Call for Abstracts for the

XV CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES

Chateau Laurier Hotel, Ottawa, Ontario

June 18th — 21st, 1980

ABSTRACTS FOR SCIENTIFIC PAPERS

Abstracts submitted 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. Papers accepted for platform delivery will be allotted 10 minutes for presentation and 5 minutes for discussion.

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

POSTER SESSIONS

Since the number of platform presentations is limited 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. All posters will be available throughout the entire duration for the Congress. Abstracts of poster presentations will be published in the same fashion as platform presentations.

ALL ABSTRACTS SHOULD BE MAILED TO:

Dr. L.P. Ivan
Scientific Program
Division of Neurosurgery
Children's Hospital of Eastern Ontario
401 Smyth Road.
Ottawa, Ontario
K1H 8L1

The deadline for receipt of abstracts is **Monday, March 3, 1980.**

Annonce du Programme scientifique et invitation à présenter des résumés pour le

XVe CONGRÈS CANADIEN DES SCIENCES NEUROLOGIQUES

Hôtel Château Laurier, Ottawa, Ontario

du 18 au 21 juin 1980

RÉSUMÉS DES ARTICLES SCIENTIFIQUES

Les résumés soumis 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. Les communications orales seront limitées à 10 minutes plus 5 minutes de discussion.

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

PRÉSENTATIONS PAR AFFICHES

Puisque le nombre de communications orales est limité, les résumés seront considérés pour la présentation par affiches sauf demande à l'effet du contraire (voir au verso). Les présentations par affiches seront organisées de façon à permettre des discussions avec leurs auteurs. Toutes affiches seront visibles pendant toute la durée du Congrès. Les résumés des présentations par affiches seront publiés comme ceux des communications orales.

SOUMETTRE LES RÉSUMÉS À:

Dr. L.P. Ivan
Scientific Program
Division of Neurosurgery
Children's Hospital of Eastern Ontario
401 Smyth Road.
Ottawa, Ontario
K1H 8L1

avant **lundi le 3 mars 1980.**

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

Depa

valproic acid

A major advance in anti-convulsant therapy that could bring more epileptic patients closer to normal.
as sole and adjunctive treatment of simple or complex absence seizures, including petit mal.
as adjunctive therapy of multiple seizures that include absence attacks.

a unique chemical structure

DEPAKENE is a simple fatty acid, chemically unrelated to other anticonvulsants.

a physiological mode of action

DEPAKENE appears to increase GABA (γ-aminobutyric acid) levels in the brain and cerebellum. GABA is known to inhibit neuronal excitability.[1]

Depakene extends the range

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

kene

"remarkably free of side effects in the general context of antiepileptics"[3]

Patients taking DEPAKENE have been reported to be more lively and alert and better able to carry out their daily tasks.[3]

DEPAKENE has not been associated with cosmetically undesirable side effects such as hirsutism, acne and gum hyperplasia. Although inhibition of platelet aggregation and leukopenia have been occasionally reported, it has not been associated with aplastic anemia or agranulocytosis. And DEPAKENE has no record of tolerance in long-term use.[2]

world-wide documentation of effectiveness

Numerous publications and clinical trials involving more than 4000 patients whose ages ranged from 5 months to 71 years, have demonstrated the antiepileptic efficacy of DEPAKENE.

An overview of clinical studies[2] involving valproic acid in 1020 patients demonstrates an excellent (75-100%) reduction in seizure frequency in 45.7% of patients, and satisfactory results (33-74% reduction of seizures) in 25.4% more.

of anticonvulsant therapy.

Depakene
valproic acid

Prescribing Information

CLINICAL PHARMACOLOGY

Depakene (valproic acid) has anticonvulsant properties. Although its mechanism of action has not yet been established, it has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA).

Valproic acid is rapidly absorbed after oral administration. Peak serum levels occur approximately one to four hours after a single oral dose. The serum half-life ($t_{0.5}$) of valproic acid is approximately 8 to 12 hours. Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. The therapeutic plasma concentration range is believed to be from 50 to 100 μg/mL.

Excretion of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The principal metabolite formed in the liver is the glucuronide conjugate.

INDICATIONS AND CLINICAL USE

Depakene (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. Valproic acid may also be used adjunctively in patients with multiple seizure types which include absence.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS

Depakene (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Hepatic failure resulting in fatalities, has occurred in patients receiving Depakene (valproic acid). These events have occurred during the first six months of treatment with valproic acid. Caution should be observed when administering Depakene to patients with pre-existing liver disease. Liver function tests should be performed prior to therapy and every two months thereafter. The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing doses. Therefore, the benefit gained by increased seizure control must be weighed against the increasing incidence of adverse effects.

Use in pregnancy

The safety of Depakene (valproic acid) during pregnancy has not been established, however, animal studies have demonstrated teratogenicity. Therefore, the physician should weigh the potential benefits against the possible risks in treating or counselling women of childbearing age who have epilepsy.

Recent reports indicate an association between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women this incidence may be increased two to threefold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsant drugs, including trimethadione and paramethadione. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation might be indicated.

Nursing Mothers

Depakene is secreted in breast milk. As a general rule, nursing should not be undertaken while a patient is receiving valproic acid.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment I fertility studies in rats have shown that doses up to 350 mg/kg/day for 60 days have no effect on fertility. The effect of Depakene (valproic acid) on the development of the testis and on sperm production and fertility in humans is unknown.

PRECAUTIONS

General

Because of reports of thrombocytopenia and platelet aggregation dysfunction, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients receiving Depakene (valproic acid) be monitored for platelet count prior to planned surgery. Clinical evidence of hemorrhage, bruising or a disorder of hemostasis/coagulation is an indication for reduction of Depakene (valproic acid) dosage or withdrawal of therapy pending investigation.

Because valproic acid may interact with other anticonvulsant drugs, periodic serum level determinations of such other anticonvulsants are recommended during the early part of therapy (see Drug Interactions).

Valproic acid is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

Driving and Hazardous Occupations

Valproic acid may produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions

Depakene (valproic acid) may potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, although the mechanism is unknown. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

Primidone is metabolized into a barbiturate, and therefore, may also be involved in a similar or identical interaction.

There is conflicting evidence regarding the interaction of valproic acid with phenytoin. It is not known if there is a change in unbound (free) phenytoin serum levels. The dose of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may produce absence status.

Caution is recommended when valproic acid is administered with drugs affecting coagulation, e.g. acetylsalicylic acid and warfarin (see Adverse Reactions).

ADVERSE REACTIONS

The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since Depakene (valproic acid) has usually been used with other anticonvulsants, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

Gastrointestinal

Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects

Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes," tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients who were also on phenobarbital.

Dermatologic

Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric

Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration have been reported.

Musculoskeletal

Weakness has been reported.

Hematopoietic

Thrombocytopenia has been reported. Valproic acid inhibits the secondary phase of platelet aggregation. (see Drug Interactions). This may be reflected in altered bleeding time. Bruising, hematoma formation and frank hemorrhage have been reported. Relative lymphocytosis and hypofibrinogenemia have been noted. Leukopenia and eosinophilia have also been reported.

Hepatic

Increases in serum alkaline phosphatase and elevation of serum glutamic oxaloacetic transaminase (SGOT) have been noted. Elevation of SGOT may be dose-related. Elevations of SGPT and LDH have been noted less frequently. Isolated cases of severe hepatotoxicity have been reported, but do not appear to be dose-related (see Warnings).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In a reported case of overdosage with Depakene (valproic acid) after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION

Depakene (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dose is 60 mg/kg/day. When the total daily dose exceeds 250 mg, it is given in a divided regimen.

The frequency of adverse effects (particularly elevated liver enzymes) may increase with increasing dose. Therefore, the benefit gained by increased seizure control must be weighed against the increased incidence of adverse effects.

Table of Initial Doses by Weight (based on 15 mg/kg/day)

Weight		Total Daily Dose (mg)	Number of Capsules or Teaspoonsful of Syrup		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	0	0	1
25-39.9	55-87.9	500	1	0	1
40-59.9	88-131.9	750	1	1	1
60-74.9	132-164.9	1,000	1	1	2
75-89.9	165-197.9	1,250	2	1	2

As the dosage of valproic acid is raised, blood levels of phenobarbital and/or phenytoin may be affected (see Precautions).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. The capsules should be swallowed without chewing to avoid local irritation of the mouth and throat.

AVAILABILITY

Depakene (valproic acid) is available as orange-coloured soft-gelatin capsules of 250 mg in bottles of 100 (Number 5681, DIN 443840), and as a red syrup containing the equivalent of 250 mg valproic acid, as the sodium salt, per 5 mL in bottles of 450 mL. (Number 5682, DIN 443832). Depakene is a prescription drug (Schedule F).

1. Roberts, E.: Formation and utilization of gamma-aminobutyric acid in brain. In: S.R. Korey & J.I. Nurnberger (Eds.). Progress in Neurobiology. I. Neurochemistry. Hoeber-Harper, New York 1956, pp. 11-25.
2. Simon, D., Penry, K.J.: Sodium Di-N-Propylacetate (DPA) in the Treatment of Epilepsy. Epilepsia 16, 549-573, 1975.
3. Pinder, R.M. et al. Sodium valproate: A Review of its Pharmacological Properties and Therapeutic Efficacy in Epilepsy. Drugs 13, 81-123, 1977.

PHARMACEUTICAL PRODUCTS DIVISION
ABBOTT LABORATORIES, LIMITED
MONTREAL, CANADA H4P 1A5

Full product monograph on request.

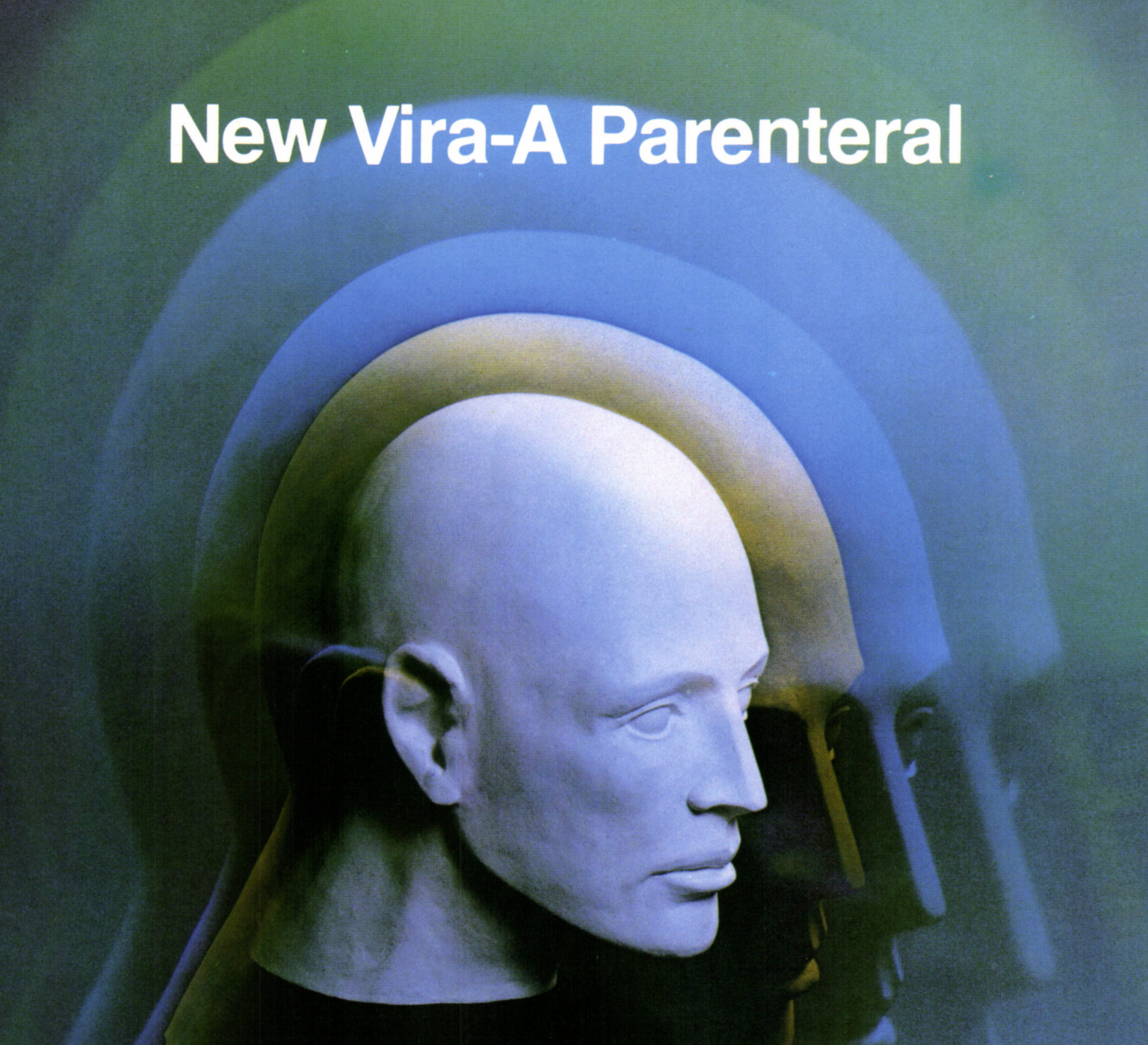
* T.M.

PAAB

MEMBER PMAC

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

New Vira-A Parenteral



Reduces the Mortality Rate Caused by Herpes Simplex Encephalitis from 70% to 28%.

Vira-A Parenteral, a major new development from Parke-Davis Research, significantly reduces the mortality rate of patients with herpes simplex encephalitis.

In controlled studies, Vira-A Parenteral (vidarabine for infusion) reduced the mortality rate caused by herpes simplex encephalitis from 70% to 28%. Over 50% of treated survivors had no or only moderately debilitating neurologic sequelae. (1)

Additional evidence suggests that Vira-A Parenteral prevents the reproduction of herpes simplex without substantial interference with the normal function of the patient's own cells. (2)

All hospital pharmacies have been provided with full prescribing information. If further information is required, contact the Medical Director, Parke, Davis and Company, Ltd.

PARKE-DAVIS

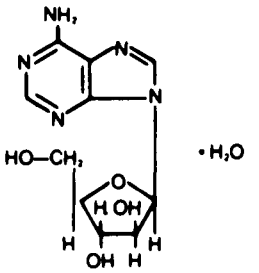
Vira-A

(Sterile Vidarabine for Infusion)

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Antiviral Agent

STRUCTURAL FORMULA AND CHEMISTRY



Molecular Formula: $C_{10}H_{13}N_5O_4.H_2O$

Molecular Weight: 285.2

Chemical Name: 9-β-D-arabinofuranosyl-adenine monohydrate.

Description: Vira-A (Vidarabine) is a white, crystalline solid. The solubility is 0.45 mg/ml at 25°C; and the melting point ranges from 260° to 270°C.

Action. Vira-A, an antiviral drug, is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. Vira-A possesses *in vitro* and *in vivo* antiviral activity against *Herpesvirus* Simplex (Herpes Simplex virus) types 1 and 2 .

The antiviral mechanism of action has not yet been established. The drug is converted into nucleotides which appear to be involved with the inhibition of viral replication. In KB cells infected with Herpes Simplex virus type 1, Vira-A inhibits viral DNA synthesis.

Excretion of Vira-A is principally via the kidneys. Vira-A is rapidly deaminated to Ara-Hx (arabinosylhypoxanthine), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is significantly less than Vira-A . Forty-one to 53% of the daily dose is cumulatively recovered in the urine as Ara-Hx with 1 to 3% appearing as the parent compound. Steady state urinary excretion of Vira-A and Ara-Hx is attained by day 3 following the first infusion. The urinary excretion rate of Vira-A is generally constant over the 12 hours during infusion and the 12 hours post-infusion. There is no evidence of fecal excretion of drug or metabolite.

Indications and Clinical Use. Vira-A is indicated in the treatment of Herpes Simplex virus encephalitis. Controlled studies indicate that Vira-A therapy reduced the mortality rate due to Herpes Simplex virus encephalitis from 70 to 28% .

Vira-A treatment has no beneficial effect on the neurological sequelae present at the time of initiation of therapy. Therefore, early diagnosis and treatment are essential.

Herpes Simplex virus encephalitis should be suspected in patients with a history of an *acute febrile encephalopathy associated with disordered mentation, altered level of* consciousness and focal cerebral signs.

Studies which may support the suspected diagnosis include examination of cerebrospinal fluid and localization of an "intra-cerebral lesion" by brain scan, electroencephalography or computerized axial tomography (CAT).

Brain biopsy is required in order to confirm the etiological diagnosis by means of viral isolation in cell cultures.

Detection of Herpes Simplex virus in the biopsied brain tissue can also be reliably done *by specific fluorescent antibody techniques. Detection of Herpes virus-like particles by* electron microscopy or detection of intranuclear inclusions by histopathologic techniques only provides a presumptive diagnosis.

There are no reports available to indicate that Vira-A for infusion is effective in the management of encephalitis due to varicella-zoster or vaccinia viruses. Vira-A is not effective against infections caused by adenovirus or RNA viruses. It is also not effective against bacterial or fungal infections. There are no data to support efficacy of Vira-A against cytomegalovirus, vaccinia virus, or smallpox virus.

Contraindications. Vira-A is contraindicated in patients who develop hypersensitivity reactions to it.

Warnings. Vira-A should not be administered by the intramuscular or subcutaneous route because of its low solubility and poor absorption.

Precautions. Treatment should be discontinued in the patients with a brain biopsy negative for Herpes Simplex virus in cell culture, unless an obvious diagnosis of Herpes Simplex encephalitis is strongly suspected on the basis of patient history and clinical evaluation.

Special care should be exercised when administering Vira-A to patients susceptible to fluid overloading or cerebral edema. Examples are patients with CNS infections and impaired renal function.

Patients with impaired renal function, such as post-operative renal transplant recipients, may have a slower rate of renal excretion of Ara-Hx. Therefore, the dose of Vira-A may need to be adjusted according to the severity of impairment. These patients should be very carefully monitored.

Patients with impaired liver function should also be monitored for possible adverse effects.

Appropriate hematologic tests are recommended during Vira-A administration since hemoglobin, hematocrit, white blood cells, and platelets may be depressed during therapy.

In addition to hematologic values, close monitoring of liver function, renal function, and neurological status is strongly encouraged while using Vira-A.

A case of post-infectious encephalomyelitis resulting in a lasting mental impairment of the patient has been reported after an initially successful treatment of Herpes Simplex encephalitis with Vira-A. A second course of treatment with the same drug did not alleviate the symptoms . It is important to monitor this complication in patients who survive the acute encephalitic phase of herpes simplex virus infection.

Some degree of immunocompetence must be present in order for Vira-A to achieve clinical response.

Usage In Pregnancy. Vira-A given parenterally is teratogenic in rats and rabbits. Doses of 5 mg/kg or higher given intramuscularly to pregnant rabbits during organogenesis induced fetal abnormalities. Doses of 3 mg/kg or less did not induce teratogenic changes in pregnant rabbits. Vira-A doses ranging from 30 to 200 mg/kg were given intramuscularly to pregnant rats during organogenesis; signs of maternal toxicity were induced at doses of 100 mg/kg or higher and frank fetal anomalies, with an incidence of >90%, were found at dose levels of 150 mg/kg and higher. Lower doses (30-100 mg/kg) had inconsistent, though positive, effects.

A safe dose for the human embryo or fetus has not been established. Consequently, the use of Vira-A in pregnant patients should be limited to life-threatening illnesses where the possible benefits outweigh the potential risks involved.

It is not known whether Vira-A is excreted in human milk. As a general rule nursing should not be undertaken while a patient is under treatment since many drugs are excreted in human milk. However, Vira-A is rapidly deaminated in the gastro-intestinal tract.

Adverse Reactions. The principal adverse reactions involve the gastro-intestinal tract and are anorexia, nausea, vomiting, and diarrhea. These reactions are usually mild to moderate, and seldom require termination of Vira-A therapy. Occasional cases with severe discomfort requiring cessation of therapy have been reported.

Neurological complications have been reported at therapeutic doses. These are tremor, dizziness, hallucinations, disorientation, major motor seizures, confusion, psychosis, and ataxia.

Hematologic clinical laboratory changes noted in controlled studies were a decrease in hemoglobin or hematocrit, total white blood cells, granulocytes and platelets. SGOT elevations were also observed. Other changes occasionally observed were decreases in reticulocyte count and elevated total bilirubin.

Other symptoms which have been reported are sharp pain of parotid or masseter muscles, weight loss, malaise, pruritus, rash, hematemesis, and pain at the injection site.

Symptoms, and Treatment Of Overdosage. Acute massive overdose of the intravenous form has been reported without any serious evidence of adverse effect. Acute water overloading would pose a greater threat to the patient than Vira-A, due to its low solubility. Doses of Vira-A over 20 mg/kg/day can produce bone marrow depression with concomitant thrombocytopenia and leukopenia. If a massive overdose of the intravenous form occurs, hematologic, neurologic, liver, and renal functions should be carefully *monitored. Treatment should be chiefly symptomatic.*

Acute massive oral ingestion is not expected to be toxic because drug absorption from the gastrointestinal tract is minimal. The oral LD_{50} for Vira-A is greater than 5,020 mg/kg in mice and rats.

Dosage and Administration. CAUTION—THE CONTENTS OF THE VIAL MUST BE DILUTED IN AN APPROPRIATE INTRAVENOUS SOLUTION PRIOR TO ADMINISTRATION. RAPID OR BOLUS INJECTION MUST BE AVOIDED.

Dosage. *Herpes Simplex virus encephalitis 15 mg/kg/day for 10 days.*

Method of Preparation. Each vial contains 200 mg of Vira-A per ml of suspension. The solubility of Vira-A in intravenous infusion fluids is limited. Each one mg of Vira-A requires 2.22 ml of intravenous infusion fluid for complete solubilization. Therefore, each one litre of intravenous infusion fluid will solubilize a maximum of 450 mg of Vira- A.

The following intravenous infusion fluids are compatible with Vira-A and may be used as diluents:

5% Dextrose injection USP

5% Dextrose plus 0.9%, 0.33% or 0.45% sodium chloride injection USP *or* Lactated Ringer's injection USP.

Biologic or colloidal fluids (e.g., blood products, protein solutions, etc.) are not suitable as diluents.

Shake the Vira-A well to obtain a homogeneous suspension before measuring and transferring.

Prepare the Vira-A solution for intravenous administration by aseptically transferring *the proper dose of Vira-A into an appropriate intravenous infusion fluid. The intravenous* infusion fluid used to prepare the Vira-A solution may be prewarmed to 36° to 40°C (95° to 100°F) to facilitate solution of the drug following its transference. Depending on the dose to be given, more than one litre of intravenous infusion fluid may be required. Thoroughly agitate the prepared admixture until *completely* clear. Complete solubilization of the drug, as indicated by a completely clear solution, is ascertained by careful visual inspection. Final filtration with an in-line membrane filter (0.45 μ pore size or smaller) is necessary.

Dilution should be made just prior to administration and the solution should be used *within 48 hours. Any unused portion should be discarded.*

Administration. Using aseptic technique, slowly infuse the total daily dose by intravenous infusion (prepared as discussed above) at a constant rate over a 12- to 24-hour period.

Availability. Vira-A (Vidarabine for Infusion), a sterile suspension containing 200 mg/ml is supplied in 5 ml Steri-Vials; packages of 10.

Animal Toxicology

Acute Toxicity. The intraperitoneal LD_{50} for Vira-A ranged from 3,890 to 4,500 mg/kg in mice, and from 2,239 to 2,512 mg/kg in rats, suggesting a low order of toxicity to a single parenteral dose. Hepatic megalocytosis was observed in rats after single, intraperitoneal injections at doses near and exceeding the LD_{50} value. The hepatic megalocytosis appeared to regress over several months. Acute intravenous LD_{50} values could not be obtained because of the limited solubility of Vira-A.

Subacute Toxicity. Rats, dogs, and monkeys have been given daily intramuscular injections of Vira-A as a 20% suspension for 28 days. These animal species showed dose related decreases in hemoglobin, hematocrit, and lymphocytes. Bone marrow depression was also observed in monkeys. Except for localized, injection-site injury and weight gain inhibition or loss, rats tolerated daily doses up to 150 mg/kg, and dogs tolerated daily doses up to 50 mg/kg. Megalocytosis was not seen in the rats dosed by the intramuscular route for 28 days.

In rats, all drug-treated males and the high and mid-dose females had moderate to marked increase in spleen weight at the end of the treatment period.

Rhesus monkeys were particularly sensitive to Vira-A. Daily intramuscular doses of 15 mg/kg were tolerable, but doses of 25 mg/kg or higher induced progressively severe clinical signs of CNS toxicity. Three monkeys given slow intravenous infusions of Vira-A in solution at a dose of 15 mg/kg daily for 28 days had no significant adverse reactions.

Tumorigenicity. Chronic parenteral (IM) studies of vidarabine have been conducted in mice and rats.

In the mouse study, there was a statistically significant increase in liver tumor incidence among the vidarabine-treated females. In the same study, some vidarabine-treated male mice developed kidney neoplasia. No renal tumors were found in the vehicle-treated control mice or the vidarabine-treated female mice.

In the rat study, intestinal, testicular, and thyroid neoplasia occurred with greater frequency among the vidarabine-treated animals than in the vehicle-treated controls. The increases in thyroid adenoma incidence in the high-dose (50 mg/kg) males and the low-dose (30 mg/kg) females were statistically significant.

Hepatic megalocytosis, associated with vidarabine treatment, has been found in short- and long-term rodent (rat and mouse) studies. It is not clear whether or not this represents a preneoplastic change.

Mutagenicity. Results of *in vitro* experiments indicate that vidarabine can be incorporated into mammalian DNA and can induce mutation in mammalian cells (mouse L5178Y cell line). Thus far, *in vivo* studies have not been as conclusive, but there is some evidence (dominant lethal assay in mice) that vidarabine may be capable of producing mutagenic effects in male germ cells.

It has also been reported that vidarabine causes chromosome breaks and gaps when added to human leukocytes *in vitro*. While the significance of these effects in terms of mutagenicity is not fully understood, there is a well-known correlation between the ability of various agents to produce such effects and their ability to produce heritable genetic damage.

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

Prolopa® Roche®

Rx Summary

Indications
Treatment of Parkinson's syndrome with the exception of drug-induced parkinsonism.

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

Warnings
Discontinue levodopa therapy at least 12 hours before initiating 'Prolopa' therapy. Increase dosage of 'Prolopa' 100-25 gradually to avoid inducing CNS side effects (abnormal movements). Observe patients for signs of depression with suicidal tendencies or other serious behavioural changes. Caution in patients with history of psychotic disorders or those receiving reserpine, phenothiazines or tricyclic antidepressants.
Administer with care to patients with history of myocardial infarction or who have atrial, nodal or ventricular arrhythmias.
Safety in patients under 18 years has not been established. In women who are or may become pregnant benefits should be weighed against possible hazards to mother and fetus. Should not be given to nursing mothers.

Precautions
Caution in patients with history of convulsive disorders. Upper gastrointestinal hemorrhage possible in patients with history of peptic ulcer.
Normal activity should be resumed gradually to avoid risk of injury.
Administer with caution to patients on antihypertensive medication; discontinue 12 hours before anesthesia.
Monitor intraocular pressure in patients with chronic wide-angle glaucoma.

Adverse reactions
Most common are abnormal involuntary movements, usually dose dependent, and may disappear or become tolerable after dosage reduction.
Most serious after prolonged therapy are periodic oscillations in performance (end of dose akinesia, on-off phenomenon and akinesia paradoxica).
Nausea, vomiting, arrythmias and orthostatic hypotension occur less frequently than with levodopa alone.
Psychiatric disturbances, including mild elation, depression, anxiety, agitation, aggression, hallucinations and delusions have been encountered.
Consult monograph for complete list of reported adverse effects.

Dosage
Recommended initial dose is one capsule 'Prolopa' 100-25 once or twice daily, increased carefully by one capsule every third or fourth day until an optimum therapeutic effect is obtained without dyskinesias. At upper limits of dosage increments should be made slowly at 2 to 4-week intervals.
Optimal dosage for most patients is 4 to 8 capsules of 'Prolopa' 100-25 daily (400–800 mg levodopa) divided into 4 to 6 doses. Most patients require no more than 6 capsules 'Prolopa' 100-25 (600 mg levodopa) per day.
'Prolopa' 200-50 capsules are intended only for maintenance therapy once the optimal dosage has been determined using 'Prolopa' 100-25 capsules. No patients should receive more than 5 to 6 capsules 'Prolopa' 200-50 daily (1000 to 1200 mg levodopa) during the first year of treatment.
For patients previously treated with levodopa discontinue for 12 hours and initiate with 'Prolopa' 100-25 to provide approximately 15% of previous levodopa dosage. The initial daily dose, however, should not exceed 6 capsules 'Prolopa' 100-25 divided into 4 to 6 doses.

Supply
Blue, flesh-coloured capsules imprinted ROCHE C and PROLOPA 100-25 (black ink) alternating between body and cap each containing 100 mg levodopa and 25 mg benserazide.
Blue, caramel-coloured capsules imprinted ROCHE C and PROLOPA 200-50 (black ink) alternating between body and cap, each containing 200 mg levodopa and 50 mg benserazide.
Bottles of 100.
Product monograph available on request.

® Reg. Trade Mark

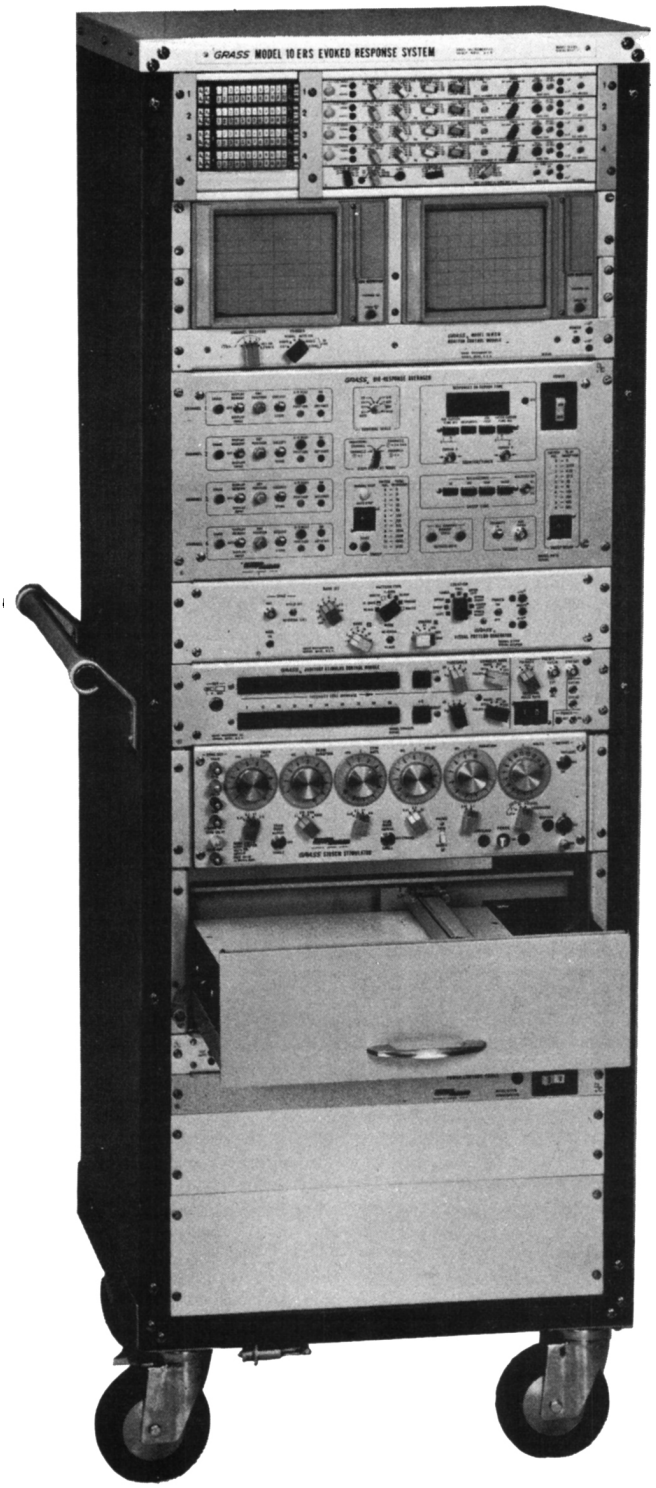
'Prolopa' is listed in provincial formularies. PAAB CCPP

ROCHE® Hoffmann-La Roche Limited
Vaudreuil, Québec J7V 6B3

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

EVOKED RESPONSE SYSTEM

by GRASS



MODEL 10 ERS

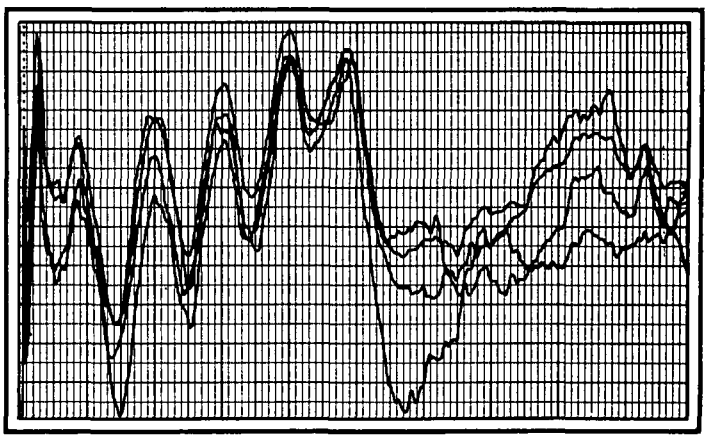
Evoke, amplify, average and record multi-modality cortical potentials with one compact, totally compatible system by Grass. The Model 10 has had lengthy and highly successful clinical and research field trials.

THE BASIC RECORDING SYSTEM:

- **A SIGNAL CONDITIONING MODULE** with 11 position electrode selection, Electrode test, individual channel bandwidth control and calibrator.
- **ISOLATED INPUTS** for electrical safety.
- **BIO-RESPONSE AVERAGER** with a full 1 K memory for each channel for greater resolution. There are four separate 1 K memories, therefore there is no memory division when multiple channels are used. Designed for short latency, rapid-rise time brainstem responses where 1000 or more trials are often needed to extract and resolve submicrovolt signals from noise within a 10 milliseconds post-stimulus period.
- **MODULAR CONSTRUCTION** for 2 or 4 channel recording.
- **DATA DISPLAY — TWO CRT MONITORS** for ongoing data and stored data, plus an X-Y plotter.

OPTIONAL STIMULATORS

- **VISUAL PATTERN GENERATOR** for flash, bars or checks.
- **AUDITORY STIMULUS CONTROL** for click and for masking noise.
- **SOMATOSENSORY STIMULATING MODULE.**



®GRASS MEDICAL INSTRUMENTS SINCE 1935

QUINCY, MASS. 02169 • 617/773-0002

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

a new way to help prevent **migraine**

Until recently, migraine therapy has frequently been inadequate. Agents used to abort or prevent migraine attacks were not only often ineffective but also had many serious limitations due to toxicity. Now, INDERAL has been shown to prevent the pain of migraine attacks effectively, with a low incidence of adverse effects. Its twice daily dosage and high response rate may enhance patient compliance and convenience.

At last, low toxicity and effective prophylaxis for migraine attacks

Clinical studies demonstrate a significant degree of effectiveness in the prevention of migraine attacks.[1,2] Patient response is excellent. A majority of patients respond with decreased frequency and/or severity of migraine attacks.[3,4] INDERAL, however, should be used only prophylactically and is not indicated in the acute treatment of migraine.

Well tolerated: low incidence of adverse effects

INDERAL has been shown to be well tolerated by most patients.[1] The infrequent and usually mild adverse effects are similar to those experienced by patients being treated for hypertension or angina pectoris.

Easy dosage guideline—twice daily

Dosage must be individualized. The initial dose is 40 mg twice daily. The dose may then be gradually increased until optimum migraine prophylaxis is achieved. The usual effective dose range is 80-160 mg per day.

Product Monograph available on request.

REFERENCES:

1. *Børgesen, S.E., Postgrad. Med. J., Vol. 52, (Suppl 4), pp. 163-165, 1976.*
2. *Forssman, B., K-G., Henriksson, V. Johannsson et al., Headache, Vol. 16, pp. 238-245, November 1976.*
3. *Diamond, Seymour and Jose L. Medina, Headache, Vol. 16, No. 1, pp. 24-27, March 1976.*
4. *Malvea, B.P., N. Gwon, J.R. Graham, Headache, Vol. 12, pp. 163-167, January 1973.*

Help prevent the pain of migraine with

inderal*

(propranolol)

...a decade ahead of other beta-blockers

PAAB MEMBER PMAC

*Reg'd TM

2491

Ayerst Laboratories
Division of Ayerst, McKenna & Harrison Inc., Montreal, Canada
Made in Canada by arrangement with IMPERIAL CHEMICAL INDUSTRIES LIMITED

Ayerst Quality has no substitute

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

inderal*

(Propranolol Hydrochloride)

A Beta-Adrenergic Receptor Blocking Agent

INDICATIONS:
a) Hypertension INDERAL is indicated in the treatment of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL can, however, in certain patients be used alone or as an initial agent in those patients in whom, in the judgment of the physician, treatment should be started with a beta-blocker rather than a diuretic. The combination of INDERAL with thiazide-like diuretics and/or peripheral vasodilators has been shown to be compatible and generally more effective than INDERAL alone. Experience with most commonly used antihypertensive agents has not suggested evidence of incompatibility. INDERAL by itself is not recommended for the emergency treatment of hypertensive crises. It is, however, sometimes used as an adjunct to counteract the unwanted effect (tachycardia) of the primary agents used in these situations. **b) Angina Pectoris** INDERAL is indicated for the prophylaxis of angina pectoris. **c) Migraine** INDERAL is indicated for the prophylaxis of migraine headache. It is not indicated for the treatment of acute migraine attacks. **CONTRAINDICATIONS:** INDERAL is contraindicated in: (1) bronchospasm including bronchial asthma; (2) allergic rhinitis during the pollen season; (3) sinus bradycardia and greater than first degree block; (4) cardiogenic shock; (5) right ventricular failure secondary to pulmonary hypertension; (6) congestive heart failure (See WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL. **WARNINGS: Cardiac Failure** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure; therefore, inhibition by means of beta-adrenergic blockade is a potential hazard as it may further depress myocardial contractility and precipitate cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction. **Abrupt Cessation of Inderal Therapy in Angina Pectoris** Severe exacerbation of angina and the occurrence of myocardial infarction have been reported in some patients with angina pectoris following abrupt discontinuation of INDERAL therapy. Therefore, when discontinuation of INDERAL is planned in patients with angina pectoris, the dosage should be gradually reduced over a period of about two weeks and the patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, INDERAL dosage should be reduced stepwise, in four days under close observation. If angina markedly worsens, or acute coronary insufficiency develops, it is recommended that treatment with INDERAL be reinstituted promptly, at least temporarily. In addition, patients with angina pectoris should be warned against abrupt discontinuation of INDERAL. **In Patients Undergoing Elective or Emergency Surgery** The management of patients with angina, being treated with beta-blockers and undergoing elective or emergency surgery, is controversial because beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli, but abrupt discontinuation of therapy with INDERAL may be followed by severe complications. In emergency surgery, since INDERAL is a competitive inhibitor of beta-adrenergic receptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or levarterenol. **PRECAUTIONS:** Some slowing of heart due to unopposed vagal activity is usual in patients receiving INDERAL, however, occasionally severe bradycardia occurs and may lead to vertigo, syncopal attacks or orthostatic hypotension. Patients, especially those with limited cardiac reserve should be monitored for signs of excessive bradycardia. Should the patient become symptomatic the dose of INDERAL should be decreased or, if necessary, the drug should be discontinued. If it is essential to correct the bradycardia, intravenous atropine or isoproterenol should be considered. **ADVERSE REACTIONS:** The most serious adverse effects encountered with INDERAL are congestive heart failure and bronchospasm. Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhea, abdominal pain) are the most common adverse effects reported. Other less frequently reported adverse effects are: (in descending order) cold extremities and exacerbation of Raynaud's phenomenon; congestive heart failure; sleep disturbances including vivid dreams; dizziness, fatigue and bronchospasm. **DOSAGE AND ADMINISTRATION: Oral—Hypertension** Therapeutic response to a given dosage varies between patients therefore dosage must be individually titrated and should be carefully monitored. In the treatment of hypertension INDERAL may be started by administering the drug in two equal daily doses of 40 mg. This may be increased, if necessary, in one week, to 80 mg twice daily, before breakfast and at bedtime. If necessary, the drug may be increased again to 160 mg twice daily. For most patients the dosage is within the range of 160-320 mg daily. A small number of patients may respond to 80 mg daily. Experience to date suggests that in some resistant patients increasing the dosage above 320 mg/day may have an additional effect. Doses above 320 mg/day should be given on a tid or qid regimen. The time course of full blood pressure response is variable. The antihypertensive effect will usually occur within 3 to 7 days after reaching the effective dose. The maximum decrease in blood pressure may occur two to four weeks after initiation of treatment. **Angina pectoris** Dosage must be individualized. Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be increased gradually at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg per day. Occasionally, in resistant patients, dosage as high as 320-400 mg per day has been administered with beneficial results. If treatment is to be discontinued, reduce dosage gradually over a period of about two weeks (See WARNINGS). **Migraine** Dosage must be individualized. The initial dose is 40 mg twice daily. The dose may then be gradually increased until optimum migraine prophylaxis is achieved. The usual effective dose range is 80-160 mg per day. **AVAILABILITY: Tablets** No. 3461 Each scored tablet contains 10 mg propranolol hydrochloride. No. 3464 Each scored tablet contains 40 mg propranolol hydrochloride. No.3468 Each scored tablet contains 80 mg propranolol hydrochloride. No. 3469 Each scored tablet contains 120 mg propranolol hydrochloride.

Product Monograph available on request.

Ayerst Quality has no substitute

AYERST LABORATORIES
Division of Ayerst, McKenna & Harrison Inc.
Montreal, Canada
Made in Canada by arrangement with
IMPERIAL CHEMICAL INDUSTRIES LIMITED

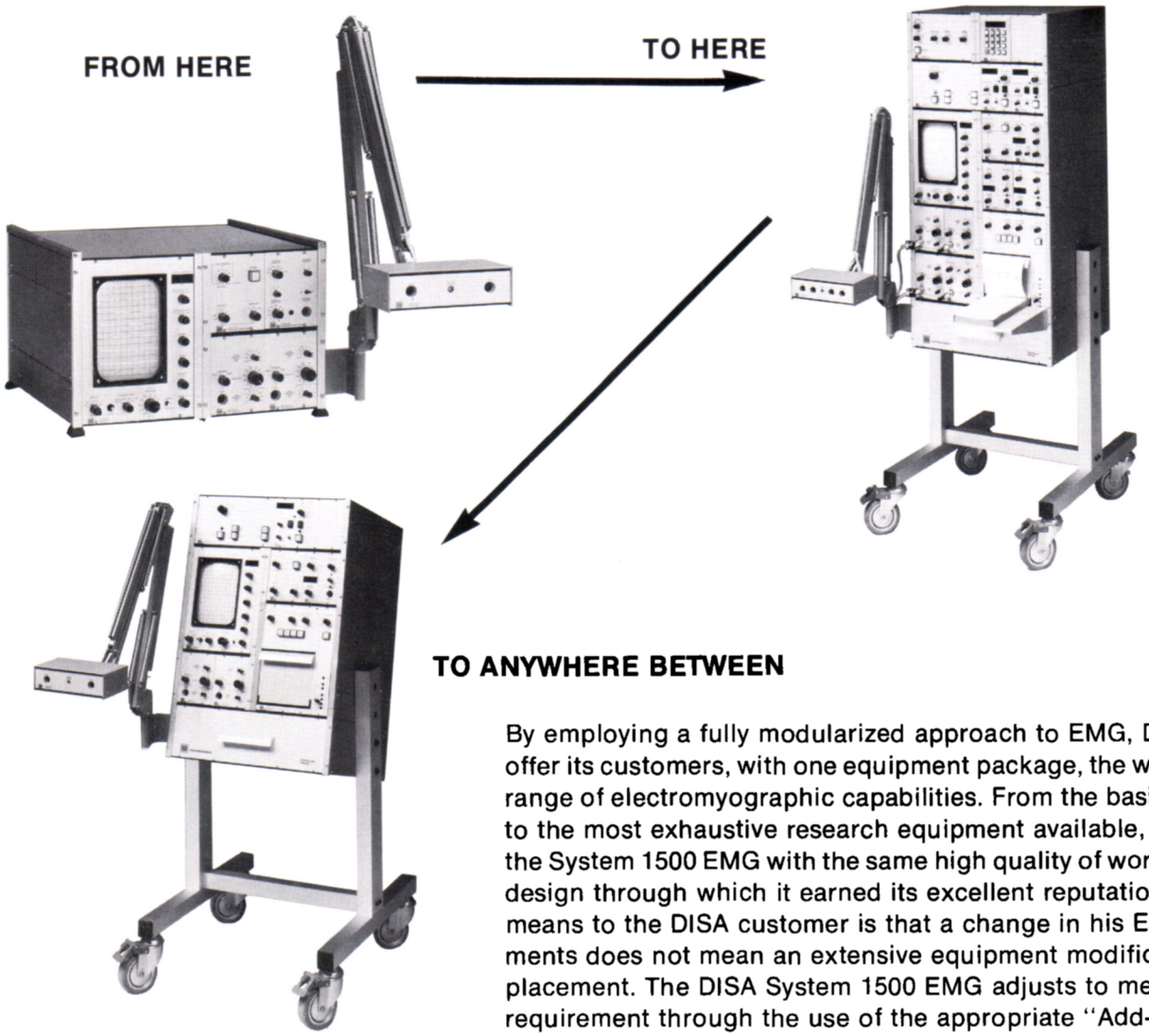
*Reg'd TM
2263

PAAB MEMBER PMAC

https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

DISA

1500 DIGITAL EMG SYSTEMS



By employing a fully modularized approach to EMG, DISA is able to offer its customers, with one equipment package, the widest possible range of electromyographic capabilities. From the basic clinical tool to the most exhaustive research equipment available, DISA employs the System 1500 EMG with the same high quality of workmanship and design through which it earned its excellent reputation. What this means to the DISA customer is that a change in his EMG requirements does not mean an extensive equipment modification or replacement. The DISA System 1500 EMG adjusts to meet the new requirement through the use of the appropriate "Add-On" Module.

DISA has maintained its leading position in the field of EMG development through the recent presentation of the following new capabilities available as 1500 Modules:

- Ultra Low Noise Sensory Amplifier
- Multistim Stimulator
- Alphanumeric Data Printer
- EMG Analyzer
- Interpack Module for Minicomputer Hook-Up

For further information please phone or write to:

DISA ELECTRONICS LTD., 140 Shorting Road, Scarborough, Ont. M1S 3S6
Telephone: (416) 298-2091 Telex: 065-25137

In USA: DISA Electronics, 779 Susquehanna Ave., Franklin Lakes, N.J. 07417 (201) 891-9460
DISA Electronics, 4676 Admiralty Way, Suite 507, Marine Del Ray, CA 90291 (213) 827-1485

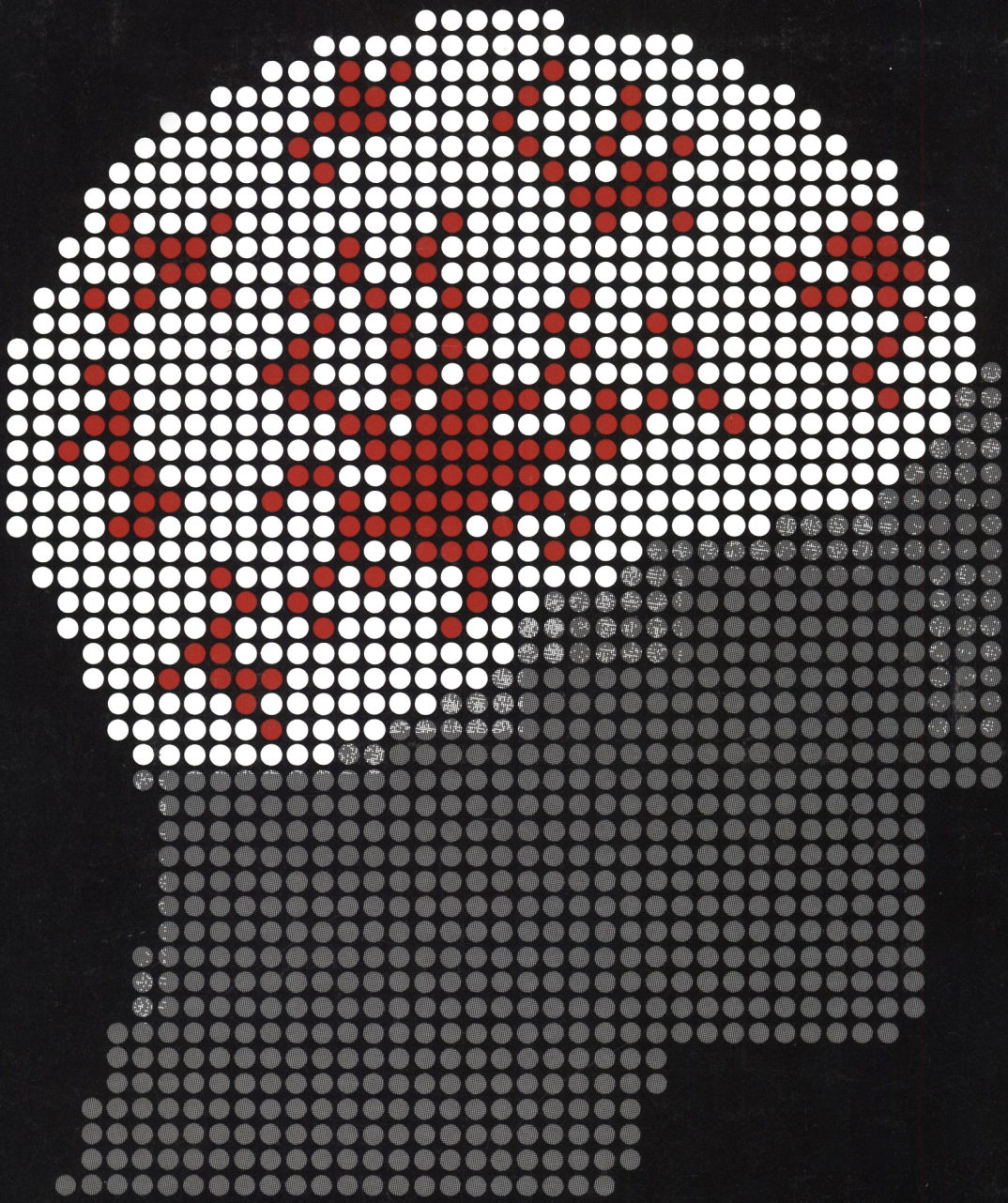
https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

Tegretol®

carbamazepine

To help control refractory generalized tonic-clonic seizures

without excessive sedation



https://doi.org/10.1017/S0317167100023611 Published online by Cambridge University Press

Geigy

For Brief Prescribing Information see Page (V)