

THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES

LE JOURNAL CANADIEN DES SCIENCES NEUROLOGIQUES

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QUEBEC COOPERATIVE STUDY ON

FRIEDREICH'S ATAXIA

PHASE TWO

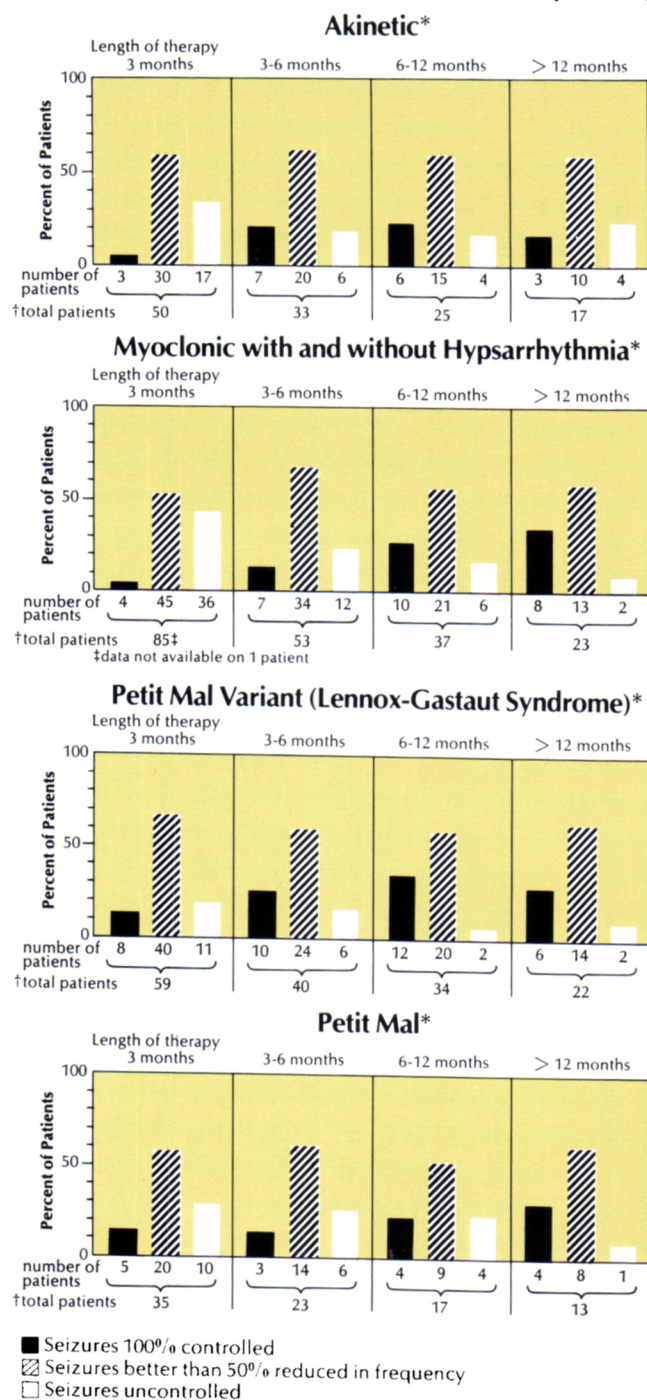
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- used alone or as an adjunct, RIVOTRIL can reduce the frequency and/or severity of akinetic, myoclonic and petit mal variant (Lennox-Gastaut syndrome) seizures.
- it may be of value as principal medication in petit mal where succinimide therapy has failed.
- the most frequently noted side effects, drowsiness and ataxia, generally are dose related and can often be controlled by dosage adjustments.

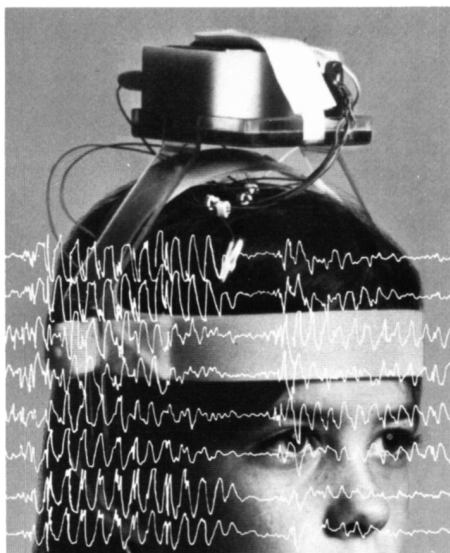
Effect of RIVOTRIL on seizure frequency



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‡ Patients dropped from the study for a variety of reasons as well as those treated for less than 12 months account for the decrease in total patient population.

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Brief Prescribing Information

Action

RIVOTRIL is a benzodiazepine and has sedative, hypnotic, and anticonvulsant properties characteristic of this class of drugs. As an anticonvulsant, it decreases the frequency, amplitude, duration, and spread of discharges in minor motor seizures and suppresses the spike-and-wave discharge in absence seizures.

The maximum blood level of clonazepam after a single oral dose is reached within 1 to 2 hours. The half-life of clonazepam is approximately 18 to 50 hours, and the main route of excretion is in the urine.

Indications

RIVOTRIL has been found useful when used alone or as an adjunct in the management of myoclonic and akinetic seizures and petit mal variant (Lennox-Gastaut syndrome).

RIVOTRIL may also be of value in patients with petit mal (absence spells) who have failed to respond satisfactorily to succinimides.

If a loss of anticonvulsant effect occurs, dosage adjustment may re-establish efficacy in some cases.

Contraindications

In patients with:

- known hypersensitivity to benzodiazepines
- significant liver disease
- narrow-angle glaucoma

Warnings

RIVOTRIL should be used by women of child-bearing potential only when the expected benefits to the patient warrant the possible risks to the fetus. Women who become pregnant should consult their physician promptly with regard to continuing antiepileptic medication.

Mothers receiving RIVOTRIL should not breast feed their infants.

Because adverse effects may possibly become apparent only after years of administration, a risk/benefit consideration of long-term use of RIVOTRIL is important in pediatric patients.

Precautions

The use of multiple anticonvulsants may increase CNS-depressant effects and the dosage of each drug may need adjustment to obtain the optimum effect.

To avoid precipitation of status epilepticus, abrupt withdrawal of RIVOTRIL must be avoided. Substitution of another anticonvulsant may be indicated during RIVOTRIL withdrawal.

In a very few patients, RIVOTRIL may cause a paradoxical increase in seizure activity or new types of seizures. RIVOTRIL may precipitate the onset of grand mal or increase its incidence. The addition of appropriate anticonvulsants or an increase in their dosage may be necessary.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and should also be warned against the concomitant use of alcohol or other CNS-depressant drugs.

Patients who may be prone to increase drug dosage on their own should be monitored carefully when receiving RIVOTRIL, as benzodiazepines have produced habituation, dependence, and withdrawal symptoms.

RIVOTRIL should be administered with caution to patients with impaired renal function.

Periodic liver function tests and blood counts are recommended during long-term therapy with RIVOTRIL.

Treatment with RIVOTRIL should be instituted with caution in patients with chronic respiratory disease, because of the possibility of hypersecretion in the upper respiratory passages.

Adverse reactions

Drowsiness has occurred in 50% and ataxia in 30% of the patients treated with RIVOTRIL. In some cases these effects have diminished with time. Behaviour problems have been noted in approximately 25% and increased salivation in 7% of the patients.

Please see product monograph for a complete list of other possible adverse reactions.

Dosage and administration

Dosage of RIVOTRIL must be determined for each patient according to clinical response and tolerance. Dosage depends, above all, on the age of the patient.

The daily requirement should be given in 2 or 3 divided doses. If the doses are not equal, the larger dose should be given before retiring.

Children up to 10 years or 30 kg: In order to minimize drowsiness, the initial dosage should usually be between 0.01 and 0.03 mg/kg/day and must not exceed 0.05 mg/kg/day.

The dosage should be increased by 0.25 to 0.5 mg/day every third day, unless seizures are controlled or side effects intervene, until a maintenance dosage of 0.1 to 0.2 mg/kg/day has been reached.

Adults: The initial dosage should not exceed 1.5 mg/day.

The dosage should be increased by 0.5 to 1 mg every third day, until seizures are controlled or side effects intervene. The recommended maintenance dosage for adults is 8 to 10 mg/day in 3 divided doses. Dosages in excess of 20 mg/day should be administered with caution.

Whenever RIVOTRIL is added to an anticonvulsant regimen, it should be borne in mind that the use of multiple anticonvulsants may result in increased depressant adverse effects.

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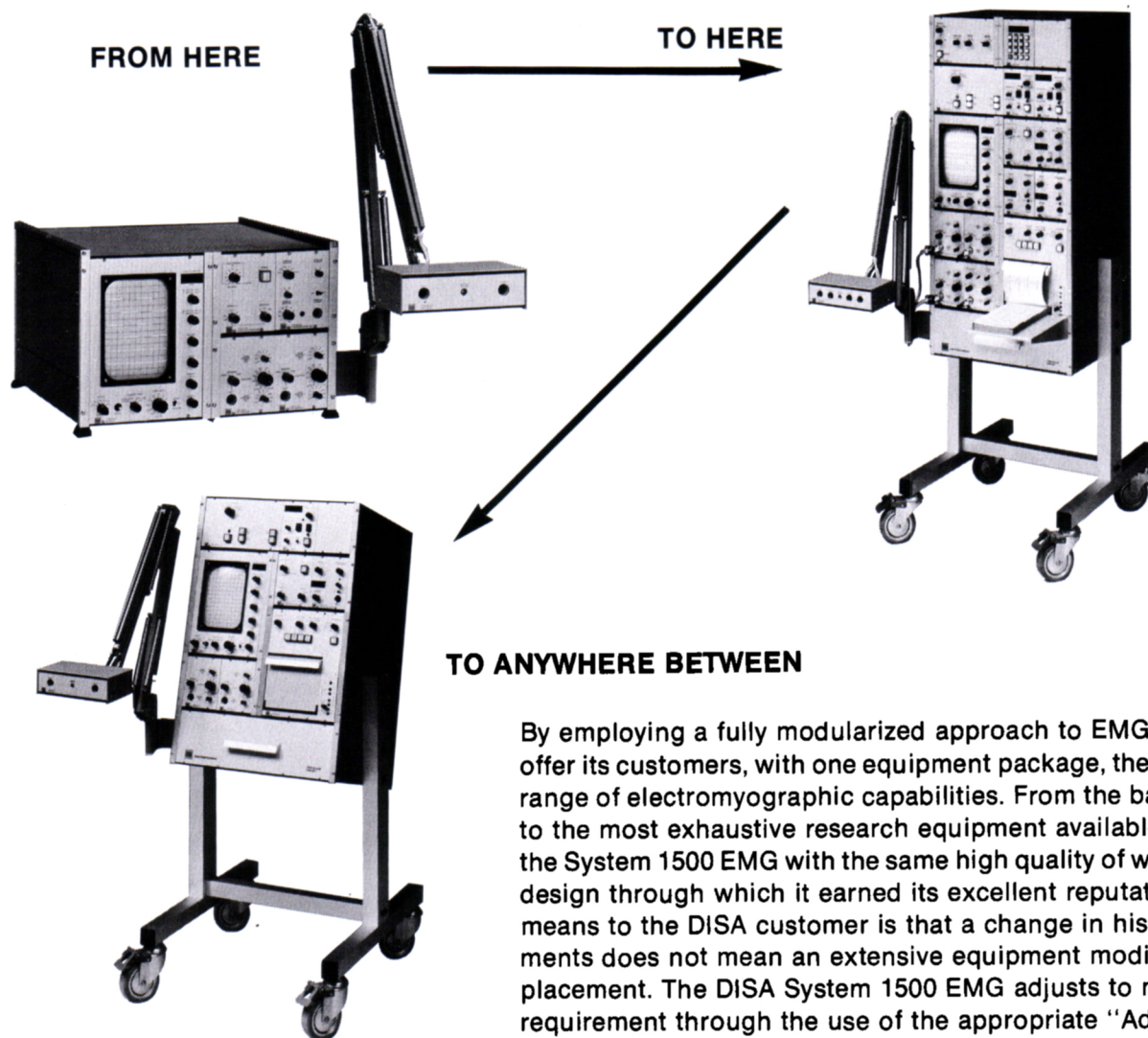
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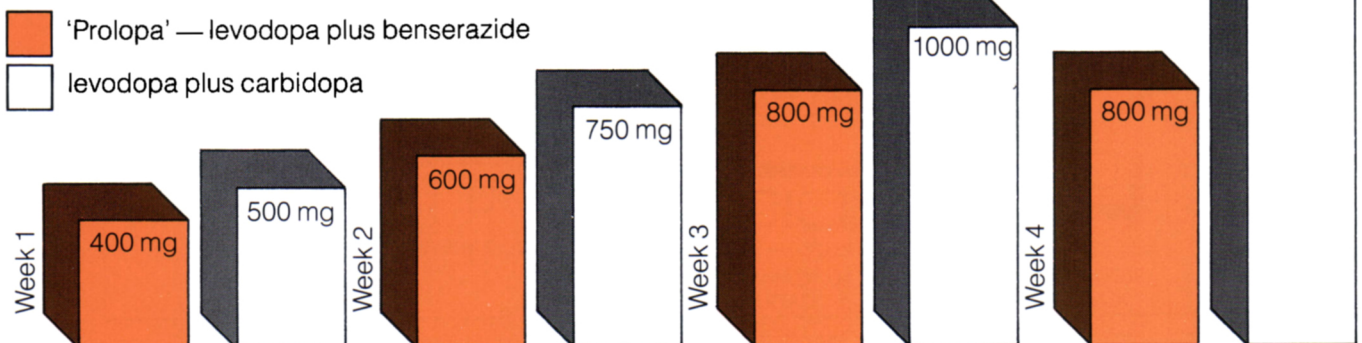
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- 1977** Continuous research and clinical trials enables Roche to introduce 'Prolopa' (levodopa plus the decarboxylase inhibitor benserazide in a 4:1 ratio). 'Prolopa' provides significant advantages for the patient and physician:
- An equal degree of improvement to that obtained with levodopa alone in the signs and symptoms of Parkinson's disease.¹
 - A marked reduction (approximately fivefold) in the daily dosage of levodopa needed to obtain a satisfactory response from patients.^{2,3}
 - A more rapid clinical response. Maximum benefit achieved in days as opposed to months with levodopa.⁴
 - Less frequent occurrences of the side effects of nausea and vomiting with 'Prolopa' than with levodopa only.⁵
 - A simpler dosage regimen.²
 - Within the range of recommended doses, less levodopa is required to reach optimal dosage for most patients than with the combination of L-dopa plus carbidopa.⁶

Levodopa daily intake based on the maximum recommended doses for a patient not receiving levodopa. (Calculated from Manufacturers' Product Monographs.)



'Prolopa': Initially, one capsule b.i.d., increasing by one capsule every three days to a maximum of eight capsules. Combination of levodopa plus carbidopa: Initially ½ tablet b.i.d., increasing by ½ tablet every three days to a maximum of five tablets.

Brief Prescribing Information

Classification

Antiparkinsonism agent

Indications

The treatment of Parkinson's syndrome with the exception of drug-induced parkinsonism.

Contraindications

Patients with a known sensitivity to levodopa or benserazide. In patients in whom sympathomimetic amines are contraindicated; in conjunction with monoamine oxidase inhibitors or within two weeks of their withdrawal. Clinical or laboratory evidence of uncompensated cardiovascular, endocrine, renal, hepatic, hematologic or pulmonary disease; in narrow angle glaucoma (may be used in wide-angle glaucoma provided that the intra-ocular pressure remains under control). History of melanoma or with suspicious undiagnosed skin lesions.

Warnings

Discontinue levodopa therapy at least twelve hours before initiation of 'Prolopa' therapy. To avoid inducing central nervous system side effects (abnormal movements) dosage of 'Prolopa' 100-25 should be increased gradually. Observe patients for signs of depression with suicidal tendencies or other serious behavioural changes. Exercise caution in patients with a history of psychotic disorders or who are receiving psychotherapeutic agents such as reserpine, pheno-thiazines or tricyclic anti-depressants.

Administer with care to patients with a history of myocardial infarction or who have atrial, nodal or ventricular arrhythmias. The safety of 'Prolopa' in patients under 18 years has not been established. In women of childbearing potential who are or who may become pregnant the anticipated benefits of the drug should be weighed against the possible hazards to mother and fetus. 'Prolopa' should not be given to nursing mothers.

Precautions

Patients with a history of convulsive disorders should be treated cautiously with 'Prolopa'. Upper gastrointestinal hemorrhage may occur in patient with a history of peptic ulcer.

Patients who improve on 'Prolopa' therapy should be advised to resume normal activities gradually as rapid mobilization may increase the risk of injury. 'Prolopa' should be administered with caution to patients on antihypertensive medication.

Adverse Reactions

Abnormal involuntary movements are the most common adverse reactions with 'Prolopa'. These are usually dose-dependent and may disappear or become tolerable after dose reduction. Periodic oscillations in performance, end-of-dose akinesia, on-off phenomenon and akinesia paradoxa constitute the most serious problems encountered after prolonged 'Prolopa' therapy.

Side effects such as nausea and vomiting, which are frequently observed during the initial stages of levodopa therapy, are much less common in patients treated with 'Prolopa'. Cardiovascular disturbances such as arrhythmias and orthostatic hypotension are less frequent than in patients treated with levodopa alone. Psychiatric disturbances including mild elation, depression, anxiety, agitation, aggression, hallucinations and delusions are also encountered.

Dosage

Recommended initial dose is one capsule of 'Prolopa' 100-25 once or twice a day. This dose may be carefully increased by one capsule every third or fourth day until an optimal therapeutic effect is obtained without dyskinesias. Near the upper limits of dosage, the increments should be made slowly, at 2-4 week intervals.

Optimal dosage for most patients is 4-8 capsules of 'Prolopa' 100-25 daily (400-800 mg levodopa), divided into 4-6 doses. Most patients require no more than 6 capsules of 'Prolopa' 100-25 (600 mg levodopa), per day.

'Prolopa' 200-50 capsules are intended only for maintenance therapy once the optimal dosage has been determined using 'Prolopa' 100-25 capsules. No patient should receive more than 5-6 capsules of 'Prolopa' 200-50 daily (1000-1250 mg levodopa in combined therapy), during the first year of treatment.

Supply

'Prolopa' 100-25 capsules containing 100 mg levodopa and 25 mg benserazide and 'Prolopa' 200-50 capsules containing 200 mg levodopa and 50 mg benserazide, in bottles of 100.

References

1. Fazio, C. et al.: Treatment of Parkinson's Disease with L-dopa and Association L-dopa plus a DOPA Decarboxylase Inhibitor. *Z. Neuro.*, 202:347. (1972).
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6. Manufacturers' Product Monographs.


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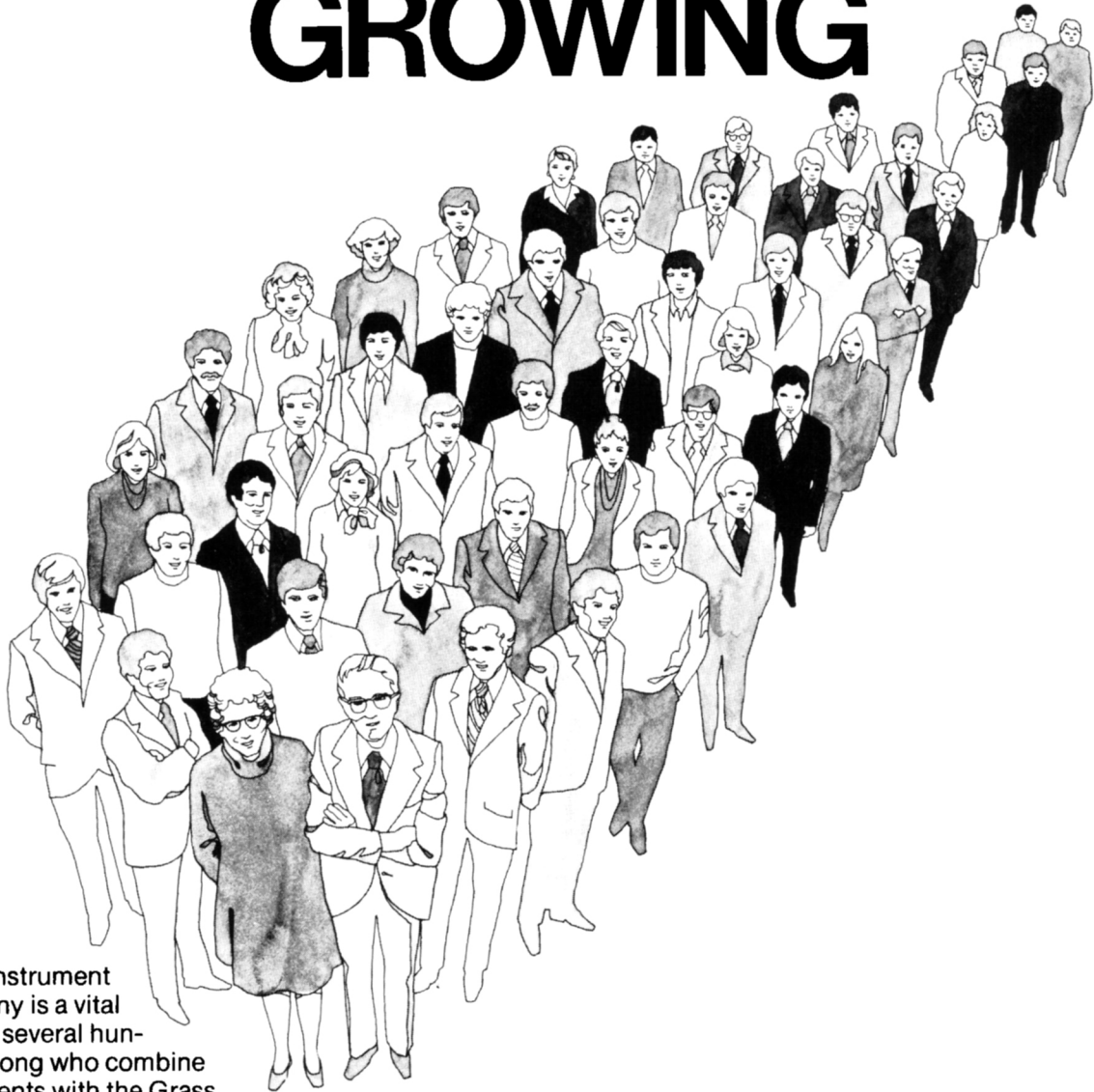
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Carbamazepine

Brief prescribing information
Tegretol[®] 200 mg
Carbamazepine

Indications and clinical use

A. Trigeminal Neuralgia:

Tegretol is indicated for the symptomatic relief of pain of trigeminal neuralgia only during periods of exacerbation of true or primary trigeminal neuralgia (tic douloureux). It should not be used 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 in:

- 1) 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.

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

Contraindications

Tegretol should not be administered to patients with a history of hepatic disease or serious blood disorder.

Tegretol should not be administered immediately before, in conjunction with, or immediately after a monoamine oxidase inhibitor. When it seems desirable to administer Tegretol to a patient who has been receiving an MAO inhibitor, there should be as long a drug-free interval as the clinical condition allows, but in no case should this be less than 14 days. Then the dosage of Tegretol should be low initially, and increased very gradually.

Safe use in pregnancy has not been established. Therefore, Tegretol should not be administered during the first three months of pregnancy.

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 (See Reproductive Studies). Because of demonstrated toxicity in nursing animals Tegretol should not be administered to nursing mothers.

Because of the similarity of chemical structure, Tegretol should not be administered to patients with known hypersensitivity to any of the tricyclic compounds, such as amitriptyline, trimipramine, imipramine, or their analogues or metabolites.

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.

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. Careful clinical and laboratory supervision should be maintained throughout treatment, including frequent performance of complete blood counts, in order to detect any early signs or symptoms of blood dyscrasia. Should any signs or symptoms or abnormal laboratory findings suggestive of blood dyscrasia or liver disorder occur, Tegretol should be immediately discontinued until the case is carefully reassessed.

Urinary Retention and Increased Intraocular Pressure:

Because of its anticholinergic action, Tegretol should be given cautiously, if at all, to patients with increased intraocular pressure or urinary retention. Such patients should be followed closely while taking the drug.

Occurrence of Behavioural Disorders:

Because it is closely related to the other tricyclic drugs, there is some possibility that Tegretol might activate a latent psychosis, or, in elderly patients, produce agitation or confusion, especially when combined with other drugs. Caution should also be exercised in alcoholics.

Use in Patients with Cardiovascular Disorders:

Tegretol should be used cautiously in patients with a history of coronary artery disease, organic heart disease, or congestive failure.

Driving and Operating Hazardous Machinery:

Because dizziness and drowsiness are possible side effects of Tegretol, patients should be warned about the possible hazards of operating machinery or driving automobiles.

Adverse reactions:

The reactions which have been most frequently reported with Tegretol are drowsiness, unsteadiness on the feet, vertigo, dizziness, gastrointestinal disturbances, and nausea. These reactions usually occur only during the initial phase of therapy. They have rarely necessitated discontinuing Tegretol therapy, and can be minimized by initiating treatment at a low dosage.

The more serious adverse reactions observed are the haematologic, hepatic, cardiovascular and dermatologic reactions, which require discontinuation of therapy.

The following adverse reactions have been reported:

Haematological reactions:

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

Hepatic disturbances:

During the long-term administration of Tegretol, abnormalities in liver function tests and cholestatic or hepatocellular jaundice have been observed.

Dermatological reactions:

The following reactions occurred during treatment with Tegretol: 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:

The reactions reported as occurring during treatment with Tegretol include vertigo, somnolence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements and increase in motor seizures. In addition, peripheral neuritis and paresthesia, depression with agitation, talkativeness, nystagmus, and tinnitus have been reported but only very rarely. There have been some reports of paralysis and other symptoms of cerebral arterial insufficiency but no conclusive relationship to the administration of Tegretol could be established.

Cardiovascular systems:

Recurrence of thrombophlebitis in patients with a prior history of thrombophlebitis, congestive heart failure, aggravation of hypertension, hypotension, syncope and collapse, edema, aggravation of coronary artery disease. Some of these complications have resulted in fatalities.

Other cardiovascular complications (including myocardial infarction and arrhythmia) have been associated with other tricyclic compounds. Whether all these complications are drug-related is not known at this time.

Genitourinary reactions:

Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, and impotence. Elevation of BUN, albuminuria and glycosuria also have been observed.

Digestive tract:

Disturbances associated with Tegretol therapy have included nausea, vomiting, gastric or abdominal discomfort, diarrhoea, anorexia and 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 slit-lamp fundoscopy and tonometry, are recommended.

Other reactions reported during treatment with Tegretol include fever and chills, lymphadenopathy, aching joints and muscles, leg cramps and conjunctivitis.

Dosage and administration

Use in psychomotor and other secondary or partial seizures:

A low initial daily dosage with a gradual increase in dosage is advised. Dosage should be adjusted to the needs of the individual patient.

Initially:

100 to 200 mg once or twice a day depending on the severity of the case and previous therapeutic history. The initial dosage is progressively increased, until the best response is obtained, up to 600 mg daily. The usual optimal dosage is 600 mg daily, but occasionally dosages 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.


Use in trigeminal neuralgia:

The initial daily dosage should be small; 200 mg, taken in two doses of 100 mg each is recommended. The total daily dosage can be increased by 200 mg per day until relief of pain is obtained. This is usually achieved at a dosage between 200 and 800 mg daily, but occasionally up to 1200 mg per day 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 of the drug in trigeminal neuralgia is not recommended.

Tegretol should be taken in two or three divided doses daily, with meals whenever possible.

Dosage forms

Tegretol is available as a 200 mg white, round, single-scored tablet, engraved with  signet.

Availability

Bottles of 50 and 500 tablets. Protect from moisture.

References

1. Livingston, S.: "Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence". Springfield, Charles C. Thomas, 1972
2. Braunhofer, J.: Med Klin. 60: 343-348, 1965

Lerman, P., and Kivity-Ephraim, S.: Carbamazepine Sole Anticonvulsant for Focal Epilepsy of Childhood. *Epilepsia*, 15: 229-234, 1974, New York

Full information is available on request.

Geigy

Dorval, P.Q., H9S 1B1

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syndrome



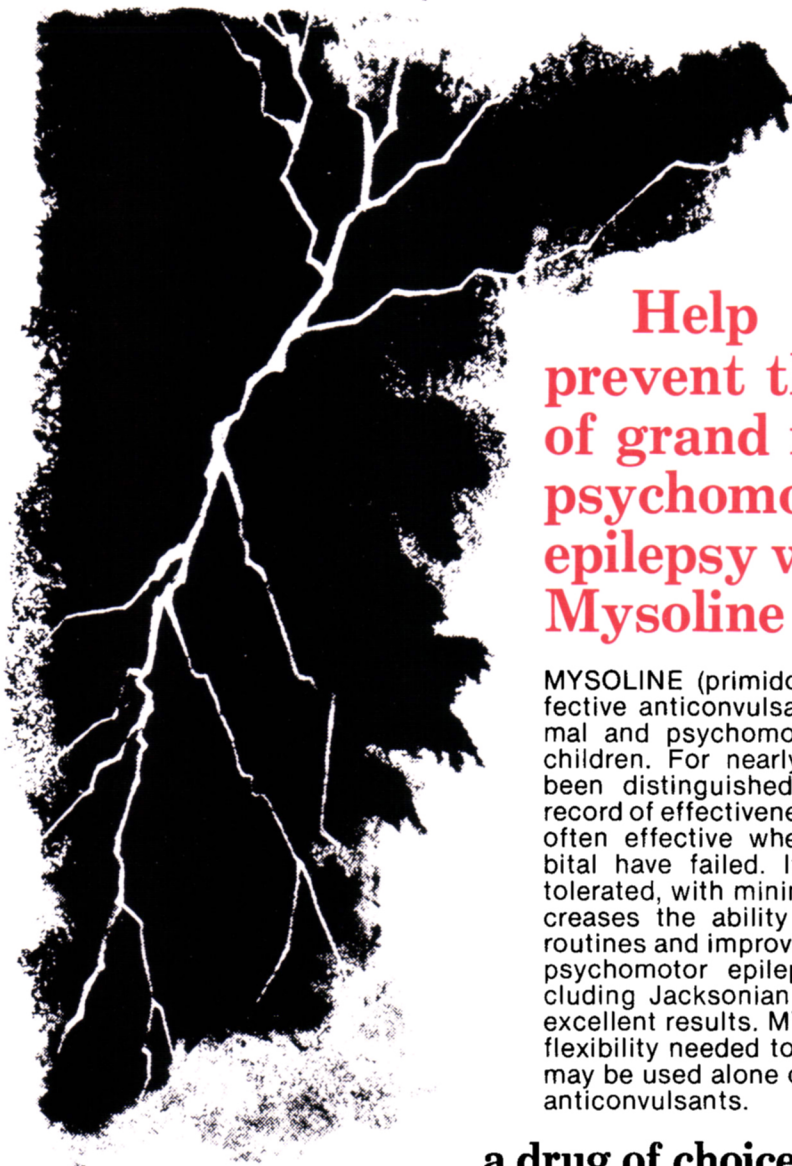
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Common adverse reactions that can occur with SINEMET^{*} are abnormal involuntary movements and, less frequently, mental changes. These usually can be diminished by dosage reduction.

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Mysoline*

Dosage: Adults and children over 8 years—week I: 250 mg h.s.; week II: 250 mg b.i.d.; week III: 250 mg t.i.d.; week IV: 250 mg q.i.d. Dosage may be increased until seizures are controlled but should not exceed 2 gm daily. Children under 8 years—half the adult dosage. In patients already receiving other anticonvulsants, dosage is gradually increased while the dosage of the other drug(s) is gradually decreased. **Adverse Effects:** Drowsiness, ataxia, vertigo, anorexia, irritability, general malaise, nausea and vomiting. These reactions are usually minor and transitory tending to disappear as therapy is continued or dosage is adjusted. No serious irreversible toxic reactions have been observed. (Occasionally, megaloblastic anemia has been reported, which is reversible by folic acid, 15 mg daily, while MYSOLINE is continued). As with any drug used over prolonged periods, routine laboratory studies at regular intervals are recommended. **Supplied:** Tablets—250 mg and 125 mg Suspension—250 mg/5ml. Complete prescribing information available on request.



* T. M. Reg.

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