BROMOCRIPTINE IN OBSTETRICS AND GYNAECOLOGY

Pages with reference to book, From 224 To 229

Parveen Haider (Department of Obstetrics and Gynaecology, Jinnah Postgraduate Medical Centre, Karachi.)

Bromocriptine, the active ingredient of Parlodel is a specific dopamine receptor agonist available for use in clinical practice. It has been successfully used in the treatment of hyperprolactinemia with associated amenorrhea, galactorrhea and infertility; in the inhibition of postpartum lactation; acromegaly and in Parkinson's disease. Its role in obstetrics and gynaecology is strategic since it restores gonadal function and fertility. It decreases the size of prolactin secreting pituitary tumors, and has been used with varying degrees of success in the treatment of menstrual disorders, premenstrual syndrome and polycystic ovarian disease. Its role in the treatment of carcinoma cervix is beneficial, but not proven. Withdrawal of bromocriptine therapy however is associated with reversal of its beneficial effects and return of hyperprolactinemia. In this article the current knowledge about the pharmacologic effects and individual clinical applications oLbromocriptine pertaining to obstetrics and gynaecology have been reviewed.

Pharmacology

2 Br - alpha - ergokryptine mesylate (Bromocriptine) is a semisynthetic ergot alkaloid, that was specifically developed in 1967, as an inhibitor of prolactin secretion. It was introduced into clinical research in 1969 and was shown to directly stimulate neuronal dopamine receptors[1-3]. Since prolactin is undertonic inhibition of dopamine[4,5] bromocriptine acting as a receptor agonist markedly inhibits its secretion[6]. After oral administration, 28% is absorbed from gastrointestinal tract, and peak plasma concentration. is achieved 1 to 3 hours after ingestion[2,3]. First pass metabolism of the absorbed dose is extensive (94%) and only 6% reaches the systemic circulation unchanged. Excretion occurs exclusively in faeces (98%) and only 2% of the dose appears in urine[1-3]. Serum prolactin levels remain suppressed for about 14 hours after a single dose and after that no bromocriptine is detectable in circulation[2]. Side effects can be separated into two major groups, those noticed with initiation of therapy and those associated with long term treatment. Initial effects include nausea, vomiting and orthostatic hypotension, that can be minimized by starting therapy with alow dose given at bed time with food, and gradually increasing it until a therapeutic response is achieved ,3 With long term treatment headache, fatigue, abdominal cramps, constipation, nasal congestion and digital vasospasm may be noted. Intense visual hallucinations, erythromelalgia, reversible, pleuropulmonary changes including pleural thickening and effusion and even urinary incontinence have been described[2,3,7]. The therapeutic role of bromocriptine in different disorders is discussed below.

Hyperprolactinemia

Hyperprolactinemia is an increasingly recognized cause of amenorrhea, galactorrhea and infertility in females and impotence and infertility in males[2,8]. Its incidence ranges from 13 to 50% (mean 24%) in women with amenorrhea. Galactorrhea is present in 30-79% of hyperprolactinemic women, although it is less common in men[8]. The commonest cause is a pituitary tumor[2]. This may be a macroadenoma (greater than 10mm diameter) or a microadenoma (less than 10mm diameter) [9]. In general serum prolactin levels may reflect tumor size. In patients with levels less than 100ng/ml, often no discrete tumour is identifiable at surgery. Patients with prolactin levels of 100-250ng/ml usually have microadenomas, and those with levels greater than 250ng/ml have macroadenomas[2]. It has been shown that about 12% non-pregnant women with amenorrhea during their reproductive life have 'pituitary prolactinoma syndrome' and this proportion rises to 50% if galactorrhea is also present[10]. Hyperprolactinemia may also result from hypothalamic damage due to infection, tumor, trauma or

irradiation; or may be drug induced (reserpine, methyldopa, phenothiazines, metoclopramide). It may be seen in hypothyroidism, renal or liver diseases, following physical or psychological stress, breast stimulation, chest wall lesions and with the use of oral contraceptives[2,8,10]. In the absence of any other cause, it is usually considered that hyperprolactinemia is due to pituitary disease, even if the lesion is not demonstrable radiographically[11]. Since its introduction into clinical practice, 'bromocriptine' has been shown to reduce circulating prolactin levels irrespective of the cause[12,13]. Many studies have shown the efficacy of bromocriptine in decreasing prolactin levels, suppressing galactorrhea and restoring cyclic menses in women[8,14,15]. Reviewing the literature Vance et al[2] have shown that within a month of beginning, of bromocriptine therapy, 73 - 100% women will attain normal menstrual function and documented ovulation in 57 to 100% cases. Whereas most patients have a lowering of prolactin levels to normal range, afewmaynot achieve this response. However these patients may also attain gonadal function despite the lack of complete suppression of prolactin[12]. Additionally, bromocriptine is also effective in restoring fertility in normoprolactinemic women with unexplained infertility and galactorrhea[16]. Bromocriptine is now proposed as the first line of treatment for prolactinomas[13]. In patients with macroadenomas, there have been many reports of the efficacy of bromocriptine in suppressing prolactin levels, reducing tumor size, improving visual fields and restoring gonadal function[2,8,17-20]. Dramatic clinical improvement and reduction in tumor size without the risk of hypopituitarism is compelling evidence for recommending bromocriptine in treatment of macroadenomas[2,8]. Bromocriptine also has a beneficial effect in reducing serum prolactin levels and decreasing the size of prolactin secreting microadenomas with cessation of galactorrhea and return of cyclic menses[21]. Non- functioning pituitary tumors may also be responsive to bromocriptine therapy, [22]but this suggestion is controversial and requires further evaluation. The beneficial effect of bromocriptine on pituitary tumors is achieved by various mechanisms. Other than lowering prolactin levels, it has been shown to have a specific antimitotic action on pituitary tumors in animal models[22]. The reduction in tumor size is also accomplished by a direct necrosing or a cytocidal effect on tumor cells[20]. Nevertheless, bromocriptine therapy does not result in a permanent cure, for withdrawal results in return of hyperprolactinemia and tumor re-expansion2'8'23.

Hyperprolactinemia and pregnancy

When a woman with hyperprolactinemia is successfully treated, her chances of becoming pregnaat are the same as those of a normal woman[2]. In bromocriptine treated hyperprolactinemic women with pituitary tumors, conception rate varies from 37.5 to 81%[2]. The main problem encountered during pregnancy is the risk of pituitary tumor expansion[10]. Genizel and Wang[9] have estimated this risk to be 35% in women with macroadenomas; but in women with microadenomas, the risk of pregnancy induced tumor expansion is much less. Bromocriptine not only restores fertility, but it has been observed that in bromocriptine induced pregnancies, the risk of tumor related complication is much smaller[24,25]. Bergh et al[25] reported the clinical course and outcothe of 19 bromocriptine induced term pregnancies and found severe pituitary tumor related complication in one patient only. Mornex et al[24] did not report any complication in 7 pregnant women with clear cut adenomas. This can be attributed to the anti-mitotic action of bromocriptine[22] that can possibly shrink pituitary tumors. Pregnancy does not have any long term adverse effect on hyperprolactinemic state. Fifty eight women with at least one bromocriptine induced pregnancy were followed up for 13 to 108 months. Following pregnancy, prolactin levels decreased by more than 50% in 20 women. Only 2 women shoWed an increase in prolactin levels, during long term follow up. This suggests that pregnancy does not make prolactin hypersecretion worse[26]. Teratogenicity and outcome of pregnancy have been carefully assessed. Turkalj et al[27] reporting the outcome of 1410 pregnancies, found no associated increased risk to the

fetus. The incidence of spoutaneous abortion, extra uterine pregnancy and malformations in offsprings of women treated with bromocriptine during a portion of pregnancy were comparable to normal population. Even continuous administration of bromocriptine throughout pregnancy resulted in the birth of children whose subsequent mental and physical development observed upto the age of 6 years. was normal[28]. Nevertheless it is recommended that bromocriptine therapy should be discontinued soon after conception on general principle that unnecessary medication should be avoided during pregnancy. Furthermore bromocriptine crosses placenta and suppresses fetal qrolactin levels, and long term effects of this are unknown[2].

Puerperal lactation

Although several hormones interact at the breast for puerperal lactation to occur, prolactin secretion is needed for initiation and maintenance of galactopoiesis[4,5]. Therefore a logical method to suppress lactation is to reduce prolactin secretion. Treatment of puerperal women with bromocriptine inhibits both basal and suckling induced prolactin secretion and provides a more physiological method of suppressing lactation[2,29]. Within 24 to 48 hours after beginning treatment, bromocriptine lowers prolactin levels to normal, blocks initiation of lactation and prevents breast engorgement and mastodynia[2]. Controlled trial of bromocriptine compared with placebo has proved its superiority in preventing breast congestion and engorgement. However 25% incidence of rebound breast engorgement was observed when bromocriptine was given for 8 days only[30]. Cook and associates[31] found a 14 day course of 2.5mg twice daily effective in lowering prolactin levels, reducing milk production, breast congestion and pain as compared to placebo. Comparing bromocriptine and estrogen treatment, bromocriptine has been found to be more effective in preventing rebound mammary engorgement, although both agents effectively suppress lactation[30,32]. Moreover there is no risk of thromboembolic disease with bromocriptine, and this is a distinct advantage over estrogen preparation[2]. Bromocriptine has been equally effective in suppressing lactation once it is established32 and in reducing milk yield in puerperae with polygalactia[33]. The most effective dose schedule is 2.5mg twice daily during the first two weeks followed by 2.5mg once daily for the third week[2].

Luteal phase insufficiency

Menstrual cycle with a short luteal phase may be a distinct entity occurring in 3 to 11% of infertile women[34,35]. The syndrome is characterized by inadequate secretion of progesterone and early regression and degeneration of corpus luteum with menses occurring 6 to 9 days after the mid cycle peak of lutenizing hormone[2]. The etiology is unknown but subnormal levels of 17 estradiol and FSH suggest an inadequate replication & follicular cells with delayed development of a small follicle and consequent evolution of a defective corpusiuteum. Alternately the cause could he attributed to a primary ovarian defect[34]. Prolactin directly appears to influence steroid secretion[36] and the function of corpus luteum[2]. Mild hyperprolactincmia has been found in 40-47% women with luteal insufficiency[37,38]. Bromocriptine 2.5mg daily, resulted in reduction of serum progesterone levels and prolongation of luteal phase. It was also effective in prolonging luteal phase in normoprolactinemic women. [37] Using the same dose, Lehtovirta et al[38] also demonstrated the beneficial effect of bromocriptine in luteal insufficiency. Luteal phase was significantly prolonged but plasma proçsterone levels remained unchanged. However Smith et al[39] failed to demonstrate lengthening of luteal phase with bromocriptine therapy. But because a significant percentage of women have responded to bromoeriptine, a trial of 2.5mg twice daily may. be worth while; success however may not be absolute[2].

Idiopathic edema

It is a poorly understood disorder occurring predominantly in women of reproductive age, and involves fluid retention in absence of any cardiac, hepatie or renal pathology[2]. A gain in excess of 1.4kg during

the day is an essential clement in the diagnosis[2]. The cause is not fully understood, but there appears to be an alteration of peripheral dopaminergie function as evidenced by decreased urinary excretion of dopamine[40] Norbiato et al[41] have suggested a dopaminergic control of renin and aldosterone and an alteration of this control may play a role in the pathogenesis of idiopathic edema. Dopamine agonists therefore have a place in the treatment of this condition. Dent and Edwards[42] reported beneficial effect of bromoeriptine in a study of 5 women with idiopathic edema. Three had a significant decrease in diurnal weight gain and 2 reported symptomatic improvement. Sowers and colleagues[43] examined the effect of bromoeriptine therapy (2.5mg three times a day) in patients with idiopathic edema and found a favourable response. Bromocriptine therefore appears to be beneficial in the treatment of this subgroup of patients.

Premenstrual syndrome

It is characterized by mental symptoms, headache, mastodynia, peripheral edema and abdominal distension[2]. The etiology remains unknown, however suggestions have ranged from cyclic fluctuation of sex steroids to psycho genie influences, but no theory has gained general acceptance[2]. Horrobin (1974) and Halbriech et al (1976) have reported an association between elevated levels of prolactin and premenstrual tension syndrome[44]. Bromoeriptine can therefore play an important role in alleviating premenstrual symptoms. Anderson and collegues,44 comparing the effect of placebo and bromocriptine, showed that medication considerably improved all the premenstrual symptoms, but mastodynia was the only one where bromocriptine was better than placebo. Elsner et al[45] reported significant improvement in breast tenderness, bloating and depression on bromocriptine therapy. Durning and Sellwood[46] also proved the superiority of bromocriptine over placebo in reducing cyclical breast pain, tenderness and nodularity. Comparing bromocriptine and norethisterone Ylostab et al[47] proved the effectiveness of bromoeriptine with regards to premenstrual symptoms. However nore thisterone was better tolerated. Anderscb et al[48] compared bromocriptine and diuretic bumetanide in 19 women. Overall[11] of the 19 women thought that bromocriptine was more effective. The dose in all these studies was 2.5mg twice daily. Although the results of these studies are provocative yet bromocriptine does not appear to be consistently effective in the treatment of premenstrual syndrome.

Polycystic ovarian syndrome

The syndrome of polycystic ovarian disease results from excessive androgen production stimulated by elevated levels of lutenizing hormone. These elevated LH levels can be reduced by dopamine infusion[49] suggesting a relative dopamine deficiency in women with polycystic ovarian syndrome. Gonzalez[50] and Buvat et al[51] have suggested that women with polycystic ovarian syndrome may have a defect in central dopaminergic tone. There are therefore theoretical reasons for bromocriptine to become a therapeutic option in these patients[50]. Adrenal involvement in PCOS has also been proved and bromocriptine is known to decrease the adrenal contribution to androgenic pool in these patients[52]. This could be another mechanism whereby bromocriptine exerts its beneficial effect. Spruce et al[53] reported favourable response in 20 patients with PCOS treated with 7.5mg bromocriptine daily for upto 1 year. and found a significant reduction in LHlevels, LH/FSH ratios and plasma testosterone leading to restoration of cyclic ovarian function and a subjective improvement in hirsutism. However Murdoch et al[54] unable to find any evidence to support a therapeutic role for bromocriptine in these patients. There were no significant changes in biochemical parameters; no improvement in hirsutism[54,55]. and the ovulatory response was disappointingly low[55]. Nevertheless to ascertain the role of bromocriptine in PCOS, further trials are required.

Carcinoma cervix

In 1981, Guthrie et al[56] reported a case of advanced carcinoma cervix that achieved remission lasting

more than 7 years when treated with a combination of bromocriptine and aprotinin. In a subsequent trial, on bromocriptine alone, out of 18 patients with Ca cervix all having received primary treatment, he reported tumor stasis in three and very long remissions in five cases. [57] Encouraged by thise results Donath and Schindler[58] began a trial of bromocriptine in women with persistent cervical intra epithelial neoplasia and reported a positive influence. In all these trials, bromocriptine was given in a dose of 2.5mg twice daily for prolonged periods. However Praest and Klem[59] using the same dose failed to demonstrate a beneficial effect of the drug on reôurrent squamous cell Ca of cervix. The rationale for treating cancer patients with bromocriptine was that prolactin may depress certain anticancer defense mechanism, but precisely how this effect is achieved is still a matter of debate. Elevated levels of prolactin reduce cell mediated and enhance bumorally mediated responses. Hence bromocriptine by modulating immune responses can achieve favourable results. Alternately cervix could be a hormone target organ in relation to prolactin. If this is so,it is possible that certain carcinomas of cervix may be prolactin dependent and hence bromocriptine therapy could be effective in the same wçç as hormone therapy in Ca of breast and endometrium[56,57]

Breast cancer

Prolactin is a known mammary epithelial growth promoter. It is an important, perhaps anessentialhormone in the development phases of mouse mammary tumorigenesis[60] but its role in human breast cancers has to be ascertained. Bromocriptine has a beneficial effect on mammary tumors in mice, 0 but in patients with breast cancer it has been used with little success[61]. However used as an adjuvant perioperative therapy in a trial, bromocriptine has exerted a positive effect on primary tumor and can therefore modify the clinical course of the disease[62]. Larger trials are however required before bromocriptine can be accepted for adjuvant therapy in breast tancers.

Adenomyosis

Endocrine mechanisms for the geneses of adenomyosis are not clearlyunderstood. Based on an animal model Mori et al[63] have suggested that prolactin plays an important role in the development of this pathological state. Huseby and Thurlow[64] have also attributed chronic hyperprolactinemia as an etiologic factor in genesis of lesions resembling adenomyosis in a strain of mice. Consequently bromocriptine has been shown to exert a beneficial effect by completely inhibiting the development of experimental adenomyosis in animals[65]. However its role in human beings remains undetermined.

Other uses of bromocriptine

The beneficial effects of bromocriptine are not merely confined to obstetrics and gynaecology. There is documented evidence regarding its efficacy in Parkinson's disease and as adjuvant therapy in acromegaly[2]. It has been used in the management of various psychiatric disorders, hepatic encephalopathy, neuroleptic malignant syndrome. Huntington's chorea and tardive dyskinesia[2,66]. There have been reports of its use in benign prostatic bypertrophy, [67] in prostatic cancers, [68] in dermatological condilions like psoriasis[69] and in the prevention of cocaine craving[70] and alcohol withdrawal syndrome[71].

CONCLUSION

Bromocriptine hq been in clinical use for over 20 years. Although it was initially approved for the treatment of byperprolactinemia, suppiession of lactation and Parkinson's disease, the spectrum of its usefulness has now extended considerably. As more and more dilemmas about prolactin are being revealed, more and more indications for its use are coming up. Till safer and more effective dopamine agonists are available, bromocriptine will continue to enjoy the existing position it has in obstetrics and gynaecology.

ACKNOWLEDGEMENT

My sincere gratitude and thanks to Prof. S. Jafarey, Head of Department of Obstetrics and Gynaecology (JPMC) for the encouragement and help in the preparation of this paper.

REFERENCES

1. Bowman, W.C. and Rand, Mi. The endocrine system and drugs affecting endocrine system, in textbook of pharmacology 2nd ed. Oxford, Blackwell, Scientific Publications, 1980, p. 1910.
2. Vance, M.L., Evans, W.S. and Thorner, M.O. Bromocriptine diag. nosis and treatment drugs five years later. Ann. Intern. Med., 1984; 100 : 78.
3. Bianchine, J.R. Drugs for Parkinson's disease, spasticity, and acute muscle spasm, in Goodman and Gillman's the pharmacological basis of therapeutics. 7th ed. New York, Mac Millan, 1985, p. 473.
4. Best, C.H. and Taylor, N.B. The hypothalamic pituitary control system - prolactin, in physiological basis of medical practice. Edited by John B. West, 11th ed. London, William & Wilkins, 1985, p. 865.
5. Ganong, W.F. The pituitary gland, in review of medical physiology. 14th ed. Narwalk, Appleton & Lange, 1989, p. 338.
6. Fluckiger, E., Doepener, W., Marko, M. and Niederer, W. Effects of ergot alkaloids on the hypothalamic pituitary axis. Postgrad. Med. J., 1976; 52 (suppl. 1): 57.
7. Caine, M. Bromocriptine and urinary incontinence. Lancet, 1984; 1:228.
8. Johnston, D.G., Prescott, R.W.G., Kendalt Taylor, P., Hall, K. and Crombie, AL. Hyperprolactinemia. Long term effects of Bromocriptine. Am. J. Med., 1983; 75 : 868.
9. Gemzell, C. and Wang, C.F. Outcome of pregnancy in women with pituitary adenoma. Fertil. Steril., 1979; 31: 363.
10. DeSwiet, M. Diseases of pituitary and adrenal glands, in medical disorders in obstetrics and practice. Oxford, Blackwell, 1984, p.405.
11. Thorner, M.O., Edwards, C.R.W., Charlesworth, M., Dacie, J.E., Moult, P.J.A., Rees, L.H., Jones, A.E. and Besser, G.M. Pregnancy in patients presenting with hyperprolactinemia. Br. Med. J., 1979; 2:771.
12. Thorner, M.O., Schran, H.P., Evans, W.S., Rozol,A.D., Morris,J.L. and Mac Leod, R.M. A broad spectrum of prolactin suppression by bromocriptine in hyperprolactinemic women; a study of serum prolactin and bromocriptine levels after acute and chronic administration of bromocriptine. J. Clin. Endocrinol. Metab., 1980; 50 1026.
13. Prolactinomas; Bromocriptine. Rules O.K. Lancet, 1982; 1: 430.
14. Spark, R.F., Pallotta, J., Naftolin, F., Clemens, R. Galactorrhea -amenorrhea syndromes: etiologyand treatment. Ann. Intern. Med., 1976; 84:532.
15. Gomez, F., Reyes, F. I. and Faiman, C. Nonpuerperal galactorrhea and hyperprolactinemia; clinical findings, endocrine features and therapeutic responses in 56 cases. Am. J. Med., 1977; 62: 648.
16. DeVane, G.W. and Guzick, D.S. Bromocriptine therapy in normoprolactinemic women with unexplained infertility and galactorrhea. Fertil. Steril., 1986; 46: 1026.
17. Von Werder, K., Fahlbusch, It, Landgraf, R., Rickardt, C.R., Rjosk, H.K. and Scriba, P.C. Treatment of patients with prolactinomas. J. Endocrinol. Invest., 1978; 1: 47.
18. George, S.R., Burrow, G. N., Zinman, B. and Ezrin, C. Regression of pituitary tumors, a possible effect of bromergocryptin. Am. J. Med., 1979; 66: 697.
19. Velentzas, C., Carras, D. and Vassilouthis, J. Regression of pituitary prolactinomas with bromocriptine administration. JAMA., 1981; 245: 1149.
20. Huseman, C.A., Rizk, 0. and Hahn, F. Long-term bromocriptine treatment for prolactin-secreting macroadenoma (letter). Am. J. Dis. Chiid., 1986; 140: 1216.

21. Archer, D.F., Lattanzi, D.R., Moore, E.E., Harger, J.H. and Herbert, DL. Bromocriptine treatment of womenwith suspected pituitaryprolactin secreting microadenomas. Am. J. Obstet. Gynaecol., 1982; 143: 620,
22. Johnston, D.G., Hall, K., McGregor, A., Ross, W.M., Kendalt Taylor, P.K. and Hall, R. Bromocriptine therapy for "nonfunctioning" pituitary tumors. Am. J. Med., 1981; 71: 1059.
23. Bergh, T., Nillius, S.J. and Wide, L. Menstrual function and serum prolactin levels after long-term bromocriptine treatment of hyperprolactinemic amenorrhea. Clin. Endocrinol., 1982; 16 : 587.
24. Mornex, R., Orgiazzi, J., Hugues, B., Gagnaire, J. and Clàustrat, B. Normal pregnancies after treatment of hyperprolactinemia with bromoergocryptine despite suspected pituitary tumors. J. Clin. Endocrin. Metab., 1978; 47: 290.
25. Bergh, T., Nillius, Si., Enoksson, P., Larsson, S.G. and Wide, L. Bromocriptine-induced pregnancies in women with large prolactinomas. Clin. Endocrinol., 1982; 17: 625.
26. Rasmussen, C., Bergh, T., Nillius, 5.5. and Wide, L. Return of menstruation and normalization of prolactin in hyperprolactinemic women with bromopiptine-induced pregnancy. Fertil. Steril., 1985; 44: 31.
27. Turkalj, I., Braun, P. and Krupp, P. Surveillance of bromocriptine in pregnancy. JAMA., 1982; 247: 1589.
28. Konopka, P., Raymond, J.P., Merceron, R. E. and Seneze, 5. Continuous administration of bromocriptine in the prevention of neurological complications in pregnant women with prolactinomas. Am. J. Obstet. Gynaecol., 1982; 146: 935.
29. Jacobs, H. S. and Wright, C.S. Bromocriptine in obstetrics and gynaecology. Br. J. Hosp. Med., 1978; 20: 652.
30. Varga, L., Lutterbeck, P.M., Pryor, 5.5., Wenner, it and Erb, H. Suppression of puerperal lactation with an ergot alkaloid. A double blind study. Br. Med. 5., 1972; 2: 743.
31. Cooke, I., Foley, M., Lenton, E. et al. Treatment of puerperal lactation with bromocriptine. Postgrad. Med. J., 1976; 52 (Suppl. 1) :75.
32. Brundel, R.E.R., Del Pozo, B., De Grandi, P., Friesen, H., Hinselmann, M. and Wyss, H. Prolactin inhibition and suppression of puerperal lactatith by a Br - ergocryptine (CB 154); a comparison with estrogen. Obstet. Gynaecol., 1973; 41 : 884.
33. Peters, F., Geisthovel, F. and Breckwoldt, M. Serum prolactin levels in women with excessive milk production. Normalization by transitoryprolactin inhibition. Acta Endocrinol., 1985; 109 : 463.
34. Sherman, B. M. and Korenman, S.G. Measurement of plasma L.H., F.S.H. estradiol and progesterone in disorders of human menstrual cycle; the short luteal phase. 5. Clin. Endocrinol. Metab., 1974; 38: 89.
35. Jones, G.S. The tuteal phase defect. Fertil. Sterit., 1976; 27: 351.
36. McNatty, K.P., Sowers, R. and McNeilly, A.S. A possible role for prolactin in control of steroid secretion by the human Graafian follicle. Nature, 1974; 250 : 653.
37. Muhlenstedt, D., Bohnet, H.G., Hanker, J.P. and Schneider, H.P. Short luteal phase and prolactin. Tnt. 5. Fertil., 1978; 23 : 213.
38. Lehtovirta, P., Arjoinaa, P., Ranta, T., Laatikainen, T., Hirvonen, E. and Seppala, M. Prolactin levels and bromocriptine treatment of short luteal phase. Tnt. J. Fertil., 1979; 24: 57.
39. Smith, S.K., Sobowale, 0., Lenton, E.A. and Cooke, ID. Effect of bromocriptine on menstrual cycle length. Br. J. Obstet. Gynaecol., 1984; 91:251.
40. Kuchel, 0., Horky, K., Gregorova, I., Marek, J., Kopecka, J. and Kobilkova, J. Inappropriate response to upright posture; a precipitating factor in the pathogenesis of idiopathic edema. Ann. Intern. Med., 1970; 73: 245.
41. Norbiato, 0., Bevilacqua, M., Raggi, U., Micossi, P., Nitti, F., Lanfrçdini, M. and Barbieri, S. Effect of metoclopramide a deopaminergic inhibitor, on renin and aldosterone in idiopathic edema; possible therapeutic approach with levodopa and carbidopa. J. Clin. Endocrin. Metab., 1979; 48: 37.

42. Dent, R.G. and Edwards, O.M. Idiopathic edema; a study of the effects of bromocriptine. Clin. Endocrinol. (Oxf), 1979; 11: 75.
43. Sowers, J., Catania, R., Paris, J. and Tuck, M. Effects of bromocriptine on renin, aldosterone, and prolactin responses to posture and metoclopramide in idiopathic edema; possible therapeutic approach. J. Clin. Endocrinol. Metab., 1982; 54 :510.
44. Anderson, A.N., Larsen, J.F., Steenstrup, O.R., Svendstrup, B. and Neilsen, J. Effects of bromocriptine on the premenstrual syndrome. A double-blind clinical trial. Br. J. Obstet. Gynaecol., 1977; 84:370.
45. EIsner, C.W., Buster, J.E., Schindler, It A., Nessim, S.A. and Abraham, G.E. Bromocriptine in the treatment of premenstrual tension syndrome. Obstet. Gynaecol., 1980; 56: 723.
46. Durning, P. and Sellwood, R.A. Bromocriptine in severe cyclical breast pain. Br. J. Surg., 1982; 69: 248.
47. Ylostalo, P., Kauppila, A., Puolakka, J., Ronnberg, L. and Janne,
47. Bromocriptine and norethisterone in the treatment of premenstrual syndrome. Obstet. Gynaecol., 1982; 59: 292.
48. Andersch, B., Hahn, L., Wendestam, C., Ohman, It and Abrahamsson, L. Treatment premenstrual syndrome with bromocriptine. Acta Endocrinol., 1978; 88 (Suppl 216): 165.
49. Leblanc, H., Lachelin, G.C.L., Abu-Fadil, S. and Yen, S.S.C. Effects of dopamine infusion on pituitary hormone secretion in humans. J. Clin. Endocrinol. Metabol., 1976; 43: 668.
50. Gonzalez, E. It Dopamine agonists for polycystic ovary disease. JAMA., 1982; 248 : 514.
51. Buvat, J., Buvat-Herbaut, M., Marcolin, 0., Racadot, A., Fourlinnie, J.C. and Fossati, P. Acute effects of bromocriptine on gonadotrophin secretion in polycystic ovary syndrome. Fertil. Steril., 1985; 44: 356.
52. Tabbakh, G.H., Lutfi, LA., Azab, I., Rahman, H.A., Aleem, F. A. and Southren, L.A. A controlled clinical trial for the effect of bromocriptine on adrenal contribution in polycystic ovarian disease. Acta Endocrinol., 1987; 114: 161.
53. Spruce, B.A., Kendall- Taylor, P., Dunlop, W., Anderson, AJ., Watson, MJ., Cook, D.B. and Gray, C.The effect of bromocriptine on polycystic ovary syndrome. Clin. Endocrinol., 1984; 20 : 481.
54. Murdoch, A. P., McClean, 1(0., Watson, M.J., Dunlop, W. and Taylor, P.IC. Treatment of hirsutism in polycystic ovary syndrome with bromocriptine. Br. J. Obstet. Gynaecol., 1987; 94 :358.
55. PoIson, D.W., Mason, H.D. and Franks, S. Bromocriptine treat- ment of women with clomiphene-resistant polycystic ovary syndrome. Clin. Endocrinol., 1987; 26: 197.
56. Guthrie, D., Ross, W.M., Latner, A.L., Turner, G.A. and Way, S. Effective treatment of a patient with an advanced carcinoma of cervix with a combination of bromocriptine and aprotinin. Br. J. Clin. Pract., 1981; 35 : 330.
57. Guthrie, D. Treatment of carcinoma of the cervix with bromocriptine. Br. J. Obstet. Gynaecol., 1982; 89: 853.
58. Donath, E. M. and Schindler, A.E. Treatment of cerrvical dysplasia with bromocriptine. Lancet, 1984; 2: 157.
59. Praest, J. and Klem, V. Treatment of recurrent carcinoma of the cervix with bromocriptine. Br. J. Obstet. Gynaecol., 1986; 93 : 519.
60. Welsh, C.W.and Gribler, C. Prophylaxisofspontnneouslydeveloping mammary carcinoma in C3H/HeJ female mice by suppression of prolactin. Cancer Res., 1973; 33: 2939.
61. Schulz, LCD., Czygan, PJ., Del Pozo, E. and Friesen, H.G. Varying response of human metastasizing breast cancer to the treatment with 2 - Br - a-ergocryptine (CB-154). Case report, in human prolactin. Edited by J.L. Pasteels and C. Robyus, Amsterdam, Excerpta Medica, 1973, p. 268.
62. Fentiman, I.S., Chaudaiy, M.A., Wang, D.Y., Brame, K., Cam plejohn, R.S and Millis, R.R. Perioperativebromocriptineadjuvant treatment for operable breast cancer. Lancet, 1988; 1 : £09.
63. Mori, T., Nagasawa, H. and Takahashi, S. The induction of adrenomyosis in mice by intrauterine

pituitary isografts. Life Sci., 1981; 29: 1277.
64. Huseby, LA. and Thurlow, S. Effects of prenatal exposure of mice to “low-dose” diethylstilbestrol and the development of adenom yosis associated with evidence of hyperprolactinemia. Ant. J. Obstet. Gynaecol., 1982; 144: 939.
65. Mori, T. and Nagasawa, H. Alteration of the development of mammary hyperplastic alveolar nodules and uterine adenomyosis in S H N mice by different schedules of treatment with CB - 154. Acta Endocrinol., 1984; 107:245.
66. Jalbut, S.D. Bromocriptine treatment of neuroleptic malignant syndrome. J. Clin. Psychiatry, 1987; 48: 69.
67. Matos - Ferreira, A., Corte-Real, J., Palma, J. and Durao, V. The effect of bromocriptine in benign prostatic hypertrophy and vesico sphincteric dynamics. Br. J. Urol., 1987; 60: 143.
68. Jacobi, G.H., Altwein, J.E. and Hoherifellner, It Adjuvant bromocriptine treatment as palliation for prostate cancer; ex perimental and clinical evaluation. Scan. J. Urol. Nephrol., 1980; 55 (Suppl) : 107.
69. Weber, G., Neidhardt, M., Frey, H., Galle, K.. and Geiger, A. Treatment of psoriasis with bromocriptine. Arch. Dermatol. Res., 1981; 271 : 437.
70. Dackis, C.A., Gold, M.S., Sweeney, D.It, Byron, J.P. Jr. and dim ko, It Single-dose bromocriptine reverses cocaine craving. Psychiatry Res., 1987; 20: 261.
71. Borg, V. Bromocriptine in the prevention of alcohol abuse. Acta Psychiatr. Scand., 1983; 68: 100.