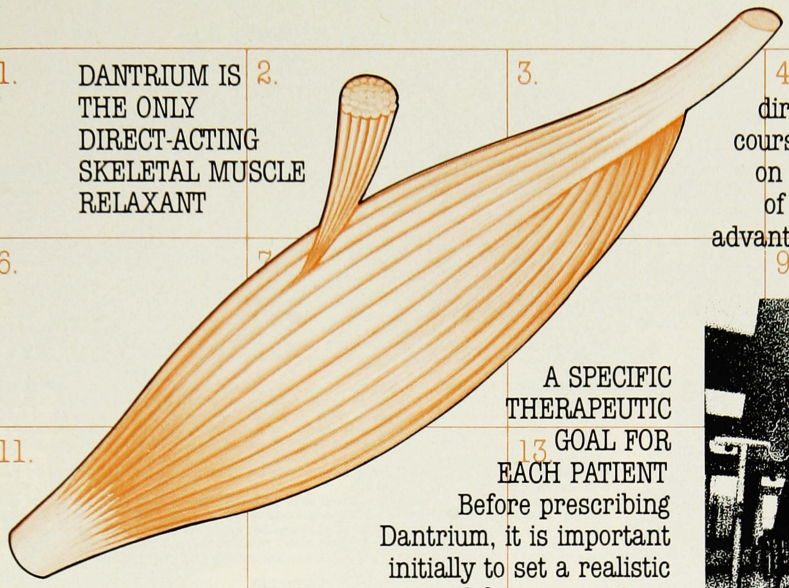
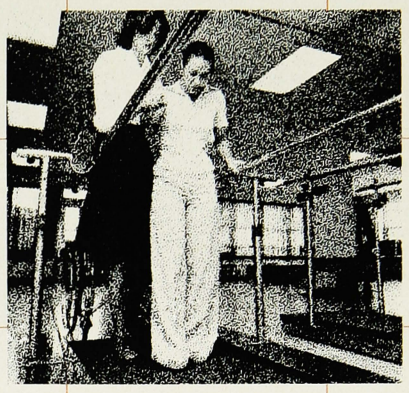
THE DANTRIUM® CONCEPT

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	

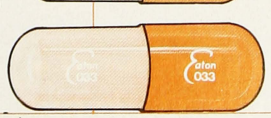
The titration chart shows the flexibility of Dantrium. Dosage is initiated at a low level and titrated according to individual response. If benefits are not evident in 45 days, therapy should be discontinued.

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]

25 mg



100 mg

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

1. Pinder RM, Brogden RN, Speight TM, et al: Dantrolene sodium: a review. Drugs 13:3-24, 1977.
2. Chyatte SB, Basmajian JV: Dantrolene sodium: long-term effects in severe spasticity. Arch Phys Med Rehabil 54:311-315, 1973.
3. Chyatte SB, Birdsong JH, Roberson DL: Dantrolene sodium in athetoid cerebral palsy. Arch Phys Med Rehabil 54:365-368, 1973.
4. Mayer N, Mecomber SA, Herman R: Treatment of spasticity with dantrolene sodium. Am J Phys Med 52:18-29, 1973.
5. Steinberg FU, Ferguson KL: J Am Geriatr Soc 23:70-73, 1975.
6. Keenan RE, Kolb ME, Horne ML: Collaborative comparison of dantrolene sodium and diazepam. Clinical Therapeutics 1:48-55, 1977.

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 ($t_{1/2}$, 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.

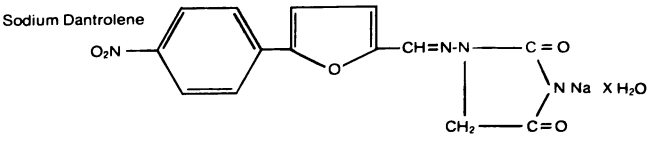
SYMPTOMS AND TREATMENT OF OVERDOSAGE

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.



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 ($CD^{\circledR}$-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
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PAAB
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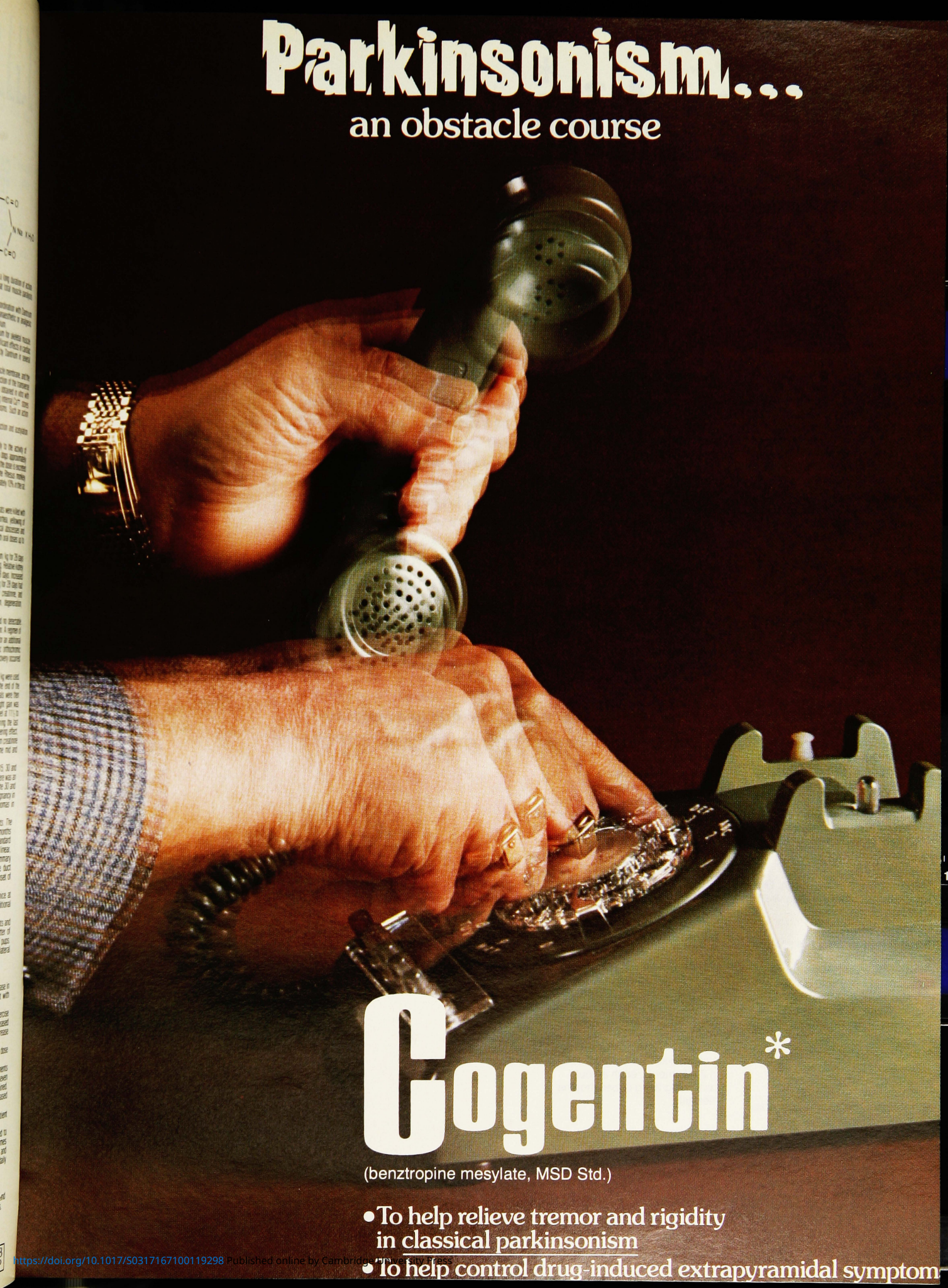


Cogentin*

Antiparkinsonian Agent

Available as:
2 ml (1 mg/ml) injection
2 mg tablets

Indications
In the symptomatic treatment of all etiological groups of parkinsonism — arteriosclerotic, postencephalitic, idiopathic, and drug-induced. Therapy is directed towards control of disturbing symptoms to permit maximum integration of functions and minimum discomfort.

Drug-Induced Parkinsonism
COGENTIN* relieves manifestations of parkinsonism that may appear during treatment with reserpine and phenothiazine derivatives.

Dosage Summary
COGENTIN* should be given in tablet form where at all possible, otherwise it may be given intramuscularly or intravenously. As COGENTIN* has cumulative action, it should be initiated in a small amount, and increased gradually by increments of 0.5 mg at 5 or 6 day intervals, to a maximum of 6 mg or until optimal results are obtained without excessive side effects.

Arteriosclerotic, Idiopathic and Postencephalitic Parkinsonism
The usual oral daily dosage is 1 to 2 mg, ranging between 0.5 to 6 mg, according to the needs of the patient.

Drug-Induced Parkinsonism
The recommended dosage is 1 to 4 mg once or twice a day orally or parenterally.

Contraindications
Children under 3 years of age. Use with caution in older children. In the presence of glaucoma.

Warnings
Safe use in pregnancy has not been established.
Benztropine mesylate may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle.

Precautions
Since COGENTIN* has a cumulative action, maintain continued supervision. Use with caution in patients with a tendency to tachycardia or patients with prostatic hypertrophy. Dysuria may occur. Glaucoma is a possibility. In large doses, weakness and inability to move muscles, mental confusion, excitement with occasional visual hallucination may occur.
Occasionally, intensification of mental symptoms in patients receiving phenothiazines or reserpine. The psychotogenic potential of antiparkinsonian drugs should be considered when planning the management of patients with mental disorders. These patients should be kept under observation, especially at the beginning of treatment and if dosage is increased. Advise patients to report gastrointestinal complaints promptly when COGENTIN* is administered with other drugs with anticholinergic activity (e.g., phenothiazines, tricyclic antidepressants). Not recommended in patients with tardive dyskinesia. As COGENTIN* may produce anhidrosis, use with caution in patients with abnormal sweating and decrease dosage if evidence of impaired ability to maintain body heat equilibrium is evident.

Adverse Reactions
May be anticholinergic or antihistaminic in nature. Dry mouth, blurred vision, nausea, nervousness, vomiting, constipation, numbness of fingers, listlessness, depression, allergic reactions, e.g., skin rash. Reduce dosage or discontinue temporarily if adverse reactions, such as dry mouth, nausea, vomiting, or skin rash, are overly troublesome.

Full prescribing information available on request

How Supplied
Ca 3172 — Tablets COGENTIN* 2 mg white, flat, discoid-shaped, quarter-sected, compressed tablets, are supplied in bottles of 100 and 1000.
Ca 3275 — Injection COGENTIN* is a clear, colorless solution, available in 2 ml ampuls, each ampul containing 2 mg of benztropine mesylate.

CGT-8-CA-527-JA

MSD | MERCK SHARP & DOHME CANADA LIMITED
P.O. BOX 1005, POINTE CLAIRE, DORVAL H9R 4P8

PAAB CCPP

SILVER JUBILEE PSYCHIATRIC RESEARCH MEETING

A multidisciplinary psychiatric research meeting will be held on May 9-11, 1979, in Saskatoon. Entitled "FROM MOLECULES TO COMMUNITY: MULTI-FACETED MENTAL HEALTH RESEARCH", the meeting is sponsored by the Psychiatric Research Division of the Saskatchewan Department of Health and the Department of Psychiatry, University of Saskatchewan. The meeting will mark the 25th Anniversary of the establishment of Psychiatric Research as an integral part of the programme of the Saskatchewan Department of Health, and in honour of this occasion, a number of distinguished guest speakers will participate and discuss recent advances in biological, clinical and psychosocial research in psychiatry.

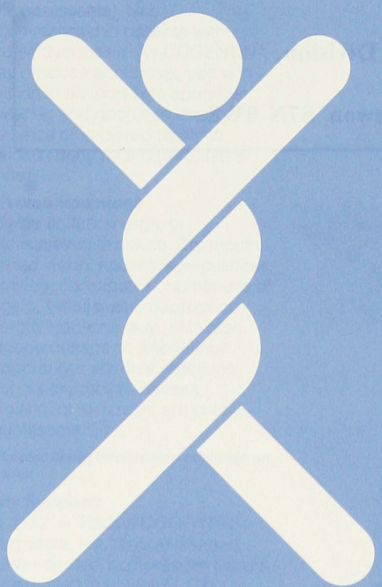
Additional information can be obtained from:

D. G. Irvine,
Psychiatric Research Division,
University Hospital,
Saskatoon, Saskatchewan S7N 0W8.

New Lioresal

baclofen

for spasticity resulting from multiple sclerosis, spinal cord injury, and spinal cord diseases.



Acts primarily at the spinal level

Lioresal is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of the afferent terminals. However, the precise mechanism of action is not fully known. Actions at supraspinal sites may also occur and contribute to the clinical effect.

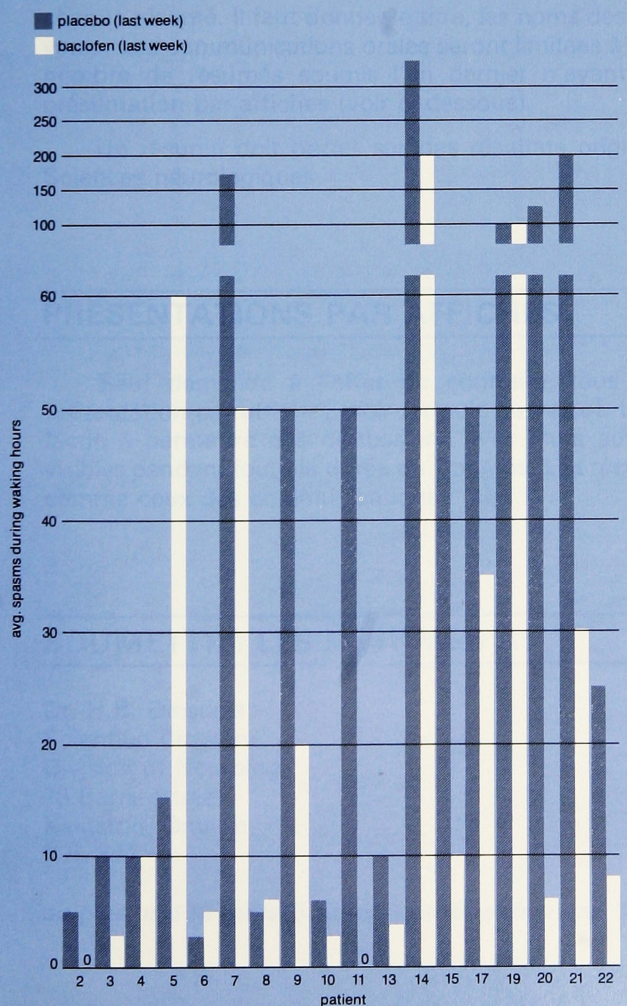
https://doi.org/10.1017/S0317167100119298 Published online by Cambridge University Press

esal®

Effective and safe

Results of a four-week, double blind crossover study of 22 patients showed 72 percent of 18 patients with spontaneous daytime spasms had a reduction in the frequency when treated with Lioresal. Furthermore, a reduction in severity amplitude, and duration of remaining spasms was also reported in patients treated with Lioresal.[1]

Figure 1. Average daily number of spasms during the last week of baclofen and placebo treatment periods in the 18 patients with spontaneous daytime spasms. (From Duncan et al[1])



When compared with placebo and diazepam in a double-blind study, Lioresal proved to be effective in reducing the number of spasms in 50% of patients who had developed tolerance to diazepam.[2]

In one study of 14 patients with spasticity, "Baclofen caused less sedation than would have been expected from comparable doses of diazepam but it did nevertheless have a tranquilizing effect..."[3]

And in one double-blind study, "No serious side effects developed and there were no signs of even transient bone marrow, liver, kidney, or gastrointestinal toxicity."[1] A few cases of increased SGOT, elevated alkaline phosphatase and elevated blood sugar have been reported but are not clinically significant. Gastrointestinal and other side effects also have been reported but generally do not persist.

Facilitates physical therapy

By relieving painful spasms Lioresal may allow more active physical therapy and daily function.

The advantages of improvement in resistance to passive movement noted in patients treated with Lioresal included more comfortable positioning and easier transfers and nursing.[1]

Effect of treatment on resistance to passive movement (Adapted from Duncan et al[1])

Stage	Baclofen	Placebo
Improved	11 **(55%)**	1 **(5%)**
Worsened	0 **(0%)**	0 **(0%)**
Unchanged	9 **(45%)**	19 **(95%)**
Total	20	20

Geigy

For Brief Prescribing Information, see page 00. G-9038

https://doi.org/10.1017/S0317167100119298 Published online by Cambridge University Press

Lioresal®baclofen
Brief Prescribing Information
Indications and clinical uses
Lioresal (baclofen) is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis.
Lioresal may also be of some value in patients with spinal cord injuries and other spinal cord diseases.
Contraindications
Hypersensitivity to **Lioresal** (baclofen).
Warnings
Abrupt Drug Withdrawal: Following abrupt withdrawal of **Lioresal** (baclofen), visual and auditory hallucinations, confusion, anxiety with tachycardia and sweating, insomnia, and worsening of spasticity have occurred. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued. *Impaired Renal Function:* Because **Lioresal** is primarily excreted unchanged through the kidneys, it should be given with caution, and it may be necessary to reduce the dosage. *Stroke:* **Lioresal** has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug. *Pregnancy:* Safe use of **Lioresal** during pregnancy or lactation has not been established. High doses are associated with an increased incidence of abdominal hernias in the fetuses of rats and of ossification defects in those of rats and rabbits. Therefore, the drug should be administered to pregnant patients, or women of child-bearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.
Precautions
Safe use of **Lioresal** (baclofen) in children under age 12 has not been established and it is, therefore, not recommended for use in children.
Because of the possibility of sedation, patients should be cautioned regarding the operation of automobiles or dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system effects of **Lioresal** may be additive to those of alcohol and other CNS depressants.
Lioresal should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function.
Extreme caution should be exercised in patients with epilepsy or a history of convulsive disorders. In such patients, the clinical state and electroencephalogram should be monitored at regular intervals during therapy, as deterioration in seizure control and EEG has been reported occasionally in patients taking **Lioresal**.
Caution should be used in treating patients with peptic ulceration, severe psychiatric disorders, elderly patients with cerebrovascular disorders, and in patients receiving antihypertensive therapy.
It is not known whether **Lioresal** is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.
Adverse Reactions
The most common adverse reactions associated with **Lioresal** (baclofen) are transient drowsiness, dizziness, weakness and fatigue. Others reported: *Neuropsychiatric:* Headache (<10%), insomnia (<10%), and, rarely, 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 (<10%), rare instances of dyspnea, palpitation, chest pain, syncope. *Gastrointestinal:* Nausea, (approx. 10%), constipation (<10%), and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool. *Genitourinary:* Urinary frequency (<10%), and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria. *Other:* Instances of 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).
Dosage and Administration
The determination of optimal dosage of **Lioresal** (baclofen) requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 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
Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (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.*
Description: 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. Available in bottles of 100 tablets.
References

1. Duncan, G. N., Shahani, B. T., and Young, R. R.: An evaluation of baclofen treatment for certain symptoms in patients with spinal cord lesions. Neurology, (May) 1976, pp. 441-446.
2. Jones, R. F.: Lioresal in the control of spasticity. Spasticity... A topical survey, Hans Huber Publishers, Bern, 1972, P. 113.
3. McLellan, D. L.: Effects of baclofen upon monosynaptic and tonic vibration reflexes in patients with spasticity. J. Neurol. Neurosurg. Psychiatry, 36(4): 555-560, (Aug.) 1973.

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INDEX TO ADVERTISEMENTS

Annonce du Programme Scientifique et
Invitation à Présenter des Résumés pour le

XIVième CONGRÈS CANADIEN DES SCIENCES NEUROLOGIQUES

Hotel Nova Scotian, Halifax, Nouvelle-Écosse
du 13 au 16 juin 1979

Les communications scientifiques seront présentées les 14, 15, 16 juin 1979.
Une journée de Neurologie des enfants et le cours précédant le Congrès auront lieu le 13 juin 1979.

En plus des membres des trois sociétés fondatrices, les membres de la Société des sciences neurologiques assisteront ou participeront au Congrès.

RÉSUMÉS DES ARTICLES SCIENTIFIQUES

Les résumés soumis en vue de leur présentation comme communications scientifiques doivent être dactylographiés, à simple interligne, dans la zone lignée au verso. Un résumé doit présenter en moins de 200 mots les données et conclusions essentielles. On demande **l'original et six (6)** copies de chaque résumé. Il faut donner le titre, les noms des auteurs et leurs villes de travail comme indiqué au verso. Les communications orales seront limitées à 10 minutes plus 5 minutes de discussion. Un grand nombre de résumés soumis l'an dernier n'ayant pu être présentés, on inaugure cette année la présentation par affiches (voir ci-dessous).

Un résumé doit porter sur des résultats originaux et sera publié dans le Journal canadien de Sciences neurologiques.

PRÉSENTATIONS PAR AFFICHES

Sauf demande à l'effet du contraire, tous les résumés soumis seront considerés pour la présentation par affiches (voir formule au verso). Les présentations par affiches seront organisées de façon à permettre des discussions avec leurs auteurs. Certaines présentations par affiches seront visibles pendant toute la durée du Congrès. Les résumés des présentations par affiches seront publiées comme ceux des communications orales.

SOUMETTRE LES RÉSUMÉS À:

Dr. H.B. Dinsdale
Scientific Program
Division of Neurology
78 Barrie Street
Kingston, Ontario
K7L 3J7

au plus tard **le lundi 5 mars.** Les résumés reçus après cette date ne seront pas considerés.

Notice of Scientific Program and Call for Abstracts for the

XIV CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES

Hotel Nova Scotian, Halifax, Nova Scotia
June 13th—16th, 1979

The Scientific Program will be held June 14th, 15th and 16th, 1979.
A day in Child Neurology and the Pre-Congress Course will be held on June 13th, 1979.

In addition to the three founding societies of the Congress there will be attendance and participation by members of the Society for Neuroscience.

ABSTRACTS FOR SCIENTIFIC PAPERS

Abstracts to be submitted for consideration for the Scientific Program must be typed, single spaced, within the ruled area on the reverse side of this announcement. Abstracts should summarize data and conclusions and contain not more than 200 words. **Seven** (7) copies of the Abstract (original and 6 photocopies) are required. The style for the title and authors' names and cities is provided at the bottom of the reverse side. Papers accepted for platform delivery will be allotted 10 minutes for presentation and 5 minutes for discussion. Because of the large number of submissions last year, many of which could not be included in the program, poster sessions are being introduced this year (see below).

Abstracts should report original material and will be published in the Canadian Journal of Neurological Sciences.

POSTER SESSIONS

All abstracts will be considered for poster presentation unless a request is made not to do so (see reverse side). Special arrangements will be made to allow time for poster presentations when presenters will be available for discussion. Some invited posters will be available throughout the entire duration of the Congress. Abstracts of poster presentations will be published in the same fashion as platform presentations.

ALL ABSTRACTS SHOULD BE MAILED TO:

Dr. H.B. Dinsdale
Scientific Program
Division of Neurology
78 Barrie Street
Kingston, Ontario
K7L 3J7

The deadline for receipt of abstracts is **Monday, March 5, 1979.** Abstracts received after that date will not be considered by the Scientific Program Committee.