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THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES

LE JOURNAL CANADIEN DES SCIENCES NEUROLOGIQUES

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NOVEMBER 1978

Rivotril®

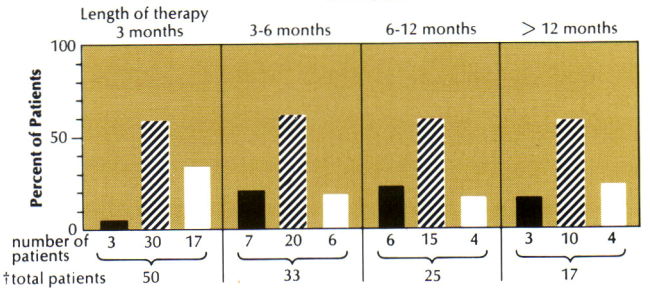
a new oral anticonvulsant from 'Roche' research

RIVOTRIL, with specific and potent anticonvulsant properties, is a new benzodiazepine in the same family as Librium®, Valium® and Dalmane® Roche®. It is therefore characterized by the same high degree of safety and efficacy.

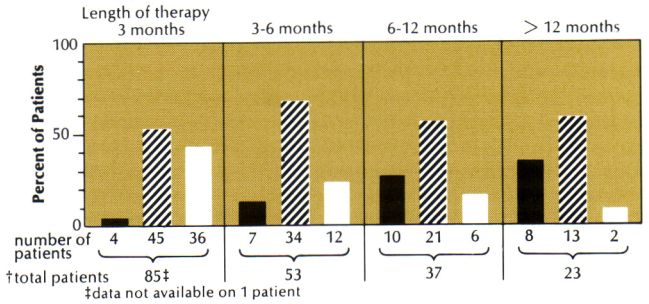
- used alone or as an adjunct, RIVOTRIL can reduce the frequency and/or severity of akinetic, myoclonic and petit mal variant (Lennox-Gastaut syndrome) seizures.
- it may be of value as principal medication in petit mal where succinimide therapy has failed.
- the most frequently noted side effects, drowsiness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

Effect of RIVOTRIL on seizure frequency

Akinetic*

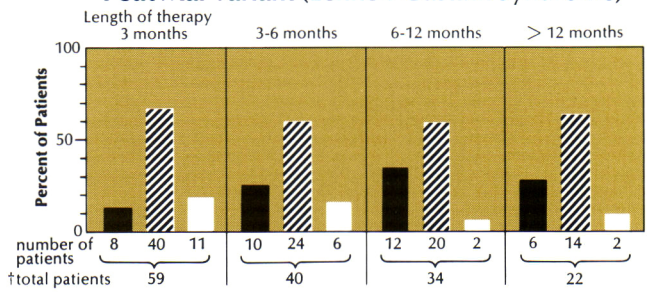


Myoclonic with and without Hypsarrhythmia*

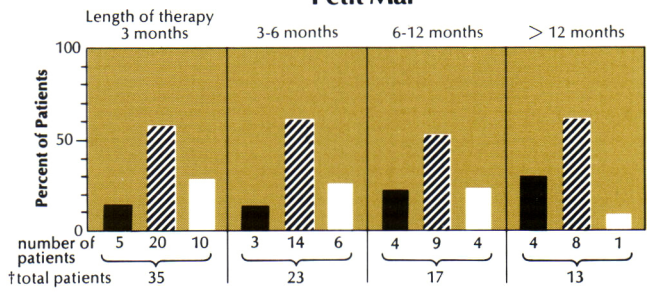


‡data not available on 1 patient

Petit Mal Variant (Lennox-Gastaut Syndrome)*



Petit Mal*



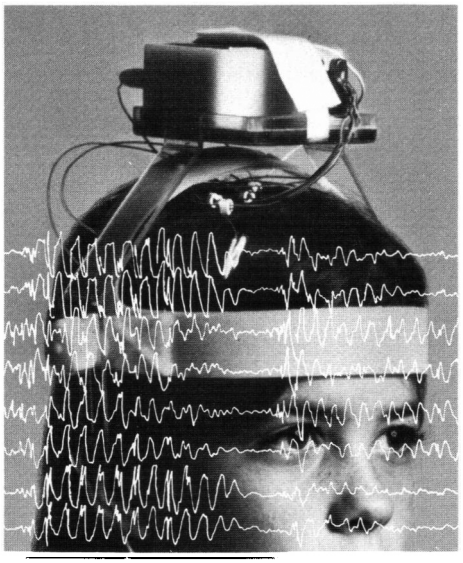
■ Seizures 100% controlled
▨ Seizures better than 50% reduced in frequency
□ Seizures uncontrolled

*Data on file, Hoffmann-La Roche Limited

†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.

https://doi.org/10.1017/S0317167100024094 Published online by Cambridge University Press

An important aid in the management of minor seizures



Noninvasive EEG telemetry device used to monitor patients in studies evaluating RIVOTRIL.

Rivotril® (clonazepam)

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.

Supply

Scored tablets, 0.5 and 2 mg. Bottles of 100.

®Reg. Trade Marks

Full prescribing information on request.

ROCHE

Hoffmann-La Roche Limited
Vaudreuil, Quebec

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why new instruments in EEG?

Because you asked for them. In reality, doctors and technologists have been the initiators for changes in instrumentation. As your needs have changed, so have your instruments.

In the mid-1950's, you wanted more reliable instruments. We introduced solid state electronics which made tube-type instruments obsolete. It was the first really innovative step forward in EEG electronics in many years.

In the early 1970's, you asked for small, mobile EEG's that could operate anywhere in a hospital or fit comfortably in an office. Again, we responded, and the Accutrace™ EEG was introduced.

In more recent years, we have heard other requests:

"Why can't I change the presets myself?"

"When will I have a mobile 16- or 20-channel EEG?"

"Why can't I visually verify my presets?"

"When will patient isolation be standard so I can use the instrument on anyone, anywhere?"

"When will I have an instrument I can service myself?"

"Why can't I economically expand the number of channels on my instrument?"

All of these ideas are logical steps in the evolution of EEG instruments, but they are no longer just ideas; they are realities in the new ACCUTRACE EEG.

The following instrument decriptions are just hints of what the actual instruments are like. All of these things are possible because once again Beckman Instruments is in the forefront by using the very latest in microprocessing electronics. At Beckman Instruments, Leadership Through Innovation isn't simply a slogan. It's a reality.

Accutrace™ Model 200 EEG

The totally mobile Accutrace Model 200 offers from 8 to 20 channels of EEG. That's right, now you can have a full 20 channels of information. But if you only need 8, 10, or even 18 channels today, it's great to know that you can economically expand the unit to as many as 20 channels tomorrow without buying a new instrument!

Patient isolation is no longer a problem because the Accutrace offers it as a standard feature. We believe patient isolation isn't something you should have to ask for; it is something you should expect.

A push-button electrode entry system allows the operator to easily enter electrodes manually. A digital display readout permits easy verification of override and preset values. As a double check, we have also incorporated a lighted head display. This visually verifies which electrodes are being used in either preset montage or override montage. It's a valuable means of verifying electrodes.

Another area of concern has always been presets. No longer must you purchase a dedicated unit limited to one set of montages. Now you can have programmable presets and change your presets at will. Sound good so far? We've even gone a few steps further.

Now at the touch of a single button, the instrument's autodiagnostic system surveys its components. Within seconds, the digital readout identifies the number of any malfunctioning module. You don't search for a problem; the instrument does it for you. Again, it's the microprocessor which surveys the electronics, eliminating time-consuming, step-by-step checks of the circuitry. It saves the EEG owner time and money.

In addition, the Accutrace 200 has an optional auto verification system which codes the patient number, preset number, and signal filtering information on each tracing.

You must admit that everything we've described makes the Accutrace sound like a dream instrument, which it is, but wait until you sit down to actually run a record. We have eliminated 90% of the surface switches and replaced them with a silent, touch-sensitive control panel for the ultimate in simplicity and convenience.

Accutrace™ Model 100 EEG

The Accutrace Model 100 EEG is a compact 8- or 10-channel mobile unit which has features not found on comparable units manufactured today. For example, the Model 100 comes standard with patient isolation and a simplified control panel for operator convenience. The instrument features a manual diagnostic system for troubleshooting, which allows the operator to devote more time to the patient. The Model 100 instruments are everything you've come to expect in an Accutrace, plus the safety and convenience not found on any other instrument except the new Accutrace Model 200's.

If you would like to learn more about these newest of EEG instruments, contact your local Beckman representative or call the EEG Product Marketing Manager collect at (312) 671-3300, or simply write Beckman Instruments, Inc., 3900 N. River Road, Schiller Park, Illinois 60176.

BECKMAN®

Accutrace™ 200 EEG

leadership through innovation

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Tegretol®
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 sensitivitiy 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 ben 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 Geigy 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

G-5052R

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THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES
LE JOURNAL CANADIEN DES SCIENCES NEUROLOGIQUES

THE EDITORIAL BOARD wishes to publish original work in the basic and clinical neurosciences on the understanding that it has not been and will not be published elsewhere. Review articles on timely subjects will be accepted. Manuscripts must be in duplicate including illustrations. One of the copies must be the original, ribbon copy. Manuscripts should be typed double spaced, on white paper.

Papers will be accepted in French or English. All papers should be accompanied by a short résumé in both languages. The résumé translation will be done by the editorial board if requested.

Papers should be identified only by the full name of the author, or authors, and the name of the place in which the work was done.

ILLUSTRATIONS: Photographs should be unmounted on glossy paper and show magnification scale. They should be marked on the back with figure number, title of paper and name of author.

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All illustrations should be referred to as figures, numbered consecutively, not included in the body of the text and all captions should be typed on a separate piece of paper.

Colored illustrations cannot usually be accepted unless the author is prepared to assist with the cost of reproduction.

REFERENCES to authors outside the context of the sentence should read (Name, Year). *i.e. "However, a recent study (Bird and Iverson, 1975) showed a decreased, etc."* Authors mentioned within the context of the sentence should read Name (Year). *"i.e. ... twenty years since Ecker and Reimenshender (1951) demonstrated, etc."* References should be typed in alphabetical order on a separate sheet and include author's name, initials, year, title, publication, volume, first and last page, i.e. Isacson, P. (1967). Myx-oviruses and autoimmunity. Progress in Allergy, 10, 256-292. Abbreviations should be the same as those used in Cumulated Index Medicus.

Textbook references should include name of text, author's name, page number, publisher and city.

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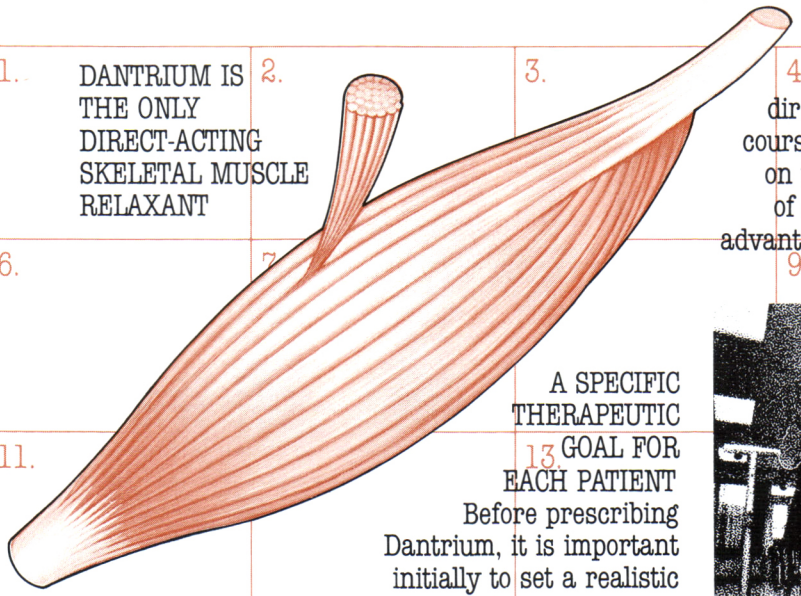
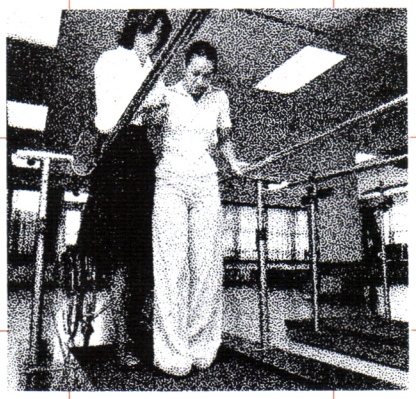
THE DANTRIUM® CONCEPT

DANTRIUM IS THE ONLY DIRECT-ACTING SKELETAL MUSCLE RELAXANT

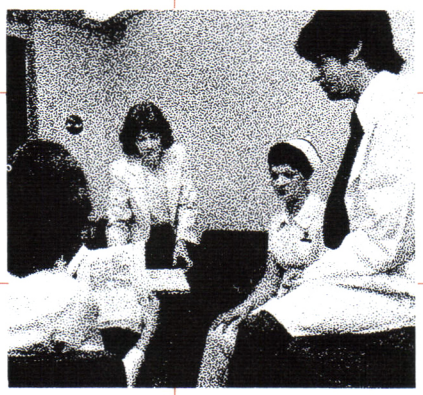


For chronic spasticity, direct action is often the best course.[1] Dantrium acts directly on the contractile mechanism of skeletal muscle. Its unique advantages can bring substantial relief to many patients.[2]



A SPECIFIC THERAPEUTIC GOAL FOR EACH PATIENT

Before prescribing Dantrium, it is important initially to set a realistic therapeutic goal for your patient. As progress is gradual, continual assessment is vital.



Response		Adults	Children
Initial, transient side effects often encountered	1st week	25 mg once daily	1.0 mg/kg once daily
	2nd week	25 mg BID	1.0 mg/kg BID
Response range for most patients	3rd week	25 mg QID	1.0 mg/kg QID
	4th week	50 mg QID	2.0 mg/kg QID
	5th week	75 mg QID	3.0 mg/kg QID
	6th week	100 mg QID	

The titration chart shows the flexibility of Dantrium. Dosage is initiated at a low level and titrated according to individual response. If benefits are not evident in 45 days, therapy should be discontinued.

Dantrium avoids persistent sedation, the major limitation of centrally acting muscle relaxants.[4,5] With Dantrium, drowsiness "...usually disappears within a few days, and it can often be avoided by starting treatment with small dosages to be increased at weekly intervals."[4] However, it can be used concomitantly with a reduced dosage of a CNS agent to achieve maximum results. It is a major breakthrough in the treatment of chronic spasticity.[6]

TEAMWORK MAKES THE DIFFERENCE

Every member of the health care team should be aware of the patient's therapeutic goal. The attending specialist, physio/occupational therapists and nursing staff can then work together in a constant feedback situation, all helping with each physical and psychological step forward. Teamwork makes The Dantrium Concept the most viable answer to many forms of chronic spasticity.[3]

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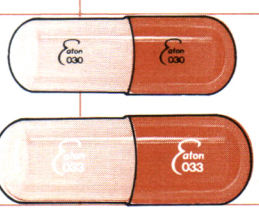

25 mg

100 mg

Norwich-Eaton Pharmaceuticals
Division of Norwich-Eaton Ltd.
P.O. Box 2002
Paris, Ontario
N3L 3G6

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Pr

Dantrium®

(dantrolene sodium capsules)

ACTIONS

Recordings of muscle tensions and electrical activity in both animal and man suggest that Dantrium has a direct inhibitory effect on the development of contractile tension. Spastic patients receiving Dantrium have shown a 40-70% reduction in the skeletal muscle tension induced by direct electrical stimulation of the motor nerve with no alteration of the EMG. This decrease in contractile tension can be attributed to an effect of Dantrium beyond the myoneural junction. Total paralysis does not occur since the Dantrium-induced change in the contractile state of skeletal muscle is limited in magnitude. The reduction in contractile activity accounts for the ability of Dantrium to diminish spasticity resulting from pathological states associated with a hyperactive stretch reflex.

Dantrium also produces central nervous system effects resulting in such manifestations as drowsiness, dizziness and generalized weakness.

Absorption of Dantrium is slow, dose-related blood levels are obtained which peak in 4 to 6 hours after a single oral dose. The peak pharmacologic effect generally occurs in 1½ to 3 hours at concentrations of 50 to 75 percent of the peak plasma level. Dantrium is highly bound to plasma protein and, to a lesser extent, red blood cells. Metabolism is rapid via hepatic microsomal enzymes. The major metabolites in humans are a 5-hydroxy analog and an acetamino analog. Urinary excretion of Dantrium and metabolites occurs in an initially rapid phase (t-½, 2.5 to 3 hours) followed by a slower phase over a 24 hour period. Dantrium is also removed by biliary excretion.

INDICATIONS

Dantrium is useful in controlling the manifestations of chronic spasticity of skeletal muscle resulting from such conditions as *spinal cord injury, cerebral palsy, multiple sclerosis, and stroke, whenever such spasticity results in a decrease in functional* use of residual motor activity. Dantrium is not indicated in the relief of skeletal muscle spasms due to rheumatic disorders.

CLINICAL USES

Dantrium has been studied in the treatment of selected patients with moderate to severe skeletal muscle spasticity resulting from stroke, spinal cord injury, cerebral palsy, multiple sclerosis, and other neuropathies. It seems to act directly on the skeletal muscle and has been found useful whenever manifestations of spasticity such as increased muscular resistance to stretch, clonus, and exaggerated reflex posturing interfere with therapeutic exercise programs, utilization of braces, transfer manoeuvres, posture equilibrium, ambulation, and activities of daily living.

Marked reduction or even cessation of spontaneous involuntary movements was observed in many patients receiving Dantrium. The extent to which Dantrium may contribute toward improvement in spasticity and activities in daily living can be tested by withdrawing the drug for 2 to 4 days and observing whether an exacerbation of the patient's condition occurs.

CONTRAINDICATIONS

Skeletal muscle spasticity without suitable volitional activity (residual motor activity) may be of value in a rehabilitation program aimed toward sustaining upright posture and balance, and may assist a patient's locomotor pattern. Relief of such spasticity would reduce rather than increase function. Therefore, in cases where spasticity is utilized to obtain or maintain increased function, Dantrium is contraindicated.

Dantrium is contraindicated in patients with compromised pulmonary function, particularly those with obstructive pulmonary disease.

WARNINGS

DANTRIUM (DANTROLENE SODIUM) HAS THE POTENTIAL TO PRODUCE HEPATOTOXICITY AND SHOULD NOT BE USED IN CONDITIONS OTHER THAN THOSE RECOMMENDED. CASES OF FATAL HEPATITIS HAVE BEEN REPORTED IN PATIENTS WHO HAD RECEIVED DANTRIUM FOR SIXTY DAYS OR LONGER. SYMPTOMATIC HEPATITIS AND LABORATORY EVIDENCE OF LIVER DYSFUNCTION HAVE ALSO BEEN REPORTED IN A NUMBER OF PATIENTS RECEIVING DANTRIUM. SOME CASES OF HEPATITIS WERE CONSIDERED TO BE DIRECTLY RELATED TO DANTRIUM ADMINISTRATION, WHEREAS OTHERS MAY HAVE BEEN DUE TO OTHER CAUSES. DANTRIUM-INDUCED HEPATOTOXICITY APPEARS TO OCCUR IN APPROXIMATELY ONE PERCENT OF THE PATIENTS RECEIVING THE DRUG. DANTRIUM MAY EXACERBATE PRE-EXISTING LIVER DYSFUNCTIONS. NO SERIOUS HEPATIC INJURY HAS YET BEEN REPORTED IN PATIENTS RECEIVING THE DRUG FOR LESS THAN 60 DAYS, ALTHOUGH LIVER ENZYME ELEVATIONS HAVE OCCURRED. RISK OF HEPATIC INJURY APPEARS TO BE GREATER IN FEMALES AND IN PATIENTS OVER 35 YEARS OF AGE. THEREFORE, DANTRIUM SHOULD NOT BE USED WITHOUT APPROPRIATE EVALUATION AND MONITORING OF HEPATIC FUNCTION BEFORE AND THROUGHOUT TREATMENT, INCLUDING FREQUENT DETERMINATIONS OF SERUM LIVER ENZYMES. A TRIAL ADMINISTRATION OF DANTRIUM IS RECOMMENDED AND IF AFTER 45 DAYS NO OBSERVABLE BENEFIT IS EVIDENT, DANTRIUM SHOULD BE DISCONTINUED. THE LOWEST POSSIBLE EFFECTIVE DOSE FOR THE INDIVIDUAL PATIENT SHOULD BE PRESCRIBED.

TOXICITY STUDIES IN ANIMALS PROVIDED EVIDENCE OF LOW-GRADE CARCINOGENIC ACTIVITY OF DANTRIUM IN THE RAT (SEE SECTION ON TOXICOLOGY). IN VIEW OF THE ANIMAL FINDINGS, POTENTIAL CARCINOGENICITY IN HUMANS CANNOT BE DISREGARDED. THEREFORE, THE POTENTIAL BENEFITS OF THE DRUG SHOULD BE WEIGHED AGAINST THE POSSIBLE RISKS OF DRUG USE FOR THE INDIVIDUAL PATIENT. CONSIDERATION SHOULD BE GIVEN AS TO WHETHER THE PATIENT HAS RESPONDED TO OTHER MEDICATION AND TO THE BENEFITS OF THE TRIAL ADMINISTRATION OF DANTRIUM AS RECOMMENDED ABOVE. IN ASSESSING RISK ACCEPTABILITY, THE AGE OF THE PATIENT, THE DEGREE OF DISABILITY AND LIFE EXPECTANCY SHOULD ALSO BE CONSIDERED. LONG TERM EFFICACY AND OTHER ASPECTS OF THE LONG TERM SAFETY OF DANTRIUM HAVE NOT YET BEEN ESTABLISHED.

Use in Children: In view of the preceding warning, it is particularly important to assess risk acceptability before Dantrium is used in pediatric patients. Since there is insufficient experience with the use of Dantrium in young children (under 5 years of age), the drug is usually not recommended in this age group.

Use in Pregnancy: The safety of Dantrium in women who are or who may become pregnant has not been established; in such patients it should be given only when the potential benefits have been weighed against possible hazard to mother and child. Dantrium should not be used in nursing mothers.

PRECAUTIONS

Although subjective weakness attributable to Dantrium is usually transient, some patients feel excessively weak as long as Dantrium therapy is continued. Such patients may not be able to manipulate rehabilitation devices such as wheelchairs, crutches, braces, walkers, or canes. Careful attention should be given to patients utilizing these devices. Dantrium should be discontinued if the weakness persists and interferes with the use of a rehabilitation device.

Dantrium should be used with caution in patients with impaired myocardial function.

Patients should be instructed not to drive a motor vehicle or participate in a hazardous occupation during the first week of Dantrium therapy. Although the primary pharmacologic effect of Dantrium is exerted directly on skeletal muscle, an apparent transient CNS effect also may exist. Therefore, caution should be exercised in the concomitant administration of tranquilizing agents.

Although photosensitization has not been a problem in clinical trials of Dantrium it is possible that in some subjects the drug might evoke a phototoxic response.

The possibility of cross-sensitivity with compounds of related chemical structure exists; however, no such reactions were reported in extensive clinical trials.

In long-term therapy, periodic clinical laboratory evaluation of organ systems, including haematopoietic, renal, and hepatic studies, should be performed.

ADVERSE REACTIONS

Side effects most frequently reported were drowsiness, weakness, dizziness, malaise, fatigue and diarrhea. Less commonly reported effects are listed by systems:

Cardiovascular: tachycardia and erratic blood pressures, phlebitis.

Gastrointestinal: constipation, anorexia, gastric irritation and bleeding, abdominal cramps, swallowing difficulty, nausea with or without vomiting and liver failure.

CNS: speech and visual disturbances, seizure, headache, lightheadedness, taste alterations, mental depression, confusion, nervousness, diplopia, insomnia.

Urogenital: increased urinary frequency, crystalluria, difficult erection, urinary incontinence and/or nocturia, difficult urination and/or urinary retention.

Musculoskeletal: myalgia, backache.

Integumentary: acne-like rash, pruritis, urticaria, eczematoid eruption, abnormal hair growth, sweating.

Other: chills, fever, excessive tearing, feeling of suffocation.

ALTERATIONS OF LIVER FUNCTION STUDIES ATTRIBUTABLE TO DANTRIUM HAVE BEEN OBSERVED. IT IS THEREFORE ADVISABLE TO PERFORM LIVER FUNCTION TESTS BEFORE AND DURING THERAPY. (SEE WARNINGS).

Side effects listed as most frequently occurring were generally transient and may be avoided with initial low doses and a gradual increase to optimal doses. Diarrhea may be of sufficient severity to warrant temporary or possibly permanent withdrawal of medication.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

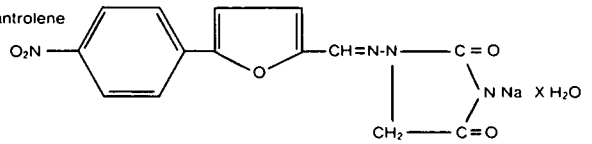
A single case has been reported of a patient with an 18-year history of multiple sclerosis who consumed 1600 mg of Dantrium per day for 13 days (a total of 20,800 mg). Other than feeling slightly weaker and "rubbery", the patient appeared to suffer no clinical manifestations of overdosage. Liver function values were transiently elevated although the patient did not become jaundiced.

For acute overdosage general supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered in fairly large quantities to avert the possibility of crystalluria. An adequate airway should be maintained and artificial resuscitation equipment made available. Electrocardiographic monitoring should be instituted, and the patient carefully observed. No experience has been reported with dialysis, hence its value in Dantrium overdosage is not known.

PHARMACOLOGY

Chemical Name: 1-[5-(p-nitrophenyl)-furfurylidene] amino hydantoin sodium hydrate.

Sodium Dantrolene



Dantrium causes marked, dose-dependent skeletal muscle relaxation in laboratory animals with a long duration of action. The pharmacologic profile of Dantrium in animals is unlike neuromuscular blocking agents in that total muscle paralysis and/or respiratory depression do not occur.

There is a wider margin between doses causing muscle relaxation and doses causing motor incoordination with Dantrium than with centrally acting muscle relaxants. Skeletal muscle relaxation is not associated with anaesthetic or analgesic action. Impairment of cornea or pinna reflexes has not been observed in animals treated with Dantrium.

Various studies both in vivo and in vitro demonstrated the apparent selectivity of action of Dantrium for skeletal muscle. There were some non-specific depressant effects seen in several smooth muscle studies and insignificant effects in cardiac muscle in doses which cause skeletal muscle relaxation. Nerve transmission was not affected by Dantrium in several animal studies.

It has been shown that Dantrium has no effect on the propagated action potential recorded on the muscle membrane, and the total membrane capacitance is not decreased by the drug, indicating that it does not disrupt the function of the transverse tubular system, and acts at a point beyond the electrically excitable surface membrane. Evidence obtained in vitro with muscle preparations exposed to caffeine, an agent known to cause muscle contractions by releasing internal Ca^{++} stores in muscle, suggests that Dantrium acts on skeletal muscle by altering the Ca^{++} release mechanisms. Such an action could explain the apparent specificity of Dantrium for skeletal muscle.

Animal studies have indicated that Dantrium is metabolized by hydrolysis, hydroxylation, nitro reduction and acetylation of the resulting amine.

Four corresponding metabolites have been identified which probably do not contribute significantly to the activity of Dantrium. Maximal blood levels following oral administration are reached in approximately 1 hour. In dogs approximately 40% of an I.V. dose of Dantrium is excreted as the hydroxylated metabolite in bile whereas only 1% of the dose is excreted in this manner by the rat. High biliary concentrations of this metabolite have also been found in the Rhesus monkey. Total excretion of known metabolites in the urine is estimated at approximately 3% in the dog and approximately 10% in the rat.

TOXICOLOGY

The oral LD_{50} of dantrolene sodium in newborn, Sprague-Dawley rats was 2902 mg/kg. No young adult rats were killed with doses up to 18,000 mg/kg. Pertinent clinical signs were inactivity, lethargy, weakness, gasping, diarrhea, yellowing of skin colour, decreased growth rate or weight loss, and death. Tubular degeneration and necrosis, cortical abscesses and pelvic necrosis occurred in kidneys. No deaths occurred within 48 hours in adult rabbits and mice, with oral doses up to 8 or 9 g/kg, respectively. Crystals were observed in the urinary and the gall bladders of rabbits.

Three subacute toxicity studies were conducted in rats with oral doses up to 500 mg of dantrolene sodium/kg for 28 days and up to 86 mg/kg for 88 days. Body weight gains were reduced significantly by doses of 43.8 mg/kg. Relative kidney and liver weights were increased by doses of 15.5 mg/kg and absolute liver weights by 86 mg/kg for 88 days. Increased serum alkaline phosphatase and SGOT occurred with doses of 62.5 mg/kg. Rats dosed with 500 mg/kg for 28 days had increased serum alkaline phosphatase, SGOT, fasting plasma glucose, plasma urea nitrogen, serum creatinine, and decreased urine specific gravity. Renal tubules were plugged by drug crystals, and tubular dilatation, degeneration, necrosis and hematuria resulted.

Chronic toxicity studies were conducted in Beagle dogs for 1 year. Oral doses of 15 mg/kg/day produced no detectable effects. At 30 mg/kg/day, there was a suppresion of weight gain and sporadic increases in BSP retention. A regimen of increasing doses (90 mg/kg for the first 206 days followed by 180 mg/kg for 14 days and 360 mg/kg for an additional 82 days) caused marked loss in body weight, increased SGOT activity and BSP retention, normocytic orthochromic anaemia, urinary anisotropic crystals and, in one dog necropsied at day 270, intrahepatic cholestasis. Recovery occurred after discontinuation of drug administration.

A one-year oral toxicity study also was conducted with Rhesus monkeys. Initial doses of 0, 15, 30 and 60 mg/kg were used. Because of the lack of clinical toxicity during the first 6 months, the dosage levels were doubled at the end of the first 6 months. At 9 months, the dosage level for the high dose group was again doubled and these animals were then maintained on 240 mg/kg/day until the termination of the study. A dose-dependent lowering of body weight gain was observed at 12 months. Urinary crystals were noted in one animal at the middle (60 mg/kg day) dosage level at 11½ to 12 months. Urinalyses at 6 and 12 months also indicated a drug-related increase in blood elements. During the last 6 months, a generally lower A/G ratio at all dosage levels, a slight, apparently dose-related cholesterol-lowering effect, a higher serum alkaline phosphatase, a high SGOT level in the two high dosage levels, and relatively lower serum creatinine levels in the high dosage groups were noted. Chronic hepatic cholangitis was observed at necropsy in some mid and high dosage level animals.

Dantrolene sodium was administered in the diet to mature Sprague-Dawley rats for 18 months at levels of 15, 30 and 60 mg/kg daily. Treated rats showed a lower body weight gain compared to controls and damage to the liver. There was an increase in the incidence of mammary adenofibromas in the females. Other drug-related changes (seen only at the 30 and 60 mg/kg daily dosage levels) were increased incidences of bile duct cystadenomas, and increased signs of malignancy in mammary tumors in females. At the 60 mg/kg daily level the number of metastasizing mammary adenocarcinomas in female rats was increased significantly; anisotropic urinary crystals were found in both male and female groups.

Because of these findings, lifetime tumorigenesis studies were conducted in Sprague-Dawley and Fischer 344 rats. The treated Sprague-Dawley rats received dantrolene sodium in the diet at levels of 15, 30 and 60 mg/kg daily for 18 months and the Fischer 344 rats received the same levels for 20 months. The animals subsequently were maintained on a standard diet until 90% of each treatment group died spontaneously. Dantrium produced in the female Sprague-Dawley rats a linear, dose-related increase in the number of rats with malignant neoplasms, and a decrease in the time of onset of mammary neoplasms. There were also increased incidences of benign hepatic tumors including lymphangiomas and bile duct cystadenomas, and angiosarcomas. In Fischer rats, there was a significant, dose-related reduction in the times of onset of mammary and testicular tumors.

A two year tumorigenesis study was conducted in Swiss mice (CD®-1 HaM/ICR). Dantrolene sodium was fed to mice at levels of 15, 30 and 60 mg/kg/day for 15 months and then the mice were maintained on a standard diet for 9 additional months. There was an increased incidence of benign angiomatous neoplasms.

Effects on Reproduction: Dietary doses of 0, 15 or 45 mg of dantrolene sodium/kg of body weight were given to rats and rabbits in classical reproductive and teratogenic studies. Significant untoward effects were not observed. One litter of 14 pups from a rat treated with 45 mg of dantrolene sodium/kg between days 6 to 15 of gestation had 6 malformed pups. Malformations included kinky tails, a short upper jaw, and renal agenesis. Two pups in another litter had unilateral microphthalmia. An association with treatment was considered doubtful.

DOSAGE AND ADMINISTRATION

Prior to the administration of Dantrium, consideration should be given to the potential response to treatment. A decrease in spasticity sufficient to allow a daily function not otherwise attainable should be the therapeutic goal of treatment with Dantrium. Refer to section on "Clinical Uses" for description of possible areas of response.

It is important to establish a therapeutic goal (regain and maintain a specific function such as therapeutic exercise program, utilization of braces, transfer manoeuvres, etc.) before beginning Dantrium therapy. Dosage should be increased until the maximum performance compatible with the dysfunction due to underlying disease is achieved. No further increase in dosage is then indicated.

Usual Dosage: It is important that the dosage be titrated and individualized for maximum effect. The lowest dose compatible with optimal response is recommended.

Adults: Begin therapy with 25 mg once daily; increase to 25 mg two, three or four times daily and then, by increments of 25 mg, to 100 mg two, three, or four times daily, if necessary. Each dosage level should be maintained for four to seven days, depending on the patient's tolerance, and should be increased only if the therapeutic goal has not been attained. Only occasionally will a dose greater than 100 mg four times daily be required in which case the dose can be increased gradually, depending on tolerance, up to 200 mg four times daily.

The dose should not be increased beyond, and may even have to be reduced to, the amount at which the patient received maximal benefit without adverse effects.

Children: A similar approach should be utilized, starting with 1.0 mg/kg of body weight once daily, this is increased to 1.0 mg/kg two, three, or four times daily and then, by increments of 0.5 mg/kg, up to 3.0 mg/kg two, three, or four times daily if necessary. Each dosage level should be maintained for four to seven days depending on the patient's tolerance, and should be increased only if the therapeutic goal has not been attained. Doses higher than 100 mg four times daily should not be used in children.

DOSAGE FORMS

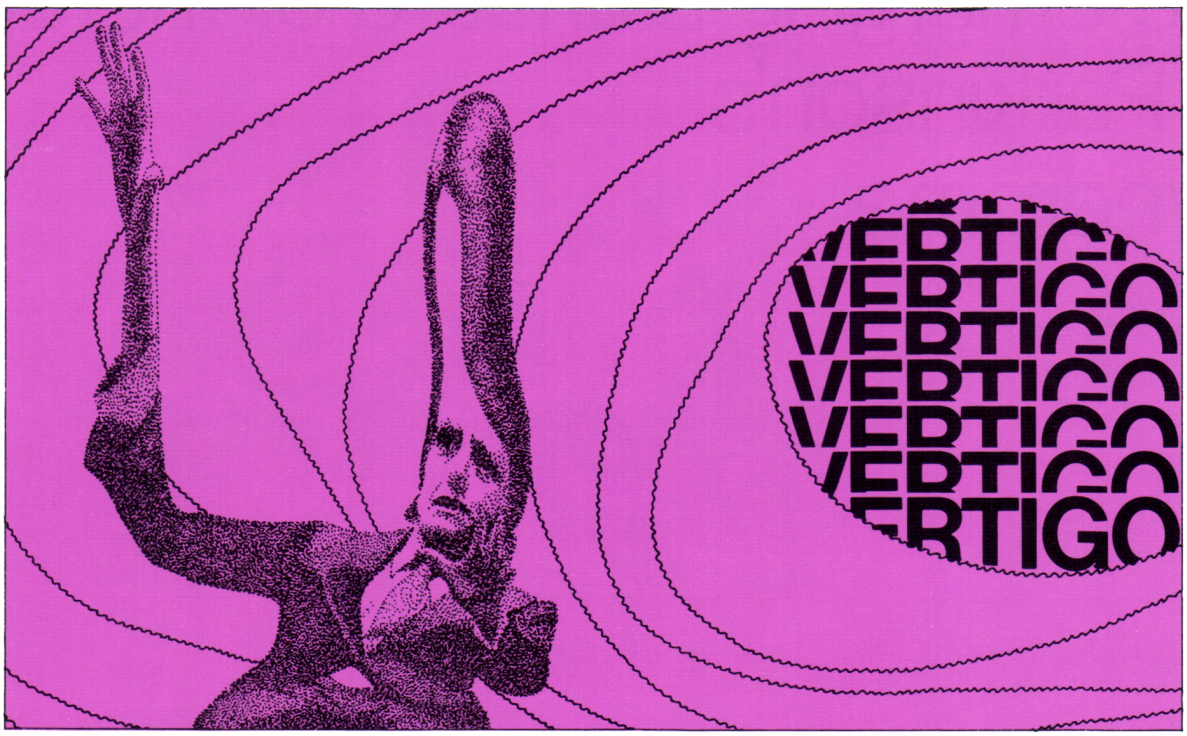
Dantrium is available in opaque orange and brown capsules of 25 mg (coded "Eaton 030" in black), and opaque orange and brown capsules of 100 mg (coded "Eaton 033" in white). They are supplied in bottles containing 100 and 500 capsules.

Dantrium is a registered trademark.

Norwich-Eaton Pharmaceuticals
Division of Norwich-Eaton Ltd.
P.O. Box 2002
Paris, Ontario
N3L 3G6

PAAB
CCPP

For the management of Vertigo in Meniere's disease



SERC®

(Betahistine hydrochloride) TABLETS

A decade of clinical success in Canada

Chemically Unique Vasoactive Compound

- Vascular responses similar to those of histamine[1, 2]
- Tends to restore, not depress vestibular response[3, 4]

May Increase Blood Flow To Inner Ear

- Increases cochlear blood flow in experimental animals[5, 6]
- Increases basilar and labyrinthine artery flow in canine studies[7, 8]

Demonstrated Efficacy and Patient Acceptance

- Reduces the number and severity of vertigo attacks[9, 10]
- Suitable for long term management[9, 10]
- Effective when other medications failed[9, 10]
- Well tolerated[2, 3, 4, 9, 10]

histaminic – not antihistaminic often a more helpful approach

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PRESCRIBING INFORMATION

DESCRIPTION AND CHEMISTRY: SERC is the proprietary name for a histamine-like drug generically designated as betahistine hydrochloride.

INDICATIONS: SERC may be of value in reducing the episodes of vertigo in Meniere's disease. No claim is made for the effectiveness of SERC in the symptomatic treatment of any form of vertigo other than that associated with Meniere's disease.

DOSAGE AND ADMINISTRATION: The usual adult dosage has been one to two tablets (4 mg. each) administered orally three times a day.

Recommended starting dose is two tablets three times daily. Therapy is then adjusted as needed to maintain patient response. The dosage has ranged from two tablets per day to eight tablets per day. No more than eight tablets are recommended to be taken in any one day.

SERC (betahistine hydrochloride) is not recommended for use in children. As with all drugs, SERC should be kept out of reach of children.

CONTRAINDICATIONS: Several patients with a history of peptic ulcer have experienced an exacerbation of symptoms while using SERC. Although no causal relation has been established SERC is contraindicated in the presence of peptic ulcer and in patients with a history of this condition. SERC is also contraindicated in patients with pheochromocytoma.

PRECAUTIONS: Although clinical intolerance to SERC by patients with bronchial asthma has not been demonstrated, caution should be exercised if the drug is used in these patients.

USE IN PREGNANCY: The safety of SERC in pregnancy has not been established. Therefore, its use in pregnancy or lactation, or in women of childbearing age requires that its potential benefits be weighed against the possible risks.

ADVERSE REACTIONS: Occasional patients have experienced gastric upset, nausea and headache.

HOW SUPPLIED: Scored tablets of 4 mg. each in bottles of 100 tablets.

Full Prescribing Information available on request.

UNIMED Pharmaceuticals Limited
Dorval, Québec, H9P 2P4

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sinemet*

(levodopa and carbidopa combination)

INDICATIONS
Treatment of Parkinson's syndrome with exception of drug induced parkinsonism.

CONTRAINDICATIONS
When a sympathomimetic amine is contraindicated; with monoamine oxidase inhibitors, which should be discontinued two weeks prior to starting SINEMET*; in uncompensated cardiovascular, endocrine, hematologic, hepatic, pulmonary or renal disease; in narrow-angle glaucoma; in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS
When given to patients receiving levodopa alone, discontinue levodopa at least 12 hours before initiating SINEMET* at a dosage that provides approximately 20% of previous levodopa.
Not recommended in drug-induced extrapyramidal reactions; contraindicated in management of intention tremor and Huntington's chorea.
Levodopa related central effects such as involuntary movements may occur at lower dosages and sooner, and the 'on and off' phenomenon may appear earlier with combination therapy.
Monitor carefully all patients for the development of mental changes, depression with suicidal tendencies, or other serious antisocial behaviour.
Cardiac function should be monitored continuously during period of initial dosage adjustment in patients with arrhythmias.
Upper gastrointestinal hemorrhage is possible in patients with history of peptic ulcer.
Safety of SINEMET* *in patients under 18 years of age* not established.
Pregnancy and lactation: In women of childbearing potential, weigh benefits against risks. Should not be given to nursing mothers. Effects on human pregnancy and lactation unknown.

PRECAUTIONS
General: Periodic evaluations of hepatic, hematopoietic, cardiovascular and renal function recommended in extended therapy. Treat patients with history of convulsions cautiously. *Physical Activity:* Advise patients improved on SINEMET* to increase physical activities gradually, with caution consistent with other medical considerations. *In Glaucoma:* May be given cautiously to patients with wide angle glaucoma, provided intraocular pressure is well controlled and can be carefully monitored during therapy. *With Antihypertensive Therapy:* As symptomatic postural hypotension has been reported occasionally, give cautiously to patients on antihypertensive drugs, checking carefully for changes in pulse rate and blood pressure. Dosage adjustment of antihypertensive drug may be required. *With Psychoactive Drugs:* If concomitant administration is necessary, administer psychoactive drugs with great caution and observe patients for unusual adverse reactions. *With Anesthetics:* Discontinue SINEMET* the night before general anesthesia and reinstitute as soon as patient can take medication orally.

ADVERSE REACTIONS
Most Common: *Abnormal Involuntary Movements*—usually diminished by dosage reduction—choreiform, dystonic and other involuntary movements. Muscle twitching and blepharospasm may be early signs of excessive dosage. **Other Serious Reactions:** Oscillations in performance: diurnal variations, independent oscillations in akinesia with stereotyped dyskinesias, sudden akinetic crises related to dyskinesias, akinesia paradoxica (hypotonic freezing) and 'on and off' phenomenon. Psychiatric: paranoid ideation, psychotic episodes, depression with or without development of suicidal tendencies and dementia. Levodopa may produce hypomania when given regularly to bipolar depressed patients. Rarely convulsions (causal relationship not established). Cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, anorexia, nausea, vomiting and dizziness.

Other adverse reactions that may occur: *Psychiatric:* increased libido with serious antisocial behaviour, euphoria, lethargy, sedation, stimulation, fatigue and malaise, confusion, insomnia, nightmares, hallucinations and delusions, agitation and anxiety. *Neurologic:* ataxia, faintness, impairment of gait, headache, increased hand tremor, akinetic episodes, "akinesia paradoxica", increase in the frequency and duration of the oscillations in performance, torticollis, trismus, tightness of the mouth, lips or tongue, oculogyric crisis, weakness, numbness, bruxism, priapism. *Gastrointestinal:* constipation, diarrhea, epigastric and abdominal distress and pain, flatulence; eructation, hiccups, sialorrhea; difficulty in swallowing, bitter taste, dry mouth; duodenal ulcer; gastrointestinal bleeding; burning sensation of the tongue. *Cardiovascular:* arrhythmias, hypotension, nonspecific ECG changes, flushing, phlebitis. *Hematologic:* hemolytic anemia, leukopenia, agranulocytosis. *Dermatologic:* sweating, edema, hair loss, pallor, rash, bad odor, dark sweat. *Musculoskeletal:* low back pain, muscle spasm and twitching, musculoskeletal pain. *Respiratory:* feeling of pressure in the chest, cough, hoarseness, bizarre breathing pattern, postnasal drip. *Urogenital:* urinary frequency, retention, incontinence, hematuria, dark urine, nocturia, and one report of interstitial nephritis. *Special Senses:* blurred vision, diplopia, dilated pupils, activation of latent Horner's syndrome. *Miscellaneous:* hot flashes, weight gain or loss. Abnormalities in laboratory tests reported with levodopa alone, which may occur with SINEMET*: Elevations of blood urea nitrogen, SGOT, SGPT, LDH, bilirubin, alkaline phosphatase or protein bound iodine. Occasional reduction in WBC, hemoglobin and hematocrit. Elevations of uric acid with colorimetric method. Positive Coombs tests reported both with SINEMET* and with levodopa alone, but hemolytic anemia extremely rare.

DOSAGE SUMMARY
In order to reduce the incidence of adverse reactions and achieve maximal benefit, therapy with SINEMET* must be individualized and drug administration continuously matched to the needs and tolerance of the patient. Combined therapy with SINEMET* has a narrower therapeutic range than with levodopa alone because of its greater milligram potency. Therefore, titration and adjustment of dosage should be made in small steps and recommended dosage ranges not be exceeded. Appearance of involuntary movements should be regarded as a sign of levodopa toxicity and an indication of overdosage, requiring dose reduction. Treatment should, therefore, aim at maximal benefit without dyskinesias.
Therapy in Patients not receiving Levodopa:
Initially ½ tablet once or twice a day, increase by ½ tablet every three days if desirable. An optimum dose of 3 to 5 tablets a day divided into 4 to 6 doses.
Therapy in Patients receiving Levodopa:
Discontinue levodopa for at least 12 hours, then give approximately 20% of the previous levodopa dose in 4 to 6 divided doses.

FOR COMPLETE PRESCRIBING INFORMATION, PARTICULARLY DETAILS OF DOSAGE AND ADMINISTRATION, PLEASE CONSULT PRODUCT MONOGRAPH WHICH IS AVAILABLE ON REQUEST.

HOW SUPPLIED
Ca 8804—Tablets SINEMET* 250, dapple-blue, oval, biconvex, scored, compressed tablets coded MSD 654, each containing 25 mg of carbidopa and 250 mg of levodopa. Available in bottles of 100 and 500.

*Trademark SNM-8-480-JA

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New Accutrace™ 100 EEG

8 or 10 channels of EEG

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The new Accutrace™ 100 EEG looks similar to the original Accutrace 8 model . . . but appearances can be deceiving. It is small, mobile, and extremely accurate. But this instrument now offers up to 10 channels of EEG (with top event marker), plus the following new conveniences:

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Load or change chart paper in seconds with the new Accutrace paper feed system.

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Twenty-five leads are standard, plus a built-in impedance scale for a quick check of electrode impedances. A time-saving mini-jackbox, for easy patient hookup, plugs into the main box.

These are the most obvious conveniences on the new Accutrace 100 EEG's, but there are more. For further information, contact your Beckman representative or write: Beckman Instruments, Inc., Electronic Instruments Division, 3900 N. River Road, Schiller Park, Illinois 60176, (312) 671-3300.

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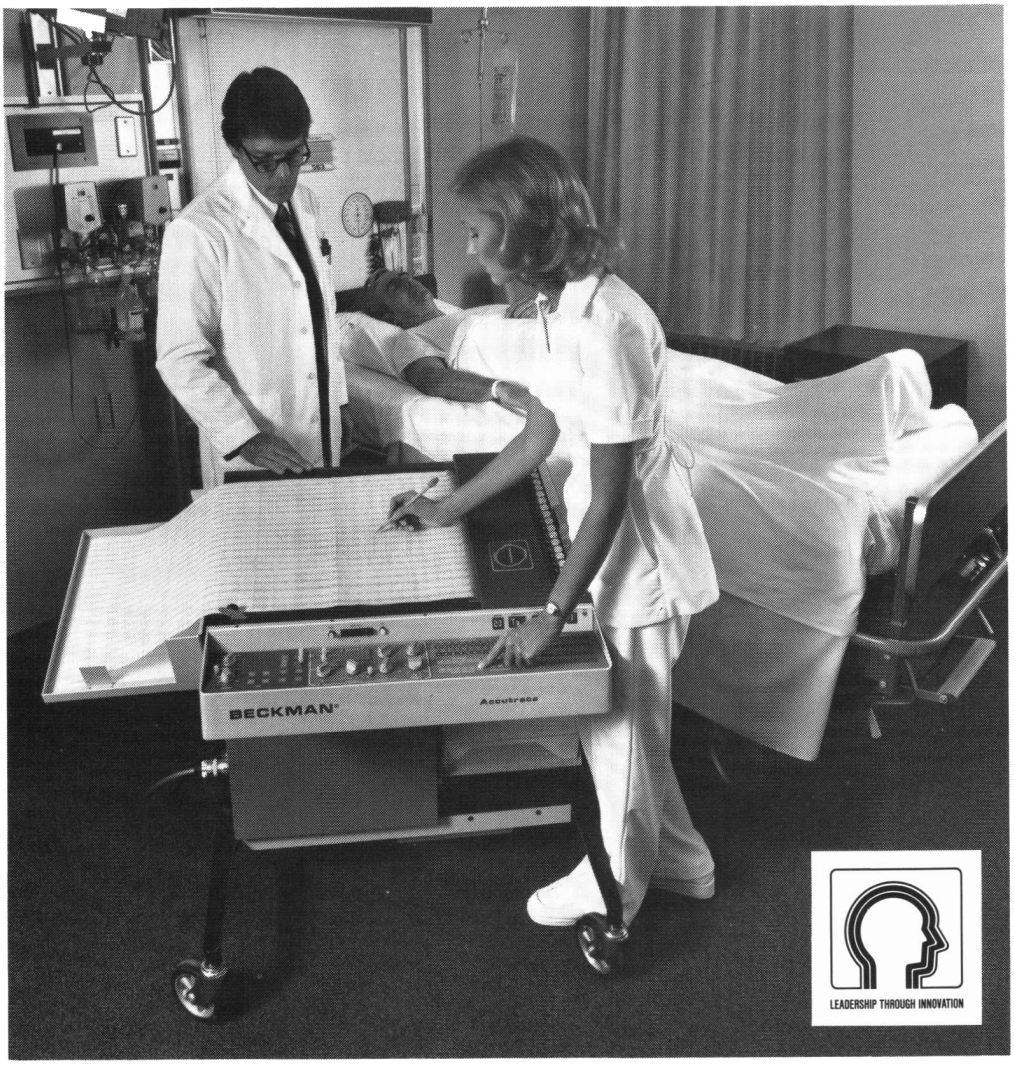

Photo taken in the ICU at Oak Park Hospital, Oak Park, Illinois.

Patient isolation– convenience or necessity?

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"Erratum. The following type was unfortunately dropped from page 328, right hand column of the August, 1978 issue, Number 3, Volume 5."

Because of these quite unexpected findings, a search of other tissues was undertaken for evidence of embolization. Similar emboli were discovered, but with more difficulty in the capillaries of renal glomeruli, myocardium and lung. None of these were associated with evidence of ischemic tissue injury. Emboli were also present in the