

The Canadian Journal of Neurological Sciences

Le Journal Canadien des Sciences Neurologiques



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The Canadian Neurological Society
The Canadian Neurosurgical Society
The Canadian Society of Clinical Neurophysiologists
The Canadian Association of Child Neurology

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May 1993



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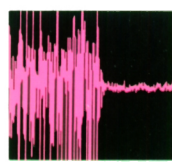
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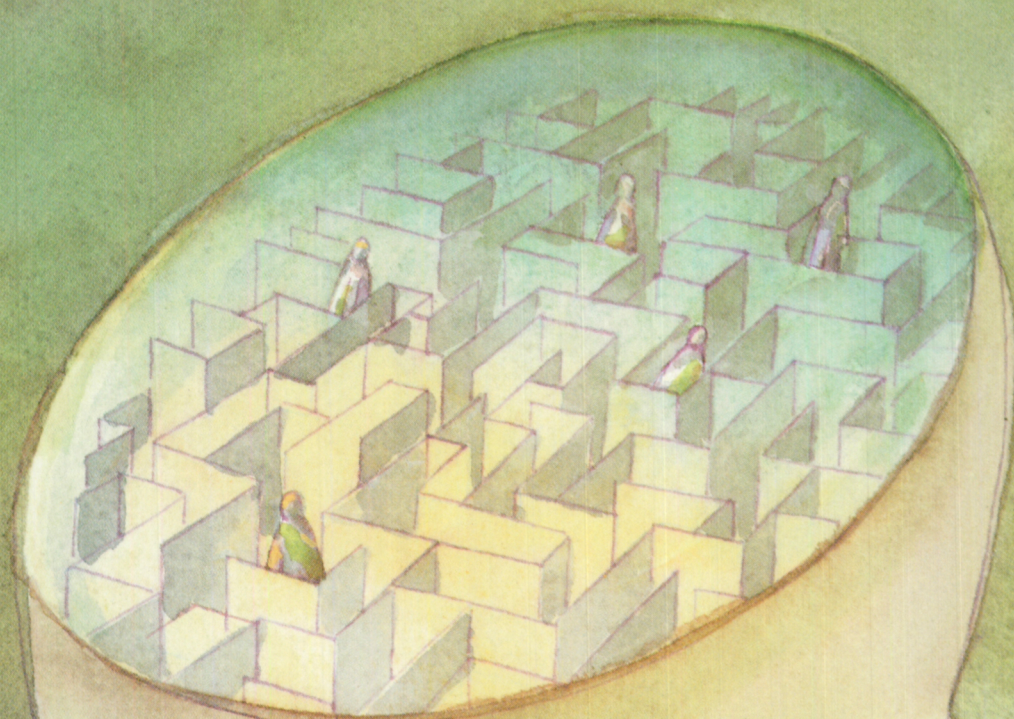
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Research led to the suspicion that GABA played a role in epilepsy, and that if GABA levels were increased, seizures might decrease.^{1,2,3,4} However, the first GABA-related medication, valproic acid, was only introduced in the early 70s in North America. Its mode of action and effect on GABA are unknown.

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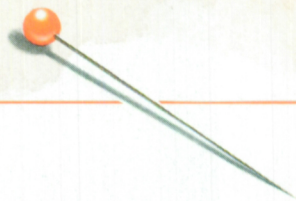
Specific GABA-T inhibitors have been discovered and tested on animals and humans. They reduce GABA-T activity and increase the pre-synaptic GABA pool.⁵

1. Ross M, Craig C J Neurosci 1981;1:1388-1396. 2. Riback C et al Science 1979;205:211-214.
3. Spero L Lancet 1982;2:1319-1322. 4. Meldrum B et al Arch Neurol 1975;32:289-294.
5. Schechter P Br J Clin Pharmacol 1985;27:196-225.

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THERAPEUTIC CLASSIFICATION Inhibitor of Platelet Function

ACTION Ticlid (ticlopidine hydrochloride) is an inhibitor of platelet aggregation. It causes a time and dose-dependent inhibition of platelet aggregation and release of platelet factors, as well as a prolongation of bleeding time. The drug has no significant *in vitro* activity.

The exact mechanism of action is not fully characterized, but does not involve inhibition of the prostacyclin/thromboxane pathways or platelet cAMP.

Ticlid interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. The effect of Ticlid on platelet function is irreversible.

Template bleeding time is usually prolonged by two to five-fold of baseline values with the therapeutic dose of Ticlid.

Upon discontinuation of Ticlid dosing, bleeding time and other platelet function tests return to normal within one week in the majority of patients.

The correlation between ticlopidine hydrochloride plasma levels and activity is still under investigation. Much of the following data was obtained from older patients corresponding to the age of patients participating in clinical trials (mean age: 63 years).

After oral administration of the therapeutic dose of Ticlid, rapid absorption occurs, with peak plasma levels occurring at approximately 2 hours after dosing. Absorption is at least 80% complete. Administration of Ticlid after meals results in an increased (20%) level of ticlopidine hydrochloride in plasma.

Steady state plasma levels of ticlopidine hydrochloride in plasma are obtained after approximately 14 days of dosing at 250 mg BID. The terminal elimination half-life is 4-5 days. However, inhibition of platelet aggregation is not correlated with plasma drug levels.

Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins in a non-saturable manner.

Ticlopidine hydrochloride is metabolized extensively by the liver; no intact ticlopidine hydrochloride is detected in the urine. Unmetabolized ticlopidine hydrochloride is a minor component in plasma after a single dose, but at steady state, ticlopidine hydrochloride is the major component.

Impaired hepatic function resulted in higher than normal plasma levels of unchanged ticlopidine hydrochloride after single doses or after multiple doses.

Inhibition of platelet aggregation is detected within 2 days of administration with 250 mg BID. Maximum platelet aggregation inhibition is achieved 8 to 11 days following dosing with 250 mg BID.

INDICATIONS AND CLINICAL USE Ticlid (ticlopidine hydrochloride) tablets are indicated for reduction of the risk of first or recurrent stroke for patients who have experienced at least one of the following events: Complete Thromboembolic Stroke, Minor Stroke, Reversible Ischemic Neurological Deficit (RIND), or Transient Ischemic Attack (TIA) including Transient Monocular Blindness (TMB).

CONTRAINDICATIONS Ticlid (ticlopidine hydrochloride) is contraindicated in the following conditions: 1. Known hypersensitivity to drug or its excipients. 2. Presence of haematopoietic disorders (such as neutropenia and/or thrombocytopenia). 3. Presence of haemostatic disorder. 4. Conditions associated with active bleeding, such as bleeding peptic ulcer or intracranial bleeding. 5. Severe liver dysfunction.

WARNINGS The following warnings were developed from clinical trial experience with over 2000 patients with cerebrovascular disease who were treated with ticlopidine for as long as 5.8 years.

Neutropenia and Thrombocytopenia: About 2.4% of ticlopidine-treated patients in clinical trials developed neutropenia (defined as an absolute neutrophil count (ANC) below 1.2×10^9 cells/L). The incidence of severe neutropenia (ANC $< 0.45 \times 10^9$ cells/L) was 0.8%. Severe neutropenia occurs during the first 3-12 weeks of therapy, and may develop quickly over a few days. The bone marrow shows a reduction in myeloid precursors. The condition is reversible, and recovery usually occurs within 1-3 weeks after discontinuation of the drug.

In clinical trials, thrombocytopenia (defined as a platelet count of $< 0.8 \times 10^{11}$ cells/L) has been observed in 0.4% of ticlopidine patients. The incidence of thrombocytopenia in patients on ASA or placebo was 0.3% or 0.4% respectively. The thrombocytopenia may occur as an isolated finding or in combination with neutropenia. Thrombocytopenia occurs during the first 3-12 weeks of therapy, and recovery usually occurs after drug discontinuation.

All patients should have a white blood cell count with a differential count and platelet count performed every 2 weeks during the first 3 months of therapy. The incidence of neutropenia or thrombocytopenia after three months of therapy is not appreciably higher than the background levels observed in control groups, and continued periodic monitoring is not warranted. However, for the duration of ticlopidine therapy, any signs or symptoms suggestive of neutropenia or thrombocytopenia should be promptly investigated with complete blood counts and platelet counts.

Hemorrhagic Complications: Prolongation of bleeding time occurs in subjects treated with Ticlid. Purpura and a few cases of more serious hemorrhagic events such as hematemesis, melena, hemorthorax and intracranial bleeding have been reported. Patients should be instructed to watch for signs of bleeding disorders and to report any abnormality to their physician immediately. Ticlid therapy has to be stopped by the patient if a physician is not immediately available for consultation.

Anticoagulant Drugs: Should be avoided as tolerance and safety of simultaneous administration with Ticlid has not been established.

Hepatic Abnormalities: Most patients receiving ticlopidine hydrochloride showed some increase of their alkaline phosphatase values above their baseline and in one-third the increase exceeded the upper reference range. In 6% the value was greater than twice the upper reference range. These increases in alkaline phosphatase were nonprogressive and asymptomatic. In clinical trials, two cases (0.1%) of cholestatic jaundice accompanied by elevated transaminases alkaline phosphatase, and bilirubin levels above $43 \mu\text{mol/L}$ have been observed. Both patients recovered promptly upon drug discontinuation.

Pregnancy: The safety of Ticlid in pregnancy has not been established. It should not be used in pregnant patients.

Pediatric Use: Safety in children has not been studied. Do not use in pediatric patients.

PRECAUTIONS

Clinical Monitoring: All patients have to be carefully monitored for clinical signs and symptoms of adverse drug reactions (see ADVERSE REACTIONS). The signs and symptoms possibly related to neutropenia (fever, chills, sore throat, ulcerations in oral cavity), thrombocytopenia and abnormal hemostasis (prolonged or unusual bleeding, bruising, purpura, dark stool), jaundice (including dark urine, light coloured stool) and allergic reactions should be explained to the patients who should be advised to stop medication and consult their physician immediately if any of these occur.

Laboratory Monitoring: All patients should have a WBC count with differential and platelet count performed every 2 weeks during the first 3 months of therapy. Thereafter, the WBC counts need only be repeated for symptoms or signs suggestive of neutropenia. Liver function tests should be conducted during therapy with Ticlid (ticlopidine hydrochloride) in response to signs and symptoms suggestive of hepatic dysfunction.

Elective Surgery: Ticlid should be discontinued 10 to 14 days prior to elective surgery or dental extraction and bleeding time and thrombocyte count performed before the procedure if clinically indicated.

Emergency Surgery: Prolonged bleeding during surgery may be a problem in ticlopidine-treated patients. Transfusions of fresh platelets would be expected to improve haemostasis in such patients, but there are no data from clinical trials to confirm this expectation. There are data from clinical pharmacology trials that indicate treatment with glucocorticosteroids can normalize bleeding time in ticlopidine treated subjects, but there is no experience with ticlopidine-treated surgical patients to show that such treatment improves haemostasis.

Selection of Patients: Ticlid should be used only for the established indications (see INDICATIONS) and should not be given to patients with haematopoietic disorders, haemostatic disorders, patients suffering from conditions associated with active bleeding (see CONTRAINDICATIONS) and patients anticipating elective surgery. In clinical trials elderly patients tolerated the drug well, but safety in children and pregnant women has not been established.

Specific Precautions: Liver: Ticlid is contraindicated in patients with severe liver dysfunction or cholestatic jaundice. Mild increase of Alkaline Phosphatase may be seen for the duration of the treatment and is inconsequential in the majority of patients (see WARNINGS and CONTRAINDICATIONS).

Kidneys: Ticlid has been well tolerated in patients with moderately decreased renal function. In severe renal disease, caution and close monitoring are recommended.

Gastrointestinal System: Conditions associated with active bleeding, such as bleeding ulcers, constitute contraindication for Ticlid. Clinical judgement and monitoring of stool for occult blood are required for patients

with a history of ulcerative lesions. Trauma: Ticlid should be discontinued temporarily until the danger of abnormal bleeding is eliminated. A single fatal case of intracranial bleeding following head trauma has been reported. The extent to which Ticlid may have contributed to the severity of the bleeding is unknown.

Drug Interactions: The following table outlines the agents which have been concomitantly administered with ticlopidine hydrochloride and the observed interaction if any:

AGENTS	OBSERVED INTERACTION
Acetylsalicylic acid (ASA)	Potential of ASA's effect on collagen-induced platelet aggregation (see WARNINGS).
Antipyrine and products metabolized by hepatic microsomal enzymes	30% increase in t1/2 of antipyrine.
Theophylline	Dose of products metabolized by hepatic microsomal enzymes to be adjusted when starting or stopping concomitant therapy with ticlopidine hydrochloride. t1/2 of theophylline increased from 8.6 to 12.2 hr along with a comparable reduction in its total plasma clearance.
Digoxin	Approximately 15% reduction in digoxin plasma levels, (little or no change in digoxin's efficacy expected).
Cimetidine	Chronic administration of cimetidine induced a 50% reduction in clearance of a single dose of ticlopidine hydrochloride.
Antacids	20% decrease in ticlopidine plasma level when administered after antacids.
Phenobarbital	No interaction reported.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, TICLID was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (however see WARNINGS) without evidence of clinically significant adverse interactions.

ADVERSE REACTIONS Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 1 to 5 years duration, discontinuation of Ticlid (ticlopidine hydrochloride) due to one or more adverse effects was required in 20.9% of patients. In these same trials, ASA and placebo led to discontinuation in 14.5% and 6.7% of patients respectively. The incidence rates of adverse reactions listed in the following table were derived from multicenter, controlled clinical trials comparing ticlopidine HCl, placebo, and ASA over study periods of up to 5 years. The rates are based on adverse reactions considered probably drug-related by the investigator. Adverse experiences occurring in greater than one percent of patients treated with Ticlid in controlled clinical trials are shown in the Table below.

PERCENT OF PATIENTS IN CONTROLLED STUDIES

Event	Ticlid (n=2048)	ASA (n=1527)	Placebo (n=536)	Ticlid (n=2048)	ASA (n=1527)	Placebo (n=536)	
	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence	
Diarrhea	12.5(6.3)*	5.2(1.8)	4.5(1.7)	Nausea	7.0(2.6)	6.2(1.9)	1.7(0.9)
Dyspepsia	7.0(1.1)	9.0(2.0)	0.9(0.2)	Rash	5.1(3.4)	1.5(0.8)	0.6(0.9)
GI Pain	3.7(1.9)	5.6(2.7)	1.3(0.4)	Neutropenia	2.4(1.3)	0.8(0.1)	1.4(0.4)
Purpura	2.2(0.2)	1.6(0.1)	0.0(0.0)	Vomiting	1.9(1.4)	1.4(0.9)	0.9(0.4)
Flatulence	1.5(0.1)	1.4(0.3)	0.0(0.0)	Pruritus	1.3(0.8)	0.3(0.1)	0.0(0.0)
Dizziness	1.1(0.4)	0.5(0.4)	0.0(0.0)	Anorexia	1.0(0.4)	0.5(0.4)	0.0(0.0)

* Percent of patients (in parentheses) discontinuing clinical trials due to event
The incidence of thrombocytopenia in these controlled studies was 0.4% in the Ticlid and placebo groups of patients and 0.3% in the ASA patient population.

The following rare events have been reported and their relationship to Ticlid is uncertain. Pancytopenia, hemolytic anemia with reticulocytosis, thrombocytopenic thrombotic purpura, jaundice, allergic pneumonitis, systemic lupus (positive ANA), peripheral neuropathy, vasculitis, serum sickness, arthropathy, hepatitis, nephrotic syndrome, myositis, and hyponatremia.

Gastrointestinal: Ticlid therapy has been associated with a variety of gastrointestinal complaints including diarrhea and nausea. The majority of cases are mild and transient in nature and occur within 3 months of initiation of therapy. Typically, events are resolved within 1-2 weeks without discontinuation of therapy. If the effect is severe or persistent, therapy should be discontinued.

Hemorrhagic: Ticlid has been associated with a number of bleeding complications such as ecchymosis, epistaxis, hematuria, conjunctival hemorrhage, gastrointestinal bleeding, and postoperative bleeding. Intracerebral bleeding was rare in clinical trials with Ticlid, and was no more than that seen with comparator agents (ASA, placebo).

Rash: Ticlopidine hydrochloride has been associated with a maculopapular or urticarial rash (often with pruritus). Rash usually occurs within 3 months of initiation of therapy, with a mean time to onset of 11 days. If drug is discontinued, recovery should occur within several days. Many rashes do not recur on drug rechallenge. There have been rare reports of more severe rashes.

Altered Laboratory Findings: Hematological: Neutropenia and rarely thrombocytopenia have been associated with Ticlid administration (see WARNINGS).

Liver: Ticlid therapy has been associated with elevations of alkaline phosphatase (See WARNINGS). Maximal changes occur within 1-4 months of therapy initiation. No further progressive increases are seen with continuous therapy. Occasionally patients developed deviations in bilirubin and SGOT.

Cholesterol: Chronic Ticlid therapy has been associated with increased serum cholesterol and triglycerides. Serum levels of HDL-C, LDL-C, VLDL-C, and triglycerides are increased 8-10% after 1-4 months of therapy. No further progressive elevations are seen with continuous therapy. The ratios of the lipoprotein subfractions are unchanged. The effect is not correlated with age, sex, alcohol use, or diabetes.

SYMPTOMS AND TREATMENT OF OVERDOSAGE One case of deliberate overdosage with Ticlid (ticlopidine hydrochloride) has been reported in a foreign postmarketing surveillance program. A 38 year old male took a single 6000 mg dose of Ticlid (equivalent to 24 standard 250 mg tablets). The only abnormalities reported were increased bleeding time and increased SGPT. No special therapy was instituted and the patient recovered without sequelae. Based on animal studies, overdosage may result in severe gastrointestinal intolerance.

In the case of excessive bleeding after injury or surgery, standard supportive measures should be carried out if indicated, including gastric lavage, platelet transfusion and use of corticosteroids.

DOSE AND ADMINISTRATION The recommended dose of Ticlid (ticlopidine hydrochloride) is 250 mg twice daily with food. Ticlid should be taken with meals to minimize gastrointestinal intolerance.

PHARMACEUTICAL INFORMATION

(i) Drug Substance

Description: Ticlopidine hydrochloride is a white crystalline solid. It is freely soluble in water and self buffers to a pH of 3.6. It also dissolves freely in methanol, is sparingly soluble in buffer solutions above pH 6.0, methylene chloride and ethanol, and is slightly soluble in acetone.


(ii) Composition: Ticlopidine hydrochloride tablets are provided, as white film coated tablets containing ticlopidine hydrochloride, citric acid, povidone, microcrystalline cellulose, corn starch, stearic acid powder, magnesium stearate and water. The coating suspension consists of hydroxypropyl methylcellulose, titanium dioxide and polyethylene glycol. The ink for printing contains D&C yellow #10 aluminum lake and FD&C blue #1 aluminum lake.

(iii) Stability and Storage Recommendations: Store at room temperature. Ticlid tablets should be dispensed in light resistant containers. Blister packs should not be exposed to light.

AVAILABILITY Ticlid 250 mg tablets are oval white film coated tablets printed using green ink with Ticlid above half an arrow on one side, "250" above half an arrow on the other side. The tablets are available in 2-week Patient Starter Packs of 28 tablets (2 blisters of 14 tablets). They are also available in boxes of 56 (4 x 14) tablets and 168 (12 x 14) tablets.

For the first 3 months of therapy, only request or dispense the 14 days supply of tablets (see PRECAUTIONS). Product Monograph available to Health Professionals on request.

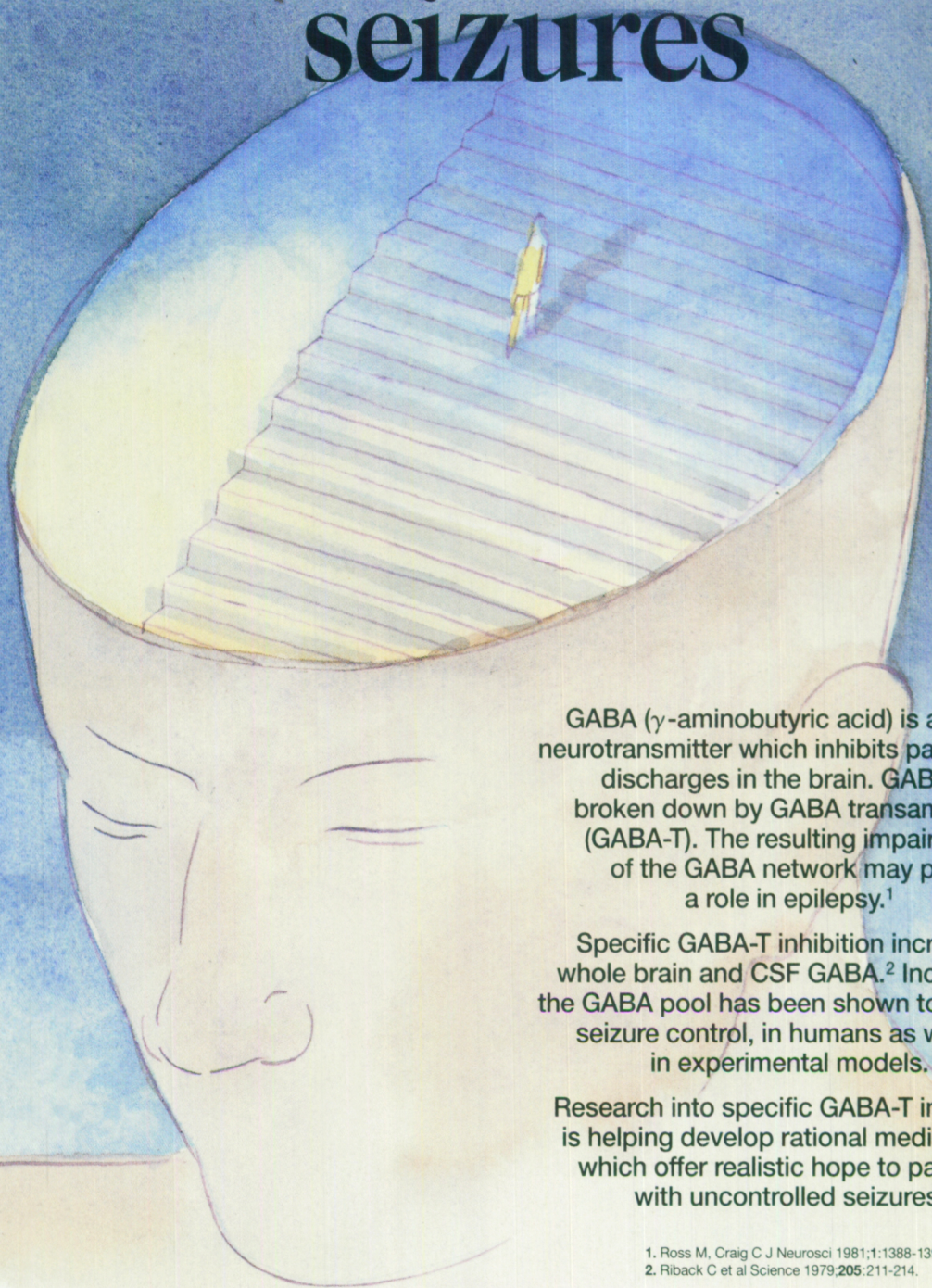
REFERENCES 1. Adapted from Feinberg W. Antithrombotic therapy in stroke and transient ischemic attacks. *American Family Physician* 1989;40(Suppl):535-95. 2. Hass WK et al. Ticlopidine Aspirin Stroke Study (TASS). A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Eng J Med* 1989;321:501-7. 3. Gent M et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *The Lancet* 1989 Jun;1215:20. 4. Ticlopidine Aspirin Stroke Study (TASS). Data on file, Syntex Inc., Vol.52, Oct 1989. 5. Compendium of Pharmaceuticals and Specialties, 1992. 6. Ticlid product monograph.

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See pages vi, vii

Towards a rational treatment of epileptic seizures



GABA (γ -aminobutyric acid) is a major neurotransmitter which inhibits paroxysmal discharges in the brain. GABA is broken down by GABA transaminase (GABA-T). The resulting impairment of the GABA network may play a role in epilepsy.¹

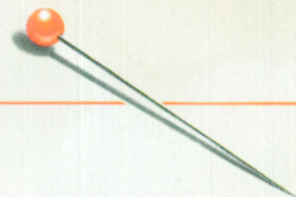
Specific GABA-T inhibition increases whole brain and CSF GABA.² Increasing the GABA pool has been shown to improve seizure control, in humans as well as in experimental models.

Research into specific GABA-T inhibition is helping develop rational medications which offer realistic hope to patients with uncontrolled seizures.

1. Ross M, Craig C J Neurosci 1981;1:1388-1396.
2. Riback C et al Science 1979;205:211-214.



Pinpointing GABA-T for better seizure control



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TRANSPLANTATION

A proven, effective treatment for end-stage organ disease.

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On peut facilement reconnaître le jeune patient épileptique traité au Tegretol® CR.

Excellent contrôle des crises

Tegretol CR (carbamazépine à libération contrôlée) maîtrise les crises chez de nombreux patients, causant peu d'impact sur la fonction cognitive^{1,2,3,4}. Contrairement aux médicaments tels la phénytoïne, Tegretol CR permet à de nombreux patients de penser clairement et de donner le meilleur d'eux-mêmes^{1,2,3,4}.

Taux sanguins uniformes

Tegretol CR cause moins de "hauts et de bas" dans les taux sanguins que le Tegretol conventionnel. Les effets secondaires sont ainsi réduits et le modèle de fonction cognitive est plus stable^{5,6}.

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Lorsque vous instituez ou remplacez un traitement, pensez au Tegretol CR. Il est présenté en comprimés à 200mg et 400 mg facilement divisibles pour une plus grande souplesse d'administration et améliorer l'observance du patient.

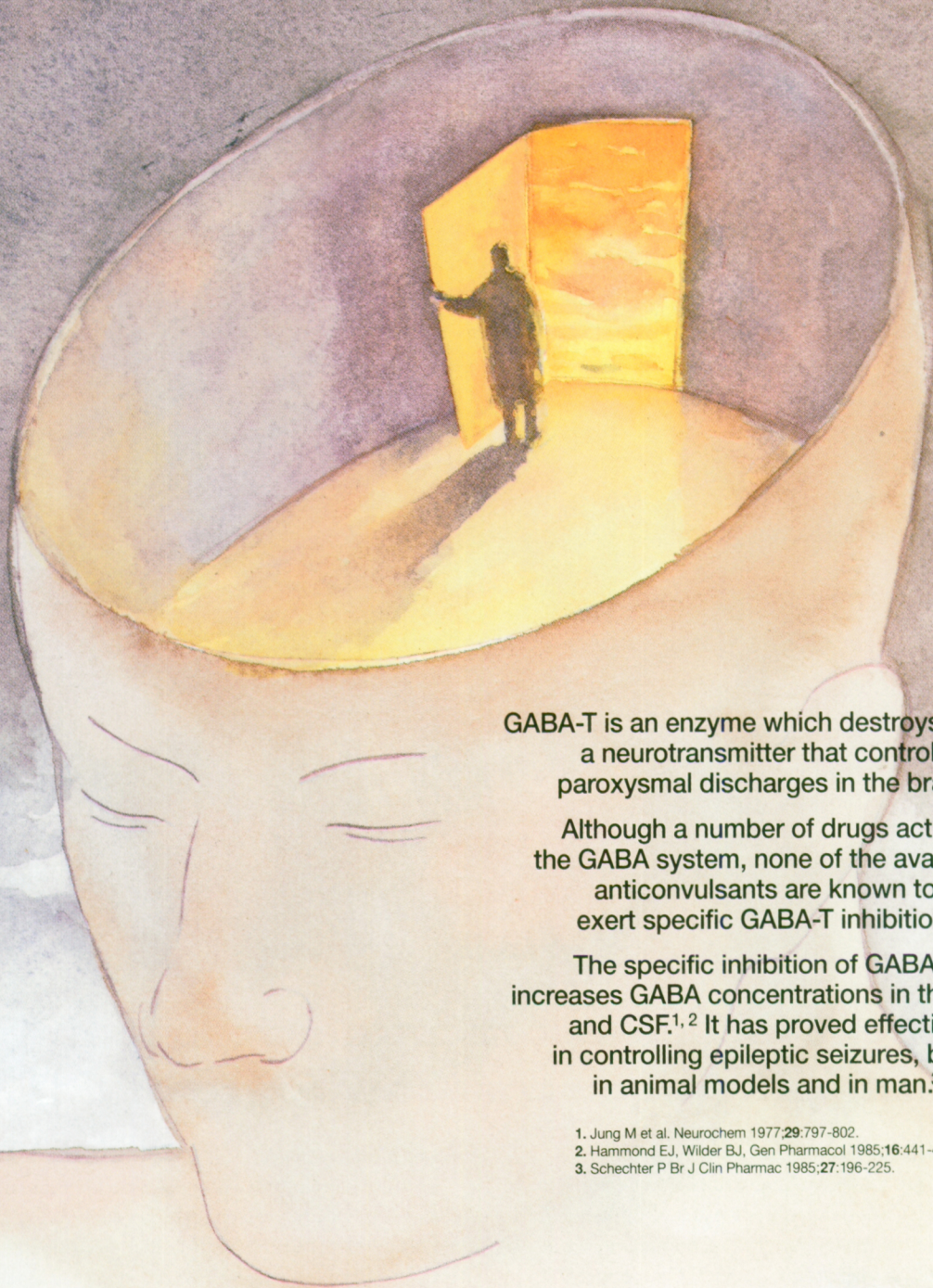


TEGRETOL® CR.
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MEMBRE
FPAAB
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New hope for better seizure control



GABA-T is an enzyme which destroys GABA, a neurotransmitter that controls paroxysmal discharges in the brain.

Although a number of drugs act on the GABA system, none of the available anticonvulsants are known to exert specific GABA-T inhibition.

The specific inhibition of GABA-T increases GABA concentrations in the brain and CSF.^{1,2} It has proved effective in controlling epileptic seizures, both in animal models and in man.³

1. Jung M et al. *Neurochem* 1977;**29**:797-802.

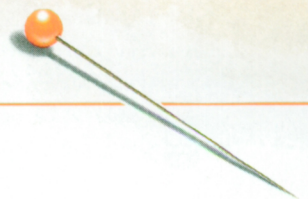
2. Hammond EJ, Wilder BJ, *Gen Pharmacol* 1985;**16**:441-447.

3. Schechter P Br J Clin Pharmacol 1985;**27**:196-225.

Pinpointing GABA-T for better seizure control



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NOW ELDEPRYL IS INDICATED FOR FIRST LINE THERAPY.

Now you can do more than deal with the disability of Parkinson's disease. You can delay it with Eldepryl first line. □ In newly diagnosed patients, Eldepryl can significantly retard the worsening of symptoms^{2,3} and delay the need for levodopa therapy.^{2,4,5} □ In fact, Eldepryl can delay the onset of disability and thereby prolong functional life by as much

as one year.^{1,4} □ As well, Eldepryl appears to have a remarkable safety profile. It has been generally well-tolerated with few side effects.^{4,6,7} □ So when you see patients with Parkinson's disease, prescribe



**HOLD BACK THE DISABILITY
OF PARKINSON'S DISEASE
FOR AN EXTRA YEAR.¹**

Eldepryl first line. It's their first line of defence against the progression of disability.

ELDEPRYL[®] FIRST LINE
selegiline hydrochloride

DELAYS THE PROGRESSION OF DISABILITY.

PAAB

For brief prescribing information see page xx



Prescribing Information

ACTION AND CLINICAL PHARMACOLOGY

SIBELIUM® (flunarizine hydrochloride) prevents the deleterious effects of cellular calcium overload by reducing excessive transmembrane fluxes of calcium. Flunarizine does not interfere with normal cellular calcium homeostasis. Flunarizine also has antihistaminic properties.

The effects of flunarizine in the prophylaxis of migraine are most pronounced with regards to the reduction of the frequency of attacks. The severity of migraine attacks improves to a lesser extent, while little or no effect is seen on the duration of migraine episodes.

The pharmacokinetic parameters of orally administered flunarizine are summarized in Table 1.

Flunarizine is well absorbed; peak plasma levels are attained 2 to 4 hours after oral administration in healthy volunteers. Plasma concentrations increase gradually during chronic administration of 10 mg daily, reaching a steady state level after 5 to 6 weeks of drug administration. Steady state plasma levels remain constant during prolonged treatment although there is substantial interindividual variation; plasma levels range between 39 and 115 ng/mL.

In 50 elderly patients (mean age 61 years), with intermittent claudication, long term (median 6 months) treatment with flunarizine, 10 mg per day, yielded fairly constant steady state plasma levels albeit with considerable interindividual differences. While plasma flunarizine levels were between 50 ng/mL and 100 ng/mL in 46% of patients, individual values ranged from less than 20 ng/mL to 580 ng/mL. Flunarizine was devoid of cumulative effects as shown by repeated measurements.

As indicated by the large apparent volume of distribution (mean = 43.2 L/kg; range = 26.7 - 79.9 L/kg) seen after the oral administration of 30 mg in healthy volunteers, flunarizine is extensively distributed to tissues. Drug concentrations in tissues, particularly adipose tissue and skeletal muscle, were several times higher than plasma levels.

Flunarizine is 99.1% bound; 90% is bound to plasma proteins and 9% distributed to blood cells, leaving less than 1% present as free drug in the plasma water.

Flunarizine is metabolized principally through N-oxidation and aromatic hydroxylation. During a 48 hour period after a single 30 mg dose, minimal urinary (<0.2%) and fecal (<6%) excretion of flunarizine and/or its metabolites was found. This indicates that the drug and its metabolites are excreted very slowly over a prolonged period of time.

Flunarizine has a long elimination half-life of about 19 days.

Table 1: Pharmacokinetic parameters of flunarizine in healthy volunteers

No. of Doses	Dose (mg)	C _{max} (ng/mL)	T _{max} (h)	AUC (ng/mL·h)	t _{1/2α} (h)	Cl _p (mL/min)	t _{1/2β} (mean days) [range]
Single Dose Studies	5	30.5	2-4	133 ^a	2.4	443.7	4 [2-8]
	10	81.5		615 ^d	2.8		
	20	117.0	1091 ^d	3.6			
	30	81.6	1169 ^d	5			
Multiple Dose Studies	5	18.1 ^b	2-6	1264 ^d 1678 ^d	301.2	[4-19]	
	14	10					38.8 ^b
	14	15					68.4 ^b
	57	10					114.5

a Area under curve 0 to 8 hours

c Area under curve 0 to 168 hours

b Plasma concentrations at 2 hours

d Area under curve 0 to 24 hours

INDICATIONS AND CLINICAL USE

SIBELIUM (flunarizine hydrochloride) is indicated in the prophylaxis of classic and common migraine. The safety of flunarizine in long-term use (i.e. for more than 4 months) has not been systematically evaluated in controlled clinical trials. Flunarizine is not indicated in the treatment of acute migraine attacks.

CONTRAINDICATIONS

SIBELIUM (flunarizine hydrochloride) is contraindicated in patients with known hypersensitivity to the drug. Flunarizine is contraindicated in patients with a history of depression or pre-existing extrapyramidal disorders.

WARNINGS

Clinical studies indicate that flunarizine treatment, even at recommended doses, can produce motor disturbances in subjects who did not show previous neurological deficits. The clinical symptoms resemble Parkinson's disease, however, they do not improve with antiparkinson medication. Experience to date suggests that in most instances the extrapyramidal symptoms tend to be reversible following discontinuation of flunarizine treatment. It is recommended that patients on flunarizine therapy be followed closely and monitored at regular intervals so that extrapyramidal symptoms may be detected early, and if necessary, treatment discontinued. Clinical studies indicate that flunarizine can, even at recommended doses, precipitate depression, mostly in younger patients.

PRECAUTIONS

Since sedation and/or drowsiness occur in some patients during treatment with SIBELIUM (flunarizine hydrochloride) (see ADVERSE REACTIONS), patients should be cautioned against activities which require alertness or rapid, precise responses (e.g. operating machinery or a motor vehicle) until the response to the drug has been determined.

Use in Pregnancy

To date, there are no data to support the use of flunarizine during pregnancy. It should therefore not be administered to pregnant women unless the anticipated benefits outweigh the potential risks.

Use During Lactation

Studies in lactating dogs have shown that flunarizine is excreted in milk. The concentration of flunarizine in milk is much greater than that in plasma. Breast feeding should therefore be discouraged in women taking flunarizine.

Use in the Elderly

The efficacy of flunarizine in the prophylaxis of migraine has not been established in elderly subjects.

Use in Children

The efficacy of flunarizine in the prophylaxis of migraine has not been established in patients younger than 18 years of age.

Use in Patients with Parkinson's Disease

Flunarizine is contraindicated in patients with pre-existing Parkinson's disease or other extrapyramidal disorders (see CONTRAINDICATIONS). Clinical studies indicate that prolonged flunarizine treatment, even at recommended doses, can produce motor disturbances in elderly subjects who did not show previous neurological deficits. The clinical symptoms resemble Parkinson's disease however, they do not improve with antiparkinson medication. Experience to date suggests that in most instances the extrapyramidal symptoms tend to be reversible following discontinuation of flunarizine treatment. It is recommended that patients on flunarizine therapy be followed closely so that extrapyramidal symptoms may be detected early and if necessary, treatment discontinued.

Use in Depressive Patients

Clinical studies indicate that flunarizine can, even at recommended doses, precipitate depression mostly in younger patients (see CONTRAINDICATIONS).

Endocrine Effects

Galactorrhea has been reported in a few female patients, some of whom were also on oral contraceptives, within the first two months of flunarizine treatment. Discontinuation of flunarizine therapy resolved the galactorrhea in most cases. Flunarizine therapy caused a mild but significant elevation of serum prolactin levels while GH, LH, FSH and TSH levels did not show significant variation. Two cases of menstrual irregularities have been reported.

Drug Interactions

Evidence from therapeutic trials in epileptic patients indicates that whereas flunarizine does not affect the kinetics of phenytoin, carbamazepine and valproic acid, it does decrease the plasma levels of mephenytoin. Furthermore, steady state levels of flunarizine are reduced by coadministration of two or more anticonvulsants. This is considered to be a result of enhanced first pass metabolism of flunarizine as a consequence of liver enzyme induction by the anticonvulsant medications.

In other studies, flunarizine was shown not to affect the anticoagulant effect of warfarin sodium or the hypoglycemic effect of glibenclamide and insulin.

Use in Patients with Impaired Hepatic Function

Flunarizine is metabolised by the liver, therefore care should be exercised when flunarizine is given to patients with compromised liver function.

ADVERSE REACTIONS

In clinical trials with SIBELIUM (flunarizine hydrochloride) migraine patients, drowsiness (also described as sedation or fatigue) as well as weight gain (and/or increased appetite) occurred fairly frequently, in the order of 20 and 15%, respectively. Of 840 migraine patients, 23 (2.7%) and 9 (1.1%) required withdrawal from flunarizine therapy due to drowsiness and weight gain, respectively.

The most serious side effect encountered in migraineurs during clinical trials was depression. Of 840 migraine patients, 11 (1.3%) were withdrawn due to depression. International post-marketing experience suggests that patients between 20 and 54 years of age with a personal or familial history of depression are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Clinical experience in other indications and epidemiologic surveys suggest that extrapyramidal symptoms may develop during flunarizine therapy. Elderly patients are particularly at risk (see CONTRAINDICATIONS and PRECAUTIONS).

Other side effects encountered in clinical trials for migraine prophylaxis included the following:

Gastrointestinal:	Heartburn, nausea, emesis, gastralgia;
Central Nervous System:	Insomnia and sleep change, anxiety, dizziness/vertigo;
Miscellaneous:	Dry mouth, asthenia, muscle aches, skin rash

SYMPTOMS AND TREATMENT OF OVERDOSE

There has been no experience to date with overdosage of SIBELIUM (flunarizine hydrochloride). Based on the pharmacological properties of the drug, sedation and asthena may be expected to occur. Treatment should consist of induction of emesis or gastric lavage and supportive measures.

DOSAGE AND ADMINISTRATION

The usual adult dosage of SIBELIUM (flunarizine hydrochloride) 10 mg per day administered in the evening. Patients who experience side effects may be maintained on 5 mg HS.

Duration of Therapy

Clinical experience indicates that the onset of effect of flunarizine is gradual and maximum benefits may not be seen before the patient has completed several weeks of continuous treatment. Therapy therefore should not be discontinued for lack of response before an adequate time period has elapsed, e.g. 6-8 weeks.

DOSAGE FORMS

Composition: Each red and grey capsule contains 5 mg flunarizine (as hydrochloride).

Availability: SIBELIUM flunarizine hydrochloride capsules are available in blister packages of 60 capsules.

Storage: SIBELIUM capsules 5 mg should be stored at or below 25°C, protected from light and moisture.

Product monograph available on request.

REFERENCES

- Edmeads J. *Advances in Migraine Prophylaxis*. Reprinted from a symposium held in Banff, Alberta at the XXVth meeting of the Canadian Congress of Neurological Sciences, June 1990. 2. Sibelium product monograph. 3. Compendium of Pharmaceuticals and Specialties, 26th edition, 1991. 4. Todd PA; Benfield P. Flunarizine: A reappraisal of its pharmacological properties and therapeutic use in neurological disorders. *Drugs* 1989; 38(4): 481-99. 5. Borgers M et al. Selective blockade of Ca²⁺-overload by flunarizine. *Inter Angio* 1984; 3:25-31. 6. Martinez-Lage JM. Flunarizine (Sibelium) in the prophylaxis of migraine. An open, long-term, multicenter trial. *Cephalalgia* 1988; 8 (Suppl 8): 15-20. 7. Amery WK et al. Flunarizine, a calcium entry blocker in migraine prophylaxis. *Headache* J 1985; 25(5): 249-54. 8. Ranskin NH. In: *Headache*. Second edition, 1988. 9. Diamond S; Millstein E. Current concepts of migraine therapy. *J Clin Pharmacol* 1988; 8: 193-9. 10. Edmeads J. *Headache*. Second edition, 1988.

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SIBELIUM
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IF YOU'RE LOOKING FOR EFFECTIVE MIGRAINE PROPHYLAXIS, YOU'VE JUST STRUCK GOLD.

Reduces migraine frequency

A recent clinical study published in *The Canadian Journal of Neurological Sciences* makes it clear; Sibelium is very effective in preventing migraine attacks.¹ In fact, the percentage reduction in attack frequency with Sibelium was twice that of propranolol.¹

Reduces migraine severity

In the most common type of migraine, migraine without aura, 73% of patients responded to Sibelium, compared with 44% to propranolol ($p=0.035$).¹ Several studies have also shown Sibelium reduces the severity of migraine and many patients have become attack-free.²⁻⁵



Offers better tolerability

Sibelium had fewer side effects and was better tolerated than propranolol.¹ There were no unwanted effects on cardiovascular function with Sibelium, whereas propranolol significantly reduced blood pressure and heart rate.¹

Suitable for many patients

Now you know what you may have already suspected. For patients who...

- suffer 3 or more attacks per month,
- have unusually severe or prolonged attacks, or
- find acute therapy ineffective,

...Sibelium is worth its weight in gold.

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Good news for patients taking oral contraceptives: Epival does not appear to be associated with O.C. failure.¹



Epival: For their epilepsy... and their lifestyles

A significant benefit for the newly diagnosed child with absence: Epival not only controls most patients with absence⁵, but is also effective against primary generalized seizures with tonic-clonic manifestations.^{4,8}



Proven efficacy in a broad range of primary generalized seizures^{4,5}

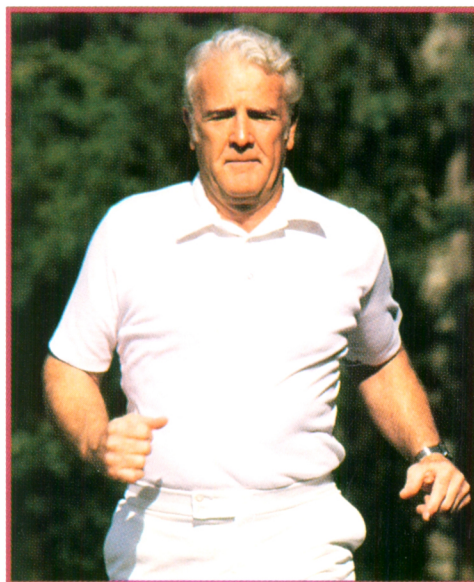
Little effect on learning and cognition³

Relatively few clinically substantiated drug interactions^{2,9}

Wide therapeutic range⁶ for easy titration

Most patients (85%) unable to tolerate other forms of valproic acid were able to take Epival⁷

A dual benefit for the elderly: Epival has relatively few clinically substantiated drug interactions^{2,9} and is rarely associated with ataxia or dyskinesias.³



Epival^{*}
divalproex sodium
A drug of choice in
primary generalized seizures

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