Volume 21 Number 4 November 1994

THE CANADIAN JOURNAL OF Neurological Sciences

LE JOURNAL CANADIEN DES Sciences Neurologiques

AN INTERNATIONAL JOURNAL / UN JOURNAL INTERNATIONAL

The official Journal of: The Canadian Neurological Society, The Canadian Neurosurgical Society, The Canadian Society of Clinical Neurophysiologists, The Canadian Association for Child Neurology

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

Volume 21 Number 4 November 1994

THE CANADIAN JOURNAL OF Neurological Sciences

LE JOURNAL CANADIEN DES Sciences Neurologiques

Volume 21 Number 4 November 1994

THE CANADIAN JOURNAL OF Neurological Sciences

LE JOURNAL CANADIEN DES Sciences Neurologiques

The official journal of: / La Revue officielle de:

The Canadian Neurological Society
La Société Canadienne de Neurologie

The Canadian Neurosurgical Society
La Société Canadienne de Neurochirurgie

The Canadian Society of Clinical Neurophysiologists
La Société Canadienne de Neurophysiologie Clinique

The Canadian Association of Child Neurology
L'Association Canadienne de Neurologie Pédiatrique

The permanent secretariat for the four societies and the Canadian Congress of Neurological Sciences is at/
Le secrétariat des quatre associations et du Congrès Canadien des Sciences Neurologiques est situe en permanence à:
810, 906 - 12 Avenue S.W., Calgary, AB Canada T2R 1K7

The Canadian Journal of Neurological Sciences is published quarterly. The annual subscription rate is $60 for members; $70 for non-members in Canada; $80 for USA and elsewhere. Residents, Interns, Pre- and Post-Doctoral Students $30 per annum (members); $40 per annum (non-members). Single copies $18 each plus postage and handling. All manuscripts and communications should be sent to: Canadian Journal of Neurological Sciences, P.O. Box 4220, Station C, Calgary, AB Canada T2T 5N1. Courier to: 810, 906 - 12th Avenue S.W., Calgary, AB Canada T2R 1K7. Telephone (403) 229-9575; Fax (403) 229-1661.

Mailed under Publications Mail registration number 3307. Postage paid at Calgary, Alberta. This journal is indexed by *Index Medicus, Excerpta Medica and Current Contents — Clinical Practice and Life Sciences.*

Le Journal Canadien des Sciences Neurologiques est publié trimestriellement. L'abonnement annuel est de 60 $ pour les membres; 70 $ pour les non-membres au Canada; 80 $ pour les Etats Unis et ailleurs. Internes, résidents, fellows pré et post doctoral: 30 $ par année (membres); 40 $ par année (non-membres). Copie simple: 18 $ plus affranchissement et manutention. Toutes les communications et les manuscrits doivent être adressés à Journal Canadien des Sciences Neurologiques, P.O. Box 4220, Station C, Calgary, AB Canada T2T 5N1. Par courrier: 810, 906 - 12th Avenue S.W., Calgary, AB Canada T2R 1K7. Téléphone (403) 229-9575; Fax (403) 229-1661.

Posté sous permis de poste-publications no 3307. Port payé à Calgary, Alberta. Le Journal est cité et indexé dans *Index Medicus, Excerpta Medica et Current Contents — Clinical Practice et Life Sciences.*

Advertising representative/Représentant de publicité:
Sally Gregg, Canadian Journal of Neurological Sciences
810, 906 - 12 Ave. S.W., Calgary, AB Canada T2R 1K7
Tel (403) 229-9575 Fax (403) 229-1661

Printer/Imprimeur:
McAra Printing Limited, 105, 2507 - 12th Street N.E., Calgary, Alberta T2E 7L5

ISSN 0317 - 1671

For brief prescribing information see page xxiv.

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

If one more walks away from

The risk of stroke is greatest within the year following a TIA.[1] So it's worth knowing that a large multicentre trial showed Ticlid prevented non-cardiogenic thromboembolic stroke twice as effectively as ASA.[2] That meant relative to ASA, Ticlid saved three more patients out of every one hundred treated from a potentially crippling or life-threatening stroke.[2]

In long-term prospective randomized trials, only Ticlid has been proven effective in women as well as in men for the prevention of recurrent and initial stroke.[3,4] ASA has not been proven to reduce the rate of recurrent stroke.[5] Nor has ASA been proven to prevent initial stroke in women.[6]

Gastrointestinal complaints such as diarrhea can be limited by taking Ticlid with full meals.[7] A temporary reduction in dose may also resolve this complaint.[3,8]

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

TIA patient stroke, it's worth it.

If rash occurs, discontinue therapy and rechallenge. Many rashes will not recur.[7]

In clinical trials there was a 2.4% incidence of neutropenia. Upon immediate discontinuation of therapy, the neutrophil count usually returned to normal within 1 to 3 weeks. White blood cell monitoring is required every two weeks for the first three months starting at baseline.[7]

Ticlid. Possibly the best opportunity a TIA patient has to walk away from stroke.

Turn the page and judge for yourself. Four independent studies attest to the value of Ticlid.

Ticlid®

ticlopidine hydrochloride 250 mg tablets

Your patients deserve all the protection they can get.

SYNTEX®

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

Four major studies establish the superior efficacy of Ticlid.

Ticlopidine Versus Aspirin for Stroke Prevention: On-Treatment Results from the Ticlopidine Aspirin Stroke Study Group

J. D. Easton, Chair, TASS Publications Committee
J Stroke Cerebrovasc Dis. Vol. 3 No. 3. 1993;3:168-176.

Ticlopidine is the newest antiplatelet agent that has been compared with aspirin for stroke prevention. Results from the intent-to-treat analysis of the Ticlopidine Aspirin Stroke Study, a randomized, triple-blind trial, showed ticlopidine to be more effective than aspirin for the prevention of threatened stroke. We present the on-treatment analysis from this study in 3,034 eligible patients receiving either ticlopidine (500 mg daily) or aspirin (1,300 mg daily). Follow-up was for 2-6 years.

During year 1, the high-risk period for stroke in patients with threatened stroke, ticlopidine reduced the risk of stroke over aspirin by 48% (p = 0.0004: the event rates were 3.4 and 6.4 respectively). The overall risk for fatal and non fatal stroke was 27% (95% confidence intervals were 6.6 and 42.3), less with ticlopidine than with aspirin. Ticlopidine significantly decreased the risk of fatal and non fatal stroke in both sexes and has a different adverse effect profile than aspirin. More adverse effects, primarily diarrhea and rash, were reported with ticlopidine.

Stroke Prevention in Women: Role of Aspirin Versus Ticlopidine

Linda A. Hershey, M.D., Ph.D., Buffalo, New York
September 1991 *The American Journal of Medicine* Vol. 91;288-292.

Summary and Conclusions: Stroke remains an important health care problem. Although the incidence of stroke and stroke mortality is lower in women than in men, the outcome in terms of major disability, decreased quality of life, economic burdens, and impact on family life is just as real for women as for men. Although aspirin has proven efficacy for preventing initial stroke, it may have limited efficacy in preventing recurrent stroke. Moreover, questions remain about the efficacy of aspirin for stroke prevention in women. There is a need for an alternative to aspirin in stroke prevention therapy.

Ticlopidine has demonstrated efficacy for both initial and recurrent stroke prevention and has been shown to be more effective than aspirin for patients at high risk for a first stroke. It is just as effective for stroke prevention in women as in men. The overall incidence of adverse effects seen with ticlopidine is not significantly different from that seen with aspirin, although careful hematologic monitoring is required with ticlopidine during the first 3 months of use. Both agents are important tools to use in addition to antihypertensive therapy and smoking cessation in stroke prevention.

Ticlopidine Versus Aspirin for the Prevention of Recurrent Stroke
Analysis of Patients With Minor Stroke From the Ticlopidine Aspirin Stroke Study

John W. Harbison. M.D., for the Ticlopidine Aspirin Stroke Study Group
Stroke 1992:1723-1727.

Background and Purpose: Ticlopidine has not been formally compared with aspirin in patients with a completed stroke. We therefore performed an analysis on a subgroup of patients from the Ticlopidine Aspirin Stroke Study (TASS) with a recent minor completed stroke as the qualifying ischemic event.

Methods: This was a multicenter, double-blind, randomized trial of patients with a recent history of cerebral ischemia. Eligible patients had a qualifying minor stroke within 3 months of study entry. All patients received either 650 mg aspirin twice daily or 250 mg ticlopidine twice daily for up to 5.8 years. The primary study end point was the first occurrence of non fatal stroke or death from any cause. A secondary end point was the first occurrence of a fatal or non fatal stroke.

Results: Minor stroke was the qualifying ischemic event in 927 patients (463 received ticlopidine and 464 received aspirin). The cumulative event rate at 1 year for non fatal stroke or death was 6.3% for patients receiving ticlopidine and 10.8% for patients receiving aspirin, a 42% risk reduction in favour of ticlopidine. For fatal or non fatal stroke, the cumulative event rate at 1 year was 4.8% for patients receiving ticlopidine and 7.5% for those receiving aspirin, a risk reduction of 36% for ticlopidine relative to aspirin. The overall risk reductions were 22.1% for non fatal stroke or death and 19.9% for fatal or non fatal stroke. Adverse reactions were reported in 58% of the ticlopidine patients and 51% of the aspirin patients.

Conclusions: The results in this subgroup are consistent with the overall TASS results and show that ticlopidine is somewhat more effective than aspirin for reducing the risk of stroke in patients with a completed minor stroke.

The Canadian American Ticlopidine Study (CATS) in Thromboembolic Stroke

Gent, J., et al. *The Lancet:* Saturday 3 June 1989.

The Canadian American Ticlopidine Study (CATS) is a randomised, double-blind placebo-controlled trial to assess the effect of ticlopidine (250 mg twice daily) in reducing the rate of subsequent occurrence of stroke, myocardial infarction, or vascular death in patients who have had a recent thromboembolic stroke. Twenty-five centres entered 1,072 patients into the study between 1 week and 4 months after their qualifying stroke. The patients were treated and followed up to 3 years (mean 24 months). In the efficacy analysis, the event rate per year for stroke, myocardial infarction or vascular death, considered together, was 15.3% in the placebo group and 10.8% in the ticlopidine group, representing a relative risk reduction with ticlopidine of 30.2% (95% confidence interval 7.5-48.3%; p=0.006). Ticlopidine was beneficial for both men and women (relative risk reductions 28.1%, p=0.037, and 34.2%, p=0.045, respectively). Analysis by intention-to-treat gave a smaller estimate of risk reduction (23.2%, p=0.020) for stroke, myocardial infarction, or vascular death. Adverse experiences associated with ticlopidine included neutropenia (severe in about 1% of cases) and skin rash and diarrhea (severe in 2% of cases each); all were reversible.

This study provides evidence of a beneficial effect of ticlopidine in both men and women with a recent thromboembolic stroke.

Ticlid®

SYNTEX®

ticlopidine hydrochloride 250 mg tablets

Your patients deserve all the protection they can get.

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

Ticlid®

ticlopidine hydrochloride 250 mg tablets

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).

Considerations in the selection of stroke prevention therapy should include the patient's current medical status and history, and their ability to comply with the required blood monitoring instructions concerning the use of ticlopidine.

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 may be life-threatening. It is usually reversible, and the recovery occurs within 1-3 weeks after discontinuation of the drug but may take longer, on occasion.

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 and platelet count performed every 2 weeks starting at baseline, before treatment is initiated, to the end of the third month of therapy with Ticlid. When the neutrophil count shows a declining trend or the neutrophil numbers have fallen below 30% of the baseline, the values should be confirmed. If the presence of neutropenia (ANC $<1.2 \times 10^9$ cells/L) or thrombocytopenia ($<0.8 \times 10^{11}$ cells/L) are confirmed, the drug should be discontinued. Because of the long plasma half-life of Ticlid, it is recommended that any patient who discontinues Ticlid for any reason within the first 90 days have an additional CBC with white cell differential count obtained two weeks after discontinuation of therapy. (See PRECAUTIONS.)

Rarely, cases of pancytopenia, aplastic anemia or thrombocytopenia, have been reported. Most cases were reversible, but some of them have been fatal. Thrombocytopenia may occur in isolation or together with neutropenia. Thrombotic thrombocytopenic purpura (TTP) has been reported, therefore careful attention to diagnosis should be made to guide treatment, platelet transfusion may be harmful in these patients.

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, hemothorax and intracranial bleeding have been reported. Patients must 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 µmol/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

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.

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 white blood cell count with a differential and a platelet count performed every 2 weeks starting at baseline, before treatment is initiated, to the end of the third month of therapy with Ticlid. When the neutrophil count shows a declining trend or the neutrophil numbers have fallen below 30% of the baseline, the value should be confirmed. If the presence of neutropenia (ANC $<1.2 \times 10^9$ cells/L) or thrombocytopenia ($< 0.8 \times 10^{11}$ cells/L) are confirmed, the drug should be discontinued. Because of the long plasma half-life of Ticlid, it is recommended that any patient who discontinues Ticlid for any reason within the first 90 days have an additional CBC with white cell differential obtained two weeks after discontinuation of therapy (see WARNINGS). 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.

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)	Potentiation of ASA's effect on collagen-induced platelet aggregation (see WARNINGS).
Antipyrine and products metabolized by hepatic microsomal enzymes	30% increase in $t^1/_2$ of antipyrine. Dose of products metabolized by hepatic microsomal enzymes to be adjusted when starting or stopping concomitant therapy with ticlopidine hydrochloride.
Theophylline	$t^1/_2$ 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

	Ticlid (n=2048) Incidence	ASA (n=1527) Incidence	Placebo (n=536) Incidence		Ticlid (n=2048) Incidence	ASA (n=1527) Incidence	Placebo (n=536) Incidence
Event							
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.

DOSAGE 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, micro-crystalline 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 a fold-over card 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. Adams HP, Gordon DL. Epidemiology of and stroke-preventive strategies for atherothromboembolic brain infarction in the elderly. *Clinics in Geriatic Medicine* 1991;7(3):401-416. **2.** Ticlopidine Aspirin Stroke Study (TASS), Data on file, Vol.52, Oct 1989 Syntex Inc.,1989. **3.** Hass WK, Easton DJ, Adams HP. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *New Engl J Med* 1989;321:501-527. **4.** Gent M, Easton DJ, Hachinski VC et al. The Canadian American Ticlopidine Study (CATS) in Thromboembolic Stroke. *The Lancet* 1989; June:1215-1220. **5.** Entrophen product monograph, 1994. **6.** Hershey LA. stroke prevention in women: Role of aspirin versus Ticlopidine. *The American Journal of Medicine* 1991;91:288-92. **7.** Ticlid product monograph, 1993. **8.** Harbison JW. Ticlopidine versus aspirin for the prevention of recurrent Stroke: analysis of patients with minor stroke from the Ticlopidine Aspirin Stroke Study. *Stroke* 1992;1723-7.

SYNTEX® Syntex Inc.* Mississauga, Ont./Montréal (Qué.)
*Registered user of all ® trademarks

PAAB CCPP MEMBER PMAC

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

For brief prescribing information see pages xix, xx.

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

INFORMATION FOR AUTHORS

The Canadian Journal of Neurological Sciences publishes original articles in neurology, neurosurgery and basic neurosciences. Manuscripts are considered for publication with the understanding that they, or the essence of their content, have not been published elsewhere except in abstract form and are not under simultaneous consideration by another journal. Manuscripts should be submitted to:

James A. Sharpe
Editor
Canadian Journal of Neurological Sciences
P.O. Box 4220, Station C
Calgary, AB Canada T2T 5N1

Manuscript Preparation

• Submit five high quality copies of the manuscript. Papers will be accepted in English or French. Manuscripts must be double spaced throughout including references, tables and legends for illustrations. Margins of at least 25mm should be left on all sides.

• After a paper has been reviewed, the author will be requested to submit four copies of the revised manuscript, including illustrations and a computer diskette (3 1/2" or 5 1/4" size) containing the article. Identify clearly first author's name, file name, word processing program and version, and system (i.e.: DOS or Mac). Clearly indicate the order and importance of headings.

• For detailed instructions regarding style and layout refer to *"Uniform requirements for manuscripts submitted to biomedical journals"*. Copies of this document may be obtained by writing to the Journal office, but the main points are summarized here. Articles should be submitted under conventional headings of *introduction, methods and materials, results, discussion,* but other headings will be considered if more suitable. Pages of text should be numbered consecutively.

• ***A title page*** should identify the title of the article and be no more than 80 characters including spaces, name of institution(s) from which the work originated and the address, telephone, and fax number of the corresponding author.

• ***Abstract*** Original articles should be accompanied by an abstract of 250 words or less on a separate page, preferably in English and French, although the Journal will provide translation if required. Abstracts of original articles should consist of four paragraphs headed: *Background (or objective), Methods, Results and Conclusions.* Review articles should be accompanied by an abstract of 150 words or less.

• ***Acknowledgements*** including recognition of financial support should be typed on a separate page at the end of the text.

• The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

• ***References*** should be numbered in the order of their citation in the text. Those cited only in tables and legends for illustrations are numbered according to the sequence established by the first identification in the text of a particular table or illustration. Titles of journals should be abbreviated according to the style used in Index Medicus. References should list the names of up to five authors; if there are more, cite the first three, then et al. Provide the full title, year of publication, volume number and inclusive pagination for journal articles. For any reference cited as "in press", five copies of the article must accompany the author's manuscript. Do not reference unpublished or "submitted" papers; these can be mentioned in the body of the text and authors must provide five copies of "submitted" manuscripts. Avoid "personal communications" and, if necessary, include them in the body of the text, not among the references. Reference citations should not include unpublished presentations or other non-accessible material. Books or chapter references should also include the place of publication and the name of the publisher. Examples of correct forms of reference follow:

Journals

Yang JF, Fung M, Edamura R, et al. H-Reflex modulation during walking in spastic paretic subjects. Can J Neurol Sci 1991; 18: 443-452.

Chapter in a book

McGeer PL, McGeer EG. Amino acid neurotransmitters. *In*: Siegel GJ, Albers RW, Agranoff BW, Katzman R, eds. Basic Neurochemistry. Boston: Little, Brown & Co., 1981: 233-254.

• ***Illustrations*** Submit five original sets of illustrations. We will not return illustrations; therefore, authors should keep negatives for all photographs. Submit high quality glossy black and white photographs preferable 127 x 173 mm (5" x 7"). Original artwork and radiographs should not be submitted. The additional cost of coloured illustrations must be borne by the author; quotations are available upon request from the Journal office. Identify each figure with a label at the back indicating top, figure number and first author. Letters and arrows applied to the figures to identify particular findings should be professional appliques suitable for publication. Photomicrographs should include a calibration bar with a scale indicated on the figure or in the legend. Legends for illustrations should be typed on a separate page from the illustrations.

• ***Tables*** Type tables double-spaced on pages separate from the text. Provide a table number and title for each. Particular care should be taken in the preparation of tables to ensure that the data are presented clearly and concisely. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

• ***Review articles*** on selected topics are also published. They are usually invited, but unsolicited reviews will be considered. It is recommended that authors intending to submit review articles contact the Editor in advance.

• ***Letters to the Editor*** concerning matters arising in recent articles are welcome. Letters should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

• ***Permissions and Releases*** Any non-original material (quotations, tables, figures) must be accompanied by written permission from the author and the copyright owner to reproduce the material in the Journal. Photographs of recognizable persons must be accompanied by a signed release from the legal guardian or patient authorizing publication.

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

Excellent contrôle des crises

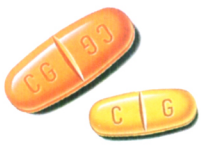
℗ Tegretol® CR (carbamazépine à libération contrôlée) maîtrise les crises chez de nombreux patients, causant peu d'impact sur la fonction cognitive[1,2]. Tegretol CR permet à de nombreux patients de penser clairement et de donner le meilleur d'eux-mêmes[1,2].

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[3,4].

Posologie b.i.d. commode

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



TEGRETOL® CR.

Aide les épileptiques à réaliser leur plein potentiel.

PAAB CCPP MEMBRE ACIM G-93095F

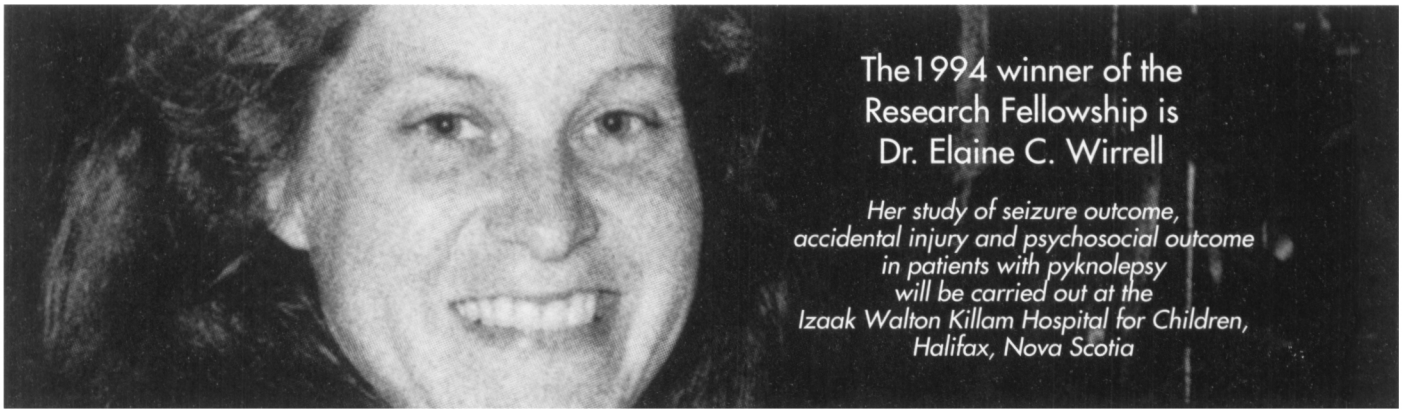
Geigy Dorval, Qué. H9S 1B1

Pour documentation voir pages xxi, xxii.

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

EPILEPSY CANADA

Parke-Davis Canada Research Fellowship



Each year Epilepsy Canada/Parke-Davis Canada provides a $35,000 Fellowship for Epilepsy Research. The aim of the Fellowship is to develop expertise in clinical or basic research and to enhance the quality of care for this neurological disorder which affects more than 280,000 Canadians.

The Fellowship is designed primarily as a training program and is not intended for individuals holding faculty appointments. Research must be carried out at a Canadian facility with ongoing clinical and research programs in epilepsy. The emphasis of the project must be on the study of epilepsy itself and not on epilepsy as part of the study of another field.

The Fellowship is presented annually by Epilepsy Canada/Parke-Davis Canada at the annual meeting of the Canadian Congress of Neurological Sciences. Applicants must have an M.D. or Ph.D. and M.D.'s must have completed residency training. The deadline for submission of applications for the 1995 award is December 1, 1994. More information and application forms are available from Epilepsy Canada.

EPILEPSY CANADA
ÉPILEPSIE CANADA
1470 Peel Street
Suite 745
Montreal, Quebec
H3A 1T1
Telephone:(514) 845-7855
Fax: (514) 845-7866

This advertisement is made possible through a grant from PARKE-DAVIS

1. Rinne UK. Strategies in the Treatment of Early Parkinson's Disease. Acta Neurol Scand. 1991; 84: Suppl 136: 95-98.

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press

Epival*

(divalproex sodium)

THERAPEUTIC CLASSIFICATION Anticonvulsant.

INDICATIONS AND CLINICAL USE Sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal; useful in primary generalized seizures with tonic-clonic manifestations. May also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

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 Should not be administered to patients with hepatic disease or significant dysfunction. Contraindicated in patients with known hypersensitivity to the drug.

WARNINGS Hepatic failures resulting in fatalities have occurred in patients receiving valproic acid and its derivatives. These incidences usually have occurred during the first six months of treatment with valproic acid. A recent survey study of valproate use in the United States in nearly 400,000 patients between 1978 and 1984, has shown that children under two years of age who received the drug as part of multiple anticonvulsant therapy were at greatest risk (nearly 20-fold increase) of developing fatal hepatotoxicity. These patients typically had other medical conditions such as congenital metabolic disorders, mental retardation or organic brain disease, in addition to severe seizure disorders. The risk in this age group decreased considerably in patients receiving valproate as monotherapy. Similarly, patients aged 3 to 10 years were at somewhat greater risk if they received multiple anticonvulsants than those who received only valproate. Risk generally declined with increasing age. No deaths have been reported in patients over 10 years of age who received valproate alone.

If Epival is to be used in children two years old or younger, it should be used with extreme caution and as a sole agent. The benefits of seizure control should be weighed against the risk.

Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as loss of seizure control, malaise, weakness, lethargy, anorexia, and vomiting. Patients and parents should be instructed to report such symptoms. Because of the non-specific nature of some of the early signs, hepatotoxicity should be suspected in patients who become unwell, other than through obvious cause, while taking Epival (divalproex sodium).

Liver function tests should be performed prior to therapy and at frequent intervals thereafter especially during the first 6 months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination. Caution should be observed in patients with a prior history of hepatic disease. Patients with various unusual congenital disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk.

In high-risk patients, it might also be useful to monitor serum fibrinogen and albumin for decrease in concentrations and serum ammonia for increases in concentration. If changes occur, the drug should be discontinued. Dosage should be titrated to and maintained at the lowest dose consistent with optimal seizure control.

The drug should be discontinued immmediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of the drug. The frequency of adverse effects, particularly elevated liver enzymes, may increase with increasing dose. Therefore, the benefit gained by improved seizure control by increasing the dosage must be weighed against the increased incidence of adverse effects sometimes seen at higher dosages.

Use in Pregnancy: According to recent reports in the medical literature, valproic acid may produce teratogenicity in the offspring of women receiving the drug during pregnancy. The incidence of neural tube defects in the fetus may be increased in mothers receiving valproic acid during the first trimester of pregnancy. Based upon a single report, it was estimated that the risk of valproic acid exposed women having children with spina bifida is approximately 1.2%. This risk is similar to that which applies to non-epileptic women who have had children with neural tube defects (anencephaly and spina bifida). Animal studies have demonstrated valproic acid induced teratogenicity, and studies in human females have demonstrated placental transfer of the drug.

Multiple reports in the clinical literature indicate an association between the use of anti-epileptic drugs and an increased 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 2-to 3-fold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, cleft lip or palate, and neural tube defects. Nevertheless, the great majority of mothers receiving anti-epileptic medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anti-epileptics. Some reports indicate a possible similar association with the use of other anti-epileptic drugs, including trimethadione, paramethadione, and valproic acid. 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.

Anti-epileptic drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risks 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 anti-epileptic medication is in doubt, appropriate consultation is indicated.

Nursing Mothers: Valproic acid is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10% of serum concentrations. As a general rule, nursing should not be undertaken while a patient is receiving Epival (divalproex sodium).

Fertility: Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses of valproic acid greater than 200 mg/kg/day in rats and 90 mg/kg/day in dogs. Segment 1 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 divalproex sodium and valproic acid on the development of the testes and on sperm production and fertility in humans is unknown.

LONG-TERM TOXICITY STUDIES IN RATS AND MICE INDICATED A POTENTIAL CARCINOGENIC RISK.

PRECAUTIONS Hepatic dysfunction: See CONTRAINDICATIONS and WARNINGS.

General: Because of reports of thrombocytopenia and inhibition of platelet aggregation, platelet counts and bleeding-time determination are recommended before instituting therapy and at periodic intervals. It is recommended that patients 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 dosage or withdrawal of therapy pending investigation.

Hyperammonemia with or without lethargy or coma has been reported and may be present in the absence of abnormal liver function tests; if elevation occurs the drug should be discontinued.

Because Epival (divalproex sodium) may interact with other anti-epileptic drugs, periodic serum level determinations of concurrently administered anti-epileptics are recommended during the early part of therapy. (See DRUG INTERACTIONS.) There have been reports of breakthrough seizures occurring with the combination of valproic acid and phenytoin.

Epival (divalproex sodium) is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

There have been reports of altered thyroid function tests associated with valproic acid; the clinical significance of these is unknown.

Driving and Hazardous Occupations: 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: May potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, by impairment of non-renal clearance. This phenomenon can result in severe CNS depression. The combination of valproic acid and phenobarbital has also been reported to produce CNS depression without significant elevations of barbiturate or valproic acid serum levels. 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 (See PRECAUTIONS - General). It is not known if there is a change in unbound (free) phenytoin serum levels. The dosage of phenytoin should be adjusted as required by the clinical situation.

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

ADVERSE REACTIONS The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since valproic acid has usually been used with other anti-epileptics, 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 anti-epileptic 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 receiving valproic acid alone or in conjunction with phenobarbital.

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

Endocrine: There have been reports of irregular menses and secondary amenorrhea in patients receiving valproic acid.

Abnormal thyroid function tests have been reported (See PRECAUTIONS).

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 second phase of platelet aggregation (See PRECAUTIONS). 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. Anemia and bone marrow suppression have been reported.

Hepatic: Minor elevations of transaminases (eg. SGOT and SGPT) and LDH are frequent and appear to be dose related. Occasionally, laboratory tests also show increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (See WARNINGS).

Metabolic: Hyperammonemia (See PRECAUTIONS). Hyperglycinemia has been reported and associated with a fatal outcome in a patient with pre-existing non-ketotic hyperglycinemia.

Pancreatic: There have been reports of acute pancreatitis occurring in association with therapy with valproic acid.

Other: Edema of the extremities has been reported.

DOSAGE AND ADMINISTRATION The recommended initial dosage 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 maximal recommended dosage is 60 mg/kg/day. When the total daily dose exceeds 125 mg, it should be given in a divided regimen (See Table).

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

As the dosage is raised, blood levels of phenobarbital 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 tablets should be swallowed without chewing.**

AVAILABILITY Epival (divalproex sodium) enteric-coated tablets are available as salmon-pink coloured tablets of 125 mg supplied in bottles of 100 tablets; peach-coloured tablets of 250 mg and lavender-coloured tablets of 500 mg are supplied in bottles of 100 and 500 tablets.

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

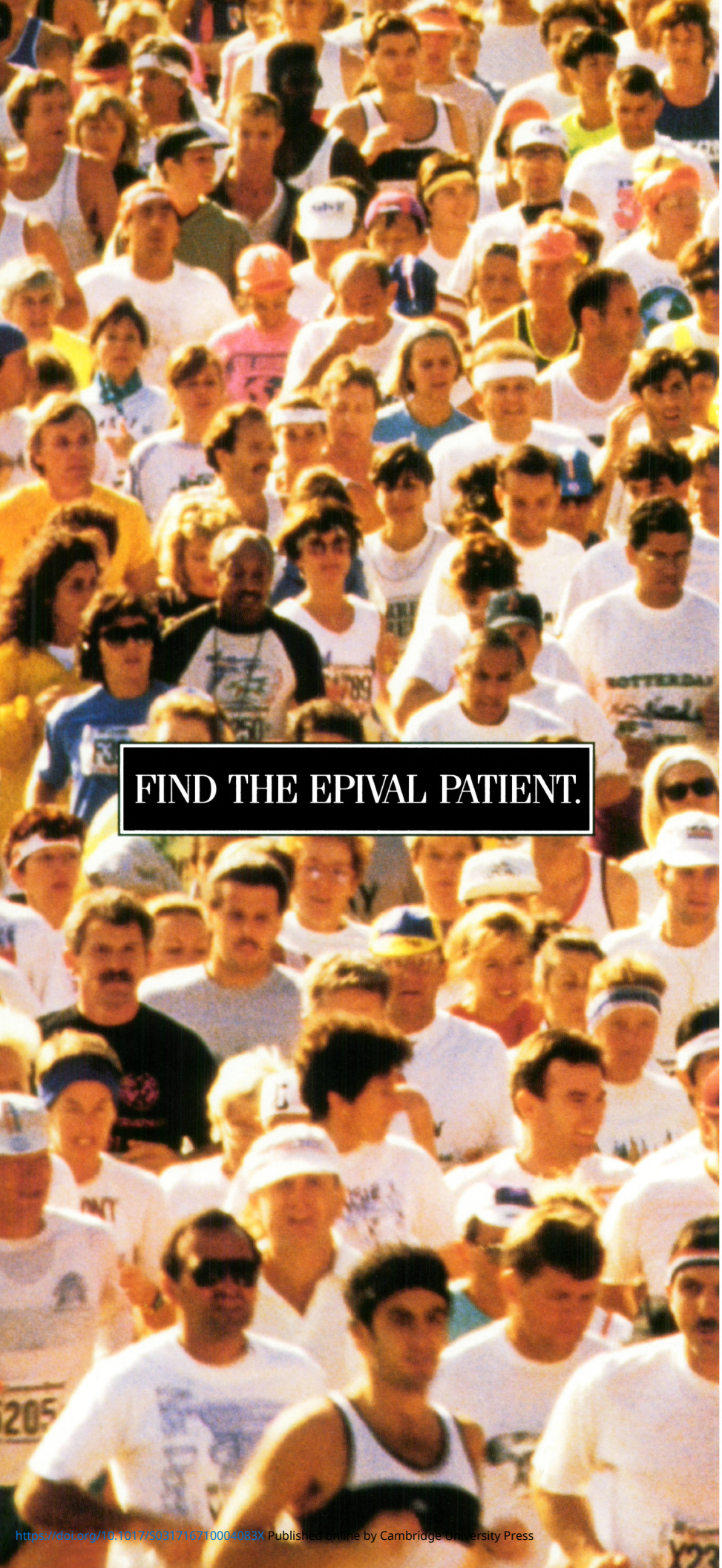
Weight		Total daily dose (mg)	Dosage (mg) Equivalent to valproic acid		
kg	lb		Dose 1	Dose 2	Dose 3
10-24.9	22-54.9	250	125	0	125
25-39.9	55-87.9	500	250	0	250
40-59.9	88-131.9	750	250	250	250
60-74.9	132-164.9	1,000	250	250	500
75-89.9	165-197.9	1,250	500	250	500

Product Monograph available on request.

References: **1.** Dreifuss FE, Langer DH. Side effects of valproate. *Am J Med* 1988;84 (suppl 1A):34-41. **2.** Dean CJ. Valproate. In: Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practices.* Philadelphia, Pa: Lea & Febiger; 1993:chap 77. **3.** Wilder BJ, Ramsay RE, Murphy JV, Karas BJ, Marquardt K, Hammond EJ. Comparison of valproic acid and phenytoin in newly diagnosed tonic-clonic seizures. *Neurology* 1983;33:1474-6. **4.** Turnbull DM, Howel D, Rawlins MD, Chadwick DW. Which drug for the adult epileptic patient: phenytoin or valproate? *Br Med J* 1985;290:815-9. **5.** Covanis A, Gupta AK, Jeavons PM. Sodium valproate: monotherapy and polytherapy. *Epilepsia* 1982;23:693-720. **6.** Kakegawa N, Miyakoshi M, Seino M. Monopharmacy by sodium valproate (SV) and the blood concentration. In: Program and abstracts of the XI Epilepsy International Symposium; September 30, 1979; Firenze, Italy. Abstract: 153. **7.** Epival (divalproex sodium). Product Monograph. Abbott Laboratories, Limited. **8.** Wilder BJ, Rangel RJ. Review of valproate monotherapy in the treatment of generalized tonic-clonic seizures. *Am J Med* 1988;84(suppl 1A):7-13.

ABBOTT LABORATORIES, LIMITED
P.O. BOX 6150, STATION CENTRE-VILLE
MONTRÉAL, QUÉBEC H3C 3K6

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press



Epival For Control Over Daily Living.

With Epival, epileptic patients can appear "just like anyone else."

Epival has been associated with little effect on learning and cognition.[1] It is effective in primary generalized epilepsy[2-4] as well as in partial seizures that secondarily generalize.[5,6,†] And it is generally well tolerated,[7] causing less GI irritation (nausea, vomiting and indigestion) than valproic acid.[8]

Prescribe Epival — by name only — to help restore your patients' control over daily living.

Because there's more to anticonvulsant therapy than seizure control.

Write it by name only...

Epival* (divalproex sodium)

Helps put patients back in control.

†For use as sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal and is useful in primary generalized seizures with tonic-clonic manifestations. EPIVAL may also be used adjunctively in patients with multiple seizure types which include either absence or tonic-clonic seizures.

PHARMACEUTICAL PRODUCTS DIVISION
ABBOTT LABORATORIES, LIMITED
SAINT-LAURENT, QUÉBEC

Product Monograph available on request.

Printed in Canada

MEMBER PAAB PMAC

https://doi.org/10.1017/S031716710004083X Published online by Cambridge University Press