PRODUCT MONOGRAPH

BROMOCRIPTINE

Bromocriptine Mesylate Tablets USP
2.5 mg

Bromocriptine Mesylate Capsules USP
5 mg

Prolactin Inhibitor

Growth Hormone Suppressant in Acromegaly

Adjunctive Medication in Parkinson's Disease

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THERAPEUTIC CLASSIFICATION

Prolactin Inhibitor

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ACTIONS AND CLINICAL PHARMACOLOGY

BROMOCRIPTINE (bromocriptine mesylate) is a dopaminomimetic ergot derivative with D_2 type dopamine receptor agonist activity, and has also D_1 dopamine receptor antagonist properties.

Bromocriptine inhibits the release and synthesis of prolactin by acting directly on the prolactin secreting cells of the anterior pituitary. In patients with acromegaly, apart from lowering prolactin and elevated levels of growth hormone, bromocriptine has a beneficial effect on clinical symptoms and on glucose tolerance.

The dopaminomimetic activity of bromocriptine in nigro-striatal pathway is considered responsible for the clinical benefits seen in patients with Parkinson's disease.

The metabolism of dopamine, from exogenous and endogenous origin, is known to involve the formation of peroxides and free radicals. It has been postulated that these agents may in fact contribute to the progression of Parkinson's disease by accelerating the rate at which neuronal cells are lost. Bromocriptine's metabolic pathway does not involve the formation of such peroxides and free radicals. It has been suggested that because bromocriptine attenuates the timing and rate of levodopa dosage increase, early use of the drug may reduce risk of formation of potentially toxic peroxides and free radicals.

In man, bromocriptine is rapidly absorbed after oral administration with an absorption half-life of approximately 0.3 hours. The amount absorbed is about 65 - 95% of the oral dose. About 7% of the dose reaches the systemic circulation unchanged, due to a high hepatic extraction rate and first pass metabolism. The plasma protein binding amounts to 96%. Bromocriptine is extensively metabolized by the liver. Only traces of the unchanged compound are found in urine, together with 2 major metabolites. Unchanged drug represents about 10 -15% of peak levels of radioactivity in plasma measured after a single dose of labelled drug. The active parent drug and the metabolites are primarily excreted via the liver, with only 6% being eliminated via the kidney. In plasma, the elimination half-life was between 2 to 8 hours for the parent drug and 50 to 70 hours for the metabolites after single oral doses.

The extreme variability in GI tract absorption and the extensive and individually variable first-pass metabolism are responsible for the broad variability in plasma concentrations of bromocriptine and, in part, for the variability in dose response.

Comparative Bioavailability

A comparative bioavailability study was performed using normal healthy human volunteers. The rate and extent of absorption after a single 7.5 mg dose of BROMOCRIPTINE 2.5 mg

tablets and PARLODEL 2.5 mg tablets was measured and compared. The results are summarized as follows:

	Bromocriptine	Parlodel₸	Percentage of Parlodel
AUC_T* (ng·h r/mL)	5.66 (16)	5.46 (23)	103.7
AUC_I* (ng·h r/mL)	7.00 (15)	6.72 (22)	104.2
C_{max}* (ng/mL)	0.99 (14)	0.99 (16)	100.0
T_{max}** (hr)	1.18 (0.33)	1.18 (0.35)	-
$t_{1/2}$** (hr)	6.09 (1.00)	5.95 (1.44)	-

* Geometric means (CV)

** Arithmetic means (SD)

₸ Parlodel (Sandoz) from a Canadian pharmacy

A second bioavailability study was performed using normal healthy human volunteers. The rate and extent of absorption after a single 10 mg dose of BROMOCRIPTINE 5 mg capsules and PARLODEL 5 mg capsules was measured and compared. The potency corrected results are summarized as follows:

	Bromocriptine	Parlodel₸	Ratio of Geometric Means (%)
AUC_T (pg · hr/mL)	511* 586 (51)**	514* 582 (47)**	99
AUC_I (pg · hr/mL)	618* 696 (48)**	610* 672 (43)**	101
C_{max} (pg/mL)	208* 224 (39)**	207* 227 (46)**	100
T_{max} (hr)	1 .39 (34)**	1 .29 (43)**	-
$t_{1/2}$ (hr)	2.44 (65)**	2.21 (53)**	-

* Geometric means
** Arithmetic means (CV)
₸ Parlodel (Sandoz) from a Canadian pharmacy

Note: The two summary tables simply serve as a convenient way of comparing the bioavailability of BROMOCRIPTINE and Parlodel within each study, not between studies. Due to advancement of analytical technology, the radioimmunoassay used in the capsule study for measuring plasma drug concentrations is evidently more selective and sensitive than the one used in the tablet study. This results in differences in observed pharmacokinetic parameter values between the two studies. Therefore, the results from these two studies should not be used as a basis for dose adjustment when switching between tablets and capsules.

INDICATIONS AND CLINICAL USE

Galactorrhea with or without amenorrhea due to hyperprolactinemia.

Prolactin-dependent menstrual disorders and infertility: e.g. secondary amenorrhea, ovulatory insufficiency and short luteal phase.

Prolactin-secreting adenomas: as a treatment for inoperable macroadenomas or prior to surgery in order to facilitate removal, and as an alternative to surgery in patients with microadenomas.

Prolactin-dependent male hypogonadism.

Acromegaly: the first-line treatment of this condition is by surgery or radiotherapy. BROMOCRIPTINE (bromocriptine mesylate) may be a useful adjunct to such treatment, and can be used as monotherapy in special cases.

Parkinson's Disease: BROMOCRIPTINE is effective when used as adjunct therapy to levodopa in the symptomatic management of Parkinson's Disease. Used concomitantly with levodopa, bromocriptine facilitates the use of lower doses of levodopa in early disease and attenuates the rate of increase in the levodopa dosages on long-term usage. In this way the risk of long–term complications such as prominent dyskinesias and/or end-of-dose failure can be reduced.

CONTRAINDICATIONS

Uncontrolled hypertension of pregnancy, a history of toxemia of pregnancy, sensitivity to ergot alkaloids. For procedure during pregnancy see "Use in Pregnancy" under PRECAUTIONS.

WARNINGS

In women with non-puerperal galactorrhea, reduction of prolactin levels may lead to resumption of normal menses. Following discontinuation of medication, galactorrhea returns in some patients and leads to suspicion of pituitary adenomas; a complete investigation at specialized units to identify these patients is advisable.

Treatment with BROMOCRIPTINE (bromocriptine mesylate) may effectively lower prolactin levels in patients with pituitary tumors but does not obviate the necessity for radiotherapy or surgical intervention where appropriate.

Long-term treatment (6-36 months) with bromocriptine in doses ranging from 20-100 mg/day has been associated with pulmonary infiltrates, pleural effusion and thickening of the pleura in a few patients. In those instances in which bromocriptine treatment was terminated, the changes slowly reverted towards normal.

To date, there have been seven (7) reported cases of retroperitoneal fibrosis occurring in parkinsonian patients on long-term treatment (15 months - 10 years) with bromocriptine at daily doses higher than 30 mg. To recognize retroperitoneal fibrosis at an early, reversible stage it is recommended to look for its manifestations (e.g. back pain, edema of the lower limbs, impaired kidney function) in this category of patients. BROMOCRIPTINE medication should be withdrawn immediately if fibrotic changes in the retroperitoneum are diagnosed or suspected.

Although there is no conclusive evidence which demonstrates the interaction between bromocriptine and other ergot alkaloids, the concomitant use of these medications is not recommended.

Particular attention should be paid to patients who have recently received other drugs that can alter the blood pressure.

PRECAUTIONS

BROMOCRIPTINE (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients, dizziness (vertigo) may occur with bromocriptine; patients should

therefore be cautioned against activities requiring rapid and precise responses such as driving an automobile or operating dangerous machinery until their response has been determined.

Care should be exercised when administering BROMOCRIPTINE concomitantly with phenothiazines or with other medications known to lower blood pressure. Dosage should be adjusted accordingly.

Alcohol should be avoided during treatment with bromocriptine. In some patients the concomitant use of bromocriptine and alcohol has given rise to alcohol intolerance and an increase in the severity and incidence of bromocriptine's possible adverse reactions.

Although there is no conclusive evidence demonstrating interactions between bromocriptine and other ergot derivatives, it is not recommended to administer concomitantly BROMOCRIPTINE and any drug with potential vasoconstrictor activity.

In patients being treated with BROMOCRIPTINE for galactorrhea, prolactin induced amenorrhea, menstrual disorders or acromegaly, infertility might be reversed by restoration of normal menses and ovulation. Women who do not wish to conceive should, therefore, use a reliable method of contraception. Since pregnancy may occur prior to initiation of menses it is recommended that a pregnancy test be conducted at least every four weeks during the amenorrheic period, and, once menses are reinitiated, every time a patient misses a menstrual period.

There have been occasional reports of gastrointestinal bleeding in acromegalic patients, both in those treated with bromocriptine and in those given a different or no medication. Until further data are available, therefore, acromegalic patients with a history or evidence of peptic ulceration should preferably be given alternative treatment. If bromocriptine must be used in such patients they should be instructed to report promptly any gastrointestinal reactions.

The use of BROMOCRIPTINE is not recommended for patients with uncontrolled hypertension or toxemia of pregnancy.

In postpartum women treated with bromocriptine mesylate, some rare serious adverse events (about 1 in 100,000) have been reported. These include hypertension, visual disturbances, myocardial infarction, seizures and strokes, or psychic disorders. In some patients the occurrence of seizures or strokes was preceded by severe headache and/or visual disturbances. Causal relationship of these events to the drug is uncertain.

Safety and efficacy of bromocriptine has not been established in patients with severe renal or hepatic disease.

Bromocriptine therapy has been demonstrated to be effective in the short term management of amenorrhea/galactorrhea. Data are not available on the safety or effectiveness of its use in long-term continuous dosage in this indication or in patients given repeated courses of treatment following recurrence of amenorrhea/galactorrhea after initial treatment. Recurrence rates are reportedly very high, ranging from 70 to 80%.

Bromocriptine should always be taken with food. In cases where adverse effects, such as nausea, vomiting and vertigo are severe or persisting, the therapeutic dosage of BROMOCRIPTINE should be reduced to half of one tablet daily (1.25 mg) and increased gradually to the recommended dose. The dopamine antagonist domperidone may be useful in the control of severe gastrointestinal side effects in Parkinsonian patients receiving bromocriptine (see Drug Interactions).

As with all medication, BROMOCRIPTINE should be kept safely out of the reach of children.

Use in Pregnancy: In patients receiving BROMOCRIPTINE, immunological confirmation of suspected conception should be performed as soon as possible and treatment stopped unless, in

the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus. In any event, the patient must be monitored closely throughout pregnancy for signs and symptoms which may develop if a previously undetected prolactin-secreting tumor enlarges.

In human studies with bromocriptine, there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took bromocriptine during early pregnancy.

Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous abortions (11.13%) in this group of pregnancies do not exceed those generally reported for such occurrences in the population at large.

Patients with pronounced enlargement of the sella turcica or a visual field defect should, in the first instance, be treated by surgery and/or radiotherapy. If pregnancy occurs in the presence of a pituitary microadenoma, close supervision throughout pregnancy is essential. This includes regular checking of the visual fields.

Small prolactin-secreting adenomas not detected previously may rapidly increase in size during pregnancy. Optic nerve compression may occur and emergency pituitary surgery or other appropriate measures may be necessary.

Use in Parkinson's Disease: Use of BROMOCRIPTINE, particularly in high doses, may be associated with mental confusion and mental disturbances. Since patients with Parkinson's Disease may manifest varying degrees of dementia, caution should be exercised when treating such patients with bromocriptine.

BROMOCRIPTINE administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction, but discontinuation of

bromocriptine may be required in some cases. Rarely, after high doses, hallucinations have persisted for several weeks following discontinuation of bromocriptine. Caution should be exercised when administering BROMOCRIPTINE to patients with a history of myocardial infarction, particularly if they have a residual atrial, nodal or ventricular arrhythmia.

Symptomatic hypotension can occur and, therefore, caution should be exercised when administering BROMOCRIPTINE, particularly in patients receiving antihypertensive medication. Periodic evaluation of hepatic, hematopoietic, cardiovascular and renal function is recommended.

Drug Interactions: The concomitant use of erythromycin may increase bromocriptine plasma levels.

Domperidone, a peripheral dopamine antagonist, may cause increases in serum prolactin. In so doing, domperidone may antagonize the therapeutically-relevant prolactin lowering effect of bromocriptine. It is possible that the anti-tumorigenic effect of bromocriptine in patients with prolactinomas may be partially blocked by domperidone administration.

ADVERSE REACTIONS

The most frequently observed adverse reactions are nausea, vomiting, headache and gastrointestinal side effects such as abdominal pain, diarrhea and constipation. All these effects may be minimized or even prevented by giving small initial doses of bromocriptine and by taking it with food.

Postural hypotension can, on rare occasions, lead to fainting, and shock-like syndromes have been reported in sensitive patients. This is most likely to occur during the first few days of BROMOCRIPTINE (bromocriptine mesylate) treatment.

In clinical studies to date, the following adverse reactions were noted:

In postpartum women treated with bromocriptine mesylate, some rare serious adverse events (about 1 in 100,000) have been reported. These include hypertension, visual disturbances, myocardial infarction, seizures and strokes, or psychic disorders. In some patients, the occurrence of seizures or strokes was preceded by severe headache and/or visual disturbances. Causal relationship of these events to the drug is uncertain.

Amenorrhea/Galactorrhea/Female Infertility/Acromegaly: The incidence of side effects in these indications is higher (68%), reflecting the larger doses required, but they are generally mild to moderate in degree. Therapy was discontinued in approximately 6% of patients because of adverse effects. In decreasing order of frequency these are: nausea 51%, headache 18%, dizziness 16%, fatigue 8%, abdominal cramps 7%, lightheadedness 6%, vomiting 5%, nasal congestion 5%, constipation 3%, and diarrhea 3%.

Parkinson's Disease: When bromocriptine is added to levodopa therapy, the incidence of adverse reactions may increase. The most common newly appearing adverse reactions in combination therapy with levodopa are: nausea, abnormal involuntary movements, hallucinations, confusion, "on-off" phenomenon, dizziness, drowsiness, faintness, fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation and vertigo.

General: Less common adverse reactions include, anorexia, anxiety, blepharospasm, dry mouth, dysphagia, edema of the feet and ankles, erythromelalgia, epileptiform seizures, fatigue, headache, lethargia, mottling of skin, nasal stuffiness, nervousness, nightmares, paresthesia, skin rash, changes in urinary frequency, urinary incontinence, urinary retention and rarely signs and symptoms of ergotism such as tingling of fingers, cold feet, numbness, muscle cramps of feet and legs or exacerbation of Raynaud's syndrome.

Abnormalities in laboratory tests may include elevation of blood urea nitrogen, SGOT, SGPT, GGPT, CPK, alkaline phosphatase and uric acid, which are usually transient and not of clinical significance.

The occurrence of adverse reactions may be lessened by temporarily reducing the dosage to 1.25 mg two or three times daily.

SYMPTOMS AND TREATMENT OF OVERDOSE

There have been several reports of acute overdosage with bromocriptine in children and adults. No life threatening reactions have occurred. Symptoms reported could have resulted from over-stimulation of dopaminergic receptors: they included nausea, vomiting, dizziness, drowsiness, hypotension, sweating and hallucinations. The management of acute intoxication is largely symptomatic. The cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

DOSAGE AND ADMINISTRATION

BROMOCRIPTINE (bromocriptine mesylate) should always be taken with food. In order to establish tolerance, the first dose of 1.25 - 2.5 mg (1/2 - 1 tablet), depending on the indication should be given at bedtime with food. Please consult the detailed dosage recommendations for each indication.

Galactorrhea with or without amenorrhea due to hyperprolactinemia:

1.25 - 2.5 mg (1/2 to 1 tablet) at bedtime with food to establish tolerance; gradually increase after 2-3 days to 2.5 mg (1 tablet) twice daily with meals. If required the dose may be increased to 2.5 mg three times daily. Continue treatment until milk secretion has ceased completely or, in the case of menstrual dysfunction, until the menstrual cycle has returned to normal.

Prolactin-dependent menstrual disorders and infertility:

1.25 - 2.5 mg (1/2 to 1 tablet) at bedtime with food to establish tolerance. Gradually increase after 2-3 days to one tablet twice daily with meals. If required the dose may be increased to 2.5 mg three times daily.

Prolactin secreting adenomas:

1.25 mg (1/2 a tablet) 2 or 3 times daily, increasing gradually (average maintenance dose: 5 - 7.5 mg daily). If necessary to keep plasma prolactin adequately suppressed, dosage may be increased gradually over a period of several weeks to 10 - 20 mg (4 to 8 tablets or 2 to 4 capsules) daily with meals.

Prolactin dependent male hypogonadism:

1.25 - 2.5 mg (1/2 to 1 tablet) at bedtime to establish tolerance. Gradually increase after 2 to 3 days to 2.5 mg twice daily with meals or more, as required to 2.5 mg three times per day with meals.

Acromegaly:

1.25 - 2.5 mg (1/2 to 1 tablet) at bedtime with food to establish tolerance, increasing gradually over a period of 2 to 4 weeks to 10 -20 mg (4 to 8 tablets or 2 to 4 capsules) daily with meals, depending on clinical response. Daily requirements of 20 mg should be taken in four equally divided doses.

For convenience and after initial titration, some patients may use the 5 mg capsules for maintenance therapy.

The maximum recommended daily dose is 20 mg (eight 2.5 mg tablets or four 5 mg capsules).

In the event of serious or persistent adverse effects, the dosage should be reduced to 1.25 mg (1/2 tablet) and increased again gradually to the recommended dose. If reactions such as nausea, vomiting, vertigo or headaches continue to be severe, BROMOCRIPTINE should be discontinued.

Parkinson's Disease:

BROMOCRIPTINE should be added to levodopa therapy. It is desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.
BROMOCRIPTINE dosage should be individualized. The initial dose is 1.25 mg (1/2 tablet) at bedtime to establish tolerance. Thereafter, the recommended dosage is 2.5 mg daily in two divided doses, with meals.

The dosage may be increased, if necessary, by adding an additional 2.5 mg per day, once every 2 to 4 weeks, taken in 2 or 3 divided doses with meals. The maximum recommended daily dosage is 40 mg. Clinical assessments are recommended during dosage titration to ensure that the lowest effective dose is employed. Where dose levels permit, use of the 5 mg capsule may be found more convenient by many patients.

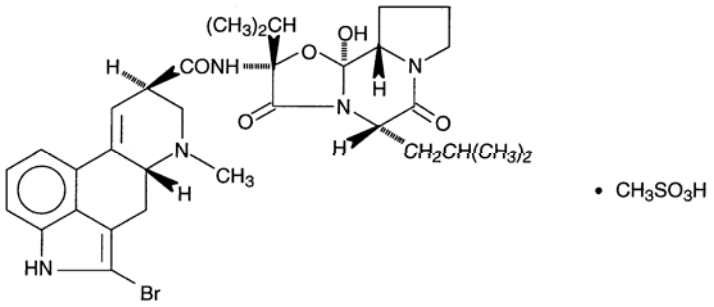
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: bromocriptine mesylate

Chemical name: 2-bromo-α-ergocryptine mesylate

Structural Formula:



Molecular formula: $C_{32}H_{40}BrN_5O_5 \bullet CH_4O_3S$

Molecular weight: 750.70

Description: Bromocriptine mesylate is a grey-tinged, white, or light yellow fine crystalline powder, odourless or with a weak characteristic odour.

Solubility: Insoluble in water, soluble in ethanol, freely soluble in methanol, very slightly soluble in chloroform.

Composition

In addition to the active ingredient bromocriptine mesylate, each tablet contains the non-medicinal ingredients lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. Each capsule contains the non-medicinal ingredients lactose, starch and stearic acid. Each capsule shell contains the non-medicinal ingredients gelatin, sodium lauryl sulfate, silicon dioxide, titanium dioxide, red iron oxide and yellow iron oxide.

Stability and Storage Recommendations

Store between 15 and 30°C (59-86°F). Protect from light. Protect tablets from moisture.

AVAILABILITY OF DOSAGE FORMS

Each white, oval-shaped tablet, scored and engraved 2.5 contains 2.5 mg bromocriptine (as mesylate). Available in bottles of 100.

Each white and caramel capsule imprinted 5 contains 5.0 mg of bromocriptine (as mesylate). Available in bottles of 100.

PHARMACOLOGY

Introduction

Bromocriptine is a semi-synthetic brominated ergot alkaloid. It is largely devoid of the pharmacological properties usually associated with ergot, such as uterotonic, vasoconstrictive or pressor effects. It is a dopamine agonist at D2-type receptors, and an antagonist at D1-type receptors.

Effects on the Endocrine System

Bromocriptine is a potent inhibitor of prolactin secretion and synthesis. This activity has been demonstrated in a variety of animal tests. Using lactation, a prolactin-dependent process, as an index, bromocriptine has been shown to inhibit milk production in a variety of animal species such as the rat, rabbit, pig and dog. This effect has been confirmed also in humans.

Bromocriptine inhibits the increase in prolactin induced by suckling stimuli in the lactating rat, and by tactile stimulation of the teat in goats and cows, but it exerts no effect on the concurrently induced release of growth hormone.

In the proestrus rat, bromocriptine blocks the natural increase in prolactin secretion (the prolactin surge), in a dose dependent manner. In the rat, it also shows antiprogestational and antifertility effects, demonstrated by the interruption of pseudopregnancy and a dose-related prevention of pregnancy in the rat, which are reversed by the administration of exogenous prolactin.

Evidence suggests that the mechanism responsible for the bromocriptine-induced antifertility effect in the rat depends on the inhibition of prolactin-induced activation of the corpus luteum, thus interfering with the progestative state, and thereby preventing implantation of the blastocyst. The antifertility effect is not due to anovulation as bromocriptine only weakly inhibits ovulation in rats. In contrast to the rat, bromocriptine exerts no antifertility effect in the rabbit, a species where luteotrophic activity is not dependent on prolactin.

Experimental evidence suggests that the mode and site of action of bromocriptine in inhibiting prolactin is by a direct action on the prolactin cells of the anterior pituitary. In cultures of rat and human pituitary cells, bromocriptine inhibits prolactin synthesis and secretion, this effect being due to its dopamine agonist property. In intact mice treated with bromocriptine, pituitary prolactin synthesis and secretion are inhibited and anterior pituitary weight decreased, without any changes in growth hormone content.

There is also evidence that bromocriptine exerts an effect on the hypothalamus. In the rat, it decreases turnover of dopamine in the median eminence and the dopaminergic tubero-infundibular region, a system which is thought to control prolactin synthesis and secretion.

Effects on the Cardiovascular System

Bromocriptine lowers blood pressure as a result of its dompaminergic effect on vascular smooth muscle, peripheral sympathetic nerve terminals and the central nervous system.

Effects on the Central Nervous System

The central nervous system effects of bromocriptine are consistent with a dopamine agonist effect in the basal ganglia, the mesolimbic system and the hypothalamus.

In small animals a biphasic effect on motor activity, similar to that of L-dopa, is seen, with initial depression being followed by strong locomotor activity. A reduced turnover of dopamine is observed.

Direct administration into both nuclei accumbens of the rat does not produce motor stimulation, but inhibits dopamine-induced hyperactivity, suggesting a dopamine antagonistic effect at this site.

Stereotyped behaviour such as repetitive sniffing, gnawing and (rarely) biting is seen after bromocriptine and can be inhibited by pimozide, a selective blocker of dopaminergic receptors. Intact synthesis and storage of dopamine appear necessary for these effects.

Bromocriptine, like other central dopamine agonists, is a potent inhibitor of behavioural depression induced by depletion of catecholamine stores.

Neurochemical investigations in the rat brain indicate that bromocriptine is a direct dopamine agonist. In addition there is evidence that it also increases noradrenaline turnover, but that it has minimal effects on serotonin turnover. In terms of ability to bind to receptor sites, bromocriptine is a mixed agonist/antagonist at both presynaptic and postsynaptic sites. Antagonistic activity at D1-type receptors is demonstrated in the dispersed bovine parathyroid cell system, where bromocriptine blocks the ability of dopamine to increase the accumulation of cyclic AMP.
Other Actions: Bromocriptine significantly inhibits the development of carcinogen-induced (DMBA) mammary tumors in female rats, and in mice it inhibits the growth of preneoplastic mammary nodules. Spontaneous mammary tumors in rats regressed during treatment with bromocriptine.

In experimental animals, dopamine agonists, including bromocriptine, have been shown to reduce the mitotic activity of pituitary cells stimulated by estrogen. There are a number of reports in the literature of regression of pituitary tumors in patients receiving bromocriptine.

TOXICOLOGY

Acute Toxicity Studies

	LD_{50} (mg/kg ± SD)	
	i.v.	p.o.
Mouse	190 ± 9.3	2620 ± 604
Rat	72 ± 3.5	~2000
Rabbit	12.5 ± 3.6	~1000

It was possible to calculate an oral $_{LD50}$ only for mice, and even here the limits of confidence had to be extrapolated since at the highest dose that it was possible to administer, mortality was only 80%. In rats and rabbits, no deaths occurred at the highest dose possible (2000 and 1000 mg/kg respectively).

Chronic Toxicity Studies

Rats: Bromocriptine, mixed in food, was given to rats at dose levels of 5, 20 and 82 mg/kg/day for 53 weeks. At the 5 mg level, no in-life drug effects were noted, but postmortem revealed increased adrenal weights and decreased pituitary weights in females. An increase in the number of cystic follicles with decreased luteal tissue in the ovaries was associated with some squamous metaplasia of the endometrium and indicated a drug effect on the pituitary

gonadotrophic axis resulting in a picture of estrogen dominance. Similar endometrial changes were observed at the two higher dose levels but were more pronounced.

A subsequent two year toxicity study in rats showed that bromocriptine treatment at doses of 1.7 to 44 mg/kg/day again caused endometrial squamous metaplasia, and that malignant neoplasms of the endometrium and myometrium occurred in a few animals. In aging female rats, the cyclicity of reproductive function is lost due to hypothalamic changes in the presence of responsive ovaries, and one of two stable conditions result: pseudopregnancy (progesterone dominance), which is a prolactin-dependent state, or continuous estrus (estrogen dominance), which occurs because of ovulation failure. The former is obviously prevented from occurring by the prolactin-inhibitory action of bromocriptine, so that nearly all bromocriptine-treated rats are brought to a continuous estrus. Both the metaplastic and the neoplastic endometrial changes are directly related to a situation of unopposed estrogen dominance peculiar to this species, and did not occur in similar studies carried out in the mouse and dog.

Dogs: Bromocriptine was given in gelatin capsules once daily to dogs 7 days a week for 62 weeks. Initial doses were small (0.1 mg/kg/day) because of emesis, but were escalated for the first ten weeks until dose levels of 1, 3 and 10 mg/kg/day were obtained and subsequently maintained for 52 weeks. During full dosage the following effects were observed: slight mydriasis, slight sedation, superficial epithelial necrosis of dependent ear margins characteristic of overdosage with ergot derivatives in dogs with low-hanging external ears, small cystic follicles and poorly formed or cystic corpora lutea in the ovaries, morphological evidence of thyroid hyperactivity, as well as non-specific pathologic changes in various organs. The above changes are all considered to be an expression of exaggerated pharmacodynamic effects. The macroscopic and microscopic appearance of the uteri of treated dogs was completely normal.

Monkeys: Bromocriptine was also given as a suspension by gavage to Rhesus monkeys, 7 days a week, for 13 weeks at doses of 2, 8 and 32 mg/kg/day. At the low and mid-dose levels, neither in-life examinations nor postmortem studies revealed drug related effects. At the high dose level of 32 mg/kg/day some swollen basophils in the anterior pituitaries of 2/4 monkeys were found. No specific toxic effects of bromocriptine emerged in this study. Eight mg/kg/day can be regarded as an oral non-toxic effect level for the Rhesus monkey.

TERATOLOGY

Bromocriptine was given to pregnant rats at 3, 10 and 30 mg/kg/day from days 6 to 15 and 6 to 18 postcoitum, administered in 2% gelatin by gavage. Bromocriptine demonstrated no embryolethal or teratogenic effect at any of the dose levels used. When the drug was given during the period of implantation, inhibition of implantation was observed with 10 and 30 mg/kg/day. Because this effect was not observed when the drug was administered later, it is most probably attributable to the prolactin-inhibiting action of bromocriptine in this species.

Bromocriptine was given to pregnant rabbits at 3, 10, 30 and 100 mg/kg/day for days 16 to 18 postcoitum, administered in 2% gelatin by gavage. Two additional doses of 300 and 1000 mg/kg/day were given to characterize the toxic effects of bromocriptine on pregnant females, so that findings in the fetuses could be set in relation to maternal toxicity. Doses of 3 and 10 mg/kg/day were well tolerated by the dams whereas higher doses were toxic. Only at doses which produced maternal toxicity did questionable increases in prenatal mortality and the incidence of fetal abnormalities occur. It is concluded that bromocriptine does not exert any embryolethal or teratogenic activity in the rabbit when given in non-toxic doses.

Female rats were given bromocriptine orally at doses of 1 and 3 mg/kg/day during the entire test period. After 14 days they were mated. Half of the animals were killed 13 days post-coitum; the other half were allowed to deliver and rear their offspring until 21 days postpartum. Bromocriptine

was found to have no effects on the fertility of the dams, embryonic development or postnatal viability of the offspring.

MUTAGENICITY

Bromocriptine has been tested in the following systems: the Ames test, using Salmonella typhimurium bacteria; micronucleus test in mice, the dominant lethal test in male mice and a cytogenetic analysis of Chinese hamster bone marrow cells (all tests for chromosome damaging potential). In none of these test systems did bromocriptine prove to be mutagenic.

CARCINOGENICITY

Bromocriptine has been subjected to prolonged toxicity studies (life time in rats and mice, 62 weeks in dogs, 13 weeks in primates) - See TOXICOLOGY.

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