Pharmacology of Ergot alkaloids

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In The Name Of Allah

First,

Our great thanks to God for giving us the ability to complete this project...

Second,

We would like to extend our hearty appreciation and to dedicate this research to our supervisor "Dr. Hanan Hajar", our parents and colleagues for being a good support for us...

And we invoke God to give its profit to the human beings...

AL-shamsi F.
AL-Bulahi H.
Al-Masary A.
AL-Hazmi A.
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Anteet
**Summary**

**Methysergide** is a non-selective 5-HT2 serotonin receptor antagonist, with partial agonistic action, but there is no agonistic action on the receptor subtype 5-HT2C. Methysergide is used as a prophylactic medication against migraine, although it cannot terminate an attack. This drug is metabolized by the cytochrome p450 system in the liver, and undergoes extensive first-pass metabolism, which contributes to its low plasma concentration after oral administration. Due to its non-selectivity, and its main metabolite, methylergonovine, methysergide has some adverse effects, which limited its clinical use.

**Ergotamine** is a non-selective 5-HT1 agonist. It also has affinities for dopamine and noradrenaline receptors. Oral absorption of ergotamine is 60-70%. The drug is metabolized in the liver by the cytochrome P450 with half life of 3-4 hrs, excreted mainly in the feces and small amount of unchanged drug is excreted in urine. Several medications are microsomal enzyme inhibitors and slow the metabolism of ergotamine, causing serious toxic effects, including ergotism, stroke, gangrene and death. Common adverse effects of ergotamine are nausea, vomiting, abdominal pain, diarrhea, peripheral paresthesias, swollen fingers, generalized weakness, and peripheral and coronary vasoconstriction. The drug is contraindicated in people with peripheral vascular disorders, coronary artery disease, stroke, severe hypertension, pregnancy, hepatic or renal failure, or sepsis.
**Bromocriptine** (parlodel) is an ergot alkaloid and it is dopamine agonist. Chemically it is a derivative of D lysergic acid. It is white, fine, crystalline powder, almost odorless & it is water insoluble. It acts as D2 dopamine receptors agonist at the level of the hypothalamus and corpus striatum. It directly stimulates ovarian dopamine receptors leading to menses in amenorrheic women & directly activates lactotrope dopamine receptors, leading to inhibition of prolactin release. It is also a free radical scavenger. Bromocriptine tablets or capsules are taken orally with water or food, or as standard oral tablets placed in the vagina. It is absorbed rapidly & good from the gastrointestinal tract, bioavailability is 6%. The peak plasma concentration & clinical improvement signs begins 1-3 hours after ingestion. It binds extensively to serum albumin (90%) and do not distribute to erythrocytes. It undergoes extensive first pass hepatic metabolism by hydrolysis to lysergic acid and peptides. Its half life is 3 hours and it is excreted mainly in feces and small amounts in urine. Bromocriptine inhibits prolactin secretion, reduces elevated levels of growth hormone in acromegaly but increase it in normal individuals, reduce size of prolactinomas and normalize luteal hormone by normalizing progesterone/estrogen imbalance. It increases dopamine leading to improvement in Parkinson's disease. It is used in hyperprolactinemia, prolactinomas regardless the etiology or sex of patient, inhibition of lactation, benign breast disease, premenstrual symptoms and in acromegaly. It is used also in Parkinson's disease alone or as adjunctive to levodopa. It can reduce body fat stores, decrease body weight and used in type-2 diabetes. It can improve psoriasis coetaneous lesions associated with prolactinomas. Its side effects are mild to moderate including nausea, vomiting, hypotension, fatigue, dizziness and nasal congestion at the
beginning of treatment. On chronic use, its major side effects are constipation or diarrhea, dyspepsia, severe hypotension, arrhythmia and exacerbation of angina. By vasoconstriction it causes digital pallor and leg cramps. It can cause psychotic hallucinations especially in Parkinsonism. While it is ergot alkaloid, it can cause retroperitoneal and pleural fibrosis. The lethal dose has not been established. It is contraindicated in sensitivity, hypertension, cardiovascular disorders and psychiatric history. It must be discontinued if pregnancy occur and in postpartum women. It has a lot of drug interactions include reduced tolerability with alcohol and raised plasma levels with cytochrome P450 inhibitors. Bromocriptine dose is 2.5 mg tablet or 5 mg capsule.

Ergometrine is an Ergot Alkaloid, which is used in prevention and treatment of postpartum hemorrhage caused by uterine atony or subinvolution. It affects primarily uterine smooth muscles producing sustained contraction and thereby shortens the third stage of labor. It is reported to be rapidly absorbed after administration by mouth and by intramuscular injection, with onset of uterine contraction in about 5 to 15 minutes after an oral dose, 2 or 3 minutes after intramuscular dose and immediately after I.V. dose. Elimination appears to be principally by metabolism in the liver. Its Main adverse effects are nausea and vomiting, abdominal pain, diarrhoea, headache, dizziness, seizures, tinnitus, chest pain, palpitations, bradycardia, hypertension, dyspnoea, leg cramps, and hematuria. Pregnancy risk factor is C. It is not recommended in lactation. It is contraindicated in hypersensitive patients, induction of labor, threatened spontaneous abortion, hypertension, impaired hepatic or renal function, toxemia, porphyria and in concurrent sympathomimetics. Use caution in patients with sepsis, obliterative vascular
disease, hepatic, or renal involvement, hypertension; administer with extreme caution if using I.V. It should not be combined with drugs as antianginal agents, β-blockers, bromocriptine, dopamine, halothane and methysergide.

**Pergolide mesylate**, a semisynthetic ergot derivative and is predominantly dopamine (D1/D2/D3) receptor agonist as well as it works on other non-dopaminergic receptors as serotonin and α-adrenoceptors which account for some of its side effects. Pergolide mesylate is absorbed orally and highly bound to plasma proteins with plasma half-life in the range of 3 to 7 hours. It undergoes extensive hepatic first pass metabolism, it is eliminated as metabolites in urine and in feces. It exerts effects on many systems of the body as the cardiovascular system, endocrine system and has anti-inflammatory activity. It may be used in the treatment of Parkinson's disease as monotherapy in the early stages it offers several theoretical advantages over levodopa. It can be used as adjunctive therapy to levodopa. It may be used in the treatment of restless leg syndrome, of macroprolactinomas, Tourette syndrome and as an antidepressant adjuvant for refractory depression. Precautions should be taken with the abrupt discontinuation of the drug and with patients with history of cardiac, respiratory problems, as well as during pregnancy or lactation. The most commonly observed adverse events associated with the use of this drug are related to nervous system, gastrointestinal, cardiovascular and respiratory system complaints.
Introduction:

History:

Ergot alkaloids are derived from the fungus *claviceps purpurea* (Pearson college website; Wooltorton 2003). Which infects rye grain and other plants (Pearson college website). Eating infected bread caused epidemics of ergotism (Eadie 2003; Wooltorton, 2003) in the middle- ages. Which manifested with gangrene (pearson college website; Wooltorton,2003) and sever peripheral burning pain known as St.Anthony's fire, spontaneous abortions and occasionally, central nervous system disturbances, such as mania and hallucinations, although, the fungus was not incriminated until 1630 by Tullier (Wooltorton,2003). European midwives noticed its oxytocic effect, even before Stearns established this medical action in 1809. The oldest record about treating migraine with ergot alkaloids was in Italian, and it goes back to 1862. The oldest paper found in English was by Edward woakes in 1868(Eadie 2003).

<table>
<thead>
<tr>
<th>Group</th>
<th>Alkaloid</th>
<th>Discovered</th>
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<tbody>
<tr>
<td>1.Ergometrine</td>
<td>Ergotmetrine</td>
<td>Dudley and Moir (1935)</td>
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<tr>
<td></td>
<td>Ergotmetrineine</td>
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<td></td>
<td>Ergotamine</td>
<td>Spiro and Stoll (1920)</td>
</tr>
<tr>
<td>2.Ergotamine</td>
<td>Ergotaminine</td>
<td></td>
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<tr>
<td></td>
<td>Ergosine</td>
<td>Smith and Timmis (1937)</td>
</tr>
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<td></td>
<td>Ergosinine</td>
<td>(1937)</td>
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<td></td>
<td>Ergocristine</td>
<td>Stoll and Burckhardt (1937)</td>
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<td>Ergocristinine</td>
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Classification:
The ergot alkaloids classified according to the chemical structure into:

1) The clavine type, such as agroclavine and elymoclavine are generally regarded as precursors to the other groups. They are not used pharmacologically, but agroclavine is a powerful uterine stimulant.

2) The water soluble lysergic acid derivatives are most often amide derivatives. The most important of these are ergonovine and methysergide. Ergonovine has potent uterine contraction activity and used in treating postpartum hemorrhages. Methysergide is used as a cranial vasodilator in the treatment of migraine headaches.

3) The water-insoluble lysergic acid derivatives are primarily peptide ergot alkaloids like ergotamine. Ergotamine, as its tartrate salt, is an analgesic specifically used for treatment of severe migraine headaches (Zavaleta et al., 2001).

<table>
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<tr>
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<th>Formula</th>
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</thead>
<tbody>
<tr>
<td>1.Ergometrine Group</td>
<td>Ergotrinine</td>
<td>C₁₉H₂₅O₂N₃</td>
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<tr>
<td></td>
<td>Ergotminine</td>
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<td></td>
<td>Ergotamine</td>
<td>C₃₃H₃₅O₅N₅</td>
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<td>2.Ergotamine Group</td>
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</tbody>
</table>
Pharmacological actions:

Methysergide:

When methysergide was administered systematically, it reached maximum vasoconstrictor effect after twenty-five minutes and decreased within 50 minutes. (Muller-Schweinitzer et al, 1985).

By methysergide's action on the 5-HT2A receptor sub-group, inhibit the release of histamine from mast cells (on 5-HT 2A receptor) (Young and Rozen 2005).

Methysergide is a non-selective serotoninergic blocker (Johnson et al., 2003). It was found that methylergometrine (one of methysergide's metabolites) is responsible for methysergide's therapeutic effects regarding migraine treatment (Muller-Schweinitzer et al., 1986). Methysergide's prophylactic action against migraine is via its non-selective action on 5-HT2c and 5-HT2b receptors (Silberstein 2002; Johnson et al., 2003) on the vascular endothelium. Johnson et al., 2003). Methysergide also has an inhibitory action on dural protein extravasation triggered by m-chlorophenylpiperazine(m-CPP), a compound known to cause migraine-like symptoms in some individuals due to release of nitric oxide (NO) due to 5-HT2b receptor activation. (Johnson et al., 2003). Methysergide (10 M) did not affect the response to cholecystokinin of a donor gallbladder. However, it considerably inhibited the response of the gallbladder to contract from a
patient with severe cholecystitis and didn't alter the gallbladder's response from a patient with mild cholecystitis \textit{(Martinez-cuesta et al., 2003)}. It was found also that methysergide decreases prolactin levels in hyperprolactinemic and normal individuals \textit{(Silberstein 1998)}.

\textit{Ergotamine}

The pharmacological properties of ergotamine are extremely complex; some of its actions are unrelated to each other, and even mutually antagonistic. The drug has partial agonist and/or antagonist activity against tryptaminergic, dopaminergic and $\alpha$-adrenerergic receptors depending upon their site, and it is a highly active uterine stimulant. It causes constriction of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The pain of a migraine attack is believed to be due to greatly increased amplitude of pulsations in the cranial arteries, especially the meningeal branches of the external carotid artery. Ergotamine reduces extracranial blood flow, causes a decline in the amplitude of pulsation in the cranial arteries, and decreases hyperperfusion of the territory of the basilar artery. It does not reduce cerebral hemispheric blood flow. Ergotamine produces constriction of both arteries and veins. In doses used in the treatment of vascular headaches, ergotamine usually produces only small increases in blood pressure but it does increase peripheral resistance and decrease blood flow in various organs. Small doses of the drug increase the force and frequency of uterine contraction; larger doses increase the resting tone of the uterus also. The gravid uterus is particularly sensitive to these effects of ergotamine. Although specific teratogenic effects attributable to ergotamine have not been found, the fetus suffers if ergotamine is given to the mother.
**Bromocriptin**

Bromocriptine mesylate is a dopamine receptor agonist (D2 receptors), which activates post-synaptic dopamine receptors. Clinically, bromocriptine mesylate significantly reduces plasma levels of prolactin in patients with physiologically elevated prolactin as well as in patients with hyperprolactinemia. The inhibition of physiological lactation as well as galactorrhea in pathological hyperprolactinemic states is obtained at dose levels that do not affect secretion of other tropic hormones from the anterior pituitary.

Bromocriptine mesylate is a nonhormonal, nonestrogenic agent that inhibits the secretion of prolactin in humans, with little or no effect on other pituitary hormones, except in patients with acromegaly where it lowers elevated blood levels of growth hormone in the majority of patients. In many acromegalic patients, bromocriptine mesylate produces a prompt and sustained reduction in circulating levels of serum growth hormone.

In about 75% of cases of amenorrhea and galactorrhea, bromocriptine mesylate therapy suppresses the galactorrhea completely, or almost completely, and reinitiates normal ovulatory menstrual cycles. Menses are usually reinitiated prior to complete suppression of galactorrhea.
Bromocriptine mesylate produces its therapeutic effect in the treatment of Parkinson’s disease, a clinical condition characterized by a progressive deficiency in dopamine synthesis in the substantia nigra, by directly stimulating the dopamine receptors in the corpus striatum.

**Ergometrine:**

Ergometrine directly stimulates contractions of uterine and vascular smooth muscle. Usual therapeutic doses of ergometrine produce intense contractions of the uterus and are usually followed by periods of relaxation.

Ergometrine increases the amplitude and frequency of uterine contractions and uterine tone which in turn impedes uterine blood flow. Contraction of the uterine wall around bleeding vessels at the placental site produces haemostasis. With larger doses, basal uterine tone is elevated and these relaxation periods will be decreased. Ergometrine also increases contractions of the cervix. The sensitivity of the uterus to the oxytocic effect is much greater toward the end of the pregnancy. The oxytocic actions of ergonovine are greater than its vascular effects. *(Gilman et al., 1985)*

Ergometrine produces vasoconstriction, mainly of capacitance vessels; increased central venous pressure, elevated blood pressure, and, rarely, peripheral ischemia and gangrene may result. Ergonovine causes vasoconstriction of coronary arteries. *(Kimball, 1989)*

Like other ergot alkaloids, ergometrine produces arterial vasoconstriction by stimulation of $\alpha$-adrenergic and serotonin receptors and inhibition of endothelial-derived relaxation factor release. The drug has only
slight $\alpha$-adrenergic blocking activity and its vasoconstrictor effects are less than those of ergotamine. (Groot et al., 1998).

In CNS, Ergonovine is a partial agonist and partial antagonist at some serotonin and dopamine receptors. Ergonovine also possesses weak dopaminergic antagonist actions in certain blood vessels and partial agonist action at serotonin receptors in umbilical and placental blood vessels. It does not possess significant $\alpha$-adrenergic blocking activity. (Gilman et al., 1985).

**Pergolide:**

Pergolide mesylate is a potent dopamine receptor agonist (D2 receptor agonist). Pergolide is 10 to 1,000 times more potent than bromocriptine. Pergolide mesylate inhibits the secretion of prolactin in humans; it causes a transient rise in serum concentrations of growth hormone and a decrease in serum concentrations of luteinizing hormone. In Parkinson’s disease, pergolide mesylate is believed to exert its therapeutic effect by directly stimulating postsynaptic dopamine receptors in the nigrostriatal system.

**Uses of Ergot Alkaloids:**

**Migraine:**

**Ergotamine** is used to abort or prevent vascular headaches, such as migraine, migraine variants, or so-called “histaminic cephalalgia”. **Methysergide** is used as prophylaxis of severe recurrent migraine, cluster headaches in patients who are refractory to other treatment and whose lives are seriously disrupted. (BMA and RPSGB, 2004; and Lacy et al., 2003)
**Parkinsonism and related disorders:**

Bromocriptine is used in Parkinsonism (but not drug-induced extrapyramidal symptoms). Pergolide is also used either alone or as adjunct to levodopa. (BMA and RPSGB, 2004; and Lacy et al., 2003)

**Endocrine disorders:**

Bromocriptine is used in amenorrhea with or without galactorrhea, infertility or hypogonadism, prolactine secreting adenomas and acromegaly. Pergolide is also used in prolactinoma. (BMA and RPSGB, 2004; and Lacy et al., 2003)

**Gynecology problems:**

Ergometrine is used in the prevention and treatment of postpartum hemorrhage due to incomplete abortion. A previous indication of Bromocriptine for prevention of postpartum lactation was withdrawn voluntarily by Sandoz Pharmaceuticals Corporation. (BMA and RPSGB, 2004; and Lacy et al., 2003)

**What is Parkinson’s Disease?**

Parkinson’s disease PD is characterized by a progressive and irreversible loss of the pigmented neurons of substantia nigra pars compacta which provide innervation to the striatum. This results in a marked loss of striatal dopamine. The cause of the disease is unknown. There is no evidence, however, that idiopathic Parkinson’s disease is caused by an environmental toxin or an infective agent. There is a combination of tremor, rigidity and akinesia (slow movements), together with changes-in-postur 0056e. The resting tremor usually most obvious in the hands (‘pill-rolling’ of the thumb and fingers), improved by voluntary movement and made worse by anxiety.
Rigidity refers to the increase in tone in the limbs and trunk. The limbs resist passive extension throughout movement. Akinesia means that there is difficulty in initiating movement (starting to walk, or rising from a chair). The face is expressionless and the speech is slow. Postural changes. A stoop is characteristic and the gait is shuffling with poor arm swinging. Balance is poor, with a tendency to fall. Other features include dribbling of saliva, dysphagia, constipation, depression and dementia in the later stages. There is gradual progression of the disease over 10-45 years, with death resulting most commonly from bronchopneumonia.

**What is Tourette Syndrome?**

Tourette Syndrome (TS) is a disorder comprised of involuntary motor and phonic tics often associated with psychiatric conditions. The etiology for TS is unclear, with both genetic and immunological theories being studied to date. TS is not a rare disorder with males have a higher incidence than females. The mean age of tic onset is typically between the ages of 6 and 7 years. Tics are sudden, brief, involuntary movements or vocalizations. They are repetitive in nature without rhythmicity. Movements and vocal tics can be either simple or complex. Tics by nature have a variable severity and duration, and no 2 patients have exactly the same symptoms (Eric; 2001).

**What is Restless Legs Syndrome?**

Restless legs syndrome (RLS), is not rare but is rarely diagnosed by clinicians. Despite a lucid description over 50 years ago by Ekbom, there is considerable misconception about RLS. RLS is characterized by periodic limb movement. Specific criteria were formulated by the International Restless
Legs Syndrome Study Group (IRLSSG). The minimal criteria include the following: 1) an intense, irresistible urge to move the legs, usually associated with sensory complaints (paresthesia or dysesthesia); 2) motor restlessness; 3) worsening of symptoms at rest and relief with motor activation; and 4) increased severity in the evening or at night. There is, however, night-to-night variability. Up to one-third to one-half of RLS cases are transmitted as an autosomal dominant trait. The observation showed that some genetic disorder may be associated with RLS as Charcot-Marie-Tooth and Autosomal dominant cerebellar ataxia. Primary (sporadic or genetic) RLS may be difficult to differentiate from RLS associated with neuropathy, uremia, iron deficiency, or other disorders (secondary RLS). (Chokroverty et al;1999)

**What is Postpartum hemorrhage?**

Defined by the WHO as postpartum blood loss ≥ 500 ml is a clinical diagnosis that encompasses excessive blood loss after delivery and, if untreated, may result in shock and death of the mother. The choice of 500 ml is arbitrary but is a loss that most mothers can tolerate without risk. In countries where many women have severe anemia, maternal blood loss of even 250 ml may be fetal. The clinical consequences of PPH depend on both the amount and the rate of blood loss and whether the mother's health is good, a factor partly included in the definition of PPH. (Groot, 1996)

**What is Migraine?**

Migraine is recurrent headache associated with both visual and gastrointestinal disturbance; in spite of the origin of the word, it does not invariably mean unilateral headache. The prevalence of migraine is
approximately 10%; some patients have a strong family history. Onset is usually before the age of 30 years. The cause of migraine remains controversial. The headache is due to vasodilatation or oedema of blood vessels, with stimulation of the nerve endings near affected extracranial meningeal arteries. The diagnosis of migraine is clinical. There are transient prodromal symptoms followed after 15—60 minutes by a throbbing headache which is often unilateral and accompanied by nausea, vomiting and photophobia. The headache may last for some days and is made worse by physical exertion. Prodromal symptoms are visual, aphasia, tingling, numbness and weakness of one side of the body. Migraine may also occur without these prodromal symptoms. The most common way in which a migraine attack resolves is through sleep.
**Chemistry:**

All ergot alkaloids are derivatives of the tetracyclic ergoline ring,

Methysergide
(Mantegani et al., 1999; Mahmood et al., 2004) which is the structural feature of them all (Mahmood et al., 2004), and similar to serotonin's structural framework (Mantegani 1999)

![The tetracyclic ergoline skeleton](image)

**Mechanism of action:**

Methysergide is a non-selective 5-HT2 receptor antagonist (Johnson et al, 2003; Fitzgerald et al., 2000), and partial agonistic action (katzung, 2001) It has a serotonergic antagonistic action peripherally, and a serotonergic agonistic action centrally.

1. 5-HT 2A: inhibit the release of histamine from mast cell (Young and Rozen 2005).
2. 5-HT 2B: methysergide exert its prophylactic effect against migraine is via its action on peripheral (outside the blood brain barrier) 5-HT 2B receptors. It was found that this receptor subtype is not directly associated with the release of inflammatory neuropeptides from the trigeminal sensory afferent as substance P and calcitonin gene-related peptide(CGRP), and so methysergide can not terminate an ongoing attack (Johnson et al, 2003).
3. 5-HT 2C: antagonistic action on this receptor subtype will alter the patient's feeling of satiety (Young and Rozen 2005).
methysergide nor its metabolite, methylergonovine has an agonistic action on this receptor subtype (Fitzgerald et al., 2000). Methysergide also has a partial agonistic action on 5-HT1, which is the cause of methsergide's adverse interaction with sumatriptan (Liston et al., 1999). Both, methysergide and methylergonovine have high-to-moderate affinity for 5-HT1D and E receptors, which will cause some vascular effects (Fitzgerald et al., 2000).

**Pharmacokinetics:**

**Absorption:**
Low absorption, which contributes to the relative availability of the drug after oral administration. (Muller-Schweinitzer et al, 1986).

**Distribution:**
It has a short distribution phase indicated by the rapid initial decrease if its concentration in plasma (Muller-Schweinitzer et al, 1986).

**Bioavailability:**
Methysergide has good tissue availability, reflected by its similar vasoconstrecting action as compared to methylergometrine with low plasma concentration after oral administration, which is due to its high firs-pass metabolism (Muller-Schweinitzer et al, 1986).
Pharmacology:

Ergotamine is metabolized in the liver by cytochrome P50 3A4 enzyme which will cause some interactions (Wooltorton, 2003). One of its metabolites is methylergometrine, or methylergonovine, produced by demethylation. Methylergonovine has a partial 5-HT2B and 5-HT2A agonist and a 5-HT2C antagonist, which is proposed to be responsible of methysergide's efficacy and side effects (as valvular lesions, because it was found to have higher plasma concentration than Methysergide after oral administration (Fitzgerald et al, 2000). This metabolite is less potent than Methysergide when administered I.V locally in producing vasoconstriction. Otherwise if injected systematically, it produces a shorter-lived action. However, their vasoconstrictive action is similar when taken orally. However, it was found that methylergometrine has a longer elimination half-life than methysergide (Muller-Schweinitzer et al, 1986). Methylergometrine has an agonistic action on 5-HT1 receptor, which gives it a prophylactic action against migraine (Bahra et al 1998), and might be used as an adjunct.
prophylactic agent in cluster headache (Mueller et al., 1997) Systemic bioavailability is about 13 percent, which due to extensive first pass metabolism in the liver (Muller-Schweinitzer, Tapparelli, 1986).

![Methylergometrine](image)

**Excretion:**
Methysergide is readily excreted in milk. 30 percent of methysergide is excreted via the kidneys.

**Elimination half-life:**
45 to 60 minutes (Muller-Schweinitzer et al, 1985, Silberstein 1998), and 220 for its metabolite methylergometrine (Silberstein 1998).

**Distribution half-life**
1.3 minutes (Muller-Schweinitzer et al, 1985).

**Pharmacological actions:**
* When methysergide was administered systematically, it reached maximum vasoconstrictor effect after twenty-five minutes and decreased within 50 minutes. (Muller-Schweinitzer et al, 1985).
* inhibit the release of histamine from mast cells (on 5-HT 2A receptor) (Young and Rozen 2005).
Methysergide is a non-selective serotonergic blocker (Johnson et al., 2003) which is the cause of Methysergide's adverse effects, thus limitation of its use. It was found that methylergometrine (one of methysergide's metabolites) is responsible for methysergide's therapeutic effects regarding migraine treatment (Muller-Schweinitzer et al., 1986). Methysergide's prophylactic action against migraine is via its non-selective action on 5-HT2c and 5-HT2b receptors (Silberstein 2002; Johnson et al., 2003) on the vascular endothelium (outside the blood-brain-barrier) (Johnson et al., 2003). Methysergide also has an inhibitory action on dural protein extravasation triggered by m-chlorophenylpiprazine(m-CPP), a compound known to cause migraine-like symptoms in some individuals due to release of nitric oxide (NO) due to 5-HT2b receptor activation (Johnson et al., 2003). By methysergide's action on the 5-HT2A receptor sub-group, it inhibits histamine release from mast cells. (Young and Rozen 2005). Methysergide (10 M) did not affect the response to cholecystokinin of a donor gallbladder. However, it considerably inhibited the response of the gallbladder to contract from a patient with sever cholecystitis and didn't alter the gallbladder's response from a patient with mild cholecystitis (Martinez-cuesta et al., 2003). It was found also that methysergide decreases prolactin levels in hyperprolactinemic and normal individuals (Silberstein 1998).

**Uses:**

1. Methysergide has a well known beneficial effect in migraine prophylaxes, but it can't terminate an attack. (Muller-Schweinitzer and Tapparelli 1986). Especially in resistant patients who have high attack
rate. It is also indicated for the treatment of cluster headache (Silberstein 1998).

2. Initially, it was used by midwives in Europe to speedup labour (Wooltorton, 2003).

3. in the treatment of cough headache (Bahra et al., 1998)

4. Although needs more research, it was found in literature that methysergide has improved the symptoms of progressive supranuclear palsy. (Rehman, 2000).

5. One of methysergide's important uses is in treating the symptoms of carcinoid tumors (Rang, 2003).

**Side effects:**

**Retroperitoneal fibrosis:**

It was proved that some drugs, as Methysergide, were the cause in third of retroperitoneal fibrosis cases (Dev et al., 1999). Retroperitoneal fibrosis presents with abdominal pain, generalized edema and pericardial effusion (Cai et al 2004). The abdominal pain may be described as dull, noncolicky pain in the back, flanks or abdomen. Patients may complain of other things as anorexia, weight loss, malaise, fever, oliguria and gastrointestinal bleeding. Patients may be complaining for an average of four months before the diagnosis (Silberstein 1998). When echocardiogram was done, it confirmed the effusion and normal ejection fraction with mild mitral, aortic and tricuspid regurgitation. Methysergide incrimination was proved by replacing it with another drug and repeating CT 2 months later, which revealed resolution of retroperitoneal fibrosis and the effusion (Cai et al, 2004). This unwanted
effect impairs the function of the gastrointestinal tract, the kidneys (renal failure), heart and lungs (Rang, 2003).

**Coronary side effects**

Therapeutic Plasma concentration levels will cause slight coronary artery constriction in patients with normal coronaries (VanDenBrink et al., 1998). However, in patients with coronary artery disease, it was found that their serotonin receptors are altered and supersensitive (Liston et al., 1999). Thus, even within therapeutic doses, myocardial infarction might occur (VanDenBrink et al., 1998)

**Cardiomyopathy:**

Methysergide-induced cardiomyopathy is due to its action on the 5-HT2B receptor sub-group, which will cause myofibroblast mitogenesis and consequently valvular regurgitation. The underlying lesion was found to fibroplasias (myofibroblast proliferation). Fitzgerald's analysis suggests that this toxicity is due to methysergide's primary metabolite methylergonovine. Not methysergide nor its metabolite methylergonovine have an agonistic action on the 5-HT2C receptor sub-group, so this receptor may not have a role in causing cardiomyopathy (Fitzgerald et al, 2000).

**Weight gain:**

Methysergide can induce weight gain (Johnson et al, 2003) by blocking some serotonergic receptors and inhibiting histamine release (5-HT 2A), which alters the patient's feeling of satiety (Young and Rozen, 2005)
Some other adverse effects:

Are nausea, vomiting, abdominal pain, diarrhea, Peripheral paresthesia, swollen fingers, generalized weakness and peripheral and coronary vasoconstriction. Some patients experienced psychic reactions, hair loss, angina and girdle and thigh claudication which might have been due to aortic, iliac and femoral artery spasm. For its many adverse effects it is essential for patients treated with methysergide to be monitored frequently for evidence of cardiac, pulmonary or peritoneal fibrosis, or any vascular complications, and it is also advised to preserve this medication for sever, resistant migraine cases (Silberstein 1998).

Contraindications:

1. Sumatriptan (a selective 5-HT 1D agonist) is contraindicated within 24 hours after methysergide administration due to the additive and/or prolonged vasoconstrictive action (Liston et al., 1999).

2. Methysergide is also contraindicated in vascular diseases (Bahra et al., 1998).

3. Methysergide is contraindicated to patients with coronary artery disease (VanDenBrink et al., 1998).

4. Methysergide is contraindicated in several other situations such as pregnancy, severe hypertension, valvular heart disease, sever arteriosclerosis, thrombophlebitis or cellulites of the legs, serious infection, fibrotic disorders, lung disease, liver or renal impairment, debilitation and peptic ulcer disease (Silberstein 1998).
**Drug interactions:**

Since the hepatic cytochrome P450 3A4 enzyme metabolizes ergots, patient on ergot drugs should avoid CYP 3A4 inhibitors, such as macrolide antibiotics (Erythromycin, Clarithromycin), antifungal drugs (Ketoconazole, Itraconazole, Fluconazole and clotrimazole), protease inhibitors (Ritonavir, Nelfinavir, Indinavir and Saquinavir), antidepressants (Nefazodone, fluoxetine and fluvoxamine), others as heparin, ampicillin, cyclosporine, tacrolimus and grapefruit juice. *(Wooltorton, 2003).* Methysergide administration within 24 hours of sumatriptan administration is contraindicated due to the additive and/or prolonged casoconstrective effect. There is a reported case of a forty five-year-old female, which was admitted through the emergency department complaining of acute onset of chest pain, tightness and shortness of breath. The symptoms appeared after ten to fifteen minutes after the patient has injected herself with subcutaneous sumatriptan after her migraine was not relieved by a two milligram of methysergide maleate, two doses, twelve hours apart. It was found that serotonin receptors are altered in the context of coronary artery disease and supersensitive. But in the case of methysergide, this adverse reaction is related to its partial agonistic action on 5-HT1 receptor (which is the same receptor sumatriptan works on), which will cause prolonged vasospastic action *(Liston et al., 1999).*

**Advantages:**

1. Unlike ergotamine, it relatively lacks the cumulative vasospastic effect *(Katzung, 2001)*
2. When infused locally in dogs, it was found that methysergide is about three hundred times more potent than its demethylated metabolite, methylergometrine, in inducing vasoconstriction.

**Pharmaceutical formulation:**

Methysergide is available in the form of oral, two-milligram tablets in the form of methysergide maleate (*Katzung, 2001*). Methysergide is known as Sansert® (*Mueller et al., 1997*).

**Dose:**

*Adult dose:* 4-8mg/day with meals. Patients must take drug holydays every six months of taking the medication of 3 – 4 weeks. To reduce the incidence of early adverse effects, patients might start of with a low dose as 1 mg a day and then increase the dose by a rate of one mg every two of three days (*Silberstein 1998*).

*Pediatric dose:* safety and effectiveness in pediatrics have not been recognized yet.

*When methysergide was given in 2 mg dose daily for 4 days, it was effective in stopping cough headaches. The dose was reduced after 2 weeks and was withdrawn in 7 weeks. The patient hasn't got any headaches since then (*bahra et al., 1998*).

Methysergide was given safely to stroke patients at doses of 2 milligrams orally 3 times a day for 14 days.
Storage:

Methysergide tablets are stored under temperatures below 30 degrees centigrade (89 Fahrenheit) (prod info Sansert®, 1999).
Ergotamine

Chemistry:

Ergotamine is one of the ergot alkaloid group. It is water-insoluble lysergic acid derivative.

Physical properties:

Ergotamine is slightly hygroscopic, colourless, odourless crystals or a white or yellowish –white crystalline powder. It may contain 2 molecules of methanol of crystallization. Soluble 1 in about 3200 of water, but soluble 1 in about 500 of water in the presence of a slight excess of tartaric acid; soluble 1 in 500 of alcohol; practically insoluble in ether. A 0.25% suspension in water has a pH of 4.0 to 5.5. Store in airtight glass containers at a temperature of 2 to 8. Protect from light.
**Mechanism of action:**

Ergotamine is nonselective serotonin 5-HT receptor agonist. It also has affinity for dopamine and noradrenaline receptors (Tfelt-Hansen et al., 2000; Villalon et al., 2003).

**Pharmacokinetics:**

Oral absorption of ergotamine is 60-70% and concurrent administration of caffeine improves both the rate and extent of absorption (Bulow et al., 1986). Ergotamine has low bioavailability and subject to substantial (greater than 90%) first-pass metabolism by the liver following oral administration, as a result very little of the unchanged parent drug reaches the circulation. However, several of the metabolites of ergotamine have biologic activity similar to that of the parent drug and are often present in concentration several times than that of the parent compound (Silberstein, 2003). Ergotamine is strongly sequestered by tissues, which could contribute to the persistence of biologic effects after the parent drug or metabolites can no longer detected in plasma (Eadie, 2001).

Little is known about the tissue distribution of ergotamine in humans. The drug is apparently distributed into the cerebrospinal fluid (Verhoeff et al., 1993). Following oral or IV administration in rats, ergotamine is distributed in
high concentrations in the liver and lung and in lower concentrations in the kidney, heart, and brain.

Ergotamine and its metabolites are excreted principally in the feces via biliary elimination. Only a small amount of Ergotamine is slightly hygroscopic, colourless, odourless crystals or a white or yellowish–white crystalline powder. It may contain 2 molecules of methanol of crystallization. Soluble 1 in about 3200 of water, but soluble 1 in about 500 of water in the presence of a slight excess of tartaric acid; soluble 1 in 500 of alcohol; practically insoluble in ether. A 0.25% suspension in water has a pH of 4.0 to 5.5. Store in airtight glass containers at a temperature of 2 to 8. Protect from light.

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Ergotamine and its metabolites are excreted principally in the feces via biliary elimination. Only a small amount of unchanged drug is excreted in urine. Elimination of ergotamine follows a biphasic pattern, with half-lives of approximately 10min and 3-4 hours (Eadie, 2001).

Unchanged drug is excreted in urine. Elimination of ergotamine follows a biphasic pattern, with mean half-lives of approximately 10min and 3-4 hours (Eadie, 2001).

**Pharmacological effects:**

Ergotamine can produce the following pharmacological actions:

1. **Constriction of meningeal arteries:**

   It has been suggested that the headache of migraine could result from dilatation of the large pain-producing conductance intracranial arteries and its relief from their constriction. Ergotamine constricts meningeal blood vessels through its agonist activity at the 5-HT1b receptors that are preferentially expressed in intracranial extra-cerebral arteries; this could contribute to its pharmacologic action by decreasing activation of perivascular trigeminal sensory nerves (Tfelt-Hansen et al., 2000; Limmroth et al., 1998).
II. Cardiovascular system:

Ergotamine can constrict coronary blood vessels through actions at 5-HT1b and 5-HT2a receptors that are present on coronary artery smooth muscle. There are more 5-HT1b receptors in the meningeal arteries than there are in the coronary arteries, and so the ergots retain selectivity for cranial over coronary blood vessels. The affinity of the ergots at constrictor 5-HT2a receptors is at least 20-fold lower than the affinity at anti-migraine 5-HT1b receptors (Rolen, 1997).

III. Inhibition of neurogenic inflammation:

The trigeminal nerve innervates the cranial blood vessels. The trigeminal sensory C fibers contain the neurokinins substance P, neurokinin A, and calcitonin gene-related peptide (CGRP). The ergot alkaloids inhibit the trigeminal sensory nerves through prejunctional 5-HT1d receptors, thereby blocking the release of vasoactive neuropeptide mediators (SP, CGRP) that could produce or exacerbate the pain and vasodilatation of migraine (Silberstein, 2003).

Uses:

Ergotamine is widely used for the treatment of severe migraine attacks. However, its adverse effects limit how much it can be used and prevents its use for prophylaxis (Lawrence, 2004).

Ergotamine was one of the main drugs used to treat acute attacks of Ergotamine may be used similarly in cluster headache to treat individual headache during a cluster period. It is also used in low doses given by mouth
or rectally for limited periods of up to 2 weeks in the prophylaxis of cluster headache during a cluster period.

Ergotamine may be used in patients with orthostatic hypotension resistant to the more usual treatment (Tfelt-Hansen, 2001).

**Adverse effects:**

The adverse effects of ergotamine may be attributed either to its effects on CNS, or to vasoconstriction of blood vessels and possible thrombi formation.

After therapeutic doses nausea and vomiting commonly occur as a result of the direct mutagenic effect of ergotamine, some patients may also experience abdominal pain. Weakness and muscle pain in the extremities and numbness and tingling of the fingers and toes may occur. There may be occasionally localized oedema and itching in hypersensitive patients. Susceptible patients, especially those with severe infections, liver disease, kidney disease, or occlusive peripheral vascular disease, may show signs of acute or chronic poisoning with normal doses of ergotamine (Meyler, 1996).

Symptoms of acute overdosage include nausea, vomiting, diarrhea, extreme thirst, coldness, tingling, and itching of the skin, a rapid and weak pulse, hypotension, shock, confusion, convulsions, and unconsciousness.

Ergotism related to chronic poisoning and resulting from therapeutic overdosage or the use of ergotamine in susceptible patients, severe circulatory disturbance may develop. The extremities, especially the feet and legs, become cold, numb, tingling, and pale or cyanotic, with muscle pain; there
may be no pulse in the affected limb. Eventually gangrene develops in the toes and sometimes the fingers. Anginal pain, tachycardia or bradycardia, hypertension or hypotension. Myocardial infarction, pleural and peritoneal fibrosis may occur with excessive use (Dresser et al., 2000).

Chronic, intractable headache (rebound headache) may occur and is also a major withdrawal symptom following the development of ergotamine dependence (Capobianco et al., 2001; Evers et al., 1999).

It has been also shown that ergotamine suppositories may lead to severe anorectal complication such as ulceration, stricture, and rectovaginal fistula with chronic use (Sayfan, 2002).

**Precautions:**

One-half the normally effective dose of ergotamine should be tried in patients on methysergide because of the vasoconstrictor action of methysergide. Triptans have a minor peripheral vasoconstrictor effect and should generally not be used together with ergotamine (Tfelt-Hansen, 2001; Lampl et al., 2002).

**Contraindications:**

Ergotamine is contraindicated in women who are or may become pregnant, since the drug may cause fetal harm such as mobius sequence which is characterized by congenital facial diplegia and external ophthalmoplegia, with variable involvement of other cranial muscles and musculoskeletal and cardiovascular systems (Smets, 2004).
Ergotamine is also contraindicated in patients with peripheral vascular diseases (Zavaleta et al., 2001), coronary heart disease (Redfield et al., 1992), uncontrolled hypertension, stroke, impaired hepatic or renal function, and sepsis (Wooltorton, 2003; Tfelt-Hansen et al., 2000).

Based on theoretical additive pharmacological effects of the drug, ergotamine should not be taken within 6 hours of the use of triptans (Tfelt-Hansen et al., 2000). It is also recommended that ergotamine should not be used in complicated migraine, migraine with prolonged aura, basal migraine, or familial hemiplegic migraine.

Ergotamine also should not be used concomitantly with certain drugs, including triacetyloleandomycin and erythromycin, which decrease metabolism of ergotamine (WHO Drug Information, 2001). The drug is also contra indicated in patients with known hypersensitivity to ergot alkaloids.

**Drug Interactions & combinations:**

The vasoconstrictor effects of ergotamine are enhanced by sympathomimetics such as adrenaline. There is also an increased risk of peripheral vasoconstriction during concomitant administration of ergotamine and beta blockers. Administration of ergotamine with a macrolide antibiotic such as erythromycin has produced ergotism (WHO Drug Information, 2001). Ergotamine should not be given until at least 6 hours after stopping a serotonin agonist such as sumatriptan, since there is an additional risk of prolonged vasospastic reactions (Lampl et al., 2002).
Arterial occlusion has been reported in patients taking methysergide and a high parenteral dosage of ergotamine concomitantly for cluster headache; the combination should be avoided.

Ergotism developed in a patient receiving treatment with ergotamine after combination antiviral treatment was started for HIV infection. Symptoms initially resolved after both ritonavir and ergotamine were withdrawn and it was suggested that the ergotism might have been caused by inhibition of ergotamine metabolism by ritonavir (Vila et al., 2001; Tribble et al., 2002).

Peripheral vasoconstriction was reported in patients with migraine after addition of propanolol to regular use of cafergot suppositories twice daily.

**Formulation & dosage:**

Most formulations of ergotamine are not very useful due to an inappropriate amount of ergotamine or compounding with other drugs, such as caffeine, chlorcyclizine, or meprobamate. Ergotamine is marketed as aerosol which is slowly being withdrawn, oral and suppository formulations. In some countries, ergotamine can be used alone in an oral formulation, or particularly in the very useful inhalation form, but most often, the suppository formulation is compounded and contains 1-2 mg of ergotamine with caffeine (Tfelt-Hansen et al., 2000; Diener et al., 1998).

The extremely low oral and rectal bioavailability of ergotamine, result in marked inter-patient variability with regard to the amount of the drug reaching the circulation. There should thus be no standard dose, but the dose should be tailored to the individual patient. The recommended starting dose for oral ergotamine is 2 mg and the maximum dose is 6 mg. For rectal...
ergotamine the recommended starting dose is 1 mg and the maximum dose is 4 mg (Ekbom et al., 1983; Tfelt-Hansen, 2001).

Bromocriptine (Parlodel)

Chemistry:

Bromocriptine is an ergot alkaloid and it is a dopamine agonist. There is a structural similarity between bromocriptine & dopamine. (See figure 1.1).
All ergot alkaloids are considered to be derivatives of the tetra-cyclic compound 6-methylergoline. The naturally occurring alkaloids contain a substituent in the $\mathcal{B}$ configuration at position 8 & a double bond in ring D.

Bromocriptine (2-bromo- $\alpha$ ergocryptine) is a semi-synthetic derivative of the ergot alkaloids and it is an amide derivative of d-lysergic acid. It is one of the earliest derivatives that have been prepared by the catalytic hydrogenation of the natural alkaloids. Bromocriptine is saturated in ring D of lysergic acid. It contains a double bond between C9 and C10 and thus belongs to the family of 9-ergoline compounds. There is optical isomerism which is due to the presence of two asymmetrical carbon atoms (position 5 and 8) in the lysergic acid portion molecule. (Gilman; 1999). The addition of the bromine atom renders this alkaloid a potent dopaminergic agonist, which is preference for D2 receptors. Bromocriptine has been studied most thoroughly and hence logically serves as a prototype for the ergolines. (Gilman; 1996).

**Physical properties:**

A white or slightly colored fine crystalline powder, almost odorless. Bromocriptine mesylate 2.87 mg is approximately equivalent to 2.5 mg of bromocriptine. Practically insoluble in water, soluble in alcohol, sparingly
soluble in dichloromethane, freely soluble in methyl alcohol. A 1% solution in a mixture of 2 parts methyl alcohol to 8 of water has a pH of 3.1 to 3.8. Store in airtight containers at a temperature not exceeding 15 degree centigrade. Protect it from light. (Parfitt; 1999)

**Mechanism of action:**

Bromocriptine is an ergot alkaloid; it is a sympatholytic dopamine D2 receptor agonist that exerts an inhibitory effect on serotonin turnover in the central nervous system. (Pijl, et al; 2000). Bromocriptine is believed to act at the level of the hypothalamus and corpus striatum as a dopamine agonist. (Russo and O'Flaherty; 2000).

Bromocriptine stimulates dopamine type-2 receptors and antagonizes type-1 receptors in the hypothalamus and the neostriatum of the central nervous system. (Roberts, et al; 2004). Also, bromocriptine may have a direct stimulatory effect on ovarian dopaminergic receptors leading to menses in amenorrheic women. Bromocriptine directly activates lactotrope dopamine receptors, leading to inhibition of spontaneous and TRH-induced release of prolactin. (Schwartz; 2004).

Bromocriptine is a free radical scavenger or an inhibitor of glutamate uptake into synaptic vesicles, but molecular basis for its neuroprotective action is not understood. Bromocriptine enhances glutamate uptake and may be important in enhancing the removal of extracellular glutamate producing similar effect as those achieved by glutamate receptor antagonists. It may serve as a prototype for the development of more specific and potent regulators of the glutamate transporters. (Yamashita, et al; 1995).
Bromocriptine can improve glucose control and glucose tolerance by resetting central (hypothalamic) circadian organization of monoamine neuronal activities leading to reverse many of the metabolic alterations associated with obesity. (Pijl, et al; 2000).

There are different ways by which bromocriptine might exert an immuno-modulatory effects, either via direct inhibition of prolactin or by inhibiting the action of human growth hormone or other factors. (Regana and Millet; 2000).

![Dopamine Agonist Effect of Bromocriptine](image)

**Figure 1.2:** The dopamine agonist effect of bromocriptine.

**Pharmacokinetics:**

**Route of administration:**

Bromocriptine tablets or capsules are taken orally by mouth; patients have to swallow them with a drink of water. It is best to take bromocriptine with food to help with symptoms such as gastric upset.
Bromocriptine is well absorbed from standard oral tablets placed in the vagina & it is sufficient to perform an action (Katz, et al; 1989).

**Absorption:**
Absorption of bromocriptine is rapid and good. Although 28% of an orally administered dose of bromocriptine is absorbed across the gastrointestinal tract, only 6% reaches the circulation (bioavailability is 6%) due to extensive first pass hepatic metabolism. The half life of absorption in healthy people is 0.2-0.5 hours. (Novartis Company Information's; 1999).

**Distribution:**
The peak plasma concentration is attained within 1-3 hours. Clinical improvement begins to take effect 1-2 hours after ingestion with peak effect after 5-10 hours.

There was however a significant relationship between plasma concentrations and concurrent changes in clinical response. Dyskinesias occurred within 90-180 minutes of dosage. Improvement is maintained for 8-12 hours. (Katz, et al; 1989).

The blood levels following a 2.5 mg dose were in the range of 2-3 mg equivalents/ml. plasma levels were in the range of 4-6 mg equivalents/ml which indicates that red blood cells did not contain appreciable amounts of drug and/or metabolites which means that bromocriptine do not distribute into erythrocytes. The drug binds extensively (90-96 %) to serum albumin.
Metabolism:
More than 90% of the absorbed dose undergoes first pass hepatic metabolism by the cytochrome P450 (CYP3A) system mainly by hydrolysis to lysergic acid & peptides, with the remainder of the dose which is hydrolyzed in the liver to inactive metabolites. (Nottingham, 2004).

Half-life:
Bromocriptine has a half life of 3 hours.

Excretion:
Excretion of the active substance is biphasic with terminal half life of approximately 15 hours. Both parent drug and metabolites are mainly eliminated in the feces via the bile with only a small amount (3-6%) is excreted by the kidney in the urine. Almost all (84.6%) of the administered dose was excreted in the feces in 120 hours.

There is no evidence that the pharmacokinetic properties tolerability of bromocriptine are altered in elderly patients. However, in patients with impaired liver function elimination may be slower, giving rise to higher plasma levels and making dose adjustment necessary. (Novartis Company Information's; 1999)

Pharmacological actions:
Bromocriptine has pharmacological actions of two categories:
1- Endocrinological actions.
2- Neurological actions.
The Endocrinological Actions of Bromocriptine:

- **By stimulating dopamine receptors it:**

  Inhibits secretion of the anterior pituitary hormone prolactin without affecting normal levels of other pituitary hormones. So, it is a potent suppressor of lactation. (McMURRAY, et al; 1995).

  Induces menses in amenorrheic women with normal levels of serum prolactin (possibly via the release of luteinizing hormone). (Cottingham; 2004)

  Reduces elevated levels of growth hormone in patients with acromegaly. (Novartis Company Informations; 1999). But bromocriptine can increase the secretion of growth hormone in normal patients. (Cottingham; 2004)

  Arrest the growth or reduce the size of prolactin-secreting pituitary adenomas (prolactinomas).

  Induces a normal pattern of luteal hormone secretion by normalizing the underlying progesterone/estrogen imbalance. (Novartis Company Information's; 1999)

-**Effect on Glucose Control:**

  Bromocriptine can reduce both fasting and postprandial plasma glucose levels, leading to improvement in glucose tolerance & insulin resistance in obese type2 diabetic patients; So, it diminishes the need for oral hypoglycemic agents. The bromocriptine-induced improvement in glycemic control is
associated with enhanced maximally stimulated insulin-mediated glucose disposal. Timed bromocriptine treatment decrease body weight and improve glucose tolerance in obese individuals who were instructed to follow a hypocaloric diet. Bromocriptine has also been shown to reduce mean daylong plasma glucose, triglyceride, and free fatty acid levels in the absence of a change in body weight in obese non-diabetic women. (Pijl, et al; 2000)

The Neurological Actions of Bromocriptine:
- By stimulating dopamine receptors it can reverse the specific nigrostriatal dopamine deficiency that characterizes Parkinson's disease.
- Due to its specific anti-depressant properties, it can improve depression symptoms. (Novartis Company Information's; 1999)

Other Actions of Bromocriptine:
- It slightly increases sodium excretion and can reduce blood pressure. High doses of the drug can induce vasoconstriction.
- It reduces the intensity of psychiatric symptoms associated with cocaine withdrawal. (Cottingham; 2004)

Uses:

A. Endocrinological uses:

In hyperprolactinemia:
Prolactin has no therapeutic value. Hyperprolactinemia is a common syndrome, however, and drugs that affect prolactin release are useful therapeutic agents for this condition.

**Prolactin-secreting tumors** are a common cause of hyperprolactinemia. It also may be caused by drugs such as dopaminergic antagonists, disorders of the hypothalamus or pituitary that interfere with the regulation of prolactin secretion, renal failure, and primary hypothyroidism associated with increase TRH levels. In women, the symptoms of hyperprolactinemia include galactorrhea, amenorrhea, and infertility. In men, the symptoms include infertility, impotence (oligospermia), loss of libido and galactorrhea. Because dopamine is an inhibitor of prolactin release, dopaminergic agents such as bromocriptine are useful and widely used in the treatment of this syndrome. (Mcmurry, et al; 1995).

About 80% of hyperprolactinemic women treated with bromocriptine resume their normal menstrual cycles, and pregnancy rates may be as high as 70%. Women undergoing bromocriptine treatment, who fail to ovulate, or ovulate but fail to conceive, can be given additional drugs to induce ovulation & achieve pregnancy.

Bromocriptine is the drug of choice for the treatment of prolactinemia regardless of the etiology or the sex of the patient. When administered to patients who have prolactin-secreting tumors, it reduces prolactin level and causes a reduction in tumor size as long as therapy continues' however tumor size usually rebounds upon cessation of treatment.

The dose of bromocriptine used for hyperprolactinemia, amenorrhea and male or female infertility is initially 1.25 to 2.5 mg once per day and then
increased to a maintenance dose of 2.5 mg 2 or 3 times daily. (Delgrange, et al; 1998).

**In prolactinomas**, bromocriptine is used as conservative treatment of pituitary micro or macroprolactinomas, in presurgical reduction of tumor size to facilitate resection, in postsurgical inhibition of persistent hyperprolactinemia.

Bromocriptine can be used also in apparently normoprolactinemic conditions: amenorrhea (with or without galactorrhea), oligomenorrhea, luteal-phase deficiency. It is used also in prolactin-independent female infertility as in: polycystic ovary syndrome, anovulatory cycles.

In all previous conditions bromocriptine dose is 1.25mg (1/2 tablet) 2 or 3 times daily, if this proves inadequate, gradually increase to 2.5 mg (one tablet) 2 or 3 times daily. Treatment should be continued until the menstrual cycle is normalized and/or ovulation occurs & if necessary, over several cycles to prevent prolapse.

In hyperprolactinemia in males the dose is 1.25 mg (1/2 tablet) 2 or 3 times daily, gradually increasing to 5-10 mg (2-4 tablets) daily.

In prolactinomas the dose is 1.25 mg (1/2 tablet) 2 or 3 times daily, gradually increasing to several tablets or capsules daily as required for control of plasma prolactin.

**In inhibition of lactation:**

Bromocriptine is used to suppress or prevent puerperal lactation for medical reasons, to prevent lactation following abortion, in puerperal breast engorgement, in incipient puerperal mastitis. (Eftekhari; 2004)

Bromocriptine was used in the past to prevent breast engorgement following delivery in women who chose not to breast feed. However, this
indication has been withdrawn because of the risk of severe postpartum side effects. Bromocriptine no longer is prescribed to prevent lactation except in unusual circumstances as stillbirth. (Mcmurry,.1995)

The dose is 1.25 mg (1/2 tablet) with the morning & again with the evening meal on the first day of treatment, followed by 2.5 mg (one tablet) twice daily for 14 days. To prevent the onset of lactation treatment should be instituted within a few hours after parturition or abortion, but not before vital signs have stabilized. Slight milk secretion occasionally occurs 2-3 days after treatment has been withdrawn. This can be stopped by resuming treatment at the same dosage for a further week.

In puerperal breast engorgement a single dose of 2.5 mg (one tablet) may be repeated after 6-12 hours without causing inappropriate suppression of lactation.

In incipient puerperal mastitis an antibiotic may be added to the regimen as required.

**In benign breast disease:**

Mastalgia (isolated or in association with premenstrual syndrome or with benign nodular or cystic changes). Benign cystic and/or nodular conditions, in particular fibrocytic breast disease. By normalizing the underlying progesterone/estrogen imbalance, bromocriptine can reduce the number of cysts and/or nodules in patients with benign breast disease and alleviates the associated pain. Bromocriptine should preferably be taken over the whole of the menstrual cycle, starting at 1.25 mg (1/2 tablet) 2 or 3 times daily and building up gradually to the full dose of 5-7.5 mg (2-3 tablets) daily.
Treatment should normally be discontinued if this dosage brings no satisfactory improvement within 3 months.

**In premenstrual symptoms:**

Breast tenderness, cyclic oedema, abdominal bloating, and mood disturbances. The dose is 1.25 mg (1/2 tablet) daily starting on day 14 of the cycle and increasing in steps of 1.25 mg daily up to 2.5 mg (one tablet) twice daily until menstruations begins. *(Delgrange, et al; 1998)*

**In acromegaly:**

Excessive secretion of growth hormone causes acromegaly in adults or gigantism, if the excessive secretion starts before epiphyseal closure. Somatotrope adenomas (growth hormone-producing adenomas) account for over 80% of the cases of acromegaly. The treatment of choice for patients with somatotrope adenomas is irradiation or surgical removal of the tumor.

Drug therapy is indicated for patients not cured by surgery and those with recurring problems. Growth hormone secretion by adenomas can be suppressed by bromocriptine. The effect of bromocriptine on growth hormone secretion is paradoxical, as it can actually increase growth hormone secretion in normal pituitary. It can reduce serum growth hormone by 50% or more in approximately ½ of patients treated, although not usually to normal levels. Since the effects of external pituitary radiation may not become maximal for several years, adjunctive therapy with bromocriptine mesylate offers potential benefit before the effects of irradiation are manifested. The dose in acromegalic patients is 1.25 mg (1/2 tablet) 2 or 3 times daily, gradually
increasing to 10-20 mg daily depending on clinical response and adverse reactions. (Cassar, et al; 1976)

B. **Neurological uses:**

**In Parkinson's disease:**

Most patients with Parkinson's disease are treated with levodopa or with dopamine agonists. Bromocriptine have been used in previously untreated patients with Parkinson's disease to prolong levodopa treatment and delay its complications. (Yamashita, et al; 1995)

While some neurologist use bromocriptine early in the treatment of Parkinsonism in an attempt to delay therapy with levodopa, others reserve it for adjunctive use when levodopa is no longer effective alone or cannot be tolerated. Bromocriptine is sometimes useful in reducing 'off' periods with levodopa and in ameliorating other fluctuations of mobility in the later stage of the disease. (Parfitt; 1999)

Bromocriptine mesylate tablets or capsules are indicated in the treatment of the signs and symptoms of idiopathic or postencephalitic Parkinson’s disease. As adjunctive treatment to levodopa (alone or with a peripheral decarboxylase inhibitor), bromocriptine mesylate therapy may provide additional therapeutic benefits in those patients who are currently maintained on optimal dosages of levodopa, those who are beginning to deteriorate (develop tolerance) to levodopa therapy, and those who are experiencing “end of dose failure” on levodopa therapy. Bromocriptine mesylate therapy may permit a reduction of the maintenance dose of levodopa and, thus may ameliorate the occurrence and/or severity of adverse reactions
associated with long-term levodopa therapy such as abnormal involuntary movements (e.g., dyskinesias) and the marked swings in motor function (“on-off” phenomenon). Continued efficacy of bromocriptine mesylate therapy during treatment of more than 2 years has not been established.

The basic principle of bromocriptine mesylate therapy is to initiate treatment at a low dosage and, on an individual basis, increase the daily dosage slowly until a maximum therapeutic response is achieved. The dosage of levodopa during this introductory period should be maintained, if possible. The initial dose of bromocriptine mesylate is ½ of a 2½ mg tablet twice daily with meals. Assessments are advised at 2-week intervals during dosage titration to ensure that the lowest dosage producing an optimal therapeutic response is not exceeded. If necessary, the dosage may be increased every 14-28 days by 2½ mg/day with meals. Should it be advisable to reduce the dosage of levodopa because of adverse reactions, the daily dosage of bromocriptine mesylate, if increased, should be accomplished gradually in small (2½ mg) increments. The safety of bromocriptine mesylate has not been demonstrated in dosages exceeding 100 mg/day. (Willis; 2005)

Figure 1.3: The cause of Parkinson’s disease.

Figure 1.4: The effect of bromocriptine in parkinsonism.
C. Other uses:

In Psoriasis:

Bromocriptine has also been used in the treatment of psoriasis. Increase in the severity and extent of psoriasis correlated with the development of a prolactin-secretory pituitary gland microadenoma. Prolactin may play role in the pathogenesis of psoriasis because it plays an important part in the immune reactions and exerts a proliferative effect on human keratinocytes. The degree of elevation of prolactin was related to the severity of psoriasis.

However, in all patients, administration of bromocriptine as a treatment of prolactinoma was associated with a better therapeutic response in psoriatic cutaneous lesions. Bromocriptine can be useful in the treatment of different autoimmune diseases. It has been used in the treatment of psoriasis vulgaris and psoriatic arthritis with a marked improvement in the lesions (Regana and Millet; 2000)

In Type II Diabetes:

Bromocriptine can be used in obese type2 diabetic patients to improve glucose tolerance and insulin resistance, also to reduce body fat stores and decrease body weight. So, patients can reduce the use of oral hypoglycemic drugs (Pijl, et al; 2000)

In Autonomic Dysfunction:

Autonomic dysfunction after traumatic brain injury is usually associated with hypertension. The hypertension encountered in traumatic brain injury is described as being part of a hyperadrenergic state because it is associated
with elevation of urine and blood catecholamine levels. Bromocriptine can cause hypotension, so, it is used in the management of labile hypertension associated with autonomic dysfunction. We start with a low dose (0.025mg/kg twice daily) and gradually increase this to 0.05mg/kg t.d.s. as required to treat the autonomic dysfunction. So, Bromocriptine is effective alternative treatment for the episodes of autonomic dysfunction due to severe traumatic brain injury or due to other causes (Russo and O'Flaherty; 2000)

**Side effects:**

The incidence of side effects is quite high (69%) but these are generally mild to moderate in degree.

Side effects of bromocriptine are generally dose-related & may therefore be more frequent with the higher doses that have been used in the treatment of Parkinsonism and acromegaly.

Reduction of the dosage of bromocriptine, followed in a few days by a more gradual increase, may alleviate many side-effects. (Parfitt; 1999). However, clinicians agree that patients with certain diseases are more sensitive to side effects than others. Furthermore, some adverse reactions are seen only with very high doses and others are only seen in patients with certain conditions- for example, psychiatric side effects in parkinsonian patients. (Thorner, et al; 1980).
Side Effects with Initiation of Therapy:

During the first few days of treatment some patients may experience nausea, & rarely, vomiting, hypotension, dizziness, syncope and fatigue. (Novartis Company Information's; 1999)

1-Nausea:

It is the most common side effect of bromocriptine therapy particularly at the beginning of treatment, occurring in approximately 50% of patients treated. Nausea may be diminished by taking bromocriptine with food. (Parfitt; 1999)

2-vomiting:

It occurs in a much lower percentage of patients.

Nausea was noted shortly following intramuscular injection of bromocriptine in 3 of 10 patients, and vomiting occurred in 1 of these 3. Gastrointestinal side effects occur frequently following intramuscular injection of bromocriptine, but they are mild and short-lived, requiring drug discontinuation in less than 10% of patients. Some patients who previously could not tolerate oral bromocriptine were able to tolerate treatment with the injectable preparation. (Maraschini et al, 1999)

Nausea and vomiting usually occur during the first few days of treatment but discontinuation of treatment is not normally necessary. If necessary, initial nausea and vomiting may be prevented by prescribing a peripheral dopamine agonist (domperidone) to be taken one hour before ingestion of bromocriptine on the first few days of treatment.

3-Hypotension:

It is a commonly occurring dose-related side effect of bromocriptine therapy. This orthostatic hypotension can occasionally resulting in collapse,
and ambulant patients’ blood pressure, therefore it should be monitored. This side effect may be troublesome but usually responds to symptomatic treatment. Hypotension was not observed following administration of intramuscular bromocriptine. (Novartis Company Information's; 1999)

A symptomatic hypotension account for the collapse that occurs in a few sensitive patients. It is essential to warn all patients starting treatment of the possibility of fainting. (Parfitt; 1999)

4-Dizziness, syncope & fatigue:
Dizziness or lightheadedness has been recorded in 7% of patients especially when getting up from a lying or sitting position.
(American Society of Health-System Pharmacists; 2005)

5-headache & nasal stiffness:
They are commonly occurred at the start of bromocriptine therapy. They are seldom severe and are often transitory. (Thorner, et al; 1980).

II. Side Effects with Chronic Use:

A- In All Groups of Patients:

-Gastrointestinal side effects:
- **Constipation:** has occurred in 3% to 4% of hyper-prolactinemic patients receiving bromocriptine. (RxList Inc.; 2004)
But it occur much more (50%) in acromegalic patients & in almost all Parkinsonian patients. In Parkinsonism it is difficult to relate this to bromocriptine, since constipation is a symptom of Parkinsonism & a complication of all anti-Parkinsonian therapies. In proportion of acromegalic patients, continuation of the drug leads to resolution of this
- **Diarrhea**: has been reported to occur in approximately 3% of patients treated with bromocriptine.

- **Anorexia**: occurs in 4% of patients treated with bromocriptine.

- **Abdominal cramps**: occurs in approximately 4% of patients receiving bromocriptine. (RxList Inc.; 2004)

- **Gastrointestinal Bleeding from Ulcers**: 6 acromegalic patients was receiving long-term bromocriptine therapy (10 to 60 mg daily) then four of them developed peptic ulcers of stomach and 2 of the duodenum.

- **Epigastric pain**: was evident in 4 patients with melena with or without hematemesis.

- **Severe gastrointestinal hemorrhages**: requiring blood transfusions were observed in 3 patients.

  4 of these 6 patients who developed peptic ulcers eventually recovered, 1 died from hemorrhage, and 1 died after gastrectomy.

  In many acromegalic patients receiving bromocriptine (10 to 40 mg daily), no evidence of peptic ulceration or gastrointestinal bleeding related to bromocriptine was documented. However, until more data on causal relationships are established, alternative therapy should be considered in acromegalics with a history of peptic ulcer. The question arisen whether or not the vascular haemostatic response to the bleeding may have been impaired by bromocriptine.

- **Dyspepsia**:

  Occurs occasionally during high-dose therapy. It is brought on by lying flat or by bending down. The symptoms are typical of esophageal
reflux. It is possible that bromocriptine may relax the physiologic cardiac sphincter. (Pandy, et al; 2005)

- **retroperitoneal fibrosis**: as other ergot derivatives, bromocriptine can cause retroperitoneal fibrosis.

- **Dry mouth and altered liver function tests** have also been reported.

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**- Cardiovascular side effects:**

Prolonged severe hypotension, arrhythmias and exacerbation of angina have been reported. (Parfitt; 1999). Other cardiovascular reactions include sinus bradycardia, ventricular tachycardia and pedal edema. (Cottigham; 2004). Aggravation of angina pectoris, bradycardia and transient disturbances of cardiac rhythm (bundle-branch block) have been reported with bromocriptine. (Novartis Company Information's; 1999). Bromocriptine is a vasoconstrictor, digital vasospasm and pallor, induced by cold, and leg cramps have also been reported. Very rarely hypertension, myocardial infarction, seizures and stroke (both sometimes preceded by severe headache or visual disturbances) have been reported in postpartum women given bromocriptine. As other ergot derivatives, bromocriptine can cause pericarditis & pericardial effusions.

- **Arrhythmias: Premature ventricular contractions**: were reported in some patients receiving 25 mg of bromocriptine four times daily. These contractions resolved with dose reduction.

- **Hypertension, myocardial infarction, seizures & stroke**:  
  
  A study involving 1813 women suggested that the risk of postpartum hypertension was increased in women who experienced pregnancy induced
hypertension and that this risk was further increased in those who took bromocriptine for suppression of lactation.

A case controlled study involving 43 women who had postpartum seizures while taking bromocriptine found that while the initial risk of seizures appeared to be lower in patients taking bromocriptine there was a small positive association with seizures occurring more than 72 hours after delivery.

Although a causal relationship between the use of bromocriptine and these adverse effects in postpartum women has not been established, the manufacturer recommends that bromocriptine should not be used postpartum or in the puerperium in women with high blood pressure, coronary artery disease, or symptoms or history of serious mental disorders. It is also recommended that when bromocriptine is used in postpartum women blood pressure should be carefully monitored, especially during the first few days and if hypertension, unremitting headache, or signs of CNS toxicity develop treatment should be discontinued immediately. (Parfitt; 1999).

- **Vasoconstriction:**
  Bromocriptine treatment is associated with peripheral vasoconstriction effects. These effects have been seen with doses as low as 7.5 mg daily or with higher doses of 60 mg. These effects include:

  *Digital vasospasm and pallor:*
  It was noticed in some patients receiving 20 to 60 mg bromocriptine daily over periods of 1 to 12 months. Pallor and painful thermal sensations of the fingers have been reported. Symptoms worsened with cold, and improved with warming temperatures, some patients wore gloves to reduce these symptoms. Dose reduction was sometimes effective in reliving symptoms, while drug withdrawal was
also required in some patients. (Parfitt; 1999). This cold-sensitive vasospasm was initially seen only when patients were treated long-term with high-dose bromocriptine. It occurs in approximately 30% of acromegalic patients & has also been reported in parkinsonian patients. It is not true ergotism, since it is painless, has ever led to ischemia of the phalanges, & can be reversed by lowering the dose. It may be prevented by keeping the fingers warm.

*Leg cramps:*

Few patients have also complained of cramps in the calves of the legs, which appear to be related to bromocriptine therapy. However, this is not a major problem. (Thorner, et al; 1980)

**Effects on mental status & nervous system:**

Psychosis with hallucinations, delusions, and confusion occurs particularly when high doses are used to treat Parkinsonism, but has also been reported with low doses. Drug related psychotic reactions have also been reported in patients with no psychiatric history. 8 of 600 patients given bromocriptine for the treatment of acromegaly or prolactinoma developed symptoms including anxiety, depression, auditory hallucinations, delusions, hyperactivity, disinhibition, euphoria and insomnia and 4 had received doses only previously associated with psychosis in susceptible patients.

A report of 2 cases of cerebrospinal fluid rhinorrhoea associated with the use of bromocriptine following partial surgical resection of prolactinoma. (Parfitt; 1999). Although CNS rhinorrhoea is rare but it can occur in patients receiving bromocriptine for the treatment of macroadenomas or in those receiving the drug post-surgically (following transsphenoid surgery). Such
patients should be observed closely for signs of CNS rhinorrhea including nasal discharge.

**-Effects on the respiratory tract:**

Because bromocriptine is ergot derivative, it can cause pleural and pulmonary fibrosis, pleural thickening and effusion.

Interstitial lung disease with dyspnoea, chest pain and cough was reported in a patient following relatively high doses of bromocriptine for Parkinsonism. Respiratory symptoms largely resolved on withdrawal of the drug, although functional respiratory changes and moderate dyspnoea persisted after 6 months. *(American Society of Health-System Pharmacists; 2005)*

**-Effects on sexual function:**

Severe hyper-sexuality has been reported in a man receiving bromocriptine and levodopa for Parkinsonism but it was apparent that addictive abuse of dopamnergic drugs had occurred.

Clitoral tumescence and increased libido has been noted in a women receiving bromocriptine to suppress lactation but there has been a report of sexual dissatisfaction and decreased libido in 3 women receiving bromocriptine for hyperprolactinemia. *(Darwish, et al; 2005)*.

**-Effects on the urinary tract:**
Urinary retention, urinary incontinence and urinary frequency have been reported in few patients receiving bromocriptine. (Cottingham; 2004). Bromocriptine has been shown to have 2 effects: one on the bladder outflow tract and one on the detrusor muscle, these effects could predispose to urinary incontinence. Symptoms resolved on discontinuing the drug and recurred on rechallenge.

**Effect on the eyes:**

Blurred vision and diplopia has been reported in several patients receiving bromocriptine. There is a report of reversible myopia developing in a patient with hyperprolactinemia given bromocriptine.

In a patient with progressive visual loss due to compression of the optic chiasma by a large pituitary tumor, administration of bromocriptine caused total visual loss within hours. Vision slowly returned to normal when the patient was placed in the supine position, the most likely cause of the visual loss was thought to be orthostatic hypotension with resultant decrease in perfusion pressure to the visual system. In some cases blurred vision and transient cortical blindness have preceded seizures and strokes. (Parfitt; 1999). Bromocriptine has been reported to cause visual cortical disturbances, myopia & ocular irritation. (Cottingham; 2004)

**Effect on the ears:**

Audiometric evidence of bilateral sensorineural hearing loss was reported in 3 patients receiving bromocriptine 15 to 20 mg daily for chronic hepatic encephalopathy. Hearing improved when the dose was reduced to 10
mg daily (Parfitt; 1999). Also, tinnitus has been reported with bromocriptine therapy. (Cottingham; 2004)

- **Effect on the blood:**
  
  Severe leucopenia and mild thrombocytopenia developed in a woman after treatment with bromocriptine 7.5 to 10 mg daily for about 3 months.

- **Effect on electrolytes:**
  
  There have been isolated reports on severe hyponitremia associated with the use of bromocriptine.

- **Oedema:**
  
  Oedema poorly responsive to diuretics has been reported in a patient given bromocriptine as part of treatment for prolactinoma. The oedema resolved when treatment was changed to other drugs.

- **Hypersensitivity:**
  
  A report of an allergic reaction due to bromocriptine in a women being treated for a prolactin-secreting microadenoma. (Parfitt; 1999).
  
  Allergic reactions can be in the form of rash and urticaria. (Cottingham; 2004)

**B-In Parkinsonism only:**
**Dyskinesia:**

Choreothetoid involuntary movements (dyskinesia) of the limbs and axial musculature (including the head and neck) are induced by bromocriptine in parkinsonian patients who have been previously developed dyskinesia. In such patients, the dose of bromocriptine must be reevaluated every 2 to 3 months so that the intake of dopaminergic drugs can be reduced if dyskinesia is prominent.

**Psychotic reactions:**

Psychiatric reactions to bromocriptine are almost entirely confined to parkinsonian patients and seem to be correlate with the severity of neurological disability. Psychotic reactions at high doses of bromocriptine are well known in patients with Parkinsonism. The earliest feature of psychiatric toxicity to bromocriptine is usually frequent & vivid dreaming. This progresses to nocturnal hallucinations, and ultimately a highly organized delusional system develops, which are usually associated with visual hallucinations & paranoid ideation. The patient is violent and aggressive. Complete withdrawal of bromocriptine may still leave a residue of severe psychotic illness. Psychosis associated with low doses of bromocriptine has often occurred in patients with a history of psychotic illness or considerable changes in behavior and mood prior to treatment. (*Besser, et al; 1980*)

A case of bromocriptine-induced musical hallucinations in a patient with dementia at dose of 7.5 mg was reported. He was given bromocriptine for the treatment of Parkinsonism. Bromocriptine is known to cause hallucinations but not musical hallucinations. The dopaminergic effect of therapy and patient's cognitive impairment might have acted together to generate the musical hallucinations. (*Kobayashi, et al; 2004*)
- **Erythromelalgia:**

  Erythromelalgic syndrome is confined to parkinsonian patients receiving prolonged, high doses of bromocriptine. It is a syndrome of red, tender, edematous extremities, often associated with a sensation of localized burning or tingling discomfort. These symptoms usually start in the feet, but may extend up to the knee, they occasionally occur in the hands. There is rarely additional polyarthritis. Histological examination of the affected skin reveals a low-grade vasculopathy characterized by mononuclear infiltration of the walls of dermal blood vessels. These symptoms heal rapidly after therapy is discontinued. *(Besser, et al; 1980)*

**C-Postpartum side effects:**

In postpartum studies with bromocriptine mesylate 23% of postpartum patients treated had at least 1 side effect, but they were generally mild to moderate in degree. Therapy was discontinued in approximately 3% of patients. The most frequently occurring adverse reactions were: headache (10%), dizziness (8%), nausea (7%), vomiting (3%), fatigue (1.0%), syncope (0.7%), diarrhea (0.4%) and cramps (0.4%). Decreases in blood pressure (≥20 mm Hg systolic and ≥10 mm Hg diastolic) occurred in 28% of patients at least once during the first 3 postpartum days; these were usually of a transient nature. Reports of fainting in the puerperium may possibly be related to this effect. In postmarketing experience in the U.S. serious adverse reactions reported include 72 cases of seizures (including 4 cases of status epilepticus), 30 cases of stroke, and 9 cases of myocardial infarction among postpartum
patients. Seizure cases were not necessarily accompanied by the development of hypertension. An unremitting and often progressively severe headache, sometimes accompanied by visual disturbance, often preceded by hours to days many cases of seizure and/or stroke. Most patients had shown no evidence of any of the hypertensive disorders of pregnancy including eclampsia, preeclampsia or pregnancy induced hypertension. One stroke case was associated with sagittal sinus thrombosis, and another was associated with cerebral and cerebellar vasculitis. One case of myocardial infarction was associated with unexplained disseminated intravascular coagulation and a second occurred in conjunction with use of another ergot alkaloid. The relationship of these adverse reactions to bromocriptine mesylate administration has not been established. (RxList Inc.; 2004)

III. -Withdrawal symptoms:

Transient galactorrhea and hyperprolactinemia occurred in a young woman after withdrawal of bromocriptine therapy for Parkinson’s disease. It was suggested the effects were due to a rebound phenomenon. (Pentald, Sawers; 1980)

IV. -Overdose (toxicity):

The most commonly reported signs and symptoms associated with acute bromocriptine mesylate overdose are: nausea, vomiting, constipation, diaphoresis, dizziness, pallor, severe hypotension, malaise, confusion, lethargy, drowsiness, delusions, hallucinations, and repetitive yawning. The lethal dose has not been established and the drug has a very wide margin of
safety. However, one death occurred in a patient who committed suicide with an unknown quantity of bromocriptine mesylate and chloroquine.

Treatment of overdose consists of removal of the drug by emesis (if conscious), gastric lavage, activated charcoal, or saline. Catharsis. Careful supervision and recording of fluid intake and output is essential. Hypotension should be treated by placing the patient in the Trendelenburg position and administering I.V. fluids. If satisfactory relief of hypotension cannot be achieved by using the above measures to their fullest extent, vasopressors should be considered. (RxList Inc.; 2004)

The highest dose known to have been ingested is 325 mg, which caused nausea, vomiting, orthostatic hypotension, drowsiness and hallucinations. The management was symptomatic. (Novartis Company Information's; 1999).

Rarely, patients treated with high-dose bromocriptine for acromegaly noted that they suffer from increased arousal and required less sleep and became more active. This side effect is seldom a problem and in fact most patients are delighted with this effect, which they consider advantageous. (Thorner, et al; 1980).

**Contraindications:**

Bromocriptine is **contraindicated** in the following conditions:

- Known hypersensitivity to any of the ingredients or to other ergot alkaloids. Inadequately controlled arterial hypertension, hypertensive states of pregnancy (including eclampsia, preeclampsia, and pregnant-
related hypertension), the postpartum or puerperium. Coronary heart disease & other severe cardiovascular disorders.

- Symptoms of severe psychiatric disorder and/or history of severe psychiatric disorder.
  - History of cerebralvascular accident, arterial occlusive disease, Raynaud's phenomenon, nicotine abuse. Treatment with methylergometrine or other ergot alkaloids. In addition, bromocriptine should not be given concomitantly with certain cytochrome P450 inhibitors. *(Novartis Company Information's; 1999)*

**Precautions:**

**General:**

Treatment should be discontinued immediately if vasospastic or thrombotic symptoms, persistent headache or any other sign of CNS toxicity develops. If the patients have gastrointestinal bleeding and gastric ulcer or he present with a history of ulcer, the drug should be discontinued or closely monitored during treatment.

Hypotensive reactions (induced by bromocriptine usually at the beginning of treatment) require a particular caution when driving or using machines. *(Novartis Company Information's; 1999)*
In hyperprolactinemia (micro- and macroadenoma)/ infertility/amenorrhoea/galactorrhoea:

Non-hyperprolactinemic women should be given bromocriptine in the lowest dose necessary to achieve relief of symptoms in order to avoid the possibility of hypoprolactinemia, with the risk of luteal function impairment.

In patients to be treated for mastalgia or nodular and/or cystic breast changes, malignancy must first be excluded by appropriate diagnostic procedures.

Since patients with pituitary macroadenoma resulting from compression or destruction of pituitary tissue may also suffer from hypopituitarism, introduction of bromocriptine should be preceded by a thorough examination of pituitary function & appropriate substitution therapy. Tumor growth must be closely monitored in patients with pituitary macroadenoma and surgery considered at the first sign of progression.

In patients with secondary adrenocortical insufficiency corticosteroid substitution is essential.

Close monitoring is necessary in adenoma patients who become pregnant during bromocriptine therapy because prolactin-secreting adenomas may grow during pregnancy.

Infertility may be reversed by bromocriptine treatment. So, women of child-bearing age who don't wish to conceive should therefore be advised to use a reliable method of contraception. (Novartis Company Information's; 1999)
**Postpartum & puerperal use:**

The drug should not be used during the post-partum period in women with a history of coronary artery disease and other severe cardiovascular conditions unless withdrawal is considered medically contraindicated. If the drug is used in the post-partum period the patient should be observed with caution. *(RxList Inc.; 2004)*

Although there is no evidence that bromocriptine can induce postpartum hypertension but regular blood pressure monitoring is essential in such patients and patients receiving bromocriptine for other indications. In the event of hypertension, increasing or persistent headache (with or without visual disturbances) or signs of CNS toxicity treatment should be discontinued immediately and the patient's condition assessed without delay. Particular caution should exercised in patients recently or currently receiving drugs that can alter blood pressure e.g. vasoconstrictors such as sympathomimetics or ergot alkaloids including ergometrine or methylergometrine. Although there is no conclusive evidence of an interaction between bromocriptine and these drugs, concomitant use is not recommended in Postpartum and puerperal women. *(Novartis Company Information's; 1999)*

**Pregnancy & lactation:**

In a patient experiences a hypertensive disorder of pregnancy, the benefit of continuing bromocriptine must be weighed against the possible risk of its use during a hypertensive disorder of pregnancy. When bromocriptine mesylate is being used to treat acromegaly, prolactinoma, or Parkinson’s disease in patients who subsequently become pregnant, a decision should be
made as to whether the therapy continues to be medically necessary or can be withdrawn. If it is continued, the drug should be withdrawn in those who may experience hypertensive disorders of pregnancy (including eclampsia, preeclampsia, or pregnancy-induced hypertension) unless withdrawal of bromocriptine is considered to be medically contraindicated. (RxList Inc.; 2004)

Reproduction studies in animals have not demonstrated a risk to the fetus but there have been no controlled trials in pregnant women. Women wishing to conceive should be told to stop taking bromocriptine- and all other drugs – as soon as pregnancy is confirmed, unless there is a medical reason for continuing to take. No increased incidence of abortion has been reported following withdrawal of bromocriptine. There is extensive evidence that administration of bromocriptine is does not adversely affect the course or outcome of pregnancy. women with a pituitary adenoma who become pregnant and discontinue bromocriptine must be closely monitored throughout the pregnancy. treatment may be resumed, or surgery considered, if evidence of pronounced prolactinoma enlargement (e.g. headache or visual field deterioration ) is found. Bromocriptine inhibits lactation & should therefore not be given to women who are breastfeeding unless there is a medical reason for its use.

**In parkinsonian patients:**

Unexplained pleuropulmonary changes or fibrosis should be thoroughly investigated and therapy discontinued if necessary. The pleuropulmonary fibrotic changes that have been observed may be associated with fibrotic
thickening of the heart valves, as has been the case in patients treated with other ergot alkaloid derivatives. Careful observation for retroperitoneal fibrosis is recommended in order to ensure detection of its manifestations (e.g. back pain, peripheral oedema, and impaired kidney function) in the early, reversible stage. Bromocriptine should be withdrawn if retroperitoneal fibrotic changes are diagnosed or suspected. (Novartis Company Information's; 1999)

**Drug interactions:**

1. **Dopamine agonists:**

   Bromocriptine and levodopa are both dopamine agonists. Concomitant use of these agents can cause additive neurologic effects. Although this combination may be necessary in some patients, dosage of levodopa may require reduction if bromocriptine is added. (Cottingham; 2004)

2. **Dopamine antagonists:**

   Such as the phenothiazines, butyrophenones, thioxanthenes, and metoclopramide might be expected to reduce the prolactin-lowering and the antiparkinsonian effect of bromocriptine. Dopamine might reduce the prolactin-lowering effect. (Parfitt; 1999)

   Drugs that increase the concentration of prolactin such as: Butyrophenones including haloperidol, loxapine, molindone, monoamine oxidase inhibitors (MAOI’s), imipramine, amitriptyline, methyldopa, phenothiazines, thioxanthines, and reserpine, can antagonize the effects of bromocriptine.
(Cottingham; 2004)

3. Octreotide:

Concomitant administration of octreotide and bromocriptine should be avoided because octreotide increases the bioavailability of bromocriptine. (Parfitt; 1999)

And due to this increase of bromocriptine plasma levels, there is an increased risk of adverse effects. (Novartis company Informations, 1999)

4. Ergot alkaloids:

Bromocriptine is an ergot alkaloid derivative. Concomitant use of it with other ergot alkaloids can lead to ergot toxicity. (Cottingham; 2004).

Concomitant treatment with methylergometrine or other ergot alkaloids should be avoided due to increased risk of adverse effects.

5. Cytochrome P450 inhibitors:

Bromocriptine is metabolized in the liver by the cytochrome P450 (CYP3A) system. Concomitant use of macrolide antibiotics (e.g. erythromycin, clarithromycin, troleandomycin, spiramycin, josamycin), azoles antimycotics (e.g. ketoconazole, itraconazole), or general cytochrome P450 inhibitors (e.g. cimetidine) may result in raised plasma bromocriptine levels, with an increased risk of adverse reactions.

6. Alcohol:

The tolerability of bromocriptine may be reduced by alcohol.
(Novartis Company Information's; 1999). High doses of bromocriptine can decrease the tolerance to ethanol, so patients should be warned of this effect and advised to lessen ethanol consumption while receiving bromocriptine. A disulfiram-like reaction can occur during concomitant use of bromocriptine and ethanol, which is manifested as chest pain, tachycardia, throbbing headache, flushing of the face, severe weakness, sweating, nausea, vomiting, & blurred vision.(Cottingham; 2004).

Mention of alcohol intolerance in some patients receiving bromocriptine 10 to 60 mg daily for the treatment of acromegaly gastrointestinal side effects with low doses of bromocriptine were markedly reduced in 2 women when they abstained from alcohol.

7. **Antibacterials:**

Drowsiness, dystonia, choreoathetoid dyskinesias, and visual hallucinations occurred when jasomycin was given to a patient receiving bromocriptine.

The systemic bioavailability of a single oral dose of bromocriptine 5 mg was markedly increased in 5 healthy subjects following treatment with erythromycin estolate 250 mg 4 times daily for 4 days; clearance of bromocriptine decreased by 70.6% and peak plasma concentrations of bromocriptine were more than 4 times higher than following the same dose before erythromycin administration. (Parfitt; 1999)

So, erythromycin has been shown to reduce the clearance of bromocriptine. Patients should be monitored for signs of bromocriptine toxicity if erythromycin is added. (Cottingham; 2004)
8. **Antifungals:**

The response to bromocriptine was blocked in a patient who was also receiving griseofulvin.

9. **Antipsychotics:**

Serum concentrations of prolactin rose and visual fields deteriorated following administration of thioridazine to a patient who was receiving bromocriptine therapy for a large prolactinoma.

10. **Sympathomimetics:**

There have been isolated reports of severe hypertension, with headache and life-threatening complications in patients receiving bromocriptine concomitantly with isomethptene mucate or phenylpropanolamine. *(Parfitt; 1999).*

Case reports have documented hypertension and seizures occurring as a result of concomitant use of bromocriptine and phenylpropanolamine. Until more data this drug combination should be avoided whenever possible.

11. **Antihypertensive drugs:**

Concomitant administration of bromocriptine and antihypertensive agents can result in additive hypotensive effects, and dosage reductions may be required.
12. **Estrogens & Progestin:**

They can produce amenorrhea or galactorrhea when administered and their use during bromocriptine administration is not recommended. *(Cottingham, 2004).*

**Pharmaceutical formulation:**

**Dose:**

Oral bromocriptine is supplied in 2.5 mg tablets and in 5 mg capsules. Also, standard oral bromocriptine tablets can be placed in the vagina. *(Katz, et al; 1989).*

Each bromocriptine mesylate tablet for oral administration contains 2.5 mg and each contains 5 mg bromocriptine (as the mesylate).

It has the following molecular formula: $C_{32}H_{40}BrN_5O_5\cdot CH_4SO_3$ with a molecular weight of: 750.70.

**2½ mg Tablets:**

*Active Ingredient:* bromocriptine mesylate, USP.

*Inactive Ingredients:* colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch, and another ingredient.
5 mg Capsules:

*Active Ingredient:* bromocriptine mesylate, USP.

*Inactive Ingredients:* colloidal silicon dioxide, gelatin, lactose, magnesium stearate, silicon dioxide, sodium lauryl sulfate, starch, titanium dioxide, yellow iron oxide, and another ingredient.

**Representative name:**

Parlodel. *(RxList Inc.; 2004).*
**Chemical Background:**

Ergometrine is an amide derivative of d-lysergic acid; it contains a double bound between C₉ and C₁₀. Upon hydrolysis, Ergometrine yields lysergic acid and an amine; consequently, it is named an amine alkaloid.

Methylergometrine is a semi synthetic amide derivative of d-lysergic acid. It contains an extra methyl group in the substituent in the β-configuration at position 8.

The enantiomers (optical isomers) are called ergometrinine and methylergometrinine. The naturally existing enantiomers are always present due to spontaneous epimerisation in the asymmetric center C₈. However, the α-configuration (-inine) forms a very small part.

Ergometrine maleate (Methergine) is another brand name which is used in USA & Canada. The molecular formula of ergometrine maleate, designated chemically as: 9, 10-didehydro -N- [(S) -2- hydroxyl -1- methylethyl] -6-methylergoline -8-carboxamide hydrogen maleate is C₁₉H₂₃N₃O₂₁, C₄H₄O₄. The structural formula of ergometrine maleate is shown in fig.1. Its molecular weight is 441.5. The CAS registry numbers is ergometrine and ergometrine maleate is 60-79-7 and 129-51-1 respectively. The pH range of the Ergometrine maleate injection is 2.7 – 3.5. *(Mayne Pharma Pty Ltd., 2004; Groot, 1998)*

**Physical Properties:**
Ergometrine maleate occurs as a white to grayish-white or faintly yellow, odourless, microcrystalline powder which darkens with age and an exposure to light. The BP states that ergometrine maleate is soluble, and the USP that it is sparingly soluble in water; and slightly soluble in alcohol; practically insoluble in chloroform and ether.

Ergometrine injection is a colourless or slightly yellowish solution for Parenteral use. (Mayne Pharma Pty Ltd., 2004)

**Mechanism of Action:**

I. **Interactions with tryptaminergic receptors**

Ergonovine has partial agonists effect in human umbilical and placental blood vessels; it selective and fairly potent antagonists in various smooth muscles; and has partial agonists and antagonists effect on some areas of CNS. (Gilman et al., 2001)

II. **Interactions with dopaminergic receptors**

It is a weak antagonists in certain blood vessels; partial agonists and antagonists in various areas of CNS; and less potent than bromocriptine in producing emesis or inhibiting secretion of prolactine. (Gilman et al., 2001)

III. **Interactions with α-adrenergic receptors**

It is partial agonists in blood vessels (less than ergotamine); and has a little antagonistic action. (Gilman et al., 2001)
**Pharmacokinetics:**

Little information is available on the pharmacokinetics of ergometrine. However, methylergometrine has been extensively studied and information from these studies is probably applicable to Ergometrine. *(Boobis et al., 1991)*

a) **Absorption**

Ergometrine is rapidly and almost completely absorbed after oral dosing or intramuscular injection. The bioavailability is probably ≥50%. Peak plasma concentrations of the drug after an oral dose occur between 60 and 90 minutes. The uterine contractile effect starts 5-15 min after oral administration, and 2-5 min after intramuscular administration. When given intravenously, the uterine contractile effect is virtually instantaneous. *(Boobis et al., 1991)*

b) **Distribution**

Distribution of ergometrine has not been fully characterized. *(Mayne Pharma Pty Ltd., 2004)*

c) **Duration of Action**

Contraction of uterus, postpartum:
- Oral: approximately 3 hours.
- Intramuscular: approximately 3 hours.
- Intravenous: 45 minutes (although rhythmic contractions may persist for up to 3 hours).

*(Lacy et al., 2003)*
d) **Metabolism**

The drug undergoes extensive hepatic metabolism. The pharmacokinetics are likely to be similar to those of methylergometrine, with an apparent volume of distribution of 0.3-0.7 l Kg-1, corresponding to total body water. *(Boobis et al., 1991)*

e) **Excretion**

It is excreted primarily in feces and urine.

Elimination is rapid by renal excretion of metabolites, with a half life that is probably less than 2 hr.

There are no reports on whether ergometrine is excreted in breast milk, although it seems probable that this will occur to some extent. There is no information on whether the drug will cross the placenta. *(Lacy et al., 2003)*

<table>
<thead>
<tr>
<th>Oral absorption</th>
<th>almost complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presystemic metabolism</td>
<td>high</td>
</tr>
<tr>
<td>Plasma half life</td>
<td>0.5 hr</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>—</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>—</td>
</tr>
</tbody>
</table>

*Table 1: Pharmacokinetics of Ergometrine (Boobis et al., 1991)*

The drug is not used in elderly, so it is not known whether its pharmacokinetics are altered in old age.

Since the total daily dose of ergometrine is usually less than 1 mg, the concentrations found in biological fluids are very low. The assay of choice is usually radioimmunoassay. The antiserum is prepared against lysergic acid
and is thus not specific for ergometrine, but also reacts with methylergometrine, lysergic acid, ergometrine, dihydroergometrine, and dihydroergotoxine. Although the antiserum apparently measures the unmetabolized drug, some cross reactivity with metabolites is possible. The lower limit of detection of the assay is 0.5-1.0 µg.l\(^{-1}\). A high pressure liquid chromatographic assay, which utilizes fluorescence detection, has been developed that should be applicable to ergometrine. This has a lower limit of detection of 100 ng.l\(^{-1}\). (Boobis et al., 1991)

**Pharmacological effects:**

Ergometrine stimulates contractions of uterine and vascular smooth muscle.

Following the administration of usual therapeutic doses of ergometrine, intense contractions of the uterus are produced and are usually followed by periods of relaxation. Larger doses of the drugs, however, produce sustained, forceful contractions followed by only short or no periods of relaxation.

Ergometrine increases the amplitude and frequency of uterine contractions and uterine tone which in turn impedes uterine blood flow. Contraction of the uterine wall around bleeding vessels at the placental site produces haemostasis. Ergometrine also increases contractions of the cervix.

Ergometrine produces vasoconstriction, mainly of capacitance vessels; increased central venous pressure, elevated blood pressure, and, rarely, peripheral ischemia and gangrene may result.

Like other ergot alkaloids, ergometrine produces arterial vasoconstriction by stimulation of α-adrenergic and serotonin receptors and
inhibition of endothelial-derived relaxation factor release. The drug has only slight $\alpha$-adrenergic blocking activity and its vasoconstrictor effects are less than those of ergotamine. (Groot et al., 1998)

I. **Uterine Stimulant**

Ergonovine directly stimulates the uterine muscle to increase force and frequency of contractions. With usual doses, these contractions precede periods of relaxation; with larger doses, basal uterine tone is elevated and these relaxation periods will be decreased. Contraction of the uterine wall around bleeding vessels at the placental site produces hemostasis.

Ergonovine also induces cervical contractions. The sensitivity of the uterus to the oxytocic effect is much greater toward the end of the pregnancy. The oxytocic actions of ergonovine are greater than its vascular effects. (Gilman et al., 1985)

II. **Vasoconstriction**

Ergonovine, like other ergot alkaloids, produces arterial vasoconstriction by stimulation of $\alpha$-adrenergic and serotonin receptors and inhibition of endothelial-derived relaxation factor release. It is a less potent vasoconstrictor than ergotamine. (Lacy et al., 2003)

III. **Diagnostic aid (coronary vasospasm)**

Ergonovine causes vasoconstriction of coronary arteries. (Kimball, 1989)
Other Actions

Ergonovine has minor actions on the central nervous system (CNS). In the CNS, Ergonovine is a partial agonist and partial antagonist at some serotonin and dopamine receptors. Ergonovine also possesses weak dopaminergic antagonist actions in certain blood vessels and partial agonist action at serotonin receptors in umbilical and placental blood vessels. It does not possess significant α-adrenergic blocking activity. (Gilman et al., 1985)

**Therapeutic Uses:**

A. **Prophylaxis**

Ergometrine is administered after the delivery of the placenta for the purpose of contracting the uterus in order to prevent postpartum and postabortion hemorrhage due to uterine atony. (Gilman et al., 2001)

B. **Treatment**

Ergometrine is administered after the delivery of the placenta to promote involution of the uterus in order to treat postpartum and postabortion haemorrhage. (Gilman et al., 2001)

C. **Diagnosing and Testing:**

Ergometrine maleate or Methylergometrine maleate have been used in a provocation for the diagnosis of variant angina (Prizmetal’s angina). Ergometrine maleate has been also used in the diagnosis of oesophageal spasm. (Schwartz and Kaufmann, 1984)
**Adverse Reactions:**

When administered in correct doses to carefully selected patients who are closely monitored, there is little risk of serious adverse systemic effects in patients receiving ergometrine. However IV administration of the drugs produces serious adverse effects if the injections are not diluted and administered slowly.

Adverse effects do not appear to occur as frequently with ergometrine as with other ergot alkaloids. Ergometrine is usually indicated for a short duration and as a consequence, many of the side effects seen with the other ergot alkaloids do not occur.

Adverse reactions which have been observed following administration of ergometrine include:

1. **Body as a Whole**
   
   Gangrene (ergometrine shows less tendency to produce gangrene than ergotamine), headache, abdominal pain, allergic phenomena (including shock, hypertension, chest pain, palpitation, dyspnoea and bradycardia). *(Boobis et al., 1991)*

2. **Cardiovascular System**
   
   Coronary artery vasospasm, peripheral vasospasm, hypotension, hypertension (possibly sudden and/or severe), thrombophlebitis, myocardial
infarction, ventricular arrhythmias; and transient chest pain, palpitation, and bradycardia alone or as part of allergic phenomena. Hypertension may occur following administration of ergometrine especially when administered IV undiluted or too rapidly or when used in conjunction with regional anesthesia or vasoconstrictors. (Lacy et al., 2003)

3. Digestive System
Diarrhoea, nausea, oesophageal spasm, vomiting, mesenteric ischemia and large bowel infarction have been reported. (Cochrane et al., 1981)

4. Metabolic and Nutritional
Water intoxication. (Mayne Pharma Pty Ltd., 2004)

5. Musculoskeletal System
Leg cramps and unmasking of myasthenia gravis. (Mayne Pharma Pty Ltd., 2004)

6. Nervous System
Dizziness, hallucinations and vertigo. (Boobis et al., 1991)

7. Respiratory System
Dyspnoea alone or as part of allergic phenomena; nasal congestion, pulmonary oedema, pleural thickening. (Parfitt, 1999)

8. Skin and Appendages
Sweating. (Lacy et al., 2003)
9. **Special Senses**
   Unpleasant foul taste and tinnitus. (Lacy et al., 2003)

10. **Urogenital System**
   Haematuria. (Parfitt, 1999)

**Contraindications:**

1. Ergometrine is contraindicated in patients who have previously displayed hypersensitivity or idiosyncratic reactions to ergometrine, other ergot alkaloids or any of the ingredients in the Ergometrine Injection preparation. (Lacy et al., 2003)

2. Ergometrine is contraindicated for the induction of labour and during the first and second stages of labour. (Lacy et al., 2003)

3. Ergometrine is contraindicated if there is any suspicion of retained placenta. (Pernoll and Benson, 1991)

4. Ergometrine is contraindicated in eclampsia or preeclampsia, and in cases of threatened spontaneous abortion. (Boobis et al., 1991)

5. Ergometrine is contraindicated in severe or persistent sepsis. (Gilman et al., 1985)

6. Ergometrine is contraindicated in patients with peripheral vascular disease or heart disease and in patients with hypertension or a history of hypertension. (Boobis et al., 1991)
7. Ergometrine is contraindicated in patients with Raynaud's phenomenon. (Dukes, 1984)

8. Ergometrine is contraindicated where impaired hepatic or renal function exists. (Boobis et al., 1991)

**Precautions:**

i. **Labour and delivery**

   *Category C.* Ergometrine induces uterine contraction and may cause premature parturition or hypertonic labour. Tetanic contractions may result in decreased uterine blood flow and foetal distress. Products containing ergometrine should therefore be avoided as far as possible during pregnancy.

   Ergometrine should not be administered prior to delivery of the placenta. Before the IV use of ergometrine during severe uterine bleeding, inspection must be made for placental fragments.

   High doses of ergometrine administered prior to delivery may cause uterine tetany and problems in the infant (hypoxia, intracranial hemorrhage).

   If ergometrine is administered during the second or third stage of labour prior to delivery of the placenta, complications such as captivation of the placenta or missed diagnosis of a second infant due to excessive uterine contraction may occur. The placenta should be delivered, and the possibility of twin pregnancy should be ruled out, before ergometrine is administered.

   Uterine overstimulation during labour can cause uterine tetany with uterine rupture, cervical or perineal lacerations, amniotic fluid embolism, or infantile trauma. (Pernoll and Benson, 1991)
ii. **In Lactation**

Ergometrine is secreted in breast milk. Ergot alkaloids have the potential to cause chronic ergot poisoning in the infant if used in higher-than-recommended doses or if used for a longer period of time than is generally recommended. Ergometrine is therefore contraindicated during breast-feeding.

The use of multiple doses in postpartum patients may lower prolactin levels and suppress lactation.

*Note:* Ergot preparations are frequently given as a single dose postpartum to control hemorrhage. A single dose of ergometrine should not prevent the mother from breastfeeding. *(Gilman et al., 1985)*

iii. **Calcium deficiency**

In patients with calcium deficiency, the uterus may not respond to ergometrine. Responsiveness can usually be restored by cautious administration of IV calcium salts. However IV calcium should be avoided in patients receiving digitalis. *(Lacy et al., 2003)*

iv. **Coronary artery disease**

Patients may be more susceptible to angina or myocardial infarction caused by ergometrine-induced vasospasm. *(Kimball, 1989)*
v. **Heart rate**

Heart rate may be decreased due primarily to an increase in vagal tone, and possibly to decreased central sympathetic activity and direct depression of the myocardium. *(Lacy et al., 2003)*

vi. **Hypertension**

Hypertension may occur following administration of ergometrine especially when administered IV undiluted or too rapidly or when used in conjunction with regional anesthesia or vasoconstrictors.

Some patients, especially eclamptic or previously hypertensive patients, may be unusually sensitive to the hypertensive effects of ergometrine; generalized headaches, severe arrhythmias, seizures, and cerebrovascular accidents have been associated with ergometrine-induced hypertension in these patients.

Blood pressure or central venous pressure may be elevated due to peripheral vasoconstriction, primarily of postcapillary vessels. This elevation has sometimes been associated with preeclampsia, history of hypertension, IV administration of ergometrine or concurrent use of local anesthetics containing vasoconstrictors. Hypotension has also been reported. *(Mayne Pharma Pty Ltd., 2004; Gilman et al., 1985)*

vii. **General anesthesia**

Because nausea and vomiting may occur, ergometrine should be administered with care to patients under general anesthesia. *(Dukes, 1984)*
viii. **Intravenous use**

IV administration of ergometrine produces serious adverse effects if the injections are not diluted and administered slowly. IV use of Ergometrine Injection should be limited to patients with severe uterine bleeding or other life-threatening emergency. IV doses should be given slowly, over a period of at least 1 minute. Some clinicians recommend diluting the IV dose to a volume of 5mL with sodium chloride injection 0.9% before administration. *(Pernoll and Benson, 1991)*

ix. **Porphyria**

Ergometrine has been associated with clinical exacerbations of porphyria. *(Mayne Pharma Pty Ltd., 2004)*

x. **Prolonged therapy**

Prolonged therapy with ergometrine may lead to gangrene and other signs of ergotism. Numbness or tingling of the extremities indicates the need to discontinue treatment. *(Mayne Pharma Pty Ltd., 2004)*

xi. **Sympathomimetics**

The vasoconstrictor effect of ergometrine is potentiated by sympathomimetics. *(Boobis et al., 1991)*

xii. **Venoatrial shunts or mitral valve stenosis**

Since ergometrine may cause serious adverse cardiovascular effects, ergometrine should be used cautiously or not at all in patients with venoatrial shunts or mitral valve stenosis. *(Boobis et al., 1991)*
xiii. **Pediatrics**

Elimination of ergometrine may be prolonged in newborns. Neonates inadvertently administered ergometrine in overdose amounts have developed respiratory depression, cyanosis, seizures, decreased urine output, and severe peripheral vasoconstriction.

There have been reports of accidental administration of adult doses of ergometrine to neonates, sometimes instead of vitamin K. Symptoms have included peripheral vasoconstriction, convulsions, respiratory failure, acute renal failure, and temporary lactose intolerance.

In two reports of accidental administration of 0.2mg of oral ergometrine maleate or of 0.5mg of IM ergometrine maleate to neonates, peripheral cyanosis and gangrene, apnea, myoclonic movements, purpuric manifestations, and mild jaundice were noted. Treatment was mainly supportive; IV chlorpromazine controlled myoclonic movements. One death has been reported in an infant who received 0.2mg of oral ergometrine maleate. (Dargavil and Campbell, 1998)

**Drug Interaction:**

A. **In Vitro:**

a) **Incompatibilities:**

Ergometrine has been reported to be incompatible with solutions containing the following: adrenaline hydrochloride, amylobarbitone sodium, ampicillin sodium, cephalothin sodium, chloramphenicol sodium succinate, chlortetracycline hydrochloride, heparin sodium, metaraminol tartrate,
methicillin sodium, nitrofurantoin sodium, novobiocin sodium, pentobarbitone sodium, sulphadiazine sodium, sulphafurazole diethanolamine, thiopentone sodium, vitamin B complex with C, warfarin sodium. (Mayne Pharma Pty Ltd., 2004)

B. In Vivo:

a) Cytochrome P450 Effect
Substrate of CYP3A4. (Lacy et al., 2003)

b) Antianginal agents
Ergot alkaloids may induce coronary vasospasm and may precipitate angina. The efficacy of glyceryl trinitrate or other antianginal agents may be reduced; increased doses of glyceryl trinitrate or antianginal agents may be necessary. (Mayne Pharma Pty Ltd., 2004)

c) β-blockers
Ergot causes vasoconstriction. The β-blockers do the same by blocking the normal β2-stimulated sympathetic vasodilatation. Ergot alkaloids have been reported to interact with β-blockers resulting in excessive, additive peripheral vasoconstriction. (Parfitt, 1999)

d) Bromocriptine
The use of ergot alkaloids may increase the incidence of rare cases of hypertension, strokes, seizures, and myocardial infarction associated with the postpartum use of bromocriptine. (Ruch and Duhring, 1989)
e) **Dopamine**

Ergot alkaloids have been reported to interact with dopamine resulting in excessive peripheral vasoconstriction. Gangrene and peripheral ischemia of hands and feet developed in a patient receiving both dopamine and ergometrine infusions. In addition, dopamine has been associated with pedal gangrene secondary to peripheral vasoconstriction and the combination of an ergot alkaloid may accentuate this effect. It would seem prudent to avoid concurrent use. *(Parfitt, 1999)*

f) **General anesthetics**

Concurrent use of general anesthetics may potentiate peripheral vasoconstriction.

Halothane in concentrations greater than 1% may interfere with the oxytocic actions of ergometrine, resulting in severe uterine hemorrhage. *(Dukes, 1984)*

g) **Methysergide**

The concurrent use of ergot alkaloids and methysergide can increase the risk of severe and persistent spasm of major arteries in some patients.

The combination should be used with great caution. *(Mayne Pharma Pty Ltd., 2004)*

h) **Nicotine**

Enhanced vasoconstriction may result from the combined effects of nicotine absorption from heavy smoking and administration of ergometrine. *(Mayne Pharma Pty Ltd., 2004)*
i) **Vasoconstrictors, including those present in some local anesthetics, or Vasopressors**

Concurrent use may result in enhanced vasoconstriction; dosage adjustments may be necessary.

The pressor effect of sympathomimetic pressor amines may be potentiated, resulting in potentially severe hypertension, headache, and rupture of cerebral blood vessels; gangrene developed in a patient receiving both dopamine and ergometrine infusions. *(Parfitt, 1999)*

j) **Effects on Laboratory Tests**

Prolactin serum concentrations may be decreased during the postpartum period. *(Mayne Pharma Pty Ltd., 2004)*

**Drug Combination:**

Bleeding due to incomplete abortion can be controlled with ergometrine and oxytocin (Syntometrine®) given intramuscularly, the dose is adjusted according to the patient’s condition and blood loss. This is commonly used before the surgical evacuation of the uterus, particularly when surgery is delayed. Oxytocin and ergometrine combined are more effective in early pregnancy than either drug alone.

For the routine management of the third stage labour ergometrine 500 micrograms with oxytocin 5 units (Syntometrine® 1 mL) is given by intramuscular injection on delivery of the anterior shoulder or, at the latest, immediately after the baby is delivered.
In excessive uterine bleeding, any placental products remaining in the uterus should be removed. In bleeding caused by uterine atony, oxytocic drugs are used in turn as follows:

- Oxytocin 5-10 units by intravenous injection.
- Ergometrine 250-500 micrograms by intravenous injection.
- Oxytocin 5-30 units in 500 mL infusion fluid given by intravenous infusion at a rate that controls the uterine atony. (BMA and RPSGB, 2004; and Lacy et al., 2003)

**Medicine Classification:**

Prescription Medicine. (Mayne Pharma Pty Ltd., 2004)

**Pharmaceutical formulations:**

1. **Oral or Sublingual:** Tablets 200 mcg (0.2 mg)  
   (Lilly-US Company \textsubscript{A}, Rec 2/89, 1988)

2. **Parenteral:**  
   50 mcg (0.05 mg) per ml (for IV use)  
   200 mcg (0.2 mg) per ml (for IV & IM)  
   250 mcg (0.25 mg) per ml (for IV & IM)  
   (Lilly-US Company \textsubscript{B}, Rec 1/89, 1988)

**Stability:**

Ampoules must be protected from light and stored at temperature 25°C (<77°F). (Hogerzeil and Walker, 1996)
Nursing Implications:
Ampoules containing discolored solution should not be used. (Lacy et al., 2003)

Dosage and administration:
Ergometrine may be administered by IM or IV injection. However, because the risk of severe adverse effects is increased with IV use of Ergometrine, its use via this route is recommended only for emergencies such as excessive uterine bleeding or any other life-threatening situation. (Pernoll and Benson, 1991)

A. Prophylaxis of postpartum hemorrhage and post-abortion hemorrhage
The immediate postpartum dose of Ergometrine maleate is 200 micrograms administered IM. The injection should not be given until completion of the delivery is assured, and until the possibility of a second twin has been excluded.

In an emergency situation, 200 micrograms may be injected intravenously. IV doses should be given slowly, over a period of at least 1 minute. Some clinicians recommend diluting the IV dose to a volume of 5mL with sodium chloride injection 0.9% before administration. (Pernoll and Benson, 1991)
B. Treatment of postpartum hemorrhage and post-abortion hemorrhage

Ergometrine maleate 200 micrograms may be injected intramuscularly. Some patients do not respond to Ergometrine because of hypocalcaemia. Cautious IV administration of calcium may restore the oxytocic action. *(Pernoll and Benson, 1991)*

**Overdose:**

A. Symptoms

The principal manifestations of serious overdose are **convulsions** and **gangrene**. Other symptoms of overdose include the following:

- Bradycardia, confusion, diarrhoea, dizziness, dyspnoea, drowsiness, fast and/or weak pulse, miosis, hypercoagulability, loss of consciousness, nausea and vomiting, numbness and coldness of the extremities, pain in the chest, peripheral vasoconstriction, respiratory depression, rise or fall in blood pressure, severe cramping of the uterus, tachycardia, tingling, unusual thirst. *(Mayne Pharma Pty Ltd., 2004)*

There have been reports of accidental administration of adult doses of Ergometrine maleate to neonates; sometimes instead of vitamin K. symptoms have included peripheral vasoconstriction, convulsions, respiratory failure, acute renal failure, and temporary lactose intolerance. *(Dargavil and Campbell, 1998)*
B. Treatment

- There is no specific antidote for the management of Ergometrine overdose. Supportive and symptomatic treatment should be initiated.
- Ergometrine should be discontinued immediately.
- Convulsions should be treated with appropriate anticonvulsants e.g. phenytoin or diazepam.
- Hypercoagulability should be controlled by the administration of heparin.
- Severe hypertension may require treatment with sodium nitroprusside or hydralazine.
- Peripheral ischemia may be treated with sodium nitroprusside or phentolamine. Gangrene may require surgical amputation.
- A vasodilator e.g. glyceryl trinitrate may be required for myocardial ischemia and/or hypertension. The vasodilator should be administered with dosage adjusted according to heart rate and blood pressure.
- ECG monitoring may be required to assess cardiac function and perfusion. Frequent monitoring of vital signs as well as blood gases and electrolytes is recommended.

(Mayne Pharma Pty Ltd., 2004)
Pergolide mesylate, a semisynthetic ergot derivative and is predominantly D2 receptor agonist, with some weak actions at the D1 and D3 (Perachon et al;1999) as well as it works on non-dopaminergic receptor.

**Chemical structure:**

Pergolide mesylate =

\[(8\text{-beta})-8-[(\text{methylthio})\text{methyl}]\text{-6-propylergoline monomethanesulfonate} = \]

LY 127,809

= CAS 66104-23-2 *(Williams;1992).*

![Chemical structure diagram]

**Physical properties (availability and storage):**

**0.05 mg:**

Each ivory-colored, modified rectangle-shaped tablet, scored and engraved with the company logo and Identi-code 4131, contains: pergolide mesylate 0.05 mg. Nonmedicinal ingredients: croscarmellose sodium, iron oxide yellow, lactose, l-methionine, magnesium stearate and povidone. Gluten- and tartrazine-free. Amber HDPE bottles of 30.
0.25 mg


1 mg:

Each pink-colored, modified rectangle-shaped tablet, scored and engraved with the company logo and Identi-code 4135, contains: pergolide mesylate 1 mg. Nonmedicinal ingredients: croscarmellose sodium, iron oxide red pure, lactose, magnesium stearate and povidone. Gluten- and tartrazine-free Amber HDPE bottles of 100. Store tablets at controlled room temperature between 59 and 86 degrees F (15 to 30 C). (www.RxMax.com)

Pharmacokinetics:

To-date only very limited pharmacokinetic data are available. It is well absorbed orally and has plasma half-life in the range of 3 to 7 hours (Gilman; 1996). Following oral administration of 4-pergolide, radioactivity in plasma appeared after 15 to 30 minutes, peaked at 1 to 2 hours, and was barely detectable after 96 hours. Radioactivity was eliminated as pergolide metabolites in urine (55%), in feces (40%) and in breath (5%). No unchanged pergolide was detected in excreta. At least 10 radioactive metabolites have been isolated including N-despropylpergolide, pergolide sulfoxide and pergolide sulfone. The latter 2 metabolites are dopamine agonists in animals.
The other detected metabolites have not been identified and it is not known whether they are pharmacologically active or not (Deleu et al; 2002).

The drug undergoes extensive hepatic first pass metabolism and is approximately 90% bound to plasma proteins. This extent of protein binding may be important to consider when pergolide is coadministered with other drugs known to affect protein binding. (Rauschenbach et al; 1995; www.RxMed.com). It differs from bromocriptine in that it has a longer half-life, substantially more potent and has D1 agonist properties (Gilman; 1996).
The rate and extent of pergolide bioavailability appears to increase proportionally with the dose (Grenier; 2003).

**The effect of pergolide on P450 hepatic enzyme:**

A study was done to estimate the effect of antiparkinsonian drugs on P450 enzymes, pergolide was among them, and to predict potential drug-drug interactions and in turn avoid inappropriate concurrent therapy is important in the successful management of this disease. It has been found that pergolide did not interfere with the following P450 enzymes:

![Table 1](image)

<table>
<thead>
<tr>
<th>P450 enzyme</th>
<th>Mother Activity</th>
<th>Pergolide</th>
<th>Ropinirole</th>
<th>Paroxetine</th>
<th>Bromocriptine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Chlorzoxazone 6-hydroxylation</td>
<td>10.2 ± 0.7</td>
<td>9.2 ± 0.1</td>
<td>9.4 ± 0.8</td>
<td>8.7 ± 0.3</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Debrisoquin 4-hydroxylation</td>
<td>10.2 ± 0.7</td>
<td>10.2 ± 0.7</td>
<td>10.1 ± 0.7</td>
<td>9.4 ± 0.3</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>O-demethylation 4-hydroxylation</td>
<td>9.2 ± 0.7</td>
<td>9.2 ± 0.7</td>
<td>9.2 ± 0.7</td>
<td>9.4 ± 0.3</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Debrisoquin 4-hydroxylation</td>
<td>10.2 ± 0.7</td>
<td>10.2 ± 0.7</td>
<td>10.1 ± 0.7</td>
<td>9.4 ± 0.3</td>
</tr>
<tr>
<td>CYP2D1</td>
<td>Paroxetine 4-hydroxylation</td>
<td>9.2 ± 0.7</td>
<td>9.2 ± 0.7</td>
<td>9.2 ± 0.7</td>
<td>9.4 ± 0.3</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Testosterone 6-hydroxylation</td>
<td>6.0 ± 0.7</td>
<td>5.0 ± 0.7</td>
<td>5.0 ± 0.7</td>
<td>4.0 ± 0.3</td>
</tr>
</tbody>
</table>

Values represent the mean (± SD) of triplicate determination by nanomolar per micromolar. The present P450 activity remaining compared with control (minus inhibitor) in CYPA 37 micromolar concentration in the presence of inhibitor (10 or 100 μM).
CYP2C9, CYP2C19, and CYP2E1 activity but pergolide were able to inhibit CYP3A4, giving that the inhibition was stronger with bromocriptine than with pergolide, and in this situation the inhibition of CYP3A4 by bromocriptine and pergolide may reflect a catalytic interaction, as CYP3A4 has been previously demonstrated to metabolize structurally similar ergot compounds (Rauschenbach et al;1995). It was also found that pergolide was similar to quinidine in its capacity to inhibit CYP2D6 activity (Wynalda et al;1997).

As pergolide interacted with at least one human cytochrome P450 enzyme and unfortunately, little is known pertaining to the in vivo pharmacokinetics of this drug other than that it is administered in low doses and are highly protein bound. The studies done, up to now, were unable to predict the likelihood of an in vivo interaction based upon the current in vitro findings. (Wynalda et al;1997)

**Pharmacodynamics:**

**Receptor-mediated effects of pergolide:**

Pergolide is a synthetic ergoline derivative and it acts on many receptors. It is a dopamine agonist which acts through dopamine D1, D2 and
D3 receptors in vivo. It has high affinity to D2 and D3, which is equipotent, and with moderate affinity to D1. It is the only antiparkinsonian drug which has been found to have high potency and intrinsic activity at the dopamine D1 receptor. While other antiparkinson dopamine agonists, as bromocriptine, pramipexole and ropinirole, act only at dopamine D2 and D3 receptors which gives pergolide additional advantage. In addition, unlike other compounds, pergolide may also promote the striatal expression of the dopamine D3 receptor (Perachon et al; 1999). It also exerts actions on non-dopaminergic receptor which includes many subtypes of 5-hydroxytrptamine (5-HT) and α-adrenoceptors (Ruffolo et al; 1987, Deleu et al; 2002).

**On dopamine receptors:**

Since pergolide is a dopamine agonist, it is crucial to understand the distribution and the effect of the dopaminergic receptors and the extent and function of the dopaminergic pathways in the central nervous system (CNS):

Dopaminergic receptors are G-protein-coupled transmembrane receptors that their signal transduction mechanisms are linked via adenylate cyclase and/or phospholipids hydrolysis. D2, D3 and D4 are linked to the inhibition of adenylate cyclase through decreasing intracellular cAMP, modulating K+ and Ca+2 current, leading to pre and postsynaptic inhibition of the nerve conduction and hormone release inhibition. Where as D1 and D5 are linked to the stimulation of adenylate cyclase.
The function of dopaminergic pathways is divided broadly into:

• **Motor control (nigrostriatal system):**
  Dopamine deficiency in this pathway results in Parkinson’s disease, a disorder in motor control. In Parkinson's disease, pergolide is believed to exert its therapeutic effect by directly stimulating postsynaptic dopamine receptors in the corpus striatum (Jenner et al; 2002).

• **Behavioural effects (mesolimbic and mesocortical systems):**
  Some suggest that schizophrenia in humans is associated with dopaminergic hyperactivity. Amphetamine, cocaine (which inhibit dopamine transporters) and other addictive drugs activate the mesocortical pathway. The main receptor seems to be D1 (Rang et al; 2003).

• **Endocrine control (tuberohypophyseal system):**
  Is involved in the prolactine secretion control. Dopamine is inhibitory and the drugs that block D2 receptors will cause increase in the hormone and
breast development and lactation as many antipsychotic drugs.
Dopamine increases the secretion of growth hormone in normal subjects.

Dopaminergic neurons have a role in producing nausea and vomiting in the chemoreceptor trigger zone which render them as constant adverse effects to the dopamine agonists which pergolide is among them (Rang et al; 2003).

As an advantage of the drug pergolide, since enzymatic conversion within the dopaminergic neurons of pergolide is not required for their activity on the dopaminergic receptors, it does not depend on the functional capacities of the nigrostriatal neurons and thus might be more effective than levodopa, the main symptomatic medication for Parkinson's disease, in the late Parkinson’s disease (Gilman; 1996). And as the dopamine agonist Pergolide does not produce oxidative stress and may reduce indirectly the risk of neurotoxic oxidative metabolism of Levodopa derived dopamine.

**On serotonin receptors:**

Since pergolide is an ergoline derivative, it shares the spectrum of adverse effects due to the powerful interaction with nearly all subtypes of 5-hydroxy tryptamine (5-HT) receptors and α-adrenoceptors (Ruffolo et al; 1987). 5-HTA receptors are distributed all over the body: in the central nervous system (mostly 5-HT2A) (Křen; 2004) where they cause a postsynaptic excitatory effect and are abundant in the cortex and limbic system and are believed to be the target of many hallucinogenic drugs (Rang et al; 2003)

**On α-adrenoceptor:**
The α-adrenoceptor-mediated effects of pergolide were investigated in a number of biochemical and pharmacological test systems. In radioligand binding studies, pergolide more effectively competed for α 2-adrenoceptors than for α 1-adrenoceptors suggesting that the α-adrenoceptor-mediated effects commonly associated with pergolide result from selective stimulation of α 2-adrenoceptors as pergolide was several orders of magnitude more effective in activating presynaptic α 2-adrenoceptors in the study to inhibit stimulation-evoked norepinephrine release than in activating postsynaptic α 1-adrenoceptors in the same tissue to produce a contractile response. And the finding that pergolide elicited a potent vasopressor response in pithed rats that was highly sensitive to antagonism by the selective α 2-adrenoceptor antagonist, yohimbine, and resistant to blockade by the selective α 1-adrenoceptor antagonist, prazosin giving that pergolide selectively activates postsynaptic vascular α 2-adrenoceptors. And all of these indicate that pergolide is a selective α 2-adrenoceptors agonist (Ruffolo et al; 1987).

**Other effects of pergolide:**

**Anti-inflammatory activity of pergolide:**

Pergolide has been shown to have anti-inflammatory activity. Studies were done to investigate the mechanism of action and to determine the pharmacologic significance of this finding. It has been found that pergolide anti-inflammatory activity was independent of its elevation of circulating glucocorticoids and it has been demonstrated that the anti-inflammatory effects of pergolide were separable from potential immunosuppressive effects, also direct effects on arachnoid acid inflammatory mediators has been ruled
out. Interactions with the autonomic nervous system were suggested, in that an α adrenergic agonist (clonidine) mimicked the activity of pergolide in the carrageenan assay, and an α adrenergic antagonist (phenoxybenzamine) blocked the anti-inflammatory activity of pergolide in that assay. Dopamine receptor antagonists (haloperidol or sulpiride) partially inhibited the effect of pergolide in the assay. However, the peripherally restricted dopamine antagonist, domperidone, was ineffective, suggesting that a central dopamine receptor was involved in the effect. Multiple dose studies indicated that tolerance might develop to the anti-inflammatory effect of pergolide (Bendele et al; 1991).

**Antioxidant effect of pergolide:**

In the rat, long term administration of pergolide appears to preserve the integrity of dopamine-containing nigrostriatal neurons with aging. The prevention of age-related degeneration may be the result of a continuous stimulation of dopamine autoreceptors and reduced conversion of dopamine to toxic compounds. Furthermore, pergolide may exert neuroprotective effects by increasing striatal superoxide dismutase activity, which has been shown following repeated administration of the compound to rats. This effect may mimic the protective increase in superoxide dismutase activity observed in Parkinson’s disease (Lange;1998, Vargas;1998). Data suggest that pergolide, independently of dopamine receptor stimulation, may interfere with the early phases of the oxidative stress-induced neurotoxic process. Pergolide protects
neuroblastoma cells from H2O2-induced neurotoxicity (Uberti et al; 2002). Pergolide was found to prevent H2O2-induced apoptosis by inhibiting NF-kB nuclear translocation and activation of p53 signalling pathway. NF-kB proteins are ubiquitous transcription factors that are activated in response to oxidative stress (Uberti et al; 2004).

**Pergolide exerts effects on many systems of the body as:**

**Cardiovascular system:**

As the effect of pergolide on cardiac sympathetic neurotransmission was examined in a previous studies and it was demonstrated that pergolide inhibits sympathetic neurotransmission to the heart by a specific activation of presynaptic dopamine receptors as positive chronotropic responses to right postganglionic cardioaccelerator nerve stimulation were significantly reduced following infusion of pergolide, which was blocked by dopamine antagonist not by adrenergic antagonist, yohimbine, whereas positive chronotropic responses to exogenous norepinephrine were unchanged (Richard et al; 1982).

Pergolide lowered both blood pressure and heart rate through its dopaminergic effect. (Terence et al; 1979).

Also pergolide was found to exert its effects on the cardiovascular system through other ways where its stimulation in the smooth muscles that will cause vasoconstriction except in the heart and skeletal muscles where it causes vasodilatation. Furthermore the stimulation of the 5-HT2A surface receptors on the platelet will cause their aggregation but is not accompanied by the release of serotonin stores in the platelet in contrast to the aggregation
induced by clot formation. And lastly is the gastrointestinal system where 5-HT2A receptors stimulation cause contraction of the smooth muscles leading to increase in the tone and facilitating peristalsis (Katzung; 2001). It has been shown that pergolide is a potent contractile partial 5-HT2A receptor agonist that its stimulation centrally may contribute to digital vasospasm and the psychic side effects (e.g. confusion, hallucinations) which has been observed as adverse effects of it in the treatment of Parkinson’s disease. These effects were found to be blocked by the 5HT2A receptor antagonist Ketanserin.

**on endocrine system:**

Pergolide mesylate inhibits the secretion of prolactin in humans and lowers serum prolactin concentrations (Berezin et al; 1991, Freda et al; 2000); it causes a transient rise in serum concentrations of growth hormone and a decrease in serum concentrations of luteinizing hormone. pergolide also lead to increase of glucocorticoid secretion from the adrenal gland (Hemrick-luecke et al; 2002)

**Indications and Clinical Uses:**

**A. Parkinson’s disease:**

**Role of pergolide in the treatment of Parkinson’s disease:**

Since its introduction, Levedopa has been considered as the sole drug in the treatment of the symptoms of Parkinson’s disease but because the many unwanted adverse effects, as long-term motor fluctuation and dyskinesia, the newly emerging therapeutic strategies suggest that initiation of Levodopa treatment should be delayed and advocate an early use of dopamine agonists which offer several theoretical advantages over levodopa. First, dopamine
agonists act directly on dopamine receptors and do not require metabolic conversion to an active product in order to exert their pharmacologic effect. They therefore act independently of the degenerating dopaminergic neurons, and through this way the increased dopamine metabolism that would results from levodopa administration which may damage the nigrostriatal system through free radical generation, as indicated by in vivo and in vitro studies, would be avoided. And nevertheless, dopamine agonists do not undergo oxidative metabolism and do not generate free radicals or induce oxidative stress. In addition, they have the potential to stimulate the presynaptic autoreceptors of dopamine and may therefore reduce endogenous dopamine turnover which is enhanced by levedopa and was proven to be potentially toxic. Second, in contrast to levodopa, circulating plasma amino acids do not compete with dopamine agonists for absorption and transport into the brain. Third, marketed dopamine agonists have a longer half-life than immediate-release and controlled-release formulations of levodopa, and individual doses therefore have the potential to provide more sustained stimulation of striatal dopamine receptors. Finally: Indeed, there is mounting evidence suggesting that they may have neuroprotective effects (Marsden et al., 1982; Lange; 1998, Olanow et al; 2001, Deleu et al; 2002).

**As monotherapy:**

As new therapeutic strategies for early PD suggest that initiation of levodopa treatment should be delayed, and advocate an early use of dopamine agonist agents, The efficacy and tolerability of pergolide were evaluated in a multicenter, double-blind, randomized clinical studies. One of which was done over 3-month trial versus placebo. Patients with a diagnosis of idiopathic PD,
a modified Hoehn & Yahr score of 1 to 3, and a score greater than 14 points on the Unified Parkinson’s Disease Rating Scale (UPDRS) part III at baseline were enrolled in the study (pergolide, n = 53; placebo, n = 52). Patient characteristics at study entry were comparable in the two study groups. The pergolide group showed a significantly greater percent of responders (defined as a ≥30% decrease in UPDRS part III score at end point) compared with placebo (57% versus 17%; p < 0.001). Pergolide-treated patients experienced a significantly greater improvement than placebo-treated patients (p < 0.001) in UPDRS (overall, part II, and part III) score, Schwab & England score, and Clinical Global Impression improvement score. By the study end the mean dose of pergolide was 2.06 mg/day. Six patients in the pergolide group versus two patients in the placebo group discontinued the study because of treatment emergent side effects (Barone P; 1999) and all of these studies supported that pergolide was safe and effective as an initial monotherapeutic agent for early Parkinson’s disease (Navan; 2002).

**As adjunctive therapy:**

Several studies have assess the efficacy of pergolide in the treatment of Parkinson’s disease as adjunctive drug to levodopa and was found to as adjuvant therapy, can significantly decrease the total daily dose of L-dopa, shorten the duration of the ‘off’ time, improve motor symptoms, extend the duration of the ‘on’ time and decrease the incidence and severity of motor complications that is improvement in the total Parkinson score (the sum of Parkinson motor score and activity of daily living score). (Sharma et al; 1999, Jenner et al; 2002, Rektorova et al; 2003).
One study, which was a double-blind controlled have demonstrated the efficacy of pergolide as adjunctive "add-on" therapy in the treatment of advanced PD. In which a study of pergolide as an adjunct to levodopa in patients with motor fluctuations, "off" time decreased by 32% in pergolide-treated patients compared with 4% in placebo-treated patients (p<0.001). Motor function improved by 35% with pergolide compared with 17% with placebo (p<0.001). In addition, pergolide permitted a mean levodopa dose reduction of 24.7% compared with 4.9% in the placebo group (p<0.001). (Olanow; 1994)

**Additional advantageous effect of pergolide treatment on Parkinson patients:**

- **for treatment of depression in Parkinson's disease:**

  only one study paid attention to this potential effect of pergolide and yet could not make any conclusions with regard to antidepressant effect of pergolide when they have studied of pergolide treatment as add-on to L-dopa therapy and observed its effect on depression in 41 non-demented patients (25 men, 16 women) suffering from both mild or moderate depression and advanced Parkinson’s disease, which arise the need of more studies to evaluate the antidepressant effect of pergolide on Parkinson’s patient suffering from depression (Rektorova et al; 2003).

- **effect on nocturnal in Parkinson’s disease:**

  Bladder dysfunction is an autonomic nervous symptom that occurs in severely affected Parkinson’s disease. It is estimated that about two-thirds of
the patients have symptomatic urinary disturbance. Above all symptoms, nocturnal, which appears during the night and early morning when the effects of L-dopa decrease, often disturbs sleep thereby impairing the patients’ quality of life.

In a study conducted to evaluate the effect of pergolide on nocturia in Parkinson’s disease on three patients with nocturia, with the exclusion of urinary tract infection, and the results were: decrease in nocturia frequency in all three patients, a decrease in irritative urinary symptoms in two and an improvement of sleep QOL "how much impact of the nocturnal symptoms on sleep" in two.

The effect of pergolide on nocturia was found to be independent of improvement of parkinsonian symptoms, suggesting a distinct mechanism from that of anti-parkinsonian effects. The study also suggests that switching from bromocriptine to pergolide improves nocturia, thereby improving sleep status of patients with Parkinson’s disease. The decrease in nocturia frequency could be due to either elimination of the action of bromocriptine in accelerating bladder contraction, suppression of bladder contraction by pergolide, or both. (Kuno et al; 2004)

B. Pergolide may be useful as an antidepressant adjuvant:

Several studies have demonstrated that direct and indirect dopamine agonists have antidepressant effect. A study conducted to assess the effect of pergolide on antidepressant-resistant depression, pergolide was found to be useful as an antidepressant adjuvant for refractory depression. However, the mechanism of action involved is not clearly understood. Which may arise the need of carefully controlled double-blind studies of pergolide versus placebo
with tricyclic or heterocyclic antidepressants will be required. (Izumi et al; 2000)

C. In the treatment of restless leg syndrome:

Pergolide was found to improve the clinical symptoms and the sleep efficiency, and reduce periodic limb movements of sleep in patients with restless leg syndrome "RLS" (Ekbom's syndrome) either from the start or after switching the patient from levodopa which showed many disadvantages as it has failed to maintain the clinical efficiency without requiring midnight or early morning dose due to its short half life and as its sustained use has produced serious problems with RLS augmentation, paradoxical worsening of symptoms. The use of pergolide in the treatment of RLS was effective without the need of early morning dose and with reduced incidence of augmentation (Earley 1998, Bassettia; 2003)

D. In the symptomatic treatment of Tourette syndrome:

Tourette syndrome is (TS) is a disorder comprised of involuntary motor and phonic tics often associated with psychiatric conditions. The etiology for TS is unclear, with both genetic and immunological theories being studied to date.

The use of dopamine agonists might be expected to have a worsening effect on tic since antipsychotic, which act solely as antagonists at dopamine receptors improve tics. However, the use of pergolide, has mixed dopaminic D3/D2/D1 agonistic effect, was found to reduce the symptoms of Tourette syndrome in children, adolescents and adults and has been found that it is an efficacious and safe medication for tic reduction in children, without the weight gain, sedation, and extrapyramidal
symptoms seen with other commonly used drug classes, and may also improve attention deficit hyperactivity disorder symptoms. A suggested explanation was that pergolide might help tic symptoms by acting as an agonist at presynaptic receptors. This was achieved by doses were considerably lower than that used to treat Parkinsonism. Adverse effects include mild sedation without extrapyramidal symptoms (Eric et al;2000, Gilbert;2003)

E. In the treatment of prolactinoma:

Although most PRL-secreting pituitary tumors are microadenomas at presentation, many, and particularly those in men, are macroadenomas (i.e. tumors.10mm ) at the time of diagnosis which often present because of symptoms of mass effect by the tumor, such as visual field loss, headache, other neurological symptoms or hypopituitarism. Therefore, the initial treatment of macroprolactinomas includes tumor shrinkage with relief of neurological symptoms, in addition to the lowering of prolactine (PRL) and restoration of gonadal function.

Medical therapy with dopamine agonists is now the preferred primary treatment in patients with macroprolactinoma as bromocriptine and, the newly introduced dopamine agonist, cabergoline. Pergolide in many occasions were found to be effectively inhibits PRL secretion and is an option for the medical treatment of prolactinomas. Pergolide is approximately 100 times more potent than bromocriptine and suppresses PRL secretion for up to 24 h after a single dose allowing effective control of hyperprolactinemia with once daily dosing. It has advantages over BC in that it only requires once-a-day dosing and is approximately one-fifth the cost .In magnetic resonance imaging (MRI).
Before the availability of cabergoline, we treated many patients with pergolide as first-line therapy and have documented its efficacy in correcting endocrine abnormalities and in shrinking macroadenomas. Although cabergoline may now be the first line therapy in many patients, pergolide remains a viable option for the treatment of macroadenomas, particularly in men and postmenopausal women.

**Fig. 1.** Coronal (a) and sagittal (b) gadolinium-enhanced T1-weighted spin-echo magnetic resonance imaging in patient 1. The images show a 2.5 × 2.5 × 4.2-cm sellar-suprasellar and right parasellar mass. It compresses and distorts the optic chiasm, the floor of the 3rd ventricle, and extends into the right middle cranial fossa to compress the medial temporal lobe. The sagittal images additionally demonstrate compression and mass effect on the midbrain and upper pons.

**Fig. 2.** Coronal (a) and sagittal (b) gadolinium-enhanced T1-weighted spin-echo magnetic resonance imaging in patient 1. The images show a 96% shrunken macroadenoma with a normal appearance to the suprasellar and right parasellar cisterns with a normal optic chiasm and now a visualized, but minimally deviated, pituitary stalk toward the left side.
In addition, it should be considered when other available therapies are not tolerated or when the cost of lifelong therapy with currently available medications is greater than patients can afford (Berezin et al; 1991, Freda et al; 2000)

**Dosage and administration:**

Administration of pergolide should be initiated with a single daily dose of 0.05 mg for the first 2 days. The dose should then be gradually increased by 0.1 to 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day every third day until an optimal dosage is achieved.

Pergolide is usually administered in divided doses 3 times/day. During dosage titration, the dosage of levodopa/carbidopa may be cautiously decreased. If the patient misses a dose, he/she should take the missed dose as soon as possible but should skip the missed dose if it is almost time for his/her next regular dose. The patient should never take two doses at the same time.

Since rapid escalation of the drug causes severe adverse reactions, it is recommended that a slow increase of pergolide be combined with a concomitant, gradual and limited reduction of levodopa dosage.

In clinical studies, the mean therapeutic dose of pergolide was 3 mg/day. The average concurrent levodopa/carbidopa daily dosage (expressed as levodopa) was approximately 650 mg/day. The safety of pergolide at doses above 5 mg/day has not been systematically evaluated (www.Rxmax.com).

**Drug Interactions:**
Dopamine antagonists such as the narcoleptics (phenothiazines, butyrophenones, and thioxanthenes) or metoclopramide ordinarily should not be administered concurrently with pergolide (a dopamine agonist) because these agents may diminish the effectiveness of pergolide.

Concurrent use of other central nervous system depressants may have additive sedative effects (Deleu et al; 2002).

Because pergolide is approximately 90% bound by plasma proteins, caution should be exercised if pergolide is coadministered with other drugs known to affect protein binding, e.g. warfarine (Deleu et al; 2002).

With levodopa: The addition of pergolide to levodopa therapy has produced an increased incidence of dyskinesias in parkinsonian patients (Lieberman et al, 1982; Diamond et al, 1985). Decreasing the levodopa dose usually reverses the dyskinesias.

Patients using antihypertensive drugs should start with lower doses in the fear to develop orthostatic hypotension (Gilman;9th edition) as lisinopril when single case was reported of a patient who was on lisinopril for 3 years when he took pergolide for the first time and developed sever hypotensive episode (Kando et al;1990, Deleu et al; 2002)

With the dopamine agonist, activity of Vitex may add to that of other dopamine agonists, increasing the risk of dopaminergic adverse effects. Vitex has been effective in alleviating luteal phase defects due to hyperprolactinemia and in relieving symptoms related to premenstrual tension syndrome so
doctors should avoid concomitant use of Vitex with pergolide (www.RxMed.com).

**Contraindications:**

Patients who are hypersensitive to this drug or other ergot derivatives.

**Precautions:**

*General: The abrupt discontinuation of pergolide in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on levodopa.*

*The administration of pergolide to patients receiving levodopa may cause and/or exacerbate pre-existing dyskinesia in parkinsonian patients; reductions in levodopa dose usually alleviates this problem (Reimer; 2002).*

*Patients with confusion, hallucinations or preexisting dyskinesia; the drug may exacerbate these symptoms.*

*Possibility of falling asleep while performing daily activities, including operation of motor vehicles (Schapira; 2000, Bassetti; 2003)*

*Cardiovascular Effects: Pergolide has not been systematically evaluated in patients with heart disease. In the multicenter clinical trial, patients with heart disease, i.e., recent angina pectoris, decompensated heart failure (New York Scale III or IV), myocardial infarction within the last 12 months, or any arrhythmia requiring antiarrhythmic therapy at the time of the study or within 12 months prior to the study were excluded.*
Since there is only limited experience with pergolide in these patients, pergolide should be administered only if in the judgment of the physician the potential benefits clearly outweigh the potential risks. *Patients with history of pleuritis, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy, or retroperitoneal fibrosis, especially if events experienced while receiving ergot derivatives. (Shaunak; et al;1999, Danoff et al; 2002).

*Pregnancy: Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only, if in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risks to the fetus.

*Lactation: It is not known whether pergolide is excreted in human milk. The pharmacologic action of pergolide suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Adverse Reactions:**

The most commonly observed adverse events associated with the use of pergolide are: nervous system complaints (including dyskinesia, dizziness, hallucinations, somnolence, and insomnia); gastrointestinal complaints (including nausea, constipation, diarrhea and dyspepsia); cardiovascular complaints,( including postural hypotension), and respiratory system complaints, including rhinitis.
Adverse Reactions Resulting in Discontinuation of Treatment:

Twenty-seven percent of approximately 1,200 patients, receiving pergolide for treatment of Parkinson's disease in premarketing clinical trials in the U.S. and Canada, discontinued treatment due to adverse reactions. Events most often causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%) (Reimer; 2002, www.Rxmax.com).

* Certain adverse experiences (e.g., dyskinesias, hallucinations) are frequently observed in patients receiving levodopa pergolide and/or other dopamine agonists. These are dose related and tend to improve with reduction of the dosage of levodopa or of Pergolide.

* Postural hypotension and nausea are most frequently reported during the initial titration phase.

* Abnormalities in laboratory tests may include elevations of AST, ALT, alkaline phosphatase and urea nitrogen.

I. Nervous system:

Frequent: dyskinesia, dystonia dizziness, are most frequently listed adverse effects central nervous system (CNS) effects during pergolide treatment. However, are the most commonly cited reasons for drug discontinuation. A variety of other sleep disturbances, mood disorders, and motor function dysfunction have been reported in premarketing clinical trials with pergolide (www.Rxmed.com). Other commonly reported CNS adverse effects
with pergolide include insomnia, anxiety, tremor and depression (www.Rxmed.com). Somnolence and sleep attacks were also encountered with pergolide (Schapira; 2000, Bassettia; 2003).

II. Psychosis:

Visual hallucinations and nightmares with pergolide were reported in several studies. These effects usually resolved when the dose was decreased, but tolerance was not observed. Patients with previous psychiatric adverse effects with levodopa and bromocriptine therapy were more prone to psychiatric effects with Pergolide.

III. Ocular effects:

Abnormal vision (6%) and diplopia, respiratory system complaints, including rhinitis

IV. *Cardiovascular:

Postural hypotension is a commonly reported (10%) adverse effect usually associated with the first dose of pergolide and does not appear to be dose-related and it was found that Tolerance can develop to this side effect, particularly with gradual dosage titration (Gilman; 1996, www.RxMed.com) and this hypotension may lead to syncope, palpitations, arrhythmia. Although restrictive valvular heart disease is considered a rare event, it is serious. It is shown here the aortic valve is thickened causing aortic
incompetence demonstrated by the echocardiography, and the other figure is after it is being excised as a consequence of treatment with pergolide (Van camp, et al; 2004). Rare: vasculitis, pulmonary hypertension, constrictive pericarditis (Shaunak; et al; 1999). In a case report a patient developed constrictive pericarditis 3–4 years after the start of treatment with pergolide. Pericardectomy was required for treatment (Balachandran; 2002). It has also side effects related to the central 5-HT2A stimulation as digital vasospasm (Gilman; 1996, Kren; 2004).

V. Respiratory:

➢ Frequent: rhinitis has been reported by 12.2% of patients taking pergolide in clinical trials, with dyspnoea noted in 5%. Epistaxis and hiccups were seen in less than 2% (www.RxMed.com). In rare cases, pleuritis, pleural effusion, or pleural fibrosis have been reported (Anon, 2003, Shaunak; et al; 1999).

➢ This chest radiograph (CT) is of a patient diagnosed with a pergolide-induced pneumonitis.
with pleural and pericardial effusions. Pergolide was stopped and the patient’s symptoms improved within 2 weeks.

Two months later, he was asymptomatic and the chest radiograph was normal. The gas transfer factor was preserved (Kastelik et al; 2002).

➢ Retroperitoneal fibrosis (Shaunak; et al;1999).

**VI. Gastrointestinal:**

Nausea occurred in nearly one-fourth of all patients in premarketing clinical trials, with constipation was noted in 10%. Diarrhea and dyspepsia occur in 6%, while anorexia, dry mouth, or vomiting are reported in 2% to 5% (www.RxMed.com). An unspecified taste perversion was noted in less than 2% of patients during premarketing clinical trials (www.RxMed.com)

**VII. Genitourinary effects:**

Urinary frequency or urinary tract infection were reported in nearly 3% of patients in premarketing clinical trials. Hematuria was noted in less than 1% (www.RxMed.com)

**VIII. Musculoskeletal:**

arthralgia or myalgia, bursitis, or muscle twitching are seen in less than 2% of patients in premarketing clinical trials(www.RxMed.com).

**IX. Skin and Appendages:**

There are several case reports of erythromelalgia in the lower extremities of parkinsonian patients on pergolide therapy (Monk et al; 1984). Erythromelalgia presented as a bilateral erythematous rash on the shins.
X. Alopecia may be induced by pergolide. The alopecia reversed partially after stopping pergolide and in some patients may be reversed completely (Tabamo; 2002).

XI. **Hematic and Lymphatic:**

Anemia.

**Withdrawal symptoms:**

Hallucinations, confusion, and paranoid ideations, as well as worsening of parkinsonian symptoms, have been observed during the first several days following abrupt withdrawal of pergolide therapy in parkinsonian patients who were also receiving chronic levodopa therapy. It is suggested that pergolide therapy be discontinued gradually when possible.

A symptom complex resembling the neuroleptic malignant syndrome (NMS), characterized by elevated body temperature, muscular rigidity, altered consciousness, and autonomic instability, has been reported in antiparkinsonian therapy. Therefore, patients should be observed carefully when the dosage of pergolide is reduced abruptly or discontinued (Reimer; 2002).
**Conclusion**

*Methysergide* is a non-selective serotonin 5-HT2 receptor subtype antagonist with some partial agonistic action. It is used in prevention of vascular headaches, but this is restricted due to its adverse effects, in which the most dangerous is retroperitoneal fibrosis.

*Ergotamine* causes long lasting (at least 24 hrs) vasoconstriction of the arteries. It is widely used for the treatment severe migraine attacks. However, its adverse effects limit how much it can be used and prevent its use for prophylaxis.

*Bromocriptine* is an ergot alkaloid. It is taken orally with drink of water or with food to reduce gastric upset. It does not require restriction of fluid intake to suppress lactation and to treat prolactinomas. It does not impair puerperal involution of the uterus or increase the risk of thromboembolism. It can normalize prolactin levels in hyperprolactinemia without affecting the release of other anterior pituitary gland hormones. Bromocriptine have been used in previously untreated patients with Parkinson's disease to prolong levodopa treatment and delay its complications.

*Ergometrine* affects primarily uterine smooth muscles producing sustained contraction and thereby shortens the third stage of labor. It is administered after the delivery of the placenta to promote involution of the uterus in order to treat postpartum and postabortion haemorrhage. It is available for oral, I.M and I.V. route. It has many adverse effects; the most serious are hypertension, stroke, myocardial infarction and pulmonary oedema. Caution must be taken in case of cardiac disease and porphyria. It is contraindicated in
cardiac disease, induction of labour, eclampsia, sepsis and severe hepatic or renal impairment.

The dopamine agonist **Pergolide** were originally introduced to overcome some of the problem associated with long term administration of levodopa in Parkinson’s disease by bypassing the degenerated nigrostriatal dopaminergic neurons. It is best used as adjuvant to levodopa therapy in Parkinson’s disease. Now new potential uses for it have emerged and it may replace other drugs for its long-life, antioxidant activity, cost effectiveness and other advantages.
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