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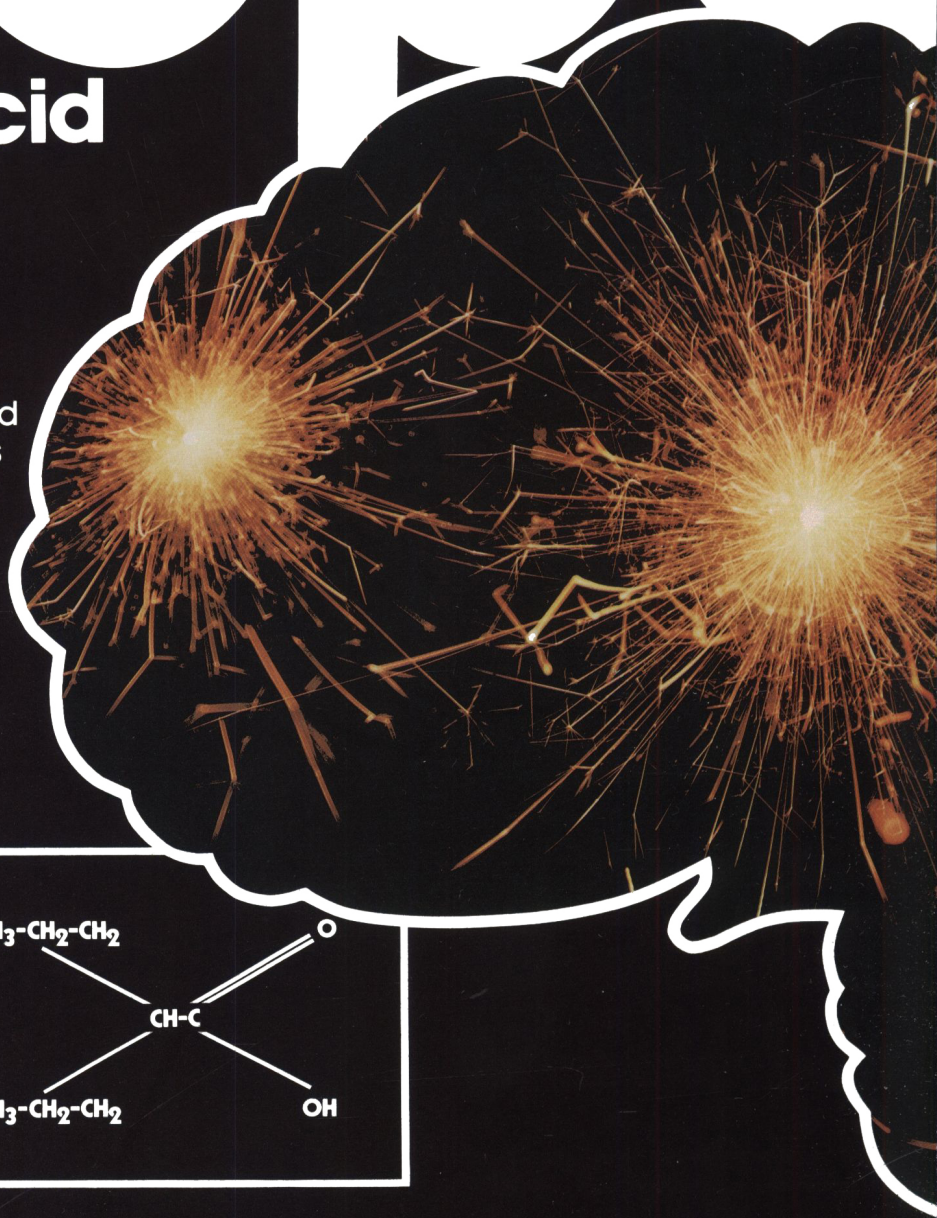
Depa

valproic acid



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

a unique chemical structure

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

a physiological mode of action

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

Depakene extends the range

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kene

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

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

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

world-wide documentation of effectiveness

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

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

of anticonvulsant therapy.

Depakene
valproic acid

Prescribing Information

CLINICAL PHARMACOLOGY

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

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

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

INDICATIONS AND CLINICAL USE

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

Use in pregnancy

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

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

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

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

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

Nursing Mothers

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

Fertility

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

PRECAUTIONS

General

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

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

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

Driving and Hazardous Occupations

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

Drug Interactions

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

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

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

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

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

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

ADVERSE REACTIONS

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

Gastrointestinal

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

CNS Effects

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

Dermatologic

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

Psychiatric

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

Musculoskeletal

Weakness has been reported.

Hematopoietic

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

Hepatic

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

AVAILABILITY

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

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3. Pinder, R.M. et al., Sodium valproate: A Review of its Pharmacological Properties and Therapeutic Efficacy in Epilepsy. Drugs 13, 81-123, 1977.

PHARMACEUTICAL PRODUCTS DIVISION
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Full product monograph on request.

* T.M.

PAAB

MEMBER PMAC

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SYMPOSIUM ON RESEARCH AND MANAGEMENT OF MULTIPLE SCLEROSIS

University Hospital
University of Western Ontario
London, Ontario, Canada

DATE: **September 3rd, 1980:** Neurovirology
September 4th, 1980: Immunology
September 5th, 1980: Physiology and Clinical Management

Invited Faculty:

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R. Baringer
J. Blavais
P. Choppin
B. Dupont
C. Gibbs
A. Haase
R. Kibler
H. Koprowski
J. Kurtzke
D. McFarlin
N. Nathanson
E. Norrby
P. Patterson
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W. Sibley
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Registration Fee: $150.00 ($50.00 for trainees)

The symposium will include state of the art presentations, and short reports of recent research or work in progress. Registrants are invited to prepare poster presentations which will be discussed at Workshops. For further information write:

Dr. Donald W. Paty OR Dr. George C. Ebers

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SENIOR NEUROLOGIST

Mount Sinai Hospital, a teaching hospital fully affiliated with the University of Toronto Faculty of Medicine, is seeking a senior Neurologist with strong clinical and teaching skills and eligible for a Faculty appointment at the Associate Professor level. A research or other academic interest would be welcomed. Mount Sinai Hospital has an active Neurology teaching program at Subspecialty Resident, General Medical Resident and Medical Student levels. Interested individuals should direct enquiries to Dr. Arnold Aberman, Physician-in-Chief, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5.

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SERC®

(betahistine hydrochloride tablets)

For the management of Vertigo in Ménière's Disease

- Tends to restore (not depress) vestibular responses [1]
- Reduces number and severity of vertigo attacks [2,3]
- Well-tolerated…suitable for longterm management [1,2,4]
- Non-sedative…acts on micro-circulation of inner ear [5,6]

REFERENCES:
1. Bertrand, R.A.: Acta Oto-Laryng. Supp. 305:48, 1972. **2.** Guay, R.M.: Applied Thera. 12:25 (Aug.) 1970. **3.** Frew, I.J.C. et al: Postgrad. Med.J. 52:501-503,1976. **4.** Wilmot, T.J. et al: J. Laryng. Otol. 9:833-840,1976. **5.** Snow, J.B.Jr. & Suga, F.: A.M.A. Arch. Otolaryng. 97:365, 1973. **6.** Martinez, D.M.: Acta. Oto-Laryng. Supp. 305:29, 1970.

PRESCRIBING INFORMATION:

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

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

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

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

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

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

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

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

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

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

Full prescribing information available on request.

UNIMED Pharmaceuticals Limited
Dorval, Quebec H9P 2P4

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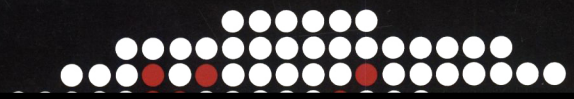
Tegretol®

carbamazepine

To help control refractory generalized tonic-clonic seizures

without excessive sedation



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