

The Canadian Journal of Neurological Sciences

Le Journal Canadien des Sciences Neurologiques



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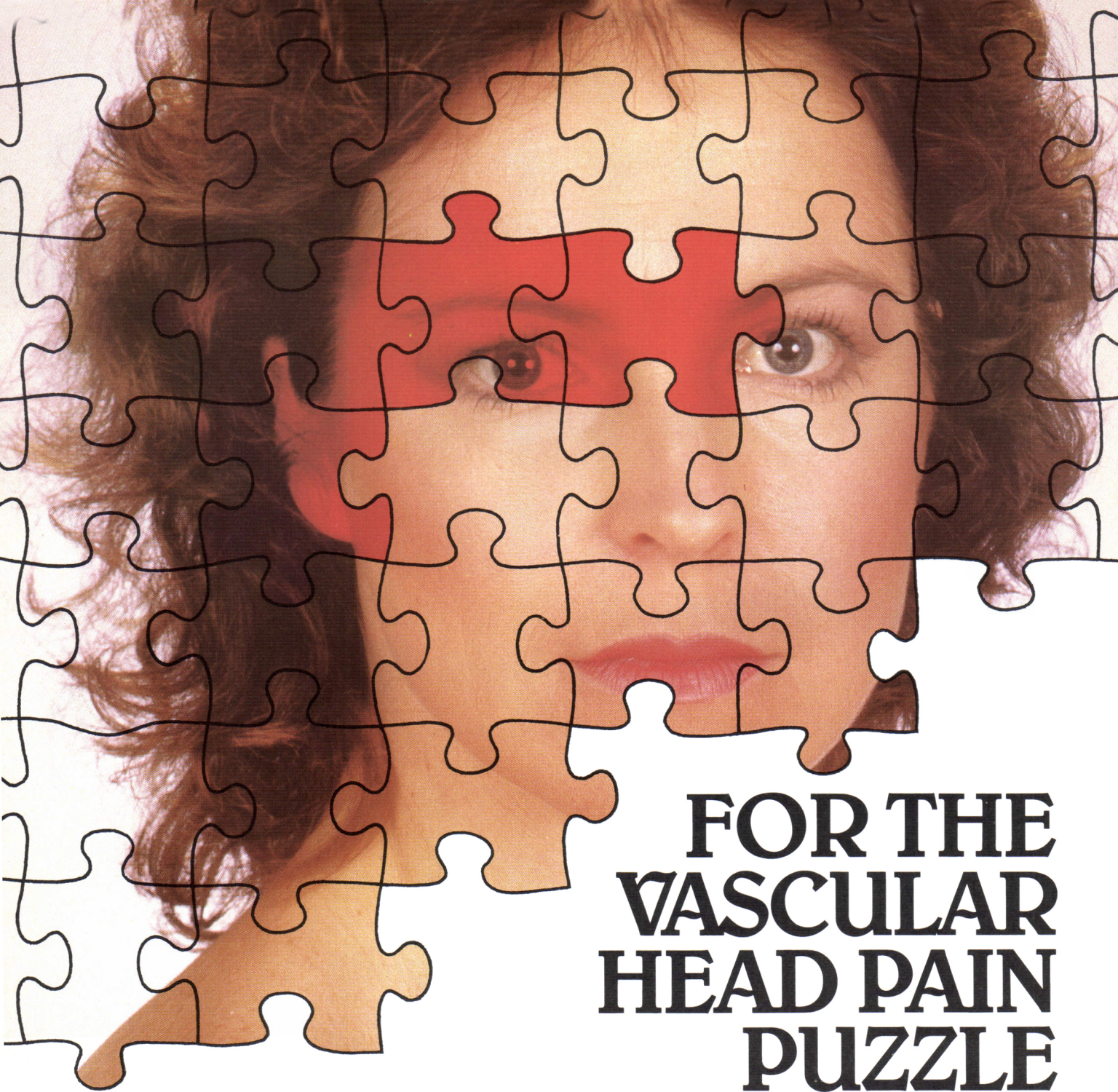
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Volume 14, No. 1

February 1987



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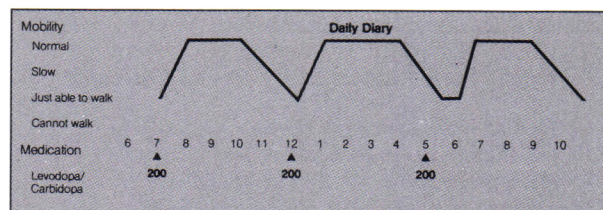
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CONFRONT THE REALITIES OF PARKINSON'S DISEASE

Problems of long-term therapy with levodopa compounds

- Performance fluctuations
- End-of-dose deterioration
- Early morning stiffness
- On-off phenomenon

During the course of a day⁽¹⁾



Once a clear pattern is determined, two treatment approaches are possible:

- Add **PARLODEL** and/or
- More frequent, smaller doses of levodopa

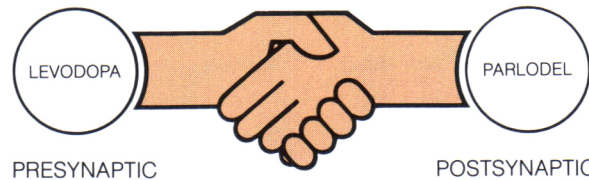


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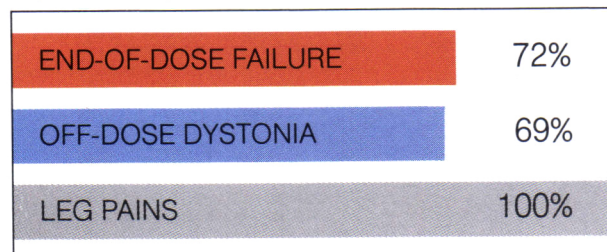
A case of study: Wearing-off of levodopa



After an average of seven years of therapy with levodopa compounds, adding Parlodel resulted in...⁽²⁾

A reduced severity of levodopa complications

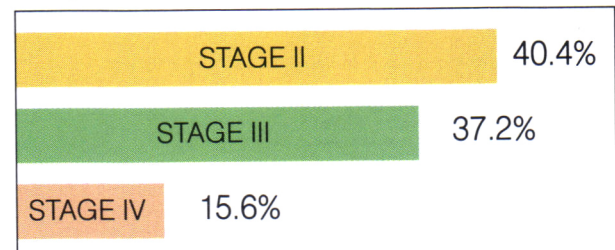
% patients improved



Adapted from the Hoehn Study⁽²⁾.
Parlodel dose range: 12.4-20 mg/day

An improvement in mean neurological scores

% improvement



Adapted from the Hoehn Study⁽²⁾.
Maximum Parlodel dosage: 20 mg/day

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ACTIONS Parlodel (bromocriptine mesylate) is a dopaminomimetic ergot derivative with D₂ type dopamine receptor agonist activity, and has also D₁ dopamine receptor antagonist properties. The dopaminomimetic 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 dopaminomimetic 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 Turkali, 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 hyperproliferative 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, lethargia, 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 overdosage 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.

DOSEAGE 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 daily, 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.

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REFERENCES:

- Grimes J.D. Medical Review Series (Handbook No. 4) 1984;14
- Hoehn M, Elton RL. Low dosages of bromocriptine added to levodopa in Parkinson's disease. *Neurology* 1985;35:199-206



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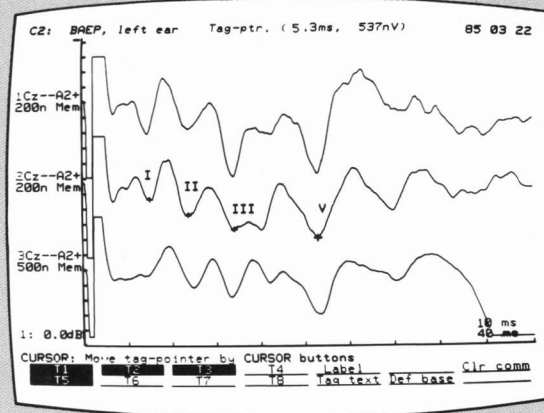
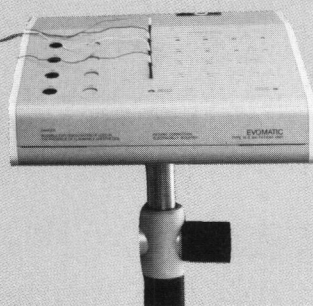
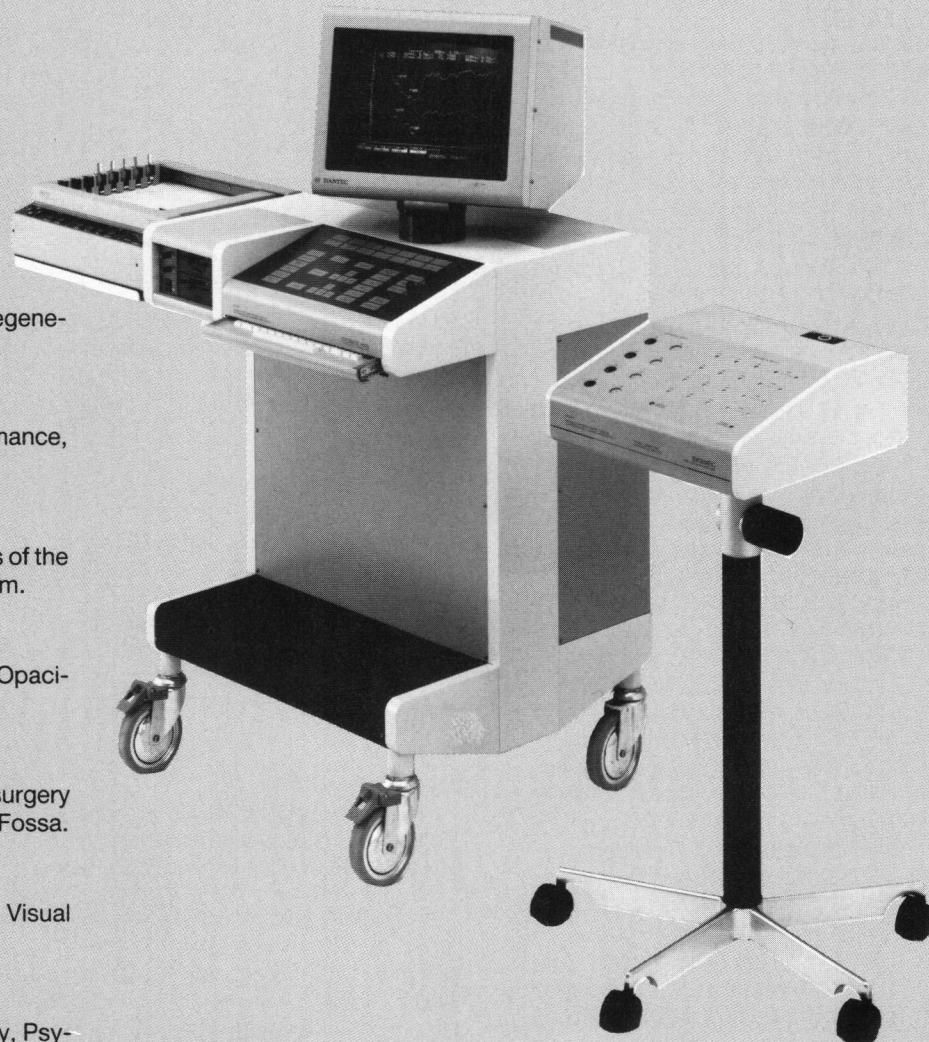
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INDICATIONS

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.

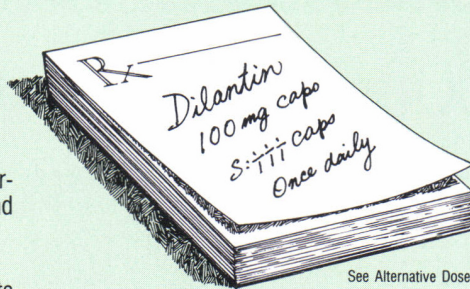
Usage in Pregnancy: The effects of Dilantin in human pregnancy and nursing infants are unknown.

The prescribing physician will have to determine the risk/benefit in treating or counselling 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



See Alternative Dose

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 morbiliform 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 periarteritis nodosa may occur and can be fatal.

MANAGEMENT OF OVERDOSE

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.

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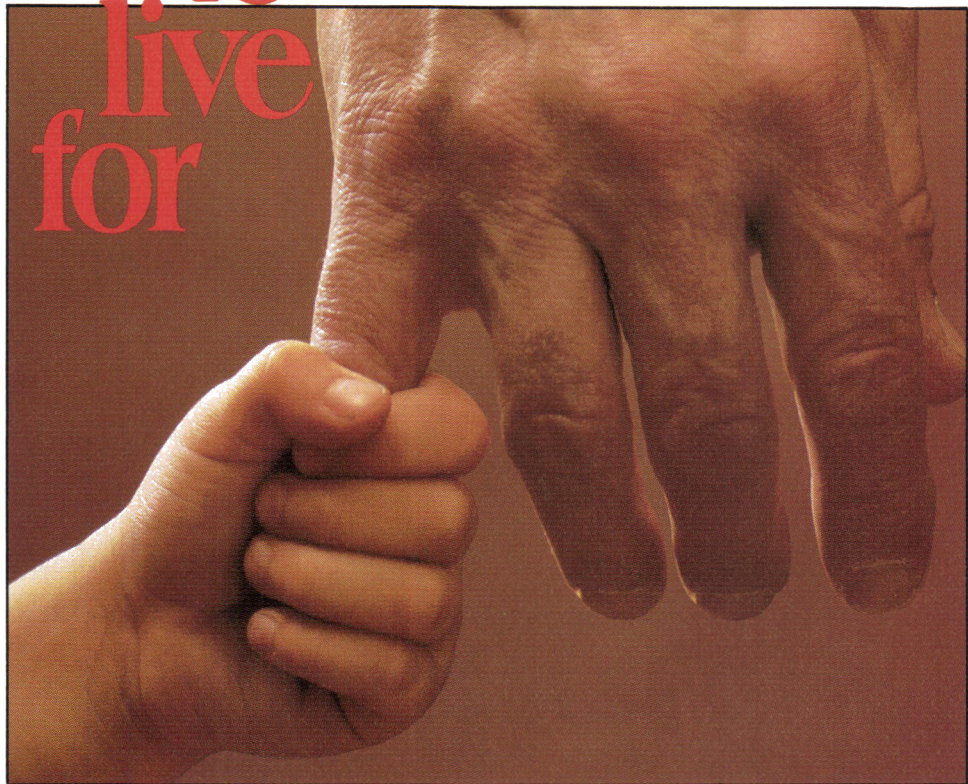


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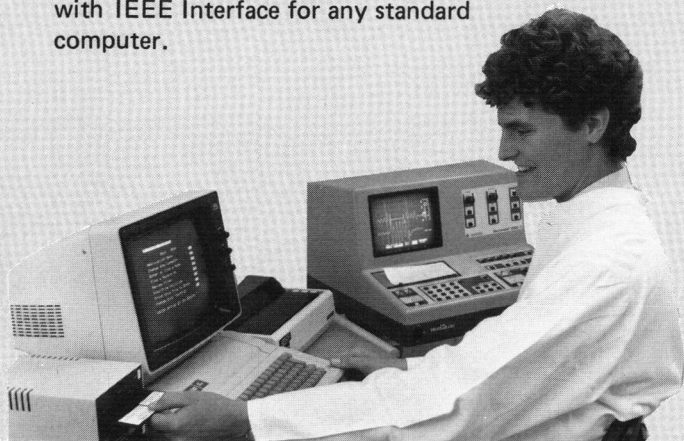
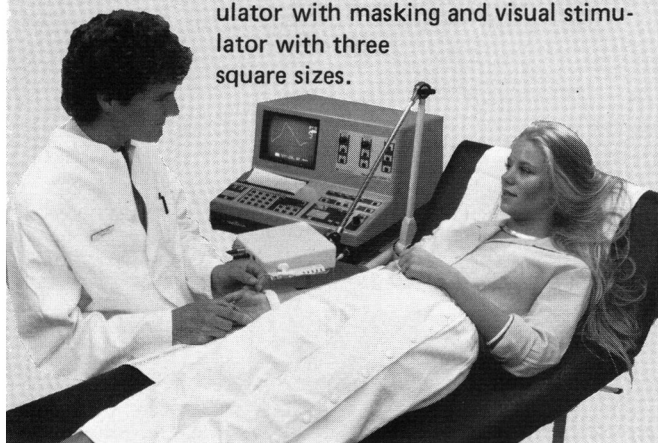


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The Neuromatic® 2000 M has superior amplifiers and powerful averagers with rejection facility. Both the C-type and the M-type can be supplied with IEEE Interface for any standard computer.



Intermediate Prescribing Information

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 leukocytosis, 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.)

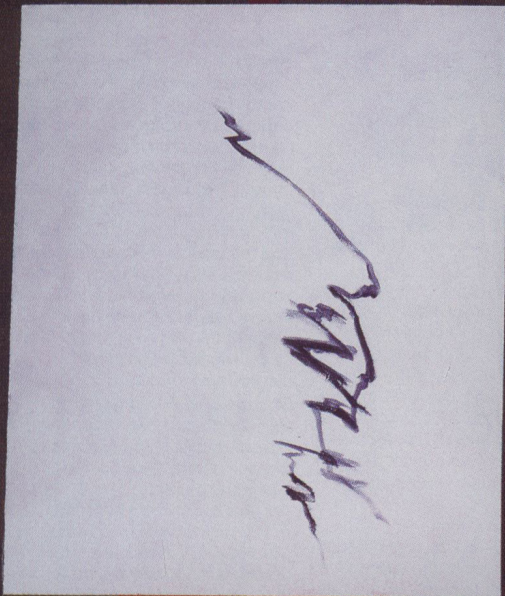
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Information for Authors

The Canadian Journal of Neurological Sciences publishes original articles in the clinical and basic neurosciences. Manuscripts are considered for publication with the understanding that, except for identified review articles, they have not been published elsewhere except in abstract form and are not under simultaneous consideration by another publication. Manuscripts should be submitted to:

The Editor
Canadian Journal of Neurological Sciences
Faculty of Medicine,
University of Calgary
3330 Hospital Drive N.W.
Calgary, Alberta T2N 4N1

Manuscripts and all illustrations should be submitted in triplicate. Papers will be accepted in English or French. All papers should be accompanied by an abstract or a résumé of approximately 150 words on a separate page, preferably in both languages, although the Journal will provide the translation if requested. All manuscripts should be double spaced throughout, including references and legends for illustrations. Margins of at least 25 mm should be left on all sides.

For detailed instructions regarding style and layout, authors should refer to "Uniform requirements for manuscripts submitted to biomedical journals". Copies of this document may be obtained by writing to the Journal office, but the main points will be summarized here. Articles should be subdivided under conventional headings of "introduction", "methods and materials", "results" and "discussion" but other headings and subheadings will be considered if more suitable for a particular manuscript. A title page should identify the title of the article, authors, name of institution(s) from which the work originated, and the address and telephone number of the author to whom communications should be addressed. Pages of text should be numbered consecutively. Acknowledgements, including recognition of financial support, should be typed on a separate page at the end of the text.

References are to be numbered in the order of citation in the text. Those cited only in tables or in legends for illustrations are numbered in accordance with a sequence established by the first identification in the text of a particular table or illustration. Titles of journals should be abbreviated according to the style used in Index Medicus. References should be complete including the names of the first three authors followed by "et al"

if there are more than three authors, full title, year of publication, volume number, and inclusive pagination for journal articles. Book or chapter references should also include the place of publication and name of the publisher. Examples of correct forms of references follow:

Journals

Poirier LJ, Filion M, Larochelle L, et al. Physiopathology of experimental parkinsonism in the monkey. *Can J Neurol Sci* 1975; 2: 255-263

Chapter in a book

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

Illustrations should be high quality glossy black-and-white photographic prints, preferably 127 x 173 mm (5 x 7"). Original artwork and radiographs should not be submitted. The additional cost of colour illustration must be borne by the author; quotations are available upon request from the journal office. All figures should be identified on the back with the author's name and figure number. Letters and arrows applied to the figures to identify particular findings should be professional appliques suitable for publication. Photomicrographs should include a calibration bar with the scale indicated on the figure or in the legend. Legends for illustrations should be typed on a separate page from the illustrations themselves.

Tables should each be on a separate page and be identified with the title or heading. Particular care should be taken in the preparation of tables to ensure that the data are presented in the most clear and precise format. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees Celsius. Other measurements should be reported in the metric system. English language text may use either British or American spelling, but should be consistent throughout.

Review articles on selected topics also are published by the Journal. These are usually invited, but unsolicited reviews will be considered. It is suggested that authors intending to submit reviews contact the Editor in advance.

Letters to the Editor are welcome. These should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

Therapy Is a Fine Art.



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Successful rehabilitation requires both spinal spasticity control and alertness. And that's why Lioresal® stands out.

Lioresal can control painful flexor spasms, but unlike diazepam, oversedation is rarely a problem^(1,2,3).

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Lioresal 10mg (initiation therapy)
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For brief prescribing information see page xii

Information aux Auteurs

Le Journal Canadien des Sciences Neurologiques publie des articles originaux dans les sciences neurologiques, cliniques et fondamentales. Les manuscrits ne sont considérés pour publication qu'à la condition expresse, à l'exception des articles de revue clairement identifiés comme tel, qu'ils n'aient pas été publiés ailleurs, sauf sous forme de résumé et qu'ils ne soient pas sous considération simultanée par un autre journal. Les manuscrits doivent être soumis à:

L'Éditeur
Journal Canadien des Sciences Neurologiques,
Faculté de Médecine,
Université de Calgary,
3330 Hospital Drive, N.W.,
Calgary, Alberta T2N 4N1

Les manuscrits et toutes les illustrations doivent être soumis en triplicata. Les articles seront acceptés en français ou en anglais. Tous les articles doivent être accompagnés d'un résumé d'environ 150 mots, sur page séparée, préférablement dans les deux langues, quoique le Journal puisse fournir cette traduction sur requête. Les manuscrits doivent être dactylographiés complètement à double interligne y compris les références et les légendes pour illustrations. Des marges d'au moins 25 mm doivent être laissées de tous les côtés.

Pour les conseils plus détaillés sur le style et la présentation du texte, les auteurs doivent se référer au texte intitulé "Règlements uniformes pour les manuscrits soumis aux journaux biomédicaux". On peut obtenir une copie de ce document en écrivant au bureau du Journal, mais en voici les principaux points: Les articles doivent être présentés selon le plan habituel: "Introduction", "Matériel et méthodes", "Résultats" et "Discussion", mais il est possible d'employer d'autres titres ou sous-titres si nécessaire pour un manuscrit en particulier. Sur une page titre séparée on doit identifier le titre de l'article, les auteurs, les institutions d'où origine le travail, ainsi que l'adresse et le numéro de téléphone de l'auteur à qui devront être adressées les communications. Les remerciements, incluant ceux pour l'appui financier, doivent être dactylographiés sur page séparée à la fin du texte. Les références doivent être numérotées dans l'ordre où elles sont citées dans le texte. Celles qui sont citées seulement dans les tableaux ou légendes d'illustrations sont numérotées selon la séquence établie par la première identification dans le texte de ces tableaux ou illustrations particulières. Les titres des Journaux doivent être abrégés selon le style utilisé dans Index Medicus. Les références doivent être complètes, incluant le nom des trois premiers auteurs suivis de "et al", s'il y a plus de trois auteurs, le titre complet, l'année de publication, le

numéro du volume et les premières et dernières pages de l'article. Les références aux livres et chapitres de livres doivent aussi inclure le lieu de la publication et le nom de la maison d'édition. Les exemples corrects suivants peuvent être utilisés:

Journaux

Poirier LJ, Filion M, Larochelle L, et al. Physiopathology of experimental parkinsonism in the monkey. *Can J Neurol Sci* 1975; 2: 255-263

Chapitre de livre

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

Les illustrations doivent être sur papier brillant de haute qualité et imprimés en blanc et noir, préférablement 127 x 173 mm (5 x 7"). Les illustrations et photographies originales ne doivent pas être soumises. Le coût supplémentaire des illustrations en couleur revient entièrement à l'auteur; les coûts détaillés peuvent être obtenus directement au bureau du Journal. Il faut identifier toutes illustrations en inscrivant au dos le nom de l'auteur et le numéro. Toutes lettres ou flèches appliquées aux illustrations pour identifier un aspect particulier doivent être de qualité professionnelle. Les photomicrographies doivent inclure une barre de calibration dont l'échelle est mentionnée dans la légende. Les légendes des illustrations doivent être dactylographiées sur une page séparée de celles-ci.

Les tableaux doivent être sur des pages séparées et être identifiés avec titre. On doit prendre un soin particulier dans la préparation de ces tableaux afin d'assurer que les données soient présentées avec le format le plus clair et le plus précis possible. Chaque colonne doit avoir un court titre. Les explications doivent être placées en dessous du tableau et non en sous-titre. Un tableau ne doit pas être soumis sous forme de photographie.

On doit employer le système international d'unités (SI) pour toutes données de laboratoire, même si celles-ci sont originellement présentées dans un autre système. Les températures doivent être citées en degrés Celcius. Les autres données doivent utiliser le système métrique. Les textes en anglais peuvent utiliser l'orthographe anglais ou américain, mais cet usage doit être constant.

Le Journal publie également des articles de revue sur des sujets sélectionnées. 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.

LIORESAL®

(baclofen)
Muscle relaxant
Antispastic agent

INDICATIONS AND CLINICAL USES

Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis. Spina cord injuries and other spinal cord diseases.

CONTRAINDICATIONS

Hypersensitivity to LIORESAL.

WARNINGS

Abrupt Drug Withdrawal: Except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued to prevent visual and auditory hallucinations, confusion, anxiety with tachycardia and sweating, and worsening of spasticity.

Impaired Renal Function: Caution is advised in these patients and reduction in dosage may be necessary.

Stroke: Has not been of benefit and patients have shown poor tolerability to the drug.

Pregnancy and Lactation: Not recommended as safety has not been established. High doses in rats and rabbits are associated with an increase of abdominal hernias and ossification defects in the fetuses.

PRECAUTIONS

Not recommended in children under 12 as safety has not been established.

Because sedation may occur, caution patients regarding the operation of automobiles or dangerous machinery, activities made hazardous by decreased alertness, and use of alcohol and other CNS depressants.

Use with caution in spasticity that is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function, epilepsy or history of convulsive disorders (clinical state and EEG should be monitored), peptic ulceration, severe psychiatric disorders, elderly patients with cerebrovascular disorders, and patients receiving antihypertensive therapy.

ADVERSE REACTIONS

Most common adverse reactions are transient drowsiness; dizziness, weakness and fatigue. Others reported:

Neuropsychiatric: Headache, insomnia, euphoria, excitement, depression, confusion, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizures.

Cardiovascular: Hypotension, dyspnea, palpitation, chest pain, syncope.

Gastrointestinal: Nausea, constipation, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.

Genitourinary: Urinary frequency, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria.

Other: Rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion.

Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

The following laboratory tests have been found to be abnormal in a few patients receiving LIORESAL: SGOT, alkaline phosphatase and blood sugar (all elevated).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and Symptoms: Vomiting, muscular hypotonia, hypotension, drowsiness, accommodation disorders, coma, respiratory depression, and seizures.

Co-administration of alcohol, diazepam, tricyclic anti-depressants, etc., may aggravate the symptoms.

Treatment: Treatment is symptomatic. In the alert patient, empty the stomach (induce emesis followed by lavage). In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis).

Maintain adequate respiratory exchange; do not use respiratory stimulants. Muscular hypotonia may involve the respiratory muscles and require assisted respiration. Maintain high urinary output. Dialysis is indicated in severe poisoning associated with renal failure.

DOSAGE AND ADMINISTRATION

Optimal dosage of LIORESAL requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually 40-80 mg daily).

The following dosage titration schedule is suggested:

5 mg t.i.d. for 3 days

10 mg t.i.d. for 3 days

15 mg t.i.d. for 3 days

20 mg t.i.d. for 3 days

Total daily dose should not exceed a maximum of 20 mg q.i.d.

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see Warnings).

AVAILABILITY

LIORESAL (baclofen) 10 mg tablets: White to off-white flat-faced, oval tablets with GEIGY monogram on one side and the identification code 23 below the monogram. Fully bisected on the reverse side.

LIORESAL D.S. 20 mg tablet: White to off-white capsule-shaped, biconvex tablets. Engraved GEIGY on one side and GW with bisect on the other.

Available in bottles of 100 tablets.

Product Monograph supplied on request.

References:

1. Carlidge, N.E.F., Hudgson, P., Weightman, D.: A comparison of baclofen and diazepam in the treatment of spasticity. *J Neurol. Sci.* 23: 17-24 (1974).
2. Young, R., Delwaide, P.: Spasticity. *New England Journal of Medicine* 304: 28-33 & 96-99 (1981).
3. From, A., Heltberg, A.: A double blind trial with baclofen and diazepam in spasticity due to multiple sclerosis. *Acta Neurol. Scandinav.* 51: 158-166, (1975).

See pages x, xi

SYMMETREL® (Amantadine HCl) Antiparkinsonian Agent

INDICATIONS: The treatment of Parkinson's syndrome and in the short-term management of drug-induced extrapyramidal symptoms.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible untoward central nervous system effects. Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL®. Safety of use in pregnancy has not been established. SYMMETREL® should not be used in women of childbearing potential, unless the expected benefit to the patient outweighs the possible risk to the fetus.

SYMMETREL® is secreted in the milk and should not be administered to nursing mothers.

PRECAUTIONS: The dose may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema or orthostatic hypotension. Since SYMMETREL® is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Care should be exercised when administering to patients with liver disease, a history of recurrent eczematoid rash, psychosis, or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when administered concurrently with central nervous system stimulants.

Patients with Parkinson's syndrome improving on SYMMETREL® should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebotrombosis. Patients receiving SYMMETREL® who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness is important.

SYMMETREL® should not be discontinued abruptly since a few patients with Parkinson's syndrome experienced a parkinsonian crisis, i.e., sudden marked clinical deterioration, when this medication was suddenly stopped.

The dose of anticholinergic drugs or of SYMMETREL® should be reduced if atropine-like effects appear when these drugs are used concurrently.

ADVERSE REACTIONS: Adverse reactions have occurred in patients while receiving SYMMETREL® alone or in combination with anticholinergic antiparkinson drugs and/or levodopa.

Important adverse reactions are orthostatic hypotensive episodes, congestive heart failure, depression, psychosis and urinary retention; and rarely convulsions, reversible leukopenia and neutropenia, and abnormal liver function test results.

Adverse reactions of less importance are: anorexia, anxiety, ataxia, confusion, hallucinations, constipation, dizziness (light-headedness), dry mouth, headache, insomnia, livedo reticularis, nausea, peripheral edema, drowsiness, dyspnea, fatigue, hyperkinesia, irritability, nightmares, rash, slurred speech, visual disturbance, vomiting and weakness; and very rarely eczematoid dermatitis and oculogyric episodes. Some side effects were transient and disappeared even with continued administration of the drug.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Limited data are available concerning clinical effects and management of SYMMETREL® overdosage. An elderly patient with Parkinson's syndrome who took an overdose of 2.8 g of SYMMETREL® in a suicidal attempt, developed acute toxic psychosis, urinary retention, and a mixed acid-base disturbance. The toxic psychosis was manifested by disorientation, confusion, visual hallucinations and aggressive behaviour. Convulsions did not occur, possibly because the patient had been receiving phenytoin prior to the acute ingestion of SYMMETREL®.

There is no specific antidote. For acute overdosing, general supportive measures should be employed, along with immediate gastric lavage or induction of emesis. Fluids should be forced, and if necessary, given I.V. The pH of the urine has been reported to influence the excretion rate of SYMMETREL®. Since the excretion rate of SYMMETREL® increases rapidly when the urine is acidic, the administration of urine acidifying fluids may increase the elimination of the drug from the body. Blood pressure, pulse, respiration and temperature should be monitored. The patient should be observed for possible development of arrhythmias, hypotension, hyperactivity, and convulsions; if required, appropriate therapy should be administered. Blood electrolytes, urine pH and urinary output should be monitored. If there is no record of recent voiding, catheterization should be done. The possibility of multiple drug ingestion by the patient should be considered.

DOSAGE AND ADMINISTRATION: Parkinson's Syndrome: Initial dose is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily. When SYMMETREL® and levodopa are initiated concurrently, SYMMETREL® should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal dose. When used alone, the usual dose of SYMMETREL® is 100 mg twice a day.

Patients whose responses are not optimal with SYMMETREL® at 200 mg daily may benefit from an increase to 300 mg daily in divided doses. Patients who experience a fall-off of effectiveness may regain benefit by increasing the dose to 300 mg daily; such patients should be supervised closely by their physicians.

DOSAGE FORMS: Capsules: (bottles of 100) - each red, soft gelatin capsule contains 100 mg of amantadine HCl. Syrup: (500 mL) - each 5 mL (1 teaspoonful) of clear colorless syrup contains 50 mg of amantadine HCl.

References:

1. Schwab RS, Poskanzer DC, England AC Jr., Young RR: Amantadine in Parkinson's disease. *JAMA* 1972;227:7.

Product monograph available on request.

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Du Pont Pharmaceuticals
Mississauga, Ontario
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See page vii

Geigy

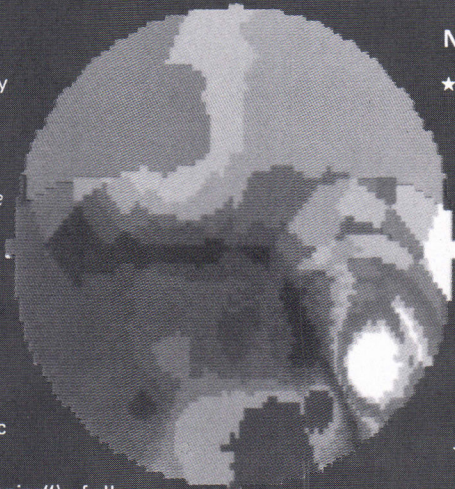
Mississauga, Ontario
L5N 2W5



New Dimension in EEG and Evoked

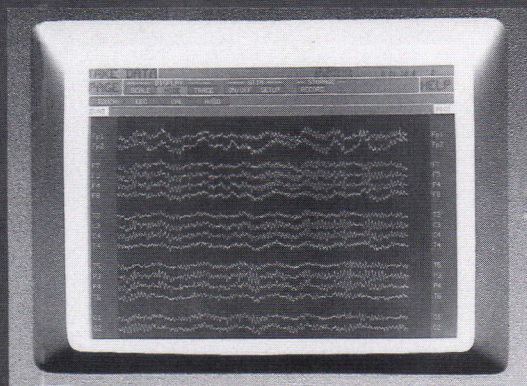
SEEG

- ★ Advanced electroencephalography and evoked potentials testing
- ★ Up to 32 recording channels
- ★ Software—control using a "mouse"
- ★ Storage of raw and digitally processed EEG on (hard)disk or streaming tape
- ★ Review of EEG in any desired montage
- ★ Software for spectral, spatial and statistical analysis and for specific applications
- ★ Topographic display ("brain—mapping") of all EEG and EP data

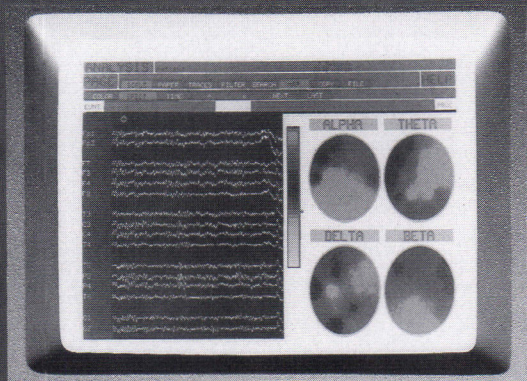


NeuroScope

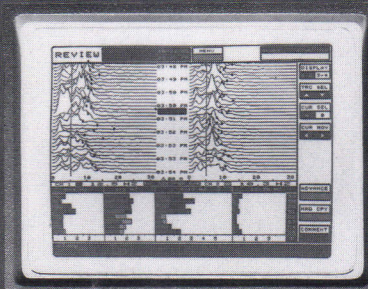
- ★ Unique touch screen control
- ★ Performs up to four—channel auditory, visual and somatosensory evoked potentials
- ★ Can be configured for EEG, CSA and EP Monitoring
- ★ Computer—generated electrode montage including impedance check
- ★ All stimulator functions for VEP, AEP and SEP
- ★ Test results on floppy disk for review and analysis
- ★ Built in thermal printer



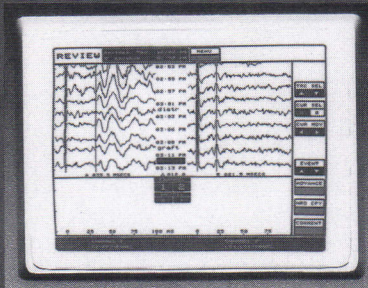
Electroencephalography



Quantitative Analysis



EEG and EP Monitoring During Carotid Endarterectomy

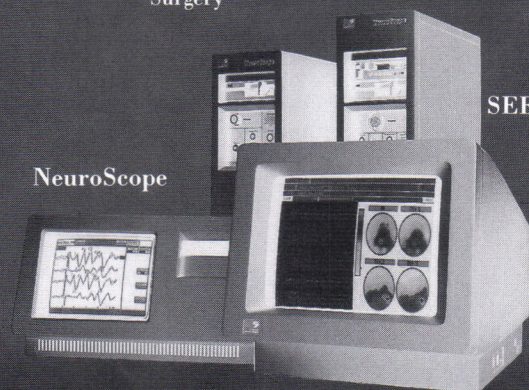


Evoked Potentials in Brain and Spinal Surgery



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Canada
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- improves motor movement rapidly²
- achieves high serum levels quickly²
- minimizes common side effects like nausea
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- all three ‘Prolopa’ dose forms contain
the established 4:1 ratio

The use of the 4:1 levodopa/decarboxylase
inhibitor combination has been shown to
reduce significantly the incidence of side
effects attributed to the 10:1 ratio^{3,4,5}

Prolopa[®]
(levodopa/benserazide) 4:1

Helps return the simple pleasures of living.

For brief prescribing information see page xvi

