

The Canadian Journal of Neurological Sciences

Le Journal Canadien des Sciences Neurologiques

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The Canadian Neurological Society
The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association for Child Neurology

When patients show prominent dyskinesia or wearing-off reactions on long-term levodopa





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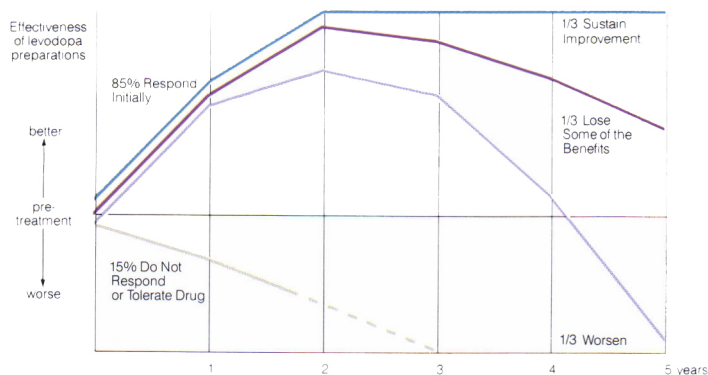
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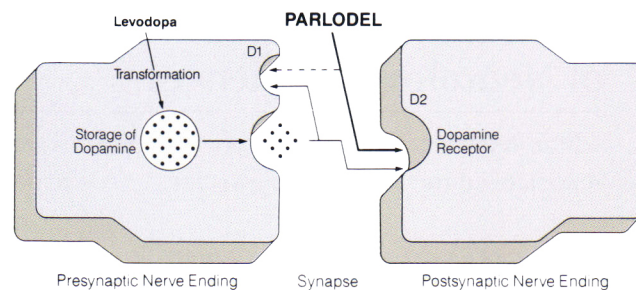
Frequent problems of long-term levodopa therapy⁸



With time, the benefits of levodopa can decline, and patients may demonstrate prominent dyskinesia or signs of wearing-off such as:

- performance fluctuations
- early morning stiffness
- foot cramps
- end-of-dose deterioration
- on-off phenomenon

Dopamine-like action³



Help protect the quality of life for your Parkinson patients over the long term with Parlodel.^{2,4} Added to levodopa, it may allow lower doses for fewer long-term levodopa side effects^{4,5,6}, and prolong the total useful period of active treatment.¹

- Primary effect is directly on postsynaptic receptors.³
- Does not require transformation for its dopaminomimetic effect.³
- Combined therapy with levodopa often leads to significantly improved control.⁹
- May permit lower levodopa doses.^{4,5}
- Longer plasma half-life (Parlodel 2-8 hours vs. levodopa 1 hour).⁹
- Mainly type D2 dopamine receptor agonist activity.

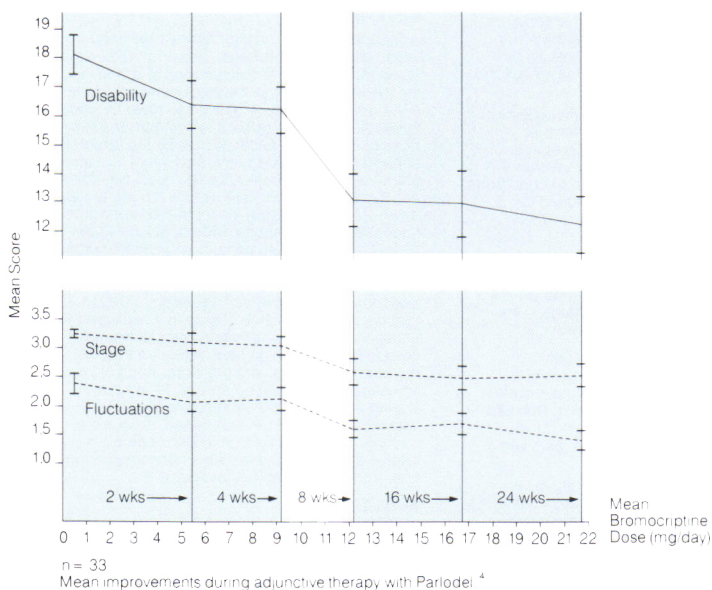
PARLODEL[®]
(bromocriptine mesylate)

Can help prolong
effective control¹

Add Parlodel for improved quality of life^{4,7}

In combination with levodopa, Parlodel may provide effective long-term control of Parkinson symptoms⁹, with decreased functional disability and increased mobility.²

Mean improvement chart



In a recently reported Canadian multicentre trial of Parlodel as adjunctive therapy⁴

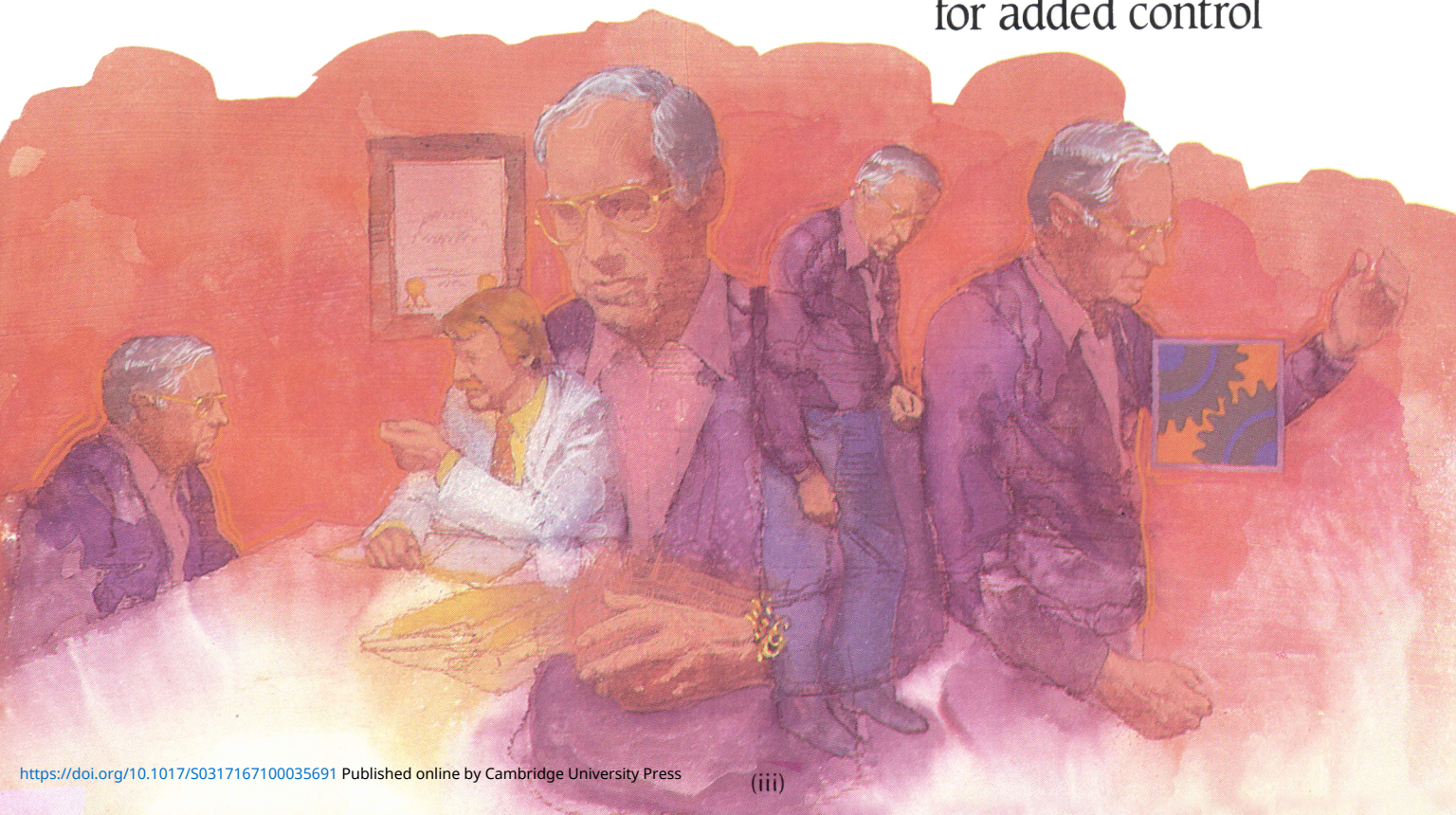
- 43% improvement in end-of-dose deterioration in a majority of patients
- 33% reduction in total disability scores
- low mean daily doses of Parlodel
12 mg (8 weeks)
22 mg (24 weeks)
- 15% average decrease of levodopa

Add Parlodel

When levodopa no longer provides sufficient control, adding Parlodel is an alternative to increasing the dose of levodopa. Likewise, Parlodel can be an important adjunct when prominent dyskinesia appear. Parlodel — a new era in the treatment of Parkinson's disease.

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(bromocriptine mesylate)

for added control



ADD[®] PARLODEL[®]

(bromocriptine mesylate)

For added control

ACTIONS Parlodel (bromocriptine mesylate) is a dopaminergic ergot derivative with D₂ type dopamine receptor agonist activity, and has also D₁ dopamine receptor antagonist properties. The dopaminergic activity of bromocriptine in the striatum is considered responsible for the clinical benefits seen in selected patients with Parkinson's Disease, when low doses of the drug are gradually added to levodopa therapy in patients on long-term treatment who develop late side effects of levodopa or no longer respond to the medication. Excessive dopaminergic drive may, however, provoke psychotic and other adverse reactions.

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

INDICATIONS* **Parkinson's Disease:** Parlodel (bromocriptine mesylate) has been found to be clinically useful as an adjunct to levodopa (usually with a decarboxylase inhibitor), in the symptomatic management of selected patients with Parkinson's Disease who experience prominent dyskinesia or wearing off reactions on long-term levodopa therapy.

Patients on long-term treatment who are beginning to deteriorate on levodopa therapy may be controlled by reducing the dose of levodopa and adjusting the frequency and schedule of drug administration. Patients maintained on optimal dosages of levodopa who still experience prominent dyskinesia and/or end-of-dose failure, may benefit from the concomitant use of Parlodel, by decreasing the occurrence and/or severity of these manifestations. Since rapid escalation of bromocriptine doses causes severe adverse reactions, it is recommended to combine a slow increase of Parlodel, usually with a concomitant, gradual and limited reduction of levodopa dosage. Continued efficacy of bromocriptine for more than two years has not been established and there is some evidence that its efficacy tends to wane. Evidence available indicates that there is no consistent benefit from bromocriptine in patients who have not responded previously to levodopa, and studies have shown significantly more adverse reactions in bromocriptine treated patients than in patients treated with levodopa. Parlodel is not recommended in the treatment of newly diagnosed patients or as the sole medication in Parkinson's Disease.

CONTRAINDICATIONS Other than sensitivity to ergot alkaloids, no absolute contraindications to treatment with Parlodel (bromocriptine mesylate) are known. For procedure during pregnancy see "Use in Pregnancy" under Precautions.

WARNINGS Long-term treatment (6-36 months) with Parlodel in doses of 20 to 100 mg/day has been associated with pulmonary infiltrates, pleural effusion and thickening of the pleura in a few patients. Where Parlodel was discontinued, these changes slowly reverted to normal.

PRECAUTIONS Parlodel (bromocriptine mesylate) may cause hypotension, primarily postural; periodic monitoring of the blood pressure, particularly during the first days of therapy, is advisable. In some patients dizziness (vertigo) may occur with Parlodel; patients should therefore be cautioned against activities requiring rapid and precise responses such as driving an automobile or operating dangerous machinery until their response has been determined.

Care should be exercised when administering Parlodel concomitantly with phenothiazines or antihypertensive agents. Due to drug interaction at the receptor site, dosage should be adjusted accordingly.

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

Parlodel should always be taken with food. In cases where severe adverse effects, such as nausea, vomiting, vertigo or headaches are severe or persisting, the therapeutic dosage of Parlodel should be reduced to one-half tablet daily (1.25 mg) and increased gradually to that recommended.

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

Use in Pregnancy If the patient wishes to become pregnant, Parlodel (bromocriptine mesylate) should be stopped as soon as possible after conception is suspected. In this event immunological confirmation should be done immediately. When pregnancy is confirmed, Parlodel, like all other drugs, should be discontinued unless, in the opinion of the treating physician, the possible benefit to the patient outweighs the potential risk to the fetus.

In human studies with Parlodel (reviewed by Turkalj, I.), there were 1410 reported pregnancies, which yielded 1236 live and 5 stillborn infants from women who took Parlodel (bromocriptine mesylate) during early pregnancy. Among the 1241 infants, 43 cases (31 minor and 12 major) of congenital anomalies were reported. The incidence (3.46%) and type of congenital malformations and the incidence of spontaneous abortions (11.13%) in this group of pregnancies does not exceed that generally reported for such occurrences in the population at large.

Gynecological Supervision All women patients receiving Parlodel continuously for six months or more should have a gynecological examination before therapy, yearly if still menstruating, and six-monthly if menopausal. The examination should include cervical and, if possible, endometrial cytology. Post-menopausal women on estrogen therapy should be excluded from Parlodel therapy at the discretion of the physician because estrogen induced uterine bleeding may mask the presence of pathological lesions.

A lifetime rat study revealed that some animals developed uterine tumors and endometrial carcinoma thought to be due to a state of induced estrogen dominance. However, clinical experience in women with a variety of hyperprolactinemic and other conditions, treated with Parlodel for months or years, failed to demonstrate abnormal trends in hormonal levels or in endometrial cytology.

Normoprolactinemic women treated with Parlodel should be given the lowest effective dose necessary to relieve their symptoms, in order to avoid the possibility of suppression of prolactin below normal levels, with a consequent impairment of luteal function.

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

Parlodel administered alone or concomitantly with levodopa may cause visual or auditory hallucinations. These usually resolve with dosage reduction, but discontinuation of Parlodel may be required in some cases. Rarely, after high doses, have hallucinations persisted for several weeks following discontinuation of Parlodel. Caution should be exercised when administering Parlodel to patients with a history of myocardial infarction, particularly if they have a residual atrial, nodal or ventricular arrhythmia.

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

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

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

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

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

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

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

The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two or three times daily.

SYMPTOMS AND TREATMENT OF OVERDOSE

There have been several reports of acute overdose with Parlodel (bromocriptine mesylate) in children and adults. No life threatening reactions have occurred. Symptoms reported included nausea, vomiting, dizziness, drowsiness, hypotension, sweating and hallucinations. Management is largely symptomatic; the cardiovascular system should be monitored. Metoclopramide can be used to antagonize the emesis and hallucinations in patients who have taken high doses.

DOSAGE AND ADMINISTRATION Parlodel (bromocriptine mesylate) should always be taken with food.

Although Parlodel (bromocriptine mesylate) has been found clinically useful in decreasing the severity and frequency of "on-off" fluctuations of late levodopa therapy, the decision to use bromocriptine as adjunctive treatment and the selection of dosage must be individualized in each case. A low dose is recommended. The initial dose of Parlodel is one half of a 2.5 mg tablet (1.25 mg) at bedtime with food to establish initial tolerance. Thereafter, the recommended dosage is 2.5 mg daily in two divided doses, with meals, (half a 2.5 mg tablet twice daily). The dosage may be increased very gradually, if necessary, by adding an additional 2.5 mg per day, once every 2 to 4 weeks, to be taken always in divided doses with meals. Increments should usually never exceed 2.5 mg. Clinical assessments are recommended at two week intervals or less during dosage titration, to ensure that the lowest effective dosage is not exceeded. The usual dosage range is from a few milligrams to 40 mg daily in two or three divided doses with meals. The median dose varies with the experience of individual investigators, but can be around 10 mg daily or higher. During initial titration it is recommended that the dosage of levodopa should be maintained, if possible. Subsequently, it might be desirable to combine a slow increase of bromocriptine with a concomitant, limited and gradual reduction of levodopa.

AVAILABILITY

1. TABLETS each containing 2.5 mg bromocriptine, as mesylate, available in bottles of 100.

Scored 7 mm, round compressed white tablets with "XC" on one side and "PARLODEL" on the reverse.

2. CAPSULES each containing 5 mg bromocriptine, as mesylate, available in bottles of 100. Caramel and white size 3 hard shell capsules with "PARLODEL" on one side and "5 mg" on the other.

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2.5 mg scored tablet



5 mg capsule

PAAB
CCPP

* For information on other approved indications, please consult the Parlodel product monograph, available to physicians and pharmacists on request.

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McGeer PL, McGeer EG. Amino acid neurotransmitters. In: Siegel GJ, Albers RW, Agranoff BW, Katzman R, eds. *Basic Neurochemistry*. Boston: Little, Brown & Co, 1981: 233-254

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Le Journal publie également des **articles de revue** sur des sujets sélectionnés. Ces articles sont généralement sur invitation, mais, à l'occasion, une revue non sollicitée peut être acceptée. Il serait préférable que les auteurs ayant l'intention de soumettre une telle revue contactent d'abord l'Éditeur.

Nous accueillons les **lettres à l'Éditeur**. Celles-ci doivent se limiter à deux pages, double interligne et peuvent contenir une seule illustration et ne citer qu'un maximum de quatre références.

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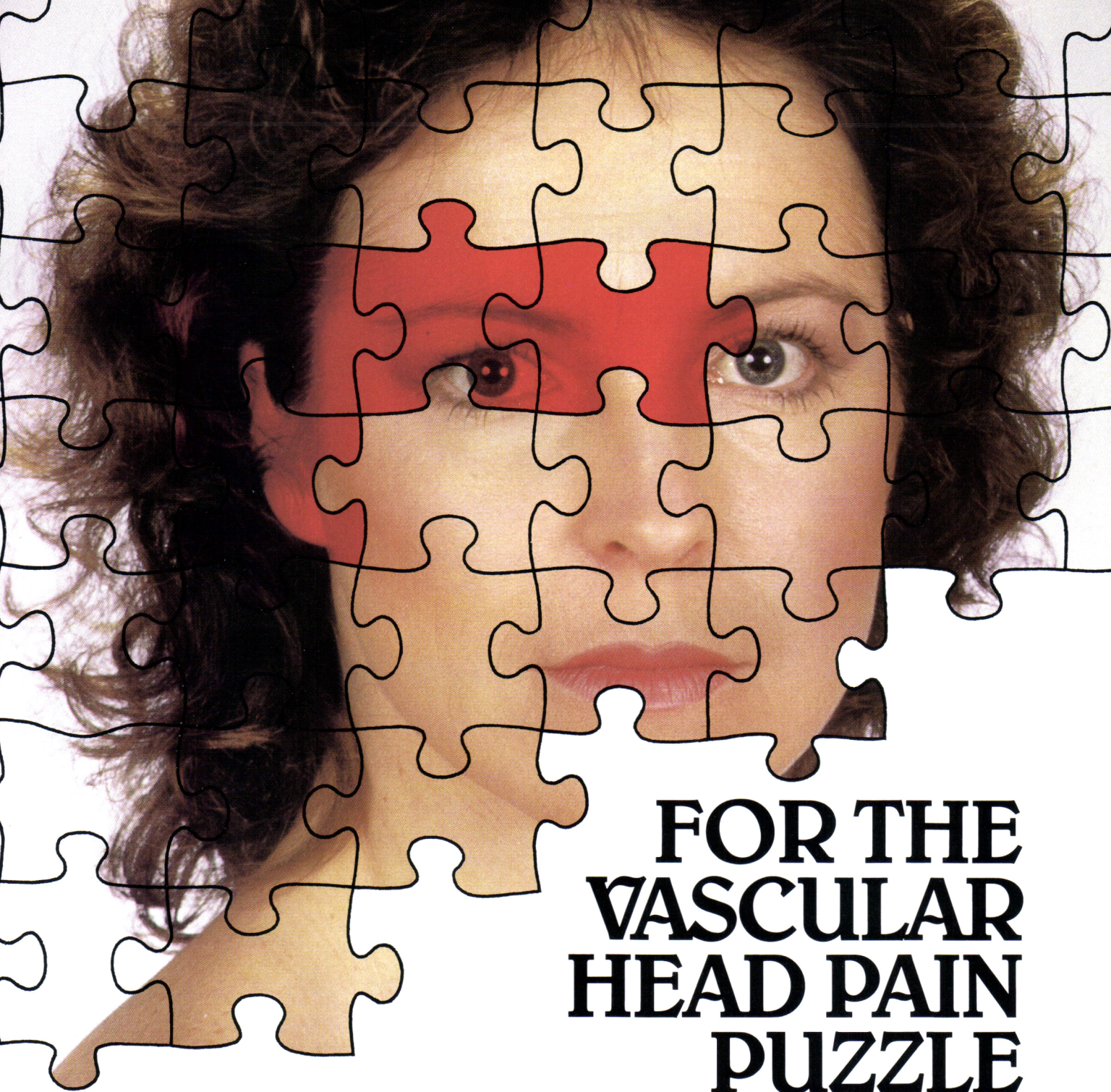
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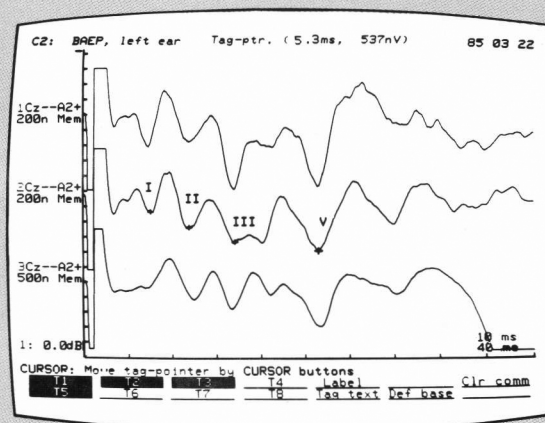
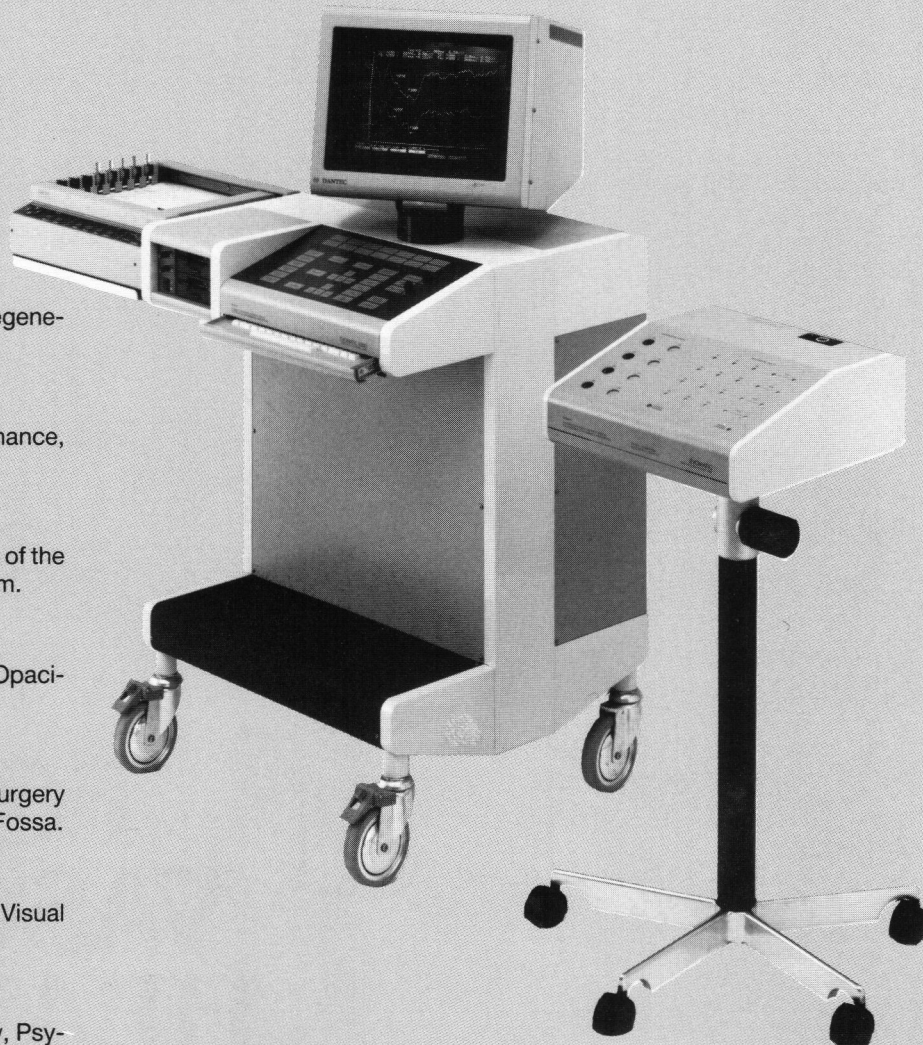
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TEGRETOL® 200 mg
(carbamazepine) tablets

TEGRETOL® Chewtabs™
(carbamazepine chewable tablets) 100 mg and 200 mg

For Symptomatic Relief of Trigeminal Neuralgia Anticonvulsant

Action:

TEGRETOL (carbamazepine) has anticonvulsant properties which have been found useful in the treatment of psychomotor and other partial epilepsies, when administered in conjunction with other anticonvulsant drugs to prevent the possible generalization of the epileptic discharge. A mild psychotropic effect has been observed in some patients, which seems related to the effect of the carbamazepine in psychomotor or temporal lobe epilepsy. TEGRETOL relieves or diminishes the pain associated with trigeminal neuralgia often within 24 to 48 hours.

Indications and Clinical Use

A. Trigeminal Neuralgia:

For the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). Do not use preventively during periods of remission. In some patients, TEGRETOL has relieved glossopharyngeal neuralgia.

For patients who fail to respond to TEGRETOL, or who are sensitive to the drug, recourse to other accepted measures must be considered.

TEGRETOL is not a simple analgesic and should not be used to relieve trivial facial pains or headaches.

B. TEGRETOL has been found useful:

- 1) in the management of psychomotor (temporal lobe) epilepsy, and,
- 2) as an adjunct, in some patients with secondary or partial epilepsy with complex symptomatology or secondarily generalized seizures, when administered in combination with other antiepileptic medication.
- 3) as an alternative medication in patients with generalized tonic-clonic seizures who are experiencing marked side effects or fail to respond to other anticonvulsant drugs.

TEGRETOL is ineffective in controlling petit mal, minor motor, myoclonic and predominantly unilateral seizures, and does not prevent the generalization of epileptic discharge.

Warnings

Although reported infrequently, serious adverse effects have been observed during the use of TEGRETOL.

Agranulocytosis and aplastic anemia have occurred in a few instances with a fatal outcome. Leucopenia, thrombocytopenia and hepatocellular and cholestatic jaundice have also been reported. It is, therefore, important that TEGRETOL should be used carefully and close clinical and frequent laboratory supervision should be maintained throughout treatment in order to detect as early as possible signs and symptoms of a possible blood dyscrasia. Long-term toxicity studies in rats indicated a potential carcinogenic risk. Therefore, the possible risk of drug use must be weighed against the potential benefits before prescribing carbamazepine to individual patients.

Contraindications

Hepatic disease, serious blood disorder, less than 14 days either before or after monoamine oxidase inhibitor (then the dosage of TEGRETOL should be low initially, and increased very gradually), atrioventricular heart block, hypersensitivity to tricyclic compounds, lactation, first trimester of pregnancy.

Usage in Pregnancy

As safety has not been established, TEGRETOL should not be given to women of childbearing potential unless, in the opinion of the physician, the expected benefits to the patient outweigh the possible risk to the foetus.

Precautions

Monitoring of Haematological and Other Adverse Reactions:

Complete blood studies, including platelet counts, and evaluation of hepatic and renal function and urinalysis should be carried out before treatment is instituted and frequent clinical and laboratory supervision should be maintained throughout treatment. If any signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur, TEGRETOL should be immediately discontinued.

Urinary Retention and Increased Intraocular Pressure:

Caution is advised in patients with increased intraocular pressure or urinary retention due to the drug's anticholinergic action.

Occurrence of Behavioural Disorders:

TEGRETOL may activate a latent psychosis, or, in elderly patients, produce agitation or confusion. Caution is advised in alcoholics.

Use in Patients with Cardiovascular Disorders:

Caution is advised in patients with a history of coronary artery disease, organic heart disease, or congestive failure. An E.K.G. should be performed if a defective conductive system is suspected before administering TEGRETOL, in order to exclude patients with atrioventricular block.

Use in Patients taking Oral Contraceptives:

Women under treatment with TEGRETOL and oral contraceptives, should be advised to use some alternative, non-hormonal method of contraception as the reliability of oral contraceptives may be adversely affected.

Driving and Operating Hazardous Machinery:

Warn patients about the possible hazards of operating machinery or driving automobiles as dizziness and drowsiness are possible side effects of TEGRETOL.

Adverse Reactions

Haematological reactions: Transitory leucopenia, eosinophilia, leucocytosis, thrombocytopenic purpura, agranulocytosis, macrocytic anemia and aplastic anemia. In a few instances, deaths have occurred.

Hepatic Disturbances: Abnormalities in liver function tests, cholestatic or hepatocellular jaundice.

Dermatological Reactions: Skin sensitivity reactions and rashes, erythematous rashes, pruritic eruptions, urticaria, photosensitivity, pigmentary changes, neurodermatitis and in rare cases Stevens-Johnson syndrome, exfoliative dermatitis, alopecia, diaphoresis, erythema multiforme, erythema nodosum, and aggravation of disseminated lupus erythematosus.

Neurological Reactions: Vertigo, dizziness, somnolence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, increase in motor seizures, peripheral neuritis, paresthesia, depression with agitation, talkativeness, nystagmus, tinnitus, paralysis and other symptoms of cerebral arterial insufficiency.

Cardiovascular Systems: Recurrence of thrombophlebitis, congestive heart failure, aggravation of hypertension, Stokes-Adams in patients with AV block, hypotension, syncope and collapse, edema, aggravation of coronary artery disease. Some of these complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds.

Genitourinary Reactions: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, impotence, elevation of BUN, albuminuria, and glycosuria.

Digestive Tract: Nausea, vomiting, gastric or abdominal discomfort, diarrhoea, anorexia, dryness of the mouth and throat, glossitis and stomatitis.

Eyes: There is no conclusive evidence that TEGRETOL produces pathological changes in the cornea, lens or retina. However, it should be recognized that many phenothiazines and related drugs have been shown to cause eye changes. By analogy, periodic eye examinations, including slitlamp funduscopy and tonometry, are recommended.

Other Reactions: Fever and chills, lymphadenopathy, aching joints and muscles, leg cramps and conjunctivitis.

Symptoms and Treatment of Overdosage

Symptoms: Dizziness, ataxia, drowsiness, stupor, nausea, vomiting, restlessness, agitation, disorientation; tremor, involuntary movements, opisthotonos, abnormal reflexes (slowed or hyperactive); mydriasis, nystagmus; flushing, cyanosis, urinary retention, hypotension, hypertension, coma. The EEG may show dysrhythmias. The laboratory findings have included leucocytosis, reduced leukocyte count, glycosuria and acetonuria.

Treatment: No known specific antidote. Induce emesis. Perform gastric lavage. Watch vital signs and administer symptomatic treatment as required. Hyperirritability may be controlled by the administration of parenteral barbiturates. Barbiturates should not be used if monoamine oxidase inhibitors have also been taken by the patient, either in overdosage or in recent therapy (within two weeks). Barbiturates may induce respiratory depression, particularly in children, therefore, have equipment available for artificial ventilation and resuscitation. Paraldehyde may be used to counteract muscular hypertonus without producing respiratory depression. Treat shock (circulatory collapse) with supportive measures, including intravenous fluids, oxygen, and corticosteroids. Electrocardiogram should be monitored, particularly in children, to detect any cardiac arrhythmias or conduction defects.

Dosage and Administration

Use in Epilepsy (see Indications): A low initial daily dosage with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient.

Adults and Children over 12 years of age: Initially: 100 to 200 mg once or twice a day. The initial dosage is progressively increased, until the best response is obtained, up to 600 mg daily. Usual Daily Dosage: 600 mg, however up to 800 to 1000 mg have been used for short periods. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Children 6-12 Years of Age: Initially, 100 mg in divided doses on the first day. Increase gradually by adding 100 mg per day until the best response is obtained. Dosage should generally not exceed 1000 mg daily. As soon as disappearance of seizures has been obtained and maintained, dosage should be reduced very gradually until a minimum effective dose is reached.

Use in trigeminal neuralgia: Initial daily dosage: 100 mg twice daily may be increased by 200 mg per day until relief of pain is obtained. Usual dosage: 200 to 800 mg daily. Up to 1200 mg daily may be necessary. As soon as relief of pain has been obtained and maintained, progressive reduction in dosage should be attempted until a minimum effective dosage is reached. Because trigeminal neuralgia is characterized by periods of remission, attempts should be made to reduce or discontinue the use of TEGRETOL at intervals of not more than 3 months, depending upon the individual clinical course.

Prophylactic use in trigeminal neuralgia is not recommended.

Administer in two or three divided doses daily, with meals whenever possible.

Dosage Forms

TEGRETOL® tablets 200 mg: Each white, round, flat, bevelled-edge double-scored tablet engraved GEIGY on one side contains 200 mg carbamazepine.

TEGRETOL® Chewtabs™ 100 mg: Pale pink, round, flat, bevel-edged tablets with distinct red spots. GEIGY engraved on one side and MR on the other. Fully bisected between the M and R. Each chewable tablet contains 100 mg carbamazepine.

TEGRETOL® Chewtabs™ 200 mg: Pale pink, oval biconvex tablets with distinct red spots. GEIGY engraved on one side and PU on the other. Fully bisected between the P and U. Each chewable tablet contains 200 mg carbamazepine.

Availability

TEGRETOL® tablets 200 mg: Bottles of 100 and 500 tablets. Protect from heat and humidity. **TEGRETOL® Chewtabs™ 100 mg:** Bottles of 100. Protect from heat and humidity.

* **TEGRETOL® Chewtabs™ 200 mg:** Bottles of 100. Protect from heat and humidity. (Available September 1985.)

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- noticeable benefits within 24 hours of start-up dose.¹
- easy usage with levodopa and anticholinergics.¹
- simple dosage regimen; simple titration.

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(amantadine HCl)

can help in Parkinson's Disease

For brief prescribing information see page xvi

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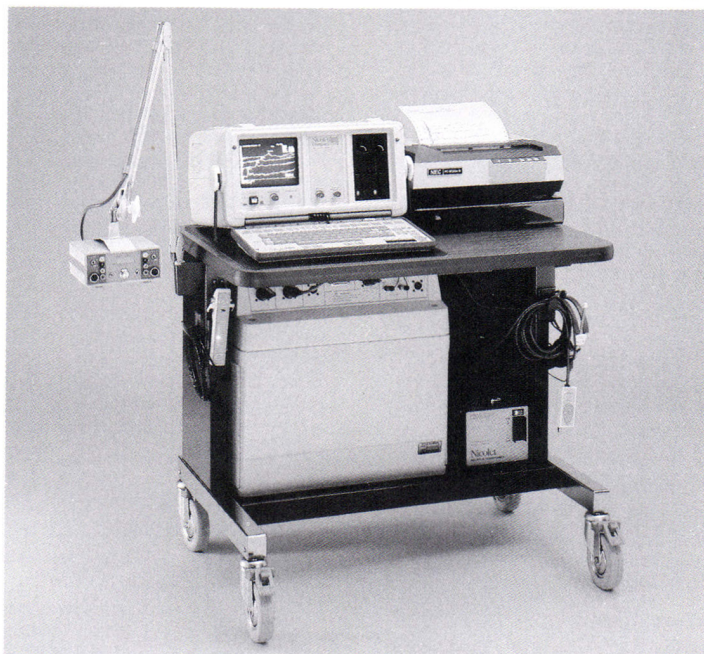
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Prolopa®

Rx Summary Indications

Treatment of Parkinson's syndrome when not drug-induced.

Contraindications

Known hypersensitivity to levodopa or benserazide; in patients in whom sympathomimetic amines are contraindicated; concomitantly with, or within 2 weeks of, MAOI administration; uncompensated cardiovascular, endocrine, renal, hepatic, hematologic or pulmonary disease; narrow-angle glaucoma.

Warnings

Discontinue levodopa at least 12 hours before initiating 'Prolopa'. See Dosage section for substitution recommendations.

Not indicated in intention tremor, Huntington's chorea or drug-induced Parkinsonism.

Increase dosage gradually to avoid CNS side effects (involuntary movements). Observe patients for signs of depression with suicidal tendencies or other serious behavioural changes. Caution in patients with history of psychotic disorders or receiving psychotherapeutic agents. In patients with atrial, nodal or ventricular arrhythmias or history of myocardial infarction initiate treatment cautiously in hospital. Caution in patients with history of melanoma or suspicious undiagnosed skin lesions.

Safety in patients under 18 years has not been established. In women who are or may become pregnant, weigh benefits against possible hazards to mother and fetus. Not recommended for nursing mothers.

Precautions

Monitor cardiovascular, hepatic, hematopoietic and renal function during extended therapy. Caution in patients with history of convulsive disorders. Upper gastrointestinal hemorrhage possible in patients with a history of peptic ulcer.

Normal activity should be resumed gradually to avoid risk of injury.

Monitor intraocular pressure in patients with chronic wide-angle glaucoma. Pupillary dilation and activation of Horner's syndrome have been reported rarely. Exercise

caution and monitor blood pressure in patients on anti-hypertensive medication. 'Prolopa' can be discontinued 12 hours prior to anesthesia. Observe patients on concomitant psychoactive drugs for unusual reactions.

Adverse Reactions

Most common are abnormal involuntary movements, usually dose dependent, which necessitate dosage reduction. Other serious reactions are periodic oscillations in performance (end of dose akinesia, on-off phenomenon and akinesia paradoxa) after prolonged therapy, psychiatric disturbances (including paranoia, psychosis, depression, dementia, increased libido, euphoria, sedation and stimulation), and cardiovascular effects (including arrhythmias, orthostatic hypotension, hypertension, ECG changes and angina pectoris).

Neurologic, intellectual, gastrointestinal, dermatologic, hematologic, musculoskeletal, respiratory, genitourinary and ophthalmologic reactions have also been reported. Consult Product Monograph for complete list.

Dosage

Individualize therapy and titrate in small steps to maximize benefit without dyskinesias. Do not exceed the recommended dosage range.

Initially, one capsule 'Prolopa' 100-25 once or twice daily, increased carefully by one capsule every third or fourth day (slower in post-encephalitic Parkinsonism) until optimum therapeutic effect obtained without dyskinesias. At upper limits of dosage, increment slowly at 2-4 week intervals. Administer with food.

Optimal dosage is usually 4-8 'Prolopa' 100-25 capsules daily, in 4-6 divided doses.

'Prolopa' 200-50 capsules are intended for maintenance therapy once optimal dosage has been determined using 'Prolopa' 100-25 capsules. No patient should receive more than 1000-1200 mg levodopa daily during the first year of treatment. 'Prolopa' 50-12.5 capsules should be used when frequent dosing is required to minimize adverse effects.

For patients previously treated with levodopa, allow at least 12 hours to elapse and initiate 'Prolopa' at 15% of previous levodopa dosage.

During maintenance, reduce dosage slowly, if possible, to a maximum of 600 mg levodopa daily.

Supply

'Prolopa' 50-12.5 capsules containing 50 mg levodopa and 12.5 mg benserazide.

'Prolopa' 100-25 capsules containing 100 mg levodopa and 25 mg benserazide.

'Prolopa' 200-50 capsules containing 200 mg levodopa and 50 mg benserazide.

Bottles of 100.

Product Monograph available on request.

References:

1. Editorial Parkinson's disease, 1984. *Lancet* 1984;1: 829-30.
2. Lieberman AN, Goldstein M, Gopmathan G, et al. Combined use of benserazide and carbidopa in Parkinson's disease. *Neurology* 1984;34:227-9.
3. Rinne UK, Mölsä P. Levodopa with benserazide or carbidopa in Parkinson's disease. *Neurology* 1979; 29:1584-9.
4. Weiner WJ, Nausieda PA. Carbidopa - levodopa ratio in Parkinson's disease. *Arch Neurol* 1981; 38:534.
5. Hoehn MM. Increased dosage of carbidopa in patients with Parkinson's disease receiving low doses of levodopa. A pilot study. *Arch Neurol* 1980; 37:146-9.

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See page vi

Original Research in Medicine and Chemistry

BRIEF PRESCRIBING INFORMATION

DILANTIN®

Extended Phenytoin
Sodium Capsules, U.S.P.
100 mg
ANTICONSULSANT

INDICATIONS

Dilantin is indicated for the control of generalized tonic-clonic (grand mal) seizures and complex partial (psychomotor) seizures.

CONTRAINDICATIONS

Dilantin is contraindicated in those patients with a history of hypersensitivity to hydantoin products.

WARNINGS

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus.

Phenytoin is not indicated in seizures due to hypoglycemia or other causes which may be immediately identified and corrected.

Phenytoin metabolism may be significantly altered by the concomitant use of other drugs such as:

A. Barbiturates may enhance the rate of metabolism of phenytoin. This effect, however, is variable and unpredictable. It has been reported that in some patients the concomitant administration of carbamazepine resulted in an increased rate of phenytoin metabolism.

B. Coumarin anticoagulants, disulfiram, phenylbutazone, and sulfaphenazole may inhibit the metabolism of phenytoin, resulting in increased serum levels of the drug. This may lead to an increased incidence of nystagmus, ataxia, or other toxic signs.

C. Isoniazid inhibits the metabolism of phenytoin so that with combined therapy, patients

who are slow acetylators may suffer from phenytoin intoxication.

D. Tricyclic antidepressants in high doses may precipitate seizures, and the dosage of phenytoin may have to be adjusted accordingly.

Usage in Pregnancy: The effects of Dilantin in human pregnancy and nursing infants are unknown.

The prescribing physician will have to determine the risk/benefit in treating or counseling epileptic women of childbearing potential.

PRECAUTIONS

The liver is the chief site of biotransformation of phenytoin, patients with impaired liver function may show early signs of toxicity. Elderly patients or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin has been associated with reversible lymph node hyperplasia. If lymph node enlargement occurs in patients on phenytoin, every effort should be made to substitute another anticonvulsant drug or drug combination.

Drugs that control generalized tonic-clonic (grand mal) seizures are not effective for absence (petit mal) seizures. Therefore, if both conditions are present, combined drug therapy is needed.

Hyperglycemia, resulting from the drug's inhibitory effect on insulin release, has been reported. Phenytoin may also raise the blood sugar level in persons already suffering from hyperglycemia.

ADVERSE REACTIONS

Central Nervous System: The most common manifestations encountered with phenytoin

therapy include nystagmus, ataxia, slurred speech, and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headache have also been observed. These side effects may disappear with continuing therapy at a reduced dosage level.

Gastrointestinal System: Phenytoin may cause nausea, vomiting, and constipation. Administration of the drug with or immediately after meals may help prevent gastrointestinal discomfort.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes.

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia.

Other: Gingival hyperplasia occurs frequently; this incidence may be reduced by good oral hygiene including gum massage, frequent brushing and appropriate dental care. Polyarthropathy and hirsutism occur occasionally. Hyperglycemia has been reported. Toxic hepatitis, liver damage, and periarthritis nodosa may occur and can be fatal.

MANAGEMENT OF OVERDOSAGE

The mean lethal dose in adults is estimated to be 2 to 5 grams. The cardinal initial symptoms are nystagmus, ataxia and dysarthria. The patient then becomes comatose, the pupils are unresponsive and hypotension occurs. Death is due to respiratory depression and apnea. Treatment is nonspecific since there is no known antidote. First, the stomach should be emptied. If the gag reflex is absent, the airway should be supported. Oxygen, vasopressors and assisted ventilation may be necessary for central nervous system, respiratory and cardiovascular

depression. Finally, hemodialysis can be considered since phenytoin is not completely bound to plasma proteins.

DOSAGE AND ADMINISTRATION

Dosage should be individualized to provide maximum benefit. In some cases, serum blood level determinations may be necessary for optimal dosage adjustments — the clinically effective serum level is usually 10-20 mcg/mL.

Adult Dose: Patients who have received no previous treatment may be started on one 100 mg Dilantin Capsule three times daily and the dose then adjusted to suit individual requirements.

Pediatric Dose: Initially, 5 mg/kg/day in two or three equally divided doses, with subsequent dosage individualized to a maximum of 300 mg daily. A recommended daily maintenance dosage is usually 4 to 8 mg/kg. Children over 6 years old may require the minimum adult dose (300 mg/day). Pediatric dosage forms available include a 30 mg Capsule, a 50 mg palatably flavoured Infatab, or an oral suspension form containing 30 or 125 mg of Dilantin in each 5 mL.

Alternative Dose: Once-a-day dosage for adults with 300 mg of Dilantin may be considered if seizure control is established with divided doses of three 100 mg Capsules daily.

HOW SUPPLIED

Dilantin 100 mg Capsules; in bottles of 100 & 1000.

Complete prescribing information available upon request.

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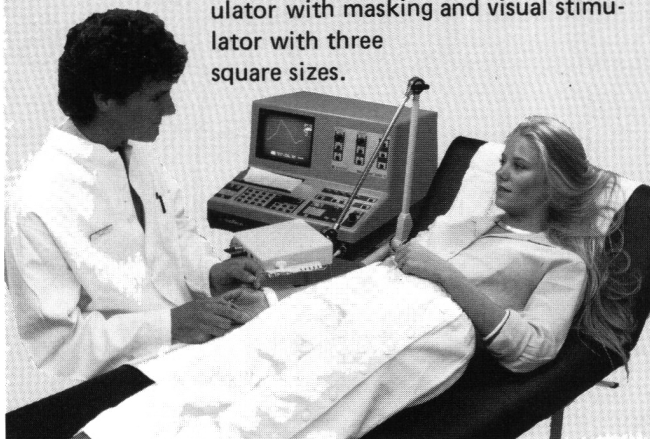
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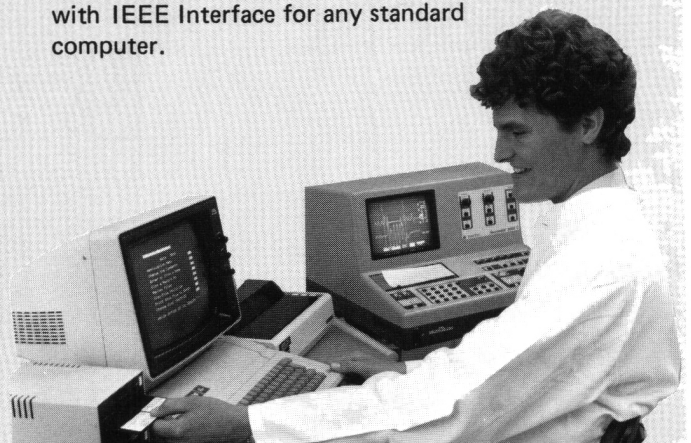
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