Bromocriptine: Past and present: From the In Vitro and In Vivo Experimental Studies to the Clinical Data

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Abstract

Bromocriptine is a drug introduced in the medical therapeutics in 1967, and since then it has been widely used in the treatment of hyperprolactinaemia. In experimental animals and in vitro experiments it inhibits prolactin secretion and the phasic secretion of gonadotrophins, while it does not seem to have an effect on growth hormone, or vasopressin secretion. Various central nervous effects, autonomic effects and cardiologic actions of bromocriptine have been reported on experimental animals during the first studies. After the initial evaluations, bromocriptine has been used in preventing lactation and galactorroea, in treating infertility, especially when related to hyperprolactinaemia, in prolactinomas of various sizes, in acromegaly and in Parkinson’s disease. Through the years of its clinical use, various acute and chronic side effects has been reported and closely monitored. Due to its need for continuous use and frequent dosage, effort has been undertaken to develop newer compounds with longer action and similar or better clinical effects. Although this has been achieved, bromocriptine due to its long clinical application and experience remains the drug with whom the actions of newer compounds are still compared. Resistance to prolactin level suppression and tumour size reduction is also frequently estimated for all dopamine agonists used in comparison with these seen after bromocriptine treatment. We present here the most important points of the numerous pharmaceutical studies on bromocriptine.

Introduction

First studies on the ergo-alkaloids and bromocriptine

Shelesnyak (1975), studying the mechanism of oocyte implantation in the rat, was the first to notice that some ergo-alkaloids decrease prolactin secretion (1). In 1954, in his first observations, Shellemsnak concluded that these drugs act either on the hypothalamus or the pituitary. Later Zeilmaier and Garlen (1962) (2) showed that one of the ergoalkaloids, ergocorcin acts directly on the pituitary. Naturally then, there was a question of how much the action of these drugs in the pituitary was clinically applicable and with what way it was connected with the other properties of these drugs. In the decade of the 60’s, a systematic research for the ergo-alkaloids and their derivatives has started with the aim to produce a compound that reduced the prolactin action. During these years the obstacle in such a research was the lack of a method to estimate prolactin levels in the blood. Thus for the initial evaluation of the action of these drugs several bioassays were used (e.g. the inhibition of leukocytosis in vaginal smears of rat with pseudocyesis, or the inhibition of oocyte implantation in fertilized rats). All these initial methods had the disadvantage that they excluded the short acting drugs (3, 4). Also another method that was used in the evaluation of these drugs was the inhibition of lactation both in humans and in mammals (5, 6). The results of these initial researchs of the decade of the 60’s led to the production of the 2Br-a-methyl-ergocriptine (CB154-bromocriptine mesylate) (Parlodol, Providel) in 1967 (illustration 1) (7, 8). Since then, many analogs have been used, but bromocriptine remains the most widely tried drug in hyperprolactinaemia.

Chemistry

The ergot alkaloids can all be considered derivatives of the tetracyclic ergoline skeleton and can be divided into two main groups based on their structural characteristics (9). The first group includes all lysergic acid derivatives of the acid amide types, such as amine alkaloids (ergonovine) and the structurally more complex ergopeptines (ergotamine, ergocristine). The second group includes the so-called “clavicle alkaloid” derivatives that contain either a methyl or a hydroxymethyl group at position 8 (9). The ergot alkaloids and their derivatives have a wide spectrum of pharmacological actions that include central, neurohumoral and peripheral effects, mediated by norepinephrine, serotonin, and dopamine receptors. The diversity of biological properties of ergot derivatives is likely to be due to diverse mechanisms of action at the cellular and molecular level (9). Because the ergot derivatives interact with different
receptor sites, it is not surprising that these drugs (as well as the natural alkaloids) display a number of side effects (9).

Bromocriptine has initially been used in the treatment of hyperprolactinaemia (8), but at the time of its discovery, the type of action of the drug was unknown. It was later that it was shown that it acts on the dopaminergic receptors; what exactly happens from the moment that the drug is bound to the cell receptors in order to exert its action still remains unclear. In fact, till the 70’s, even the existence of prolactin was not sure and then the growth hormone was thought to be the human lactogen hormone. The discovery of bromocriptine and the isolation of prolactin were almost simultaneous. Friesen and his co–workers isolated prolactin in 1971 (10), and this also led to the development of a special and sensitive radioimmunoassay for human prolactin (11).

With the use of the sensitive prolactin assays, the physiology of prolactin secretion was studied and hyperprolactinaemia was established as the commonest human hypophysial disorder (12, 13, 14). It is important to remember that it was established as a clinical entity, at the same time that the suitable drug was ready for its effective treatment. With 2-3 clinical trials, it was shown that the drug acts stimulating the dopaminergic receptors (15,16). In the next few years, dopamine was established as the basic hypothalamic factor in prolactin inhibition (17). Due to its properties, bromocriptine was also used in the treatment of both acromegaly and Parkinson’s disease.

**Endocrinological action of bromocriptine**

**Inhibition of prolactin secretion**

Bromocriptine inhibits prolactin secretion in all mammals and fishes that have so far been examined (18), either under physiological conditions or during the phase that the hormone secretion is stimulated with physiological, pharmacological or surgical criteria.

**Area of action**

When bromocriptine is added to pituitary cell cultures, it inhibits prolactin secretion in vitro (19). Thus, the belief that the drug acted directly on the lactotrophs was firmly established. The experimental in vivo experience also proved the direct effect of bromocriptine on the pituitary. The drug inhibits the TRH – induced stimulation of prolactin (20), decreases plasma prolactin in the presence of ectopic pituitary (21), and the increased prolactin levels in rats that have been treated with reserpine and a-methyl-\(\pi\)-tyrosine (22).

**Mechanism of bromocriptine action**

Bromocriptine reduces prolactin secretion without influencing directly the hormonal synthesis but with reducing the out cellular events (23). After the drug ingestion, initially an increase of pituitary prolactin is noticed (24), while protracted use leads to a decrease of the quantity and concentration of the hormone (25).

In rats, where oestrogens were given, simultaneous treatment with bromocriptine decreases prolactin levels, DNA synthesis and the mitotic activity of the pituitary (26, 27). It appears that the continuous inhibition of prolactin secretion leads to a decrease of the cell metabolism and the ability for mitotic division.

The bromocriptine-induced inhibition of prolactin secretion in the rats, is overpowered by chlorpromazine. As already known, chlorpromazine is an inhibitor of the dopamine receptors’ antagonists in a dose dependent degree (18).

Prolactin secretion in vitro is increased, when cAMP is increased (28), this ability though is inhibited in the presence of bromocriptine (29) or dopamine (30). Both dopamine and bromocriptine reduce the basic action of adenyl cyclase in rat pituitaries (31). Opposite views though have been mentioned by other researchers and a few believe that both these substances have no effect on the enzyme activity (32).

Since calcium is indispensable both for the action of potassium and TRH in the prolactin secretion and since bromocriptine antagonizes these two stimulatory influences (18, 20), it was concluded that the drug reduces the hormonal plasma levels by either decreasing the intracellular quantity of calcium or affecting the cell membrane receptors function.

Classically, dopamine receptors have been divided into D1 receptors, which stimulate adenyl cyclase activity, and D2 receptors, which inhibit this enzyme (33, 34, 35); three further discrete receptors subtypes have been described (D3, D4 and D5) with less activity on prolactin secretion (34). Dopamine inhibition of prolactin secretion is mediated by the D2 dopamine receptors expressed by the normal and tumorous lactotrophs (33, 34, 35). D2 receptors belong to the family of G protein – coupled receptors, characterized by a single polypeptide chain containing seven hydrophobic transmembrane domains; besides their effect on adenyl cyclase, they are able to inhibit...
inositol phosphate production (36) with an effect that involves G proteins sensitive to pertussis toxin (33, 34, 35, 36). Additionally, dopamine inhibits arachidonic acid release from pituitary cells independently from other mechanisms (37). Two isoforms generated by alternative spicing of the D2 receptors have been described (38). These two isoforms differ by a 29–amino acid sequence located within the intracytoplasmic domain that interacts with G proteins; dopamine inhibition of adenyl cyclase activity is observed with both isoforms.

The inhibition of cAMP levels is a key step in the inhibition of prolactin release by dopamine (39). It is likely that the dopaminergic ergot derivatives share similar mechanisms of action (40).

Dopamine agonists reduce the size of prolactinomas by causing a reduction in cell volume (via an early inhibition of the secretory mechanism, and a late inhibition of gene transcription and prolactin synthesis), as well as causing perivascular necrosis and partial cell necrosis (41). There may also be an antimitotic effect. Histologically there is a reduction in secretory activity and cell size, an increase in immunoreactive prolactin cellular content and inhibition of exocytosis (42).

Effects on other pituitary hormones

Gonadotrophins

The bromocriptine effect on the gonadotrophin secretion has also been evaluated. The drug effect may or may not be identified with the dopaminergic activity. In fact, the neural control of the gonadotrophins has not been completely understood and there is still difficulty in explaining the action of these substances in the receptors.

Secretion

Bromocriptine brings new oocytic cycles in rats with pseudocyesis, or pseudocyesis can be produced by an ectopic source of prolactin secretion (21), or after ingestion of drugs that have an effect on the neural aminic functions (43). It appears that bromocriptine restores the basic gonadotrophic secretion in several species probably because it initially reduces the prolactin levels. Having in mind that dopamine is involved in the control of the gonadotrophin secretion (44), it is possible that bromocriptine has a direct action.

Inhibition of the gonadotrophin secretion

Bromocriptine inhibits the phasic secretion of gonadotrophins and the ovulation in young rats where premature cycle is induced after giving plasma of pregnant mare (45). In such animals, when a given dose inhibits prolactin surge, simultaneously both LH surge and ovulation is inhibited (45). In adult animals big doses are usually needed for both phasic secretion of the gonadotrophins and ovulation inhibition. The doses must be greater than those needed for the inhibition of prolactin increase before ovulation. These experiments show that in young animals the neural control of the phasic gonadotrophic secretion is different that this of the adult rats. Adult rats can take bromocriptine for a long time, without disruption of their cycle periodicity. But there is a time dependent aggregation of non active luteal bodies due to the repeated inhibition of the prolactin increase before ovulation (46). Thus, dopamine is involved in the control of LH secretion. The comparison of dopaminergic compounds activity as far as ovulation inhibition and implantation inhibition lead to the initial conclusion that these two properties are different (4).

Growth hormone

Bromocriptine does not seem to affect the growth hormone in experimental animals (23). In adult rats, where oestrogens are given, bromocriptine does not affect the growth hormone response (47). In rat cell cultured lines (GH3), bromocriptine has no effect in the basal levels of growth hormone (48). In similar experiments the drug has no effect in the potassium–mediated increase of this hormone (49), at least in concentrations that reduce prolactin secretion. On the contrary, bromocriptine has been found to reduce both prolactin and growth hormone secretion in adenomatous tissue taken from acromegalic patients (50).

Adrenocorticotrophic hormone (ACTH)

There are no many studies in animals where ACTH was estimated after the ingestion of bromocriptine. Indirectly, it appears that the drug has no intense effect on ACTH levels. In rats, long duration treatment with bromocriptine has not caused increase or reduction of the weight of the adrenals or a difference in the corticosterone plasma levels (51). In cows during lactation, doses of bromocriptine that reduced prolactin secretion, had no effect on the cortisol levels (52).

Effect of bromocriptine on the hormones of the posterior pituitary

Vasopressin (AVP)
In rat experiments, bromocriptine does not affect the water excretion (18) and appears that the vasopressin secretion is not affected by the drug. Of course with long term use of bromocriptine, at least in rats, there is reduction of osmolarity (53) and the special weight (54) of urine, but it is not known if this phenomenon is due to the direct effect of the drug in renal function, in prolactin reduction, or a mild inhibition of vasopressin secretion.

Oxytocin

In rats, the oxytocin secretion that is observed as a response to nursing (milk ejection test) during lactation is reduced by many ergoalkaloids (55). Bromocriptine though does not reduce the response to nursing (ejection) (22). There must be a inhibitory dopaminergic mechanism, that regulates the oxytocin secretion in rats (in vitro studies) (56).

Effect on the peripheral endocrine system

Organs producing steroid hormones

Bromocriptine produces changes in stereoidogenesis. Initially they were thought as a result of changes in prolactin levels and not as a direct effect of the drug at the peripheral endocrine organs. When a dose of bromocriptine is injected the fifth day into the rat oocyte, an increase of the 20a hydroxy steroido-dihydrogenase is noticed, which does not happen the sixteen day of pregnancy. Prolactin injection abolishes the 20a hydroxyl steroid-dihyrogenase (57). Long term ingestion of bromocriptine in male rats causes decrease of the circulating testosterone levels (58). The role of prolactin in testicular function has been well documented in the past (59). It is also known that prolactin plays some role in the stereoidogenesis that takes place at least in the rat adrenals (60).

Other peripheral endocrine organs

Dopamine increases the cAMP production and the parathormone secretion in vitro (61). It appears that dopamine in the parathyroid cells acts through the D1 receptors (62). But the effect of bromocriptine in the cells of the parathyroid glands is not exactly known.

Renin secretion in dogs (63) and insulin and glucagon secretion in humans (64) are both stimulated by the dopamine effect. Again there are no experimental data for the bromocriptine effect on these hormones.

Effect on the central nervous system

Bromocriptine influences the extrapituitary areas of the brain. Sometimes its action is obvious in doses similar to those they cause prolactin suppression, other times though there is need for higher doses.

Autonomic functions

Bromocriptine shows strong emetic effect in dogs (ED50 7.5 µg/kg IV or 11.4 µg/kg SC). When it is given IV, bromocriptine is three times less potent (as far as the emetic behavior is concerned) from the a – ergocriptine and 2.5 times less from ergotamine. The drug reduces the body temperature of rats that have been exposed to cold environment, action that is abolished by the dopamine agonists, pimozide (65), haloperidol and sulpiride (66). It appears that the thermorythmisis is based in the dopaminergic behaviour. When reserpine is given to the rats for hypothermia induction, bromocriptine increases the body temperature, while the action is reversed by administration of sulpiride (67). Haloperidol reverses the hyperthermia induced by small bromocriptine doses, but has no effect when big doses are given. In contrast cyproheptadine suppresses the hyperthemic action of both small and big bromocriptine doses (68). This phenomenon explains that dopamine has both dopaminergic and serotoninergic action.

Movement activity

In small rodents, bromocriptine has a biphasic effect in movement activity (69). The first hour, after the subcutaneous injection of bromocriptine into the rats, a deduction in exploratory activity is observed. Similar behavioral changes are observed after apomorphine and l-dopa, while amphetamine (which releases the endogenous catecholamines) increases the exploratory activity. After the initial reduction of movement activity, both bromocriptine and l-dopa cause a stimulation of the moving behaviour which lasts from the second till the fifth hour.

Stereotypies

Like apomorphine, d-amphetamine and l-dopa, bromocriptine cause stereotypic behaviour in rodents (69) which consists of repetitive biting or sneezing. Stereotypy is achieved through stimulation of the dopaminergic receptors and is inhibited by pimozide (69), selective antagonist of the dopaminergic receptors (70). In hamsters, bromocriptine does not cause stereotypic behaviour, but the sensitivity of these animals increases with time or with the simultaneous giving of d – amphetamine or apomorphine (71).

Cardiologic action of bromocriptine
IV injection of bromocriptine in continually increasing doses up to 18.7 µg/kg in anaesthetized cats (18) has shown that after a dose of more than 0.1 µg/kg, both the cardiac rhythm and arterial blood pressure are reduced (18). While the IV injection (10 µg/kg) has no effect, when it is given inside the ventricles, reduces the blood pressure up to 30 mmHg. This action lasts approximately for 2 hours. In parallel, there is also bradycardia. Bromocriptine reduces blood pressure, when given to dogs, and its action is also proportional to the dose and to the way of the drug is given. The initial effective dose is 6 µg/kg and usually the drug should be given intravenously. In these experimental animals rarely bradycardia is encountered. The action of the drug in the cardiac rhythm and pressure can be suppressed, when haloperidol, ergometrine or methyl-ergometrine are previously given (72, 73, 74). All these initial studies have shown that the hypotensive properties of bromocriptine are due to the action of this substance in three possible areas: 1) CNS, 2) endings of the sympathetic neurons 3) smooth muscles. In all three cases, bromocriptine action is due to the stimulation of the dopaminergic receptors.

**Clinical relevance of bromocriptine (illustration 2)**

**Lactation**

The normal lactation process can be suppressed by giving 2.5 mg bromocriptine 2-3 times per day. If this dose is given for three weeks, the milk production stops and does not reappear. Comparing the bromocriptine suppressing effect on lactation to this of oestrogens, bromocriptine is safer, since the thromboembolic risk is smaller. Furthermore, after bromocriptine use, fertility reappears four weeks after delivery, in those women they nurse though three months are needed.

**Galactorroea**

Whatever the galactorroea cause, treatment with bromocriptine (5-10 mg per day) in divided doses restores both prolactin in normal levels and the milk suppression within a week. When galactorroea is due to the use of neuroleptic drugs or to very high prolactin levels, doses of bromocriptine up to 50 mg per day may be needed.

**Infertility**

Infertility may be seen even when the prolactin levels are slightly elevated. Treatment with bromocriptine restores both prolactin levels and fertility. 4-12 weeks are enough to restore the menstrual cycle in women with amenorrhoea and potency to males. In refractory cases, the treatment may be prolonged up to 6-12 months, if needed. In women with polycystic ovary syndrome (high dehydroepiandrosterone levels), commonly (20%) high prolactin levels are also noticed. Bromocriptine decreases both the increased levels of dehydroepiandrosterone and prolactin. When there is no hyperprolactinaemia, it does not appear that bromocriptine restores fertility. A similar phenomenon is seen in anorexia nervosa. Bromocriptine is effective only if there is concomitant hyperprolactinaemia. In infertile women with short luteal phase, (5 days), and temporary hyperprolactinaemia, or low progesterone values, bromocriptine restores the menstrual cycle. Thus, it is obvious that bromocriptine restores fertility that is related to hyperprolactinaemia.

**Premenstrual tension syndrome**

When bromocriptine is given at a dose of 2.5 mg 1-3 times per day, 5-15 days before the menses appear, it seems that it causes reduction of the reported symptoms.

**Breast cancer**

Bromocriptine has not shown promising results in breast cancer.

**Parkinson’s disease**

Bromocriptine has been tried in Parkinson’s disease. It appears that the dose should be high. In some cases, doses up to 200 mg per day have been used. Levodopa has been tried in Parkinson’s, but it shows many side effects. Bromocriptine can in such cases substitute levodopa, because although it has lower action, its effect has longer duration.

**Prolactinomas**

These adenomas are relatively common cause of infertility. Usually bromocriptine (2.5-10 mg three to four times daily) reduces hyperprolactinaemia and restores fertility. Furthermore, it ameliorates visual fields and reduces the size of the adenomas (75).

**Acromegaly**

Most of the acromegalics, after treatment with bromocriptine (5-10 mg three times daily), show reduction of the growth hormone levels. The growth hormone levels though do not fall as easily as prolactin ones. Although the decline of growth
hormone is obvious within the first week, clinical improvement often needs 8 weeks of treatment. Best results are obtained with high doses (10-20 mg three times daily for 6 months). The clinical improvement is greater than that expected in comparison with the reduction of the levels of growth hormone. Patients that show concomitant hyperprolactinaemia, show a better response. In no case though can bromocriptine replace the operation, when it is needed.

Side effects of bromocriptine (Illustration 3)

There is no doubt that bromocriptine has been a useful drug. Despite this, the drug administration often leads to side effects, although there has never been mentioned a permanent lesion after bromocriptine use. There are though some patients that they are more sensitive than others. Some side effects are only seen when very big doses are used. Finally, some side effects are observed especially in some patients such as psychiatric and parkinsonian ones. The bromocriptine side effects are divided in acute (onset of therapy) and chronic (after long term administration of the drug). The side effects of bromocriptine resemble very much those of l-dopa. They all stem from the diffuse stimulation of the central and peripheral dopaminergic receptors. Vasospasm, erythromelalgia, lack of tolerance of alcohol and peptic bleeding are side effects that characterize exclusively bromocriptine.

Acute side effects

Usually, nausea, emesis and orthostatic hypotension. The appearance of these side effects vary depending on the disease for which the patient is treated. Young normal subjects who took the drug experimentally taking part in clinical studies are more prone to develop acute side effects. The hyperprolactinaemic subjects are also prone to develop acute side effects, while acromegals are more resistant. It is rare to notice these symptoms in women who take bromocriptine, either after parturition or for lactation suppression. The intensity of these side effects can be reduced when the drug is given concomitantly with small quantities of food just before sleep. When the patient is lying down these side effects are usually avoided. In patients that developed these side effects it is usually preferable to increase the dose more slowly than usual. Rarely hyperprolactinaemic patients need doses more than 7.5 mg per day, while on the contrary parkinsonians and acromegals may need 10-80 mg per day. Usually with the small doses of bromocriptine, only few side effects are seen in the beginning of therapy.

Chronic side effects

When small doses of bromocriptine are used, rarely there are such side effects that demand the discontinuation of therapy. Acromegals, although they usually take big bromocriptine doses, rarely show such side effects that the treatment should be discontinued. Parkinsonians, on the contrary, many times show intense side effects that the drug may need to be discontinued.

Headaches

Mild headaches are observed often in the beginning of treatment with bromocriptine. They are rarely serious and usually are temporary.

Gastrointestinal side effects

Symptoms from the gastrointestinal system are rare. After the administration of big doses, mild dyspepsia may be noticed. Usually these symptoms resemble those of gastrooesophageal feedback and they are relieved when the patient lies down. Gastrointestinal bleeding after the administration of bromocriptine has been observed (76), but there is no evidence about its frequency.

Vasospasm

It has been noticed initially in patients taking big doses of bromocriptine. It has been seen in up to 30% of the acromegals (77, 76) and in parkinsonians (78). It is not an ergotism phenomenon, because it is not followed by pain or finger ischaemia and because it is relieved as soon as the dose of the drug is reduced.

Alcohol non tolerance

In a 10% of patients, immediately after the beginning of treatment with bromocriptine, non tolerance of alcohol develops especially for quantities they used to consumed in the past. With the continuation of therapy this side effect usually disappears.

Side effects seen in Parkinson’s disease

Dyskinesia

Choreoathetoid movements of the limbs and the head and neck muscles are a characteristic side effect of l-dopa, when it is administered in big doses for the treatment of parkinsonism. The movements can mimick any movement disorder such as dystonia and myoclonus. The precise mechanism that leads to
patients taking bromocriptine may show a syndrome erythromelalgia using small dose for the treatment of prolactinomas. These adverse effects appear to be dose-dependent and they are not usually seen when administered of l-dopa, administration of bromocriptine can produce exactly the same phenomena even if they continue taking l-dopa or not. Despite this, the dyskinesia that is produced by bromocriptine seems to be less dramatic.

Psychiatric disturbances

Parkinson’s disease, if left without treatment, shows mental disturbances, such as depression, dementia, hallucinations or illusions (79). But also any antiparkinsonic treatment can cause or worsen similar psychomental disturbances. At least 20% of the parkinsonians that take anticholinergic drugs report psychiatric disturbances. The same symptoms are also seen in patients who take l-dopa. With the administration of l-dopa, hallucinations of paranoid type may be seen. With the use of bromocriptine, the danger for such side effects is even greater. In the initial stages of toxicity, with either l-dopa or bromocriptine, the patients complain for frequent and intense dreams that quickly lead to nocturnal hallucinations. Slowly a complicated system of hallucinations is organized that is characterized by visual hallucinations and paranoid ideation. These side effects of bromocriptine are seen exclusively in patients with Parkinson’s disease. Their severity parallels the existing neurological disorder. Discontinuation of the drug leads to amelioration of the mental condition, although for full improvement a few weeks are usually needed. The decision for stopping the drug is a dilemma, because in some patients the neurological disorder is so much worsen that they face the danger of aspiration, vein thrombosis or infection of the urogenital tract. The clinician then finds him/herself in a difficult position to choose between a destructive parkinsonism and a dramatic psychotic condition.

Rarerly, in patients with Parkinson’s disease treated with very high doses of bromocriptine, pulmonary infiltrates, fibrosis, pleural effusions, pleural thickening and retroperitoneal fibrosis have been described (80, 81, 82). These adverse effects appear to be dose-dependent and they are not usually seen when using small dose for the treatment of prolactinomas.

Erythromelalgia

Patients taking bromocriptine may show a syndrome that is characterized by red, sensitive and oedematous limbs, that is followed by a sense of local heat and dysphoria. The symptoms usually affect the lower limbs, but they may affect the upper limbs or even the knees. The whole clinical picture is followed by polyarthralgia and increased sedimentation rate. This clinical picture is also exclusively seen in parkinsonic patients who take big doses of bromocriptine for a long time. Of these patients, only a 10% show erythromelalgia. After discontinuation of bromocriptine, this syndrome virtually disappears within 3 – 4 days.

On the whole, the adverse effects of bromocriptine may be grouped into three categories: gastrointestinal, cardiovascular, and neurological (83). Symptoms as already said tend to occur after the initial dose and with dosage increases, but can be minimized by introducing the drug at a low dosage (0.625 or 1.25 mg/day) at bedtime, by taking it with food, and by very gradual dose escalation (40). Sometimes, tolerance to the adverse effects develops, but occasionally, therapy withdrawal or dose reduction followed by a more gradual reintroduction is required. Up to 12% of patients are unable to tolerate therapeutic doses of bromocriptine (84). Usually though the initial side effects mentioned above can be avoided by taking the drug at bedtime or while recumbent, but tolerance usually develops rapidly making this precaution unecessary after the first few days. From the symptoms they have not been mentioned so far, some infrequent psychiatric side effects need to be considered. Bromocriptine, even in low doses has been associated with mania in postpartum patients (83, 84, 85) and signs and symptoms of psychosis or exacerbations of preexisting psychosis have been associated with the use of bromocriptine (86, 87, 88). Turnet et al., observed de novo psychotic reactions in 8 of 600 patients treated with bromocriptine or lisuride (88). The symptoms which included auditory hallucinations, delusional ideas, and mood alterations, entirely remitted when the drug was reduced in dose or discontinued (89). The safety of the drug in the psychiatric population subjects remains to be established, although in a short-term trial in which bromocriptine was given to 16 individuals with psychiatric disorders who were previously stabilized on neuroleptic agents, exacerbations of psychosis was not observed (89). Some other psychiatric symptoms associated with higher doses of bromocriptine, include anxiety, depression, confusion, auditory hallucinations, hyperactivity, disinhibition, insomnia, day-time somnolence, and paranoia (84, 88, 90). Other rarer side effects include paraesthesia, nightmares, blurred vision, diplopia (high doses) and reversible ototoxicity.
(in patients with chronic liver disease) (83, 84). CSF rhinorrhea has been reported during treatment with bromocriptine, not only post surgically, but also in the absence of prior radiotherapy or surgical intervention due to tumour shrinkage, when the tumour previously served as an obstacle for the tumour – induced skull base defect (91,92, 93, 94, 95, 96). Reports from post partum women have suggested a causal association between the use of bromocriptine and hypertension, thromboembolic events, severe leucopenia, hyponatraemia and oedema (97, 98, 99, 100, 101). Although, the causative association is not proven, in the United States, the FDA has determined that bromocriptine should not be used to treat postpartum lactation.

In a small group of patients at low doses of bromocriptine (5-10 mg/daily), transient asymptomatic increases in serum alkaline phosphatase and/or transaminases have been reported (83,84). Hyponatraemia has been associated with the use of bromocriptine in patients with cirrhosis and hepatic encephalopathy (101).

The use of bromocriptine, when taken for only the first few weeks of gestation, has not been associated with an increase in the rates of spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations in a very large number of pregnancies (102, 103). In a study which undertook a long term follow up of 64 children, between the ages of 6 months and 9 years, who were born to mothers who took bromocriptine for a limited duration in early pregnancy, have shown no adverse effects on childhood development (104). Data on infant outcomes of approximately 100 women who used bromocriptine throughout pregnancy revealed abnormalities in 2 infants, one newborn with an undescended testicle and one with a talipes deformity (105). So far from all the available data on dopamine agonists and pregnancy, bromocriptine has the largest safety database and has a proven safety record for pregnancy. The incidence of malformation in the offspring is not greater than that in the general population. In case during pregnancy, reinstitution of a dopamine agonist is needed to control tumour growth, some of the drugs that have been used are lergotrile, pergolide and lisuride. All three act by binding the dopamine receptors of the lactotrophs and showed that they are capable of reducing prolactin secretion in vitro. Clinically pergolide was the strongest drug with the longest duration of action (107, 108). In a study of 47 patients (all had hypersecretion of growth hormone (109)), pergolide was given once daily and the results were validated after three months. 35 of these patients showed normal prolactin levels after 3 months and only 2 of them had levels a bit higher than the normal range, while another 2 had a 38-58% reduction only. The clinical trial for pergolide has shown its potency to reduce tumour size as shown previously for bromocriptine. A 30 months’ study at Baylor has compared the results of both action of bromocriptine and pergolide. 40 patients (28 women and 12 men) have been studied randomly. Others took bromocriptine and others pergolide. Before the study,

Controlling high prolactin levels in most of the patients. But there have been disadvantages in bromocriptine action.

The fact that the drug usually is given at a dose of 2.5 mg three times daily, means that the patient depends absolutely from this frequent administration. In diseases such as acromegaly and parkinsonism, the doses had to be greater, the intervals of administration are many times per day. Taking tablets many times per day has been very problematic for many patients and this eventually led to patients’ reduced tolerance.

The initiation of bromocriptine treatment has been followed by side effects as presented above (eg, nausea, emesis, and arterial hypotension). These first side effects have made through the years many patients to be hesitant in the continuation of the treatment.

Discontinuation of bromocriptine administration is followed by the re – increase of prolactin levels to the initial high values. In the case the drug has caused decrease of the tumour growth, its discontinuation often is followed from its re-increase (106).

Although, the bromocriptine value is undisputable, the fact that it may given for life, and that its discontinuation may lead in the recurrence of the disease, is definitely a disadvantage. For years the researchers have tried to overcome the disadvantages of bromocriptine and discover substances with greater effectiveness, longer action and the lack of disease recurrence after their discontinuation.
it has been estimated the degree of hyperprolactinaemia based at the hour fluctuations of prolactin during a 24 hour period and the size of the tumour with computerized tomography. Both drugs proved to be effective to reduce the prolactin values and the size of the tumour. These patients that did not responded to pergolide, eventually responded to bromocriptine (108). Thus it has been proved that the patients that do not respond to one dopamine agonist may respond to another. In the past a study at St Bartholomews, compared the in vitro effect of four ergoalkaloids on prolactin secretion using the principle of a perfusion system (110). The action of lisuride (5 nmol/l), lergotrile (5nmol/l) and pergolide (50 nmol/l) was compared to this of bromocriptine (5 nmol/l). In these doses, bromocriptine and lisuride had at least 3 hour duration of action after their removal from the system, while lergotrile and pergolide had a shorter duration of action. Thus these initial studies showed that in comparison with dopamine, lergotrile was 2.5 more potent, bromocriptine 13, lisuride 15 and pergolide 23. This was the initial study that has proved that lisuride and bromocriptone were long acting drugs in vitro.

We also proved the action of the newer to bromocriptine compounds, CV 205-501 (currently quinaagolide) and COP 201-403, both produced by Sandoz Pharmaceutical Ltd) and comparing their effects we noticed that they both were effective in low doses (0.1 nM) and that their duration of action was long; a hundred times bigger dose of bromocriptine had an effect that did not last as long as these two compounds on suppressing prolactin secretion (111, 112). After this initial study on newer to bromocriptone compounds, many followed both in vitro and in vivo so new compounds evolved in the market currently used in parallel with bromocriptine and due to their longer duration of action after their removal from the system, while lergotrile and pergolide had a shorter duration of action. Thus these initial studies showed that in comparison with dopamine, lergotrile was 2.5 more potent, bromocriptine 13, lisuride 15 and pergolide 23. This was the initial study that has proved that lisuride and bromocriptone were long acting drugs in vitro.

**Dopamine agonist/bromocriptine resistance**

Although dopamine agonists are successful in normalizing plasma prolactin levels, alleviating symptoms of hyperprolactinaemia and reducing tumour size, some patients with prolactinomas do not show a satisfactory response to these drugs (113). This phenomenon means that prolactinomas show a variable response to dopamine agonists, and may respond completely at one end or at the other end of the spectrum they may show a total resistance. Resistance is not related to drug non tolerance, since the second phenomenon means that the drug side effects prevent the clinician to achieve an effective response.

Why some prolactinomas do not respond to dopamine agonists is not fully understood. There is no doubt that the substantial genetic heterogeneity of these tumours complicates our ability to find out the factors responsible for drug resistance. There is experimental evidence that some dopamine agonist-resistant prolactinomas have a reduced density of D2 receptors (114, 115, 116) The lactotroph dopamine D2 receptor is most probably involved in the pathogenesis of dopamine agonist resistance. Limited studies of prolactinomas have not revealed mutations of the D2 receptor. There is though evidence that some dopamine agonist resistant prolactinomas have lower density of D2 receptors (114). Pellegrini et al., in cell cultures of prolactinomas reported a 50% reduction of D2 dopamine receptors in drug resistant prolactinomas compared to sensitive ones (114). Some of these tumours actually showed only 10% of the binding D2 receptor sites compared with those seen in responsive prolactinomas (116). Caccavelli et al., (117) found a 4-fold lower level of D2 receptor mRNA and a 5-fold lower number of D2 binding sites among bromocriptine-resistant compared with bromocriptine-sensitive prolactinomas, but Kovacs et al. (118), demonstrated preservation of both D2 receptor mRNA and protein expression in their prolactinoma resistant to dopamine agonist therapy (118). Thus, the absence of D2 receptor expression is not a universal finding among prolactinomas resistant to dopamine agonist therapy. There is also a possibility of differences in the proportion of short (D2S) and long (D2L) dopamine receptor variants in drug resistant prolactinomas, since in sensitive prolactinomas, the short and long receptor isoforms are found in equivalent proportions (117). By contrast, the proportion of mRNA corresponding to the D2S was found to be lower in resistant prolactinomas compared to sensitive ones (119). Abnormal coupling of the D2 receptor to Gai2 proteins and a reduction in Gai content cannot be excluded (120, 121). A role of autocrine pathways of inhibitory growth signaling in the development of dopamine agonist resistance in human prolactinomas cannot also be excluded.

A nerve growth factor (NGF)-mediated autocrine loop that controls proliferation and differentiation in pituitary lactotrophs has been identified (122). Dopamine sensitive prolactinomas secrete high levels of NGF and express the NGF receptors (123). From various
in vitro studies, it appears that NGF regulates D2 receptor expression (inducing p75NGF receptor-mediated nuclear translocation and activation of nuclear factor-kB) (124, 125). NGF also promotes a conformational change in the tumour suppressor p53 that permits its nuclear translocation and reconstitutes its DNA binding activity (126). Thus, although, some resistant to dopamine agonists prolactinomas are associated with a reduction in D2 density, they do not seem to show alterations in receptors’ binding activity. Also some agonist resistant prolactinomas may exhibit disruptions in the autocrine growth factor signaling pathway mediated by NGF, and this may contribute to tumour progression.

Resistance to dopamine agonists has been estimated to be in 24, 13, and 11% of patients for bromocriptine, pergolide and cabergoline, respectively. Resistance to other dopamine agonists such as quinagolide is difficult to estimate, since there are no large published series. Most of the clinical data regarding dopamine agonist resistance involve studies investigating whether another dopamine agonist may be effective in patients resistant to bromocriptine. Of all the dopamine agonists, cabergoline has been shown to be most effective in normalizing prolactin levels in patients resistant to bromocriptine. Approximately 80% of bromocriptine resistant patients normalize their prolactin on cabergoline. Approximately 85% of 20 patients resistant to both bromocriptine and quinagolide, responded with prolactin normalization, and 70% responded with some change in tumour size (127). In a larger study, 70% of 58 patients unresponsive to bromocriptine were controlled on cabergoline, although higher than average doses were required. It is possible that cabergoline can be effective in patients resistant to bromocriptine due to its higher affinity for dopamine binding sites, its greater occupancy of the receptor, and slower elimination rate from the pituitary (128).

**Resistance to tumour reduction**

Comparison among dopamine agonists for their relative ability for tumour size reduction has been attempted in several studies. In one series of study, with 27 patients, bromocriptine normalized increased prolactin levels in 66% of patients (12 months’ assessment), and caused a 50% reduction of tumour size in 64% of patients (129). Cabergoline (24 months’ assessment), in 26 patients normalized increased prolactin levels in 100% of patients and caused a 50% tumour size reduction in 96% (130). Another study in the same series involved the effect of pergolide (27 months’ assessment) where 22 patients were studied: Plasma increased prolactin levels normalized in 68% of patients and in 86% of patients a 50% tumour reduction size was estimated (131). Since the tumour reduction in size may continue up to one year in these studies it is possible that the effect of bromocriptine on tumour mass effects is underestimated. Thus, in concluding from these studies, with respect to lack of normalization of prolactin levels, resistance is expected in 25 – 50% of patients taking bromocriptine, in 10 – 30% in those taking pergolide, and in 5 – 18% of those taking cabergoline. With respect to failure to achieve at least a 50% decrease in tumour size, resistance can be expected in about one third of those taking bromocriptine, about 15% of those taking pergolide, and 5 – 10% of those taking cabergoline.

**Dopamine agonist/bromocriptine withdrawal**

Dopamine agonist treatment of prolactinomas gives excellent results, as far as normalizing prolactin levels, restoring gonadal function and reducing tumour size, particularly in view of the reported recurrence of hyperprolactinaemia after surgery (132, 133, 134, 135). The principal disadvantage of dopamine agonist treatment has been its supposed lifelong requirement. In the first study on results on bromocriptine withdrawal, it was reported that although prolactin levels remained significantly lower than those before treatment, they remained within the normal range in only 2 of the 37 treated patients. After withdrawal of bromocriptine, remission rates have been reported from as low as 0-9% (136, 137, 138, 139) to as high as 20-44% (140, 141, 142, 143, 144, 145). In patients though with only macroprolactinomas van’t Verlaat and Croughs (146) reported a remission rate in 8% of 12 patients after 12 months. After bromocriptine discontinuation, an increase in tumour size (clear-cut reexpansion) has been found in less than 10% of cases (147, 148, 149).

**Conclusion**

Bromocriptine has been valuable in treating various disorders especially hyperprolactinaemia of variable aetiology. Due to its effectiveness and also to its long-term use in clinical practice, new drugs are being compared both in their duration of action, but also in their effectiveness in prolactin reduction levels and also tumour reduction with bromocriptine in order to draw conclusive data (150). Practically though it still constitutes one of the valid first line treatments for hyperprolactinaemia.
References


53. Mahajian KK, Manku MS, Davidson H, James MF, Robinson CJ and Horrobin DF. Renal interaction of


110. Delitala G, Yeo T, Grossman A, Hathway NR and Besser GM. A comparison of the effects of four ergot-derivatives on prolactin secretion by dispersed...


Illustrations

Illustration 1

Bromocriptine Chemistry
Illustration 2

Clinical relevance of bromocriptine

Illustration 2 : Clinical relevance of bromocriptine

1. Lactation suppression
2. Galactorroea suppression
3. Infertility treatment (hyperprolactinaemia (prolactinoma), polycystic ovary syndrome, anorexia nervosa, short luteal phase defect)
4. Premenstrual tension syndrome relieve
5. Treatment of Parkinson's disease
Acromegaly treatment
Illustration 3

Side Effects of bromocriptine

Illustration 3: Side Effects of bromocriptine

Side effects at the beginning of treatment
1. nausea
2. emesis
3. postural hypotension

Side effects during chronic treatment
A. In all patients
1. headaches
2. gastrointestinal side effects
3. vasospasm
4. alcohol non tolerance

B. In patients with Parkinson’s disease
1. dyskinesia
2. psychiatric disturbances
erythromelalgia
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