 5 to 13 years after the initial radiological examinations of the sella turcica. At the first examination standard lateral and postero-anterior coned down views of the sella turcica showed a normal sella in 16 women. Minor radiological changes classed as B1-B3 were observed in 38 women, while 19 women displayed pronounced asymmetry that was assigned to class B4-B5. In four patients there was suprasellar extension of the tumour. One patient had an empty sella. The PRL concentration in the serum before treatment ranged between 21 and 1500 ug/l (mean 108 ug/l). The mean serum PRL level was significantly higher in the B4-B5 group than in groups B0 and B1-B3. BRCR had been given in daily doses of between 2.5 mg and 50 mg for 2 to 132 months in all patients except one, who received no treatment. Sixty-seven women were normoprolactinaemic during treatment and had regular menstrual bleeding. Forty-eight BRCR-induced pregnancies occurred in 35 of the women

during the follow-up. Thirteen of them had two term pregnancies, among which ten were induced by BRCR.

Enlargement of the pituitary fossa was found in 25 (34%) of the 73 women. The serum PRL concentration in this group ranged between 21 and 1470 ug/l (mean 107 ug/l).

Seven of these 25 women showed progression of the sellar asymmetry during pregnancy, with alteration in the classification of the sella turcica. All of them had been treated with 5 mg of bromocriptine daily for 2 to 20 months (median 4 months). In all 7 patients the BRCR treatment was stopped as soon as pregnancy was confirmed. All of them were treated with BRCR postpartum. During this treatment three of them showed regression of the sellar asymmetry but without normalization of the sella. Two women had two term pregnancies, and one of them showed further progression during the second pregnancy. Marked progression during pregnancy with development of suprasellar extension of the tumour was seen in one woman. BRCR was reinstituted during the pregnancy and resulted in tumour regression. BRCR treatment was restarted after weaning and the patient conceived soon again and this time had a normal pregnancy with no further progression of the sellar asymmetry.

Non-pregnancy-related progression occurred in 18 of the 25 women. Minor progression with erosion and thinning of the laminae durae was observed in eight women and major progression with a change in the classification occurred in ten women. BRCR had been given in a mean dose of 7.3 mg daily (range 2.5 to 50 mg daily) for 18 to 132 months (median 60 months). There was no difference in the mean PRL level in the serum before treatment between the group with minor and that with major progression. During the follow-up period six of these women had one BRCR-induced term pregnancy and three of them had two such pregnancies without any progression of the asymmetry.

Radiological regression occurred in 14 (20%) of the 73 women. Three of these 14 women showed suprasellar extension of the tumour. Minor regression was noted during treatment in six women, while marked regression with a change in classification was found in five women. BRCR had been given for 38 to 112 months (median 78 months) with a mean dose of 6.9 mg. In three women with suprasellar extension of the tumour, repeated computed tomography showed regression of the extension after BRCR treatment for 4, 6 and 10 months, respectively, but there was

no further regression in the sellar asymmetry. Pregnancy had occurred during treatment with BRCR in four patients, resulting in four normal children. Two patients had had two pregnancies. There was no progression of the radiological sellar changes during or after the pregnancies. No difference in the mean PRL level in serum before treatment or in the duration of treatment was found between the group with minor and the group with major regression.

There was no difference in the mean duration of treatment between the group with regression and the group with non-pregnancy-related progression.

Thirty-four women (46%) did not show any change in their sellar configuration during the follow-up. BRCR treatment had been given for 4 to 126 months (median 58 months) in a mean dose of 7.0 mg. One BRCR-induced term pregnancy was experienced by 18 of these women, while six of them had two term pregnancies.

Within the whole group of 73 women, the mean PRL level in the serum before treatment was lower in the group with no radiological changes than in the group with regression.

Intrasellar calcifications were seen in eight of the 73 women. One woman had a curvelinear calcification in the region of the anterior superior aspect of the pituitary capsule. One woman had developed a solitary calcification after a diagnostic fine-needle aspiration of the pituitary tumour. The remaining six women displayed granular calcifications in the anterior portion of the sella turcica. Progression of these calcifications was observed in three of the women and in two of these the calcification increased in association with radiographical regression of the sellar changes. We were not able to find any factor which could predict the occurrence of the calcific deposit.

B: Treatment with a new long-acting dopamine agonist (CV 205-502) in women with hyperprolactinaemia

Short-term treatment with CV 205-502

In a dose-ranging study CV 205-502 was given to 24 hyperprolactinaemic women of ages 18 to 47 years for 7 days. Twenty-one had had BRCR treatment for 2 to 69 months before they entered the study. Three had never received any treatment with a dopamine agonist. The pretreatment PRL levels in the serum ranged between 22

and 320 ug/l (mean 85 ug/l). The women were randomly allocated double-blind to one of three treatment groups, which received CV 205-502 once daily for 7 days in a dose of 0.01 mg (group 1), 0.03 mg (group 2) or 0.06mg (group 3). Two patients in each group were given placebo. A PRL day curve was obtained during the 1st and 7th days. On day 8 blood samples were obtained 23 and 24 hours after the last treatment dose.

The serum PRL concentrations decreased dose-dependently in all patients given active substance. Group 3 (0.06 mg) showed the most pronounced effects of the drug. Four patients became normoprolactinaemic, with serum PRL levels below 10 ug/l, and in these patients the PRL secretion was suppressed for at least 24 hours. In the remaining two women the prolactin level decreased by more than 50%. The side effects were mild and transient. No patients discontinued the study.

Long-term treatment with a new non-ergot long-acting dopamine agonist, CV 205-502 in women with hyperprolactinaemia

Twenty-four hyperprolactinaemic women, aged 22 to 48 years, were treated with CV 205-502 for 6 months. All except one had been treated with BRCR for 1 to 108 months. Five of the women had discontinued the BRCR treatment because of undesirable side effects. The serum PRL concentrations ranged between 31 and 1100 ug/l (mean 84 ug/l).

A double-blind placebo-controlled design was used for the first 4 weeks, in which the patients were randomly assigned to receive either placebo or 0.05 mg of CV 205 -502 once daily. The patients who had had placebo started with 0.05 mg of CV 205 -502 at the end of week 4, while in the CV 205-502 treated patients who had not become normoprolactinaemic the daily dose was increased by 0.025 mg. Thereafter the study was open-label and the dose was increased by 0.025 mg daily every 4 weeks until the plasma PRL levels were within the normal range or until the study period ended at 6 months. All the patients, including those who started with placebo, received 6 months' treatment with CV 205-502. The maximum dose was 0.175 mg once daily.

CV 205-502 therapy decreased the serum PRL levels in all the patients. The mean PRL concentration had decreased from baseline by an average of 77% after 4 weeks of treatment and by 90% at week 24. The treatment resulted in normalization

of PRL secretion in 17 of the 24 women receiving daily doses of 0.05 to 0.15 mg (mean 0.075 mg) of the drug. The PRL level was still elevated in seven of the 24 women at the end of the study. In three of these women a marked decrease in the PRL concentration occurred, compared with the pretreatment value while four of the seven women responded to CV 205-502 with only a minor decrease within the 6 months. One of these patients had previously received BRCR with normalization of PRL secretion and restoration of menstrual function. Regular menstrual bleeding occurred in 16 of the 17 women whose PRL levels were normalized. Ovulation was confirmed by progesterone determinations in 15 women. Furthermore, regular menstrual function occurred in four of the seven women despite persistently elevated PRL levels. Ovulation was confirmed in all four women.

Mild to moderate galactorrhoea was found at the baseline examination in 19 of the 24 patients. After 6 months of treatment some mild galactorrhoea was still present in six women.

CV 205-502 was well tolerated and the side effects, which mainly consisted of nausea and tiredness, were mild and transient and occurred mostly at the beginning of the drug therapy. No patients discontinued the study.

DISCUSSION

In these studies we have investigated the long-term effects of treatment with dopamine-agonists and of pregnancy on hypersecretion of prolactin. In some patients significant changes in the PRL secretion had occurred during the study while in others the changes in serum prolactin concentrations were regarded to be within the normal variation of PRL secretion.

Prolactin is synthesized and secreted from the lactotropic cells of the adenohypophysis. The hormone is released in pulses of varying magnitude superimposed on a continuous basal secretion (45). In normal subjects the highest plasma PRL concentrations occur during sleep (72). Moreover, PRL secretion is increased by a number of physical, emotional, or combined stress stimuli. At the time of puberty in girls, the mean serum PRL level increases significantly to reach the adult female range (23) and remains unchanged until menopause. During pregnancy the serum PRL level begin to rise in the first trimester and increases

progressively to ten times or more the concentration of non-pregnant women at term (83).

Hyperprolactinaemia is often associated with hypogonadism with or without galactorrhoea. High PRL concentrations have an inhibitory effect on follicular growth and steroidogenesis (52), and in addition there is a loss of normal surge of LH secretion in response to the administration of oestrogen (32), and spontaneous pulses of LH secretion are infrequent or absent (9). Reduction of circulating PRL, by treatment with BRCR, is associated with a rise in the serum oestradiol concentration (73), a return of LH positive feedback responses (1), and restoration of LH pulsatility (9). Moult et al (56) proposed that BRCR acts directly on the pituitary to reduce the serum PRL level, and that this in turn allows hypothalamic dopamine production to fall, restoring normal LH pulsatility.

The primary reason for treatment of hyperprolactinaemia in women is infertility, but in some cases treatment may be warranted because of troublesome galactorrhoea or because of symptoms due to oestrogen deficiency. Not all patients with hyperprolactinaemia require treatment and those who do not should be kept under observation. However, there are data suggesting that patients with untreated hyperprolactinaemic amenorrhoea may be at risk of developing osteoporosis (41, 42). This possibility should be kept in mind when making the decision as to whether women with hyperprolactinaemia should be treated or not. Only limited data are available concerning the natural history of hyperprolactinaemia in patients with and without a pituitary tumour and the long-term effects of BRCR treatment and of pregnancy on these conditions.

Hyperprolactinaemia and long-term bromocriptine treatment

Hyperprolactinaemia is a common clinical disorder and has been found to be present in a significant proportion of women with amenorrhoea, with an incidence varying between 13 and 20% (2, 63). Several studies have documented that BRCR therapy effectively lowers the PRL level to normal and restores ovulatory function in more than 90% of women with hyperprolactinaemia (5, 28, 55). In addition, this drug has been found to reduce the size of a prolactinoma in a large percentage of patients (53, 80). It is still unclear, however, whether the suppressive effect of the drug on PRL hypersecretion is permanent (28).

In the present investigation we followed up 75 hyperprolactinaemic women after discontinuation of long-term BRCR treatment. Hyperprolactinaemia returned rapidly in most of the patients (56%) after withdrawal of the drug, which is in agreement with other reports (7, 50, 51, 87). However, as many as 44% of the women, who had been treated with BRCR for up to 65 months, had no need for reinstitution of therapy within 6 months. The PRL levels in this group had decreased by 55% compared with the pretreatment values. In the group of women who had discontinued BRCR treatment after another treatment period of 5 to 81 months, eight were still without need of treatment at the 6-month follow-up. Persistent serum PRL normalization occurred in three of the women in each of the two groups. Moriondo et al (55) reported persistent normalization of serum PRL levels after BRCR withdrawal in 11% and 22% of 36 women treated for 1 and 2 years, respectively. The observation time was only 45 days, which might explain the higher success rate. Maxon et al. (51) found that PRL concentrations did not usually plateau until at least 40 days after cessation of therapy and concluded that decisions regarding tumour activity based on the PRL concentration should not be made until at least 6 weeks after withdrawal of bromocriptine treatment. This is in accordance with the results in ten women followed up in our study for 5 years after discontinuation of treatment. It was found that the serum PRL levels rapidly returned within 3 months to a stable plateau and remained at this level for the rest of the follow-up period.

When the group of patients who were still without treatment were subdivided into those with serum PRL levels above and below 100 ug/l, it was found that the women with PRL levels above 100 ug/l showed a more marked decrease in their PRL secretion than those with only moderate hyperprolactinaemia. These results are in agreement with those of Eversmann et al (24), who concluded that the degree of persistent PRL suppression correlated to the height of the PRL level before treatment and to the duration of BRCR treatment. This is partially in contrast with the results of Moriondo et al (55), who found a positive correlation between basal PRL levels and those recorded after BRCR withdrawal. One explanation for the difference from our results may be that most of our patients had had treatment for a longer period than in the study by Moriondo et al (55).

In a previous study Bergh et al. (2) found that nine women with slightly elevated PRL levels had become normoprolactinaemic at follow-up after 1 to 4 years without treatment. This is in accordance with the report by Pepperell (64) who concluded

that one third of patients with mild hyperprolactinaemia can have spontaneous resolution of their hyperprolactinaemia. In a group of women with idiopathic hyperprolactinaemia, Martin et al (49) found that the PRL levels returned to normal spontaneously in 14 of 41 of the patients after a follow-up of 5 years, but that there was no spontaneous regression in patients with PRL levels above 60 ug/l. However, it is unlikely that PRL secretion would become normal spontaneously in a large group of women with marked hyperprolactinaemia. Rjosk et al (69) found no evidence of PRL normalization in 34 untreated patients with microprolactinomas who were followed up for 6 years and in another study spontaneous regression occurred in only 7% of 43 untreated patients with hyperprolactinaemia (48). None of the ten women in this study who were followed up for up to 5 years after BRCR therapy showed any signs of spontaneous regression. It is much more probable that in most of the patients the PRL decrease is related to the long-term BRCR treatment. Re-expansion of prolactinomas occurred in a large proportion of patients in a recent study when BRCR therapy was discontinued (53). In this study, BRCR had been given for only one year. Possibly a more prolonged treatment period is necessary to achieve more permanent tumour regression. One of our patients, with a large pituitary tumour with suprasellar extension and who was given BRCR treatment for 2 years, still has a nearly normal serum PRL level and normal menstruation after 8 years without therapy. Radiological follow-up has shown no evidence of tumour regrowth. This finding is in agreement with the report by Johnston et al (39), who followed up 15 hyperprolactinaemic patients after withdrawal of bromocriptine treatment which had been given for 1.5 to 7 years and concluded that rapid tumour regrowth is uncommon and of small extent.

Hyperprolactinaemia and pregnancy

Restoration of ovarian function and induction of pregnancy are now easily achieved in hyperprolactinaemic women with amenorrhoea and infertility by means of PRL-lowering treatment with BRCR (3, 63, 79). BRCR is generally found to enable about 80% or more of women with hyperprolactinaemic infertility to become pregnant (88). The major risk associated with pregnancy in women harbouring a prolactinoma is expansion of the tumour during pregnancy. However, several studies have shown that the risk of developing serious pituitary tumour complications during pregnancy

is low (3, 21, 38). Nillius et al (61) reviewed 488 pregnancies and found that only 2% of the hyperprolactinaemic women developed visual complications due to rapid prolactinoma enlargement. The risk is also small in patients with larger prolactinomas (6). In a recent review, Molitch (54) summarized 16 series reported in the literature encompassing 246 microprolactinomas and 45 macroprolactinomas left untreated before pregnancy was achieved. Only 1.6% of the women with microprolactinomas had symptoms of tumour enlargement. Of the 45 women with macroprolactinomas, 15.5% had symptomatic, and 8.9% asymptomatic tumour enlargement.

Studies on the long-term effect of pregnancy on PRL hypersecretion have been sparse. In 1979 Cowden and Thomsen (16) reported on a hyperprolactinaemic woman in whom a BRCR-induced pregnancy was followed after breast-feeding by the return of spontaneous menstruations and normoprolactinaemia. Resolution of hyperprolactinaemia after BRCR-induced pregnancy has now been decribed in several papers (4, 12, 18, 71). However, there are only few reports on the long-term effects of pregnancy in women with hyperprolactinaemia (38).

In the present study 58 hyperprolactinaemic women were followed up for 1 to 9 years after at least one BRCR-induced pregnancy. The serum PRL level decreased markedly in 20 of the women (34%) after pregnancy, lactation and weaning. Four had become normoprolactinaemic. Only two women showed a significant increase in PRL secretion after pregnancy, but they had no symptoms or signs of tumour complications.

Spontaneous uterine bleedings returned in 16 of the 58 women after pregnancy (27%). All except two of these 16 women had PRL levels of < 100 ug/l before treatment. This group of women was followed up for 6 years without any evidence being found that the PRL levels increased again. The 15 women who experienced two term pregnancies had lower PRL levels in their serum after the second pregnancy than after the first, which confirms the observation that PRL hypersecretion seems to decrease after repeted pregnancy (19).

Prolactinomas and long-term bromocriptine treatment

The prolactinomas represent a common and complex clinical entity. Autopsy series have yielded evidence that pituitary microadenomas occur in 20 to 30 % of pituitary

glands examined during routine postmortem examinations. Approximately 40 % of these tumours stain positively for PRL (11, 15).

It is likely that micro- and macroprolactinomas are two distinct entities, one destined to enlarge, possibly rapidly (82), the other remaining inconsequential throughout most of the patient's life, although gradual tumour growth over decades is possible. Sisam et al. (76) found no evidence of even subtle tumour growth in 38 untreated hyperprolactinaemic women with microprolactinomas, who were followed up for an average of 31.7 months. In another study, 43 untreated hyperprolactinaemic patients were followed up for 3 to 20 years and signs of tumour enlargement were observed in only two patients (48). On the other hand, Pontiroli and Falsetti (66) reported the sudden development of radiologically verified prolactinomas in 14 of 65 hyperprolactinaemic patients followed up for 3 years.

In this present study 73 hyperprolactinaemic women were followed up for 5 to 13 years after the initial radiological examination of the sella turcica. Radiological signs of progression were noted in 25 of the 73 patients (34%). In seven women this progression occurred during pregnancy. Evidence of minor or major non-pregnancy-related progression during the follow-up period was found in 18 of the 73 patients. We were not able to find any factor such as PRL levels or grade of sellar asymmetry which could predict this progression. It is well known that there is a risk of pituitary tumour expansion during pregnancy in hyperprolactinaemic women. However, only one woman had serious clinical complications which demanded reinstitution of BRCR therapy. Twenty-two of the women had a term pregnancy without any radiological signs of progression. These results, like those of previous studies (3, 21), show that the risk of clinically significant tumour expansion during pregnancy is low. Radiological regression occurred in 14 women (20%). There was no difference in the mean serum PRL level before treatment between the group with progression and the group which showed regression.

The normal sella turcica varies markedly in shape (60). The pituitary gland itself occupies only 50-85% of the pituitary fossa (20). The gland is surrounded by venous plexus communicating with the sinus cavernosus. Therefore, the pituitary gland can increase considerably in size at the expense of venous filling and can even double in size during pregnancy without altering the bony margins of the sella (20). It is unlikely that minor changes in the shape or the bony margins of the sella turcica constitute evidence of an intrasellar lesion. In a study of 205 autopsy cases Muhr et

al. (57) found that asymmetries of the sellar floor with a slope of 2 to 14° and minor cortical changes were frequent, and correlated poorly to the presence of microadenomas. Furthermore, a normal-sized sella turcica can well harbour an adenoma in the pituitary gland. Still, it is probable that radiographical regressive or progressive changes of the sella turcica over time in individual patients are an expression of an increased or decreased tumour size.

Annual radiological examinations of the sella turcica have previously been recommended in the follow-up of the hyperprolactinaemic patients (2). Our present study shows, however, that from a clinical point of view such short intervals are unnecessary. In none of our patients did repeat sellar x-rays give any information which altered the clinical management. Furthermore, a disadvantage of standard coned down views and multidirectional tomography is that the change in size of an adenoma is only recorded indirectly. Modern radiological technology, such as computed tomography is superior to plain sellar x-ray as it provides information not only about the sella turcica but also about the pituitary gland itself. With this technique it is possible to detect and follow the changes in a microadenoma before a change in the configuration of the sella turcica appears (10). Weiss et al (89) concluded that computed tomography rather than endocrine or ophthalmological evaluation provides the best index of early tumour growth. However, standard radiological examination of the sella turcica is an easily performed low-cost examination, involving low radiation doses. It permits a preliminary evaluation of the sella turcica, if necessary before the use of more detailed procedures. Granular calcifications, a finding of unknown clinical meaning, were found in the anterior portion of the sella turcica, in six women (8%). This incidence is in agreement with the results of a compilation of 13 radiological series (13), where the incidence of granular calcifications within a pituitary adenoma varied between 0.3 and 14%. The aetiology of the calcifications is not known. Landolt and Rothenbühler (43) reported that calcification occurred in necrotic cells and classified this as dystrophic calcification. In contrast, Rilliet et al. (68) found histologically that calcifications were most frequently located extracellularly. They concluded, like Guay et al. (33), that the presence of calcification suggests a slowly growing neoplasm. In our study two patients showed progression of the calcific deposit accompanied by radiographical signs of regression of the sellar asymmetry. In one woman progression of the sellar asymmetry occurred without any change in calcification. Thus it is still unclear why

these calcifications develop and if they are of any clinical importance.

CV 205-502, a new dopamine agonist

Bromocriptine is the most widely used drug in the treatment of hyperprolactinaemic states. Despite a relatively long duration of action, prolonged suppression of serum PRL in human subjects usually requires oral administration 2 or 3 times a day. In addition, adverse reactions including nausea, emesis and hypotension are often seen at the beginning of the treatment, and sometimes such problem persist during therapy. These adverse reactions together with the need for multiple doses during the day, have prompted a search for a new compound with greater potency for inhibiting PRL secretion without a concomitant increase in undesirable effects.

A short-term study with CV 205-502, a new long-acting dopamine agonist, showed that this drug effectively inhibited PRL secretion for at least 24 hours. It was found that the highest used dose of 0.06 mg was most effective but probably not optimal, as two of the women did not become normoprolactinaemic. In most of the patients in whom the PRL level was restored to normal, this happened within 6 hours after the first dose of CV 205-502. The side effects were all transient and mild. Several of the patients who had experienced severe side effects during bromocriptine treatment had no problem in tolerating CV 205-502.

The prolonged study confirmed the efficacy of single daily doses of CV 205-502 in suppressing PRL secretion and in restoring menstrual function. Seventy per cent of the women became normoprolactinaemic. In a previous study (5) it was found that BRCR restored ovulatory function in about 90% of patients with hyperprolactinaemia. One explanation for the difference between CV 205-502 and BRCR in the effect on the serum PRL levels may have been that the patients in the CV 205-502 trial included a high proportion of women who had been hyporesponders to previous dopamine agonist treatment. Secondly, the treatment in this study was stopped at a dose of 0.175 mg daily. The treatment continued in 21 of the 24 women for further 6 months (max dose 0,325 ug/l). At 12 months' follow-up all except two of the women now were normoprolactinaemic. Both had been hyporesponders to previous treatment with dopamine agonists. BRCR treatment has no uniform effect on PRL secretion, i.e. some patients need higher doses than others, even if their serum PRL levels are similar. According to Thorner et al. (81), it is not possible on the basis of

the pretreatment PRL level, the tumour size or the response to a single dose of bromocriptine, to determine in which patient the PRL level will fall to normal during chronic therapy. These authors speculated that the wide spectrum of results is most likely due to the differential sensitivity of the lactotrophs to dopamine stimulation. The same mechanism could explain why not all of our patients responded satisfactorily to CV 205-502 therapy.

One patient in our study achieved no therapeutic effect of CV 205-502 even though she had previously responded to BRCR. This example illustrates the fact that PRL suppression may vary significantly in the same patients in response to different dopamine agonists. Franks et al (27) showed that higher doses of pergolide mesylate did not markedly affect PRL secretion in BRCR-resistent women with hyperprolactinaemia. However, Kleinberg et al (40) described a patient in whom 30 mg of BRCR daily had no effect while 0.3 mg of pergolide mesylate per day normalized the serum PRL level. Furthermore, they found one woman who was unable to tolerate BRCR because of gastrointestinal distress but responded well to pergolide and one other woman who was unable to tolerate pergolide for the same reason but took BRCR without side effects. Thus, there seem to be marked individual variations in the response to different dopamine agonists.

Four of our hyporesponders had normal ovulatory function at the end of the study, according to the serum progesterone levels in the luteal phase of the menstrual cycle. Similar observations of restoration of gonadal function in women whose PRL levels were not suppressed to the normal range have been made previously (81). Thus the significance of the need to suppress PRL levels completely within normal limits remains to be established.

The adverse effects of CV 205-502 in this study were all mild and transient which is in agreement with another report (35). Most of the women who had experienced adverse effects during BRCR therapy had no tolerance problems while taking CV 205-502. Thus CV205-502 seems to be a valuable alternative to the dopamine agonists which are used today in the treatment of patients with PRL disorders.

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