

THE CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES

LE JOURNAL CANADIEN DES SCIENCES NEUROLOGIQUES

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Official Journal of
 The Canadian Neurological Society
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SERC®

(betahistine hydrochloride tablets)

For the management of Vertigo in Ménière's Disease

- Tends to restore (not depress) vestibular responses¹
- 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, J.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 histamine-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.

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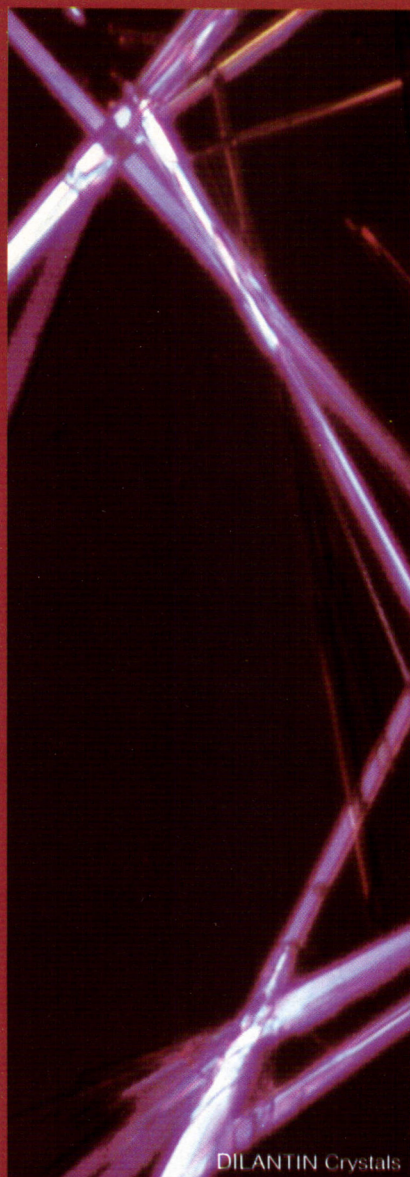
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Parke-Davis Canada Inc., Scarborough, Ontario



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Jean — myoclonic seizures



Michael — akinetic seizures



Carol — Lennox-Gastaut syndrome

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 - myoclonic seizures
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 - absence seizures (where succinimide therapy has failed)
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- no reports of incompatibility with a ketogenic diet
- economical, for long-term therapy
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'Rivotril' has not been associated with the severe side effects seen with some other anticonvulsant medications.

- No reports of serious side effects, such as hepatotoxicity.
- Very low incidence of nausea and G.I. upsets.¹
- No serious problems of drug interaction. (eg. ASA)
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- Drowsiness, which may occur, is generally dose-related and may be well controlled with proper dosage adjustment.^{2,3}



For Rx Summary, see page (xix)

Rivotril[®] for the victims of minor motor seizures

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Specific, Double Strength headache prophylaxis.

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The specific triple action of
FIORINAL[®] can give the
"uptight" headache patient
fast relief of the symptom
complex of muscle
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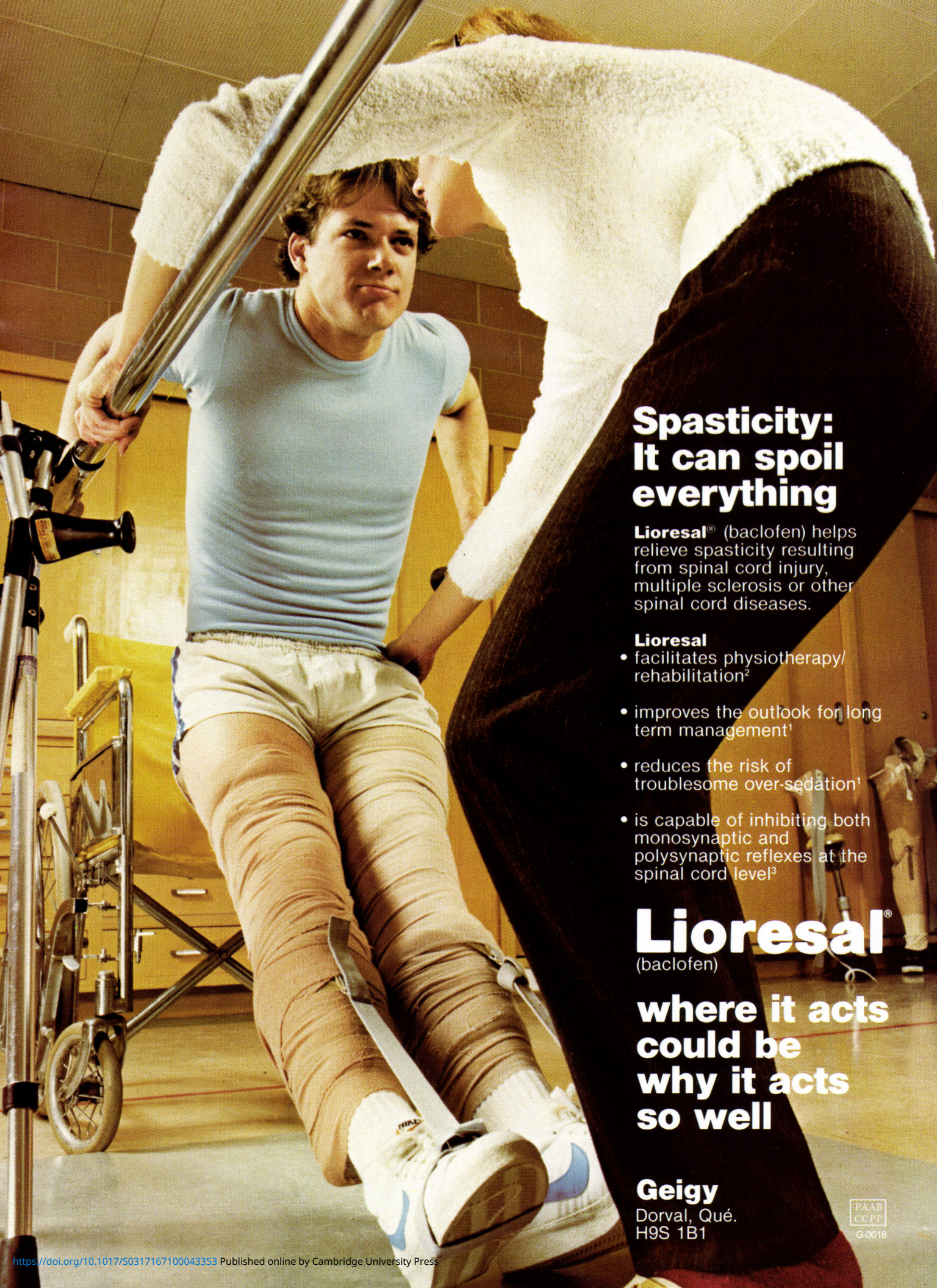
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Spasticity: It can spoil everything

Lioresal[®] (baclofen) helps relieve spasticity resulting from spinal cord injury, multiple sclerosis or other spinal cord diseases.

Lioresal

- facilitates physiotherapy/rehabilitation²
- improves the outlook for long term management¹
- reduces the risk of troublesome over-sedation¹
- is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal cord level³

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Brief Prescribing Information

Lioresal[®] baclofen

Action

The precise mechanisms of action of Lioresal (baclofen) are not fully known. It inhibits both monosynaptic and polysynaptic reflexes at the spinal level, probably by hyperpolarization of afferent terminals, although actions at supra-spinal sites may also occur and contribute to its clinical effect. Although Lioresal is an analog of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. Peak plasma concentrations of Lioresal are achieved within 2 hours and the plasma half-life is 2-4 hours.

Indications and Clinical Uses

Lioresal (baclofen) is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis.

Lioresal may also be of some value in patients with spinal cord injuries and other spinal cord diseases.

Contraindications

Hypersensitivity to Lioresal (baclofen).

Warnings

Abrupt Drug Withdrawal: Following abrupt withdrawal of Lioresal (baclofen), visual and auditory hallucinations, confusion, anxiety with tachycardia and sweating, insomnia, and worsening of spasticity have occurred.

Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued. **Impaired Renal Function:** Because Lioresal is primarily excreted unchanged through the kidneys, it should be given with caution, and it may be necessary to reduce the dosage. **Stroke:** Lioresal has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug. **Pregnancy:** Safe use of Lioresal during pregnancy or lactation has not been established. High doses are associated with an increased incidence of abdominal hernias in the fetuses of rats and of ossification defects in those of rats and rabbits. Therefore, the drug should be administered to pregnant patients, or women of child-bearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Precautions
Safe use of Lioresal (baclofen) in children under age 12 has not been established and it is, therefore, not recommended for use in children. Because of the possibility of sedation, patients should be cautioned regarding the operation of automobiles or dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system effects of Lioresal may be additive to those of alcohol and other CNS depressants. Lioresal should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function. Extreme caution should be exercised in patients with epilepsy or a history of convulsive disorders. In such patients, the clinical state and electroencephalogram should be monitored at regular intervals during therapy, as deterioration in seizure control and EEG has been reported occasionally in patients taking Lioresal. Caution should be used in treating patients with peptic ulceration, severe psychiatric disorders, elderly patients with cerebrovascular disorders, and in patients receiving antihypertensive therapy. It is not known whether Lioresal is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Adverse Reactions
The most common adverse reactions associated with Lioresal (baclofen) are transient drowsiness, dizziness, weakness and fatigue. Others reported: **Neuropsychiatric:** Headache (<10%), insomnia (<10%), and, rarely, euphoria, excitement, depression, confusion, hallucinations, paresthesia, muscle pain, tinnitus, slurred speech, coordination disorder, tremor, rigidity, dystonia, ataxia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, dysarthria, epileptic seizures. **Cardiovascular:** Hypotension (<10%), rare instances of dyspnea, palpitation, chest pain, syncope. **Gastrointestinal:** Nausea, (approx. 10%), constipation (<10%), and, rarely, dry mouth, anorexia, taste disorder, abdominal pain, vomiting, diarrhea, and positive test for occult blood in stool.

Genitourinary: Urinary frequency (<10%), and, rarely, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, hematuria. **Other:** Instances of rash, pruritus, ankle edema, excessive perspiration, weight gain, nasal congestion. Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

The following laboratory tests have been found to be abnormal in a few patients receiving Lioresal: SGOT, alkaline phosphatase and blood sugar (all elevated).

Symptoms and Treatment of Overdosage

Signs and Symptoms: Vomiting, muscular hypotonia, hypotension, drowsiness, accommodation disorders, coma, respiratory depression, and seizures. The signs and symptoms may be further aggravated by co-administration of a variety of other agents including alcohol, diazepam, and tricyclic antidepressants. **Treatment:** The treatment is symptomatic. In the alert patient, empty the stomach promptly by induced emesis followed by lavage. In the obtunded patient, secure the airway with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Maintain adequate respiratory exchange; do not use respiratory stimulants. Muscular hypotonia may involve the respiratory muscles and require assisted respiration. A high urinary output should be maintained since Lioresal (baclofen) is excreted mainly by the kidneys. Dialysis is indicated in severe poisoning associated with renal failure.

Dosage and Administration

The determination of optimal dosage of Lioresal (baclofen) requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily). The following dosage titration schedule is suggested:
5 mg t.i.d. for 3 days
10 mg t.i.d. for 3 days
15 mg t.i.d. for 3 days
20 mg t.i.d. for 3 days
Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.). The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (see Warnings).

Availability: Lioresal (baclofen) 10 mg tablets. **Description:** White to off-white flat-faced, oval tablets with Geigy monogram on one side and the identification code 23 below the monogram. Fully bisected on the reverse side. Available in bottles of 100 tablets.

References:
1. R.F. Jones, J.W. Lance, Medical Journal of Australia, 1976, May:654-657.
2. R.G. Feldman: Symposia Reporter, Vol. 3, No. 2 June 1979.
3. Lioresal Product Monograph.

Product monograph supplied on request.

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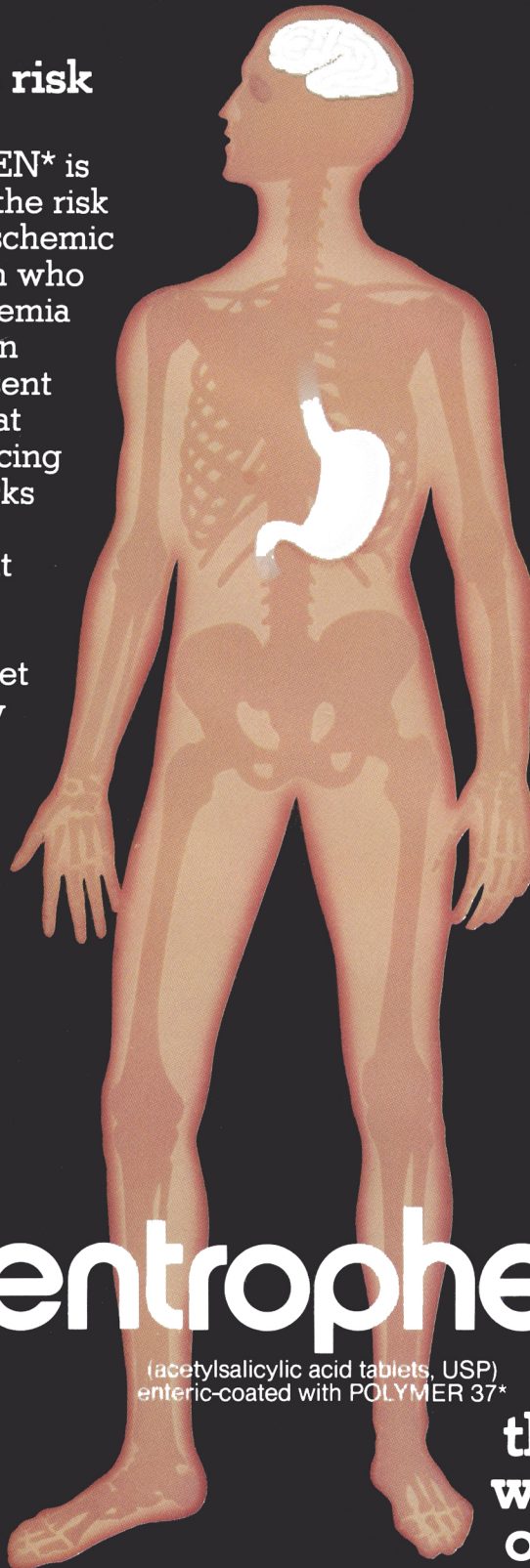
NOW IN STROKE

The Advantages of ENTROPHEN*

To reduce the risk of stroke

Now, ENTROPHEN* is indicated for reducing the risk of recurrent transient ischemic attacks or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. At present there is no evidence that ASA is effective in reducing transient ischemic attacks in women, or is of benefit in the treatment of completed strokes in men or women.

Inhibition of platelet cyclooxygenase activity by a single dose of ENTROPHEN*-10 was comparable to that of plain ASA, although the effect was delayed, reflecting the delayed appearance of ASA in the plasma.¹



with reduced risk of stomach upset

When you prescribe ASA for long-term use, it is important not to create additional problems for your patients.

While they may benefit from the therapeutic effect of ASA, there is still a potential for gastric irritation and upset, particularly when the regimen calls for continuous daily dosage.

Clinical experience has shown that ENTROPHEN*, coated with POLYMER 37* reduces gastric distress in long-term treatment with high doses of ASA.

entrophen*

(acetylsalicylic acid tablets, USP)
enteric-coated with POLYMER 37*

To reduce the risk of stroke with reduced risk of stomach upset

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1. Ali, M. et al.: Plasma acetylsalicylate and salicylate and platelet cyclooxygenase activity following plain and enteric-coated aspirin. *Stroke* 11(1):9-13, Jan/Feb 1980.

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TABLETS

entrophen*

(acetylsalicylic acid tablets, USP)

Enteric-coated with POLYMER 37*

Anti-inflammatory—Analgesic Agent

Platelet Aggregation Inhibitor

DESCRIPTION

ENTROPHEN* is an enteric-coated tablet containing acetylsalicylic acid coated with POLYMER 37*, a partially esterified polyvinyl alcohol.

ACTION

Acetylsalicylic acid (ASA) has analgesic, antipyretic and anti-inflammatory properties.

In rheumatic diseases, although the analgesic and antipyretic effects are useful, the major purpose for which ASA is used is to reduce the intensity of the inflammatory process. Inhibition of prostaglandin synthesis may be involved in the anti-inflammatory action of ASA.

ASA also alters platelet aggregation and release reaction by inhibiting prostaglandin synthesis. Thromboxane A₂ is an essential step in platelet aggregation. ASA prevents Thromboxane A₂ formation by acetylation of platelet cyclooxygenase. This inhibition of prostaglandin synthesis is irreversible and affects platelet function for the life of the platelet.

The POLYMER 37* coating substantially resists disintegration in aqueous fluids having a pH lower than 3.5 for a period of at least 2 hours and is capable of disintegrating in aqueous fluids having a pH of at least 5.5 in from 10 to 30 minutes. Thus, POLYMER 37* coating effectively inhibits the release of ASA in the stomach, whilst allowing the tablet to dissolve in the upper portion of the small intestine for absorption from the duodenal area. Clinical experience has shown that POLYMER 37* coated acetylsalicylic acid diminishes or eliminates gastric distress during long-term treatment with high doses of ASA.

INDICATIONS

ENTROPHEN* is indicated whenever gastric intolerance to ASA is of concern.

ENTROPHEN* is indicated for the relief of signs and symptoms of the following:

- Osteoarthritis
- Rheumatoid arthritis
- Spondylitis
- Bursitis

and other forms of rheumatism

Musculoskeletal disorders

Rheumatic fever, however, penicillin and other appropriate therapy should be administered concomitantly.

ASA is generally considered to be the primary therapy for most forms of arthritis.

ENTROPHEN* is also indicated for reducing the risk of recurrent transient ischemic attacks or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. At present there is no evidence that ASA is effective in reducing transient ischemic attacks in women, or is of benefit in the treatment of completed strokes in men or women.

CONTRAINDICATIONS

Sensitivity to the ingredients

Active peptic ulcer

Patients who had a bronchospastic reaction to ASA or non-steroidal anti-inflammatory drugs.

WARNINGS

ASA is one of the most frequent causes of accidental poisoning in toddlers and infants. ENTROPHEN* should, therefore, be kept well out of the reach of all children.

PRECAUTIONS

Salicylates should be administered with caution to patients with asthma and other allergic conditions, with a history of gastrointestinal ulcerations, with bleeding tendencies, with significant anemia or with hypoprothrombinemia.

Salicylates can produce changes in thyroid function tests.

Acute hepatitis has been reported rarely in patients with systemic lupus erythematosus and juvenile rheumatoid arthritis with plasma salicylate concentrations above 25 mg/100 mL.

Patients have recovered upon cessation of therapy.

Use in Pregnancy

ASA does not appear to have any teratogenic effects. ASA has been found to delay parturition in rats. This effect has also been described with non-steroidal anti-inflammatory agents which inhibit prostaglandin synthesis.

High doses (3 g daily) of ASA during pregnancy may lengthen the gestation and parturition time.

Because of possible adverse effects on the neonate and the potential for increased maternal blood loss, ASA should be avoided during the last three months of pregnancy.

Drug Interactions

Caution is necessary when ENTROPHEN* and anticoagulants are prescribed concurrently, as ASA may potentiate the action of anticoagulants. Salicylates may potentiate sulfonyleurea hypoglycemic agents. Large doses of salicylates may have a hypoglycemic action, and thus, affect the insulin requirements of diabetics.

Although salicylates in large doses are uricosuric agents, smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of probenecid, sulfipyrazone and phenylbutazone.

Sodium excretion produced by spironolactone may be decreased in the presence of salicylates. Salicylates also retard the renal elimination of methotrexate.

ADVERSE REACTIONS

Gastrointestinal reactions: nausea, vomiting, diarrhea, gastrointestinal bleeding and/or ulceration. Ear reactions: tinnitus, vertigo, hearing loss. Hematologic reactions: leukopenia, thrombocytopenia, purpura. Dermatologic and Hypersensitivity reactions: urticaria, angioedema, pruritus, various skin eruptions, asthma and anaphylaxis. Miscellaneous reactions: acute reversible hepatotoxicity, mental confusion, drowsiness, sweating and thirst.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

In mild overdosage these may include rapid and deep breathing, nausea, vomiting (leading to alkalosis), hyperpnea, vertigo, tinnitus, flushing, sweating, thirst and tachycardia. (High blood levels of ASA lead to acidosis.) Severe cases may show fever, hemorrhage, excitement, confusion, convulsions or coma, and respiratory failure.

Treatment

Treatment is essentially symptomatic and supportive. Administer water, universal antidote and remove by gastric lavage or emesis. Force fluids (e.g., salty broth) to replace sodium loss. If the patient is unable to retain fluids orally, the alkalosis can be treated by hypertonic saline intravenously. If salicylism acidosis is present, sodium bicarbonate intravenously is preferred because it increases the renal excretion of salicylates. Vitamin K is indicated if there is evidence of hemorrhage. Hemodialysis has been used with success.

Respiratory depression may require artificial ventilation with oxygen. Convulsions may best be treated by the administration of succinylcholine and artificial ventilation with oxygen. Central nervous system depressant agents should not be used.

Hyperthermia and dehydration are immediate threats to life and initial therapy must be directed to their correction and to the maintenance of adequate renal function. External cooling with cool water or alcohol should be provided quickly to any child who has a rectal temperature over 104°F.

DOSAGE AND ADMINISTRATION

Analgesic; antipyretic

Up to 2.925 g daily as necessary.

Anti-inflammatory

Because the suppression of inflammation increases with the dose of salicylate even beyond the point of toxicity, the therapeutic objective is to employ as large a dose as possible short of toxicity. Most patients will tolerate blood salicylate levels in the range of 20 to 25 mg per cent. The most common reason for failing to obtain a therapeutic response to ASA is the administration of inadequate doses.

The generally accepted way to achieve effective 'anti-inflammatory' salicylate blood levels of 20 to 25 mg per cent is to titrate the dosage by starting with 2.6 to 3.9 g daily, according to the size, age and sex of the patient. If necessary, the dosage is then gradually adjusted by daily increments of 0.65 g until symptoms of salicylism e.g., auditory symptoms, occur. Then, the dosage is decreased by 0.65 g daily until these symptoms disappear and maintained at that level as long as necessary.

In adults the median dose at which tinnitus develops is 4.5 g per day, but the range extends from 2.6 to 6.0 g per day.

Intermittent administration is ineffective. Patients should be advised not to vary the dose from day to day depending on the level of pain because that often fluctuates independently of the intensity of the inflammation. A continuous regimen of 0.65 g four times daily is considered to be minimum therapy for adults. ENTROPHEN* should be administered four times daily. For nighttime and early morning benefits, the last dose should be given at bedtime.

Once maintenance dose is established, ENTROPHEN*-15 may be useful to encourage patient compliance.

Optimally, salicylate therapy should be monitored by periodic blood salicylate level determinations. If this is not practical, the appearance of auditory symptoms in the form of tinnitus or deafness are acceptable as an indication of the maximum tolerated salicylate dose.

There is an inverse relation between blood salicylate levels at which auditory symptoms appear and the age of the patient. In the young adult, this is usually in the range of 20 to 30 mg per cent. In children, however, the level may be much higher, or the effect apparently absent. Because salicylate toxicity may appear without such warning in children, the usual practice is to give ASA in a daily dose of 50 to 100 mg per kilogram of body weight and to follow blood levels aiming for a concentration of about 30 mg per cent.

Rheumatic Fever

A total daily dosage of 100 mg per kilogram of body weight administered in divided doses to allay the pain, swelling and fever.

Cerebral ischemic attacks (men)

The recommended dosage is 1,300 mg per day (650 mg twice a day or 325 mg four times a day).

AVAILABILITY

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Photo taken in the ICU at Oak Park Hospital, Oak Park, Illinois.

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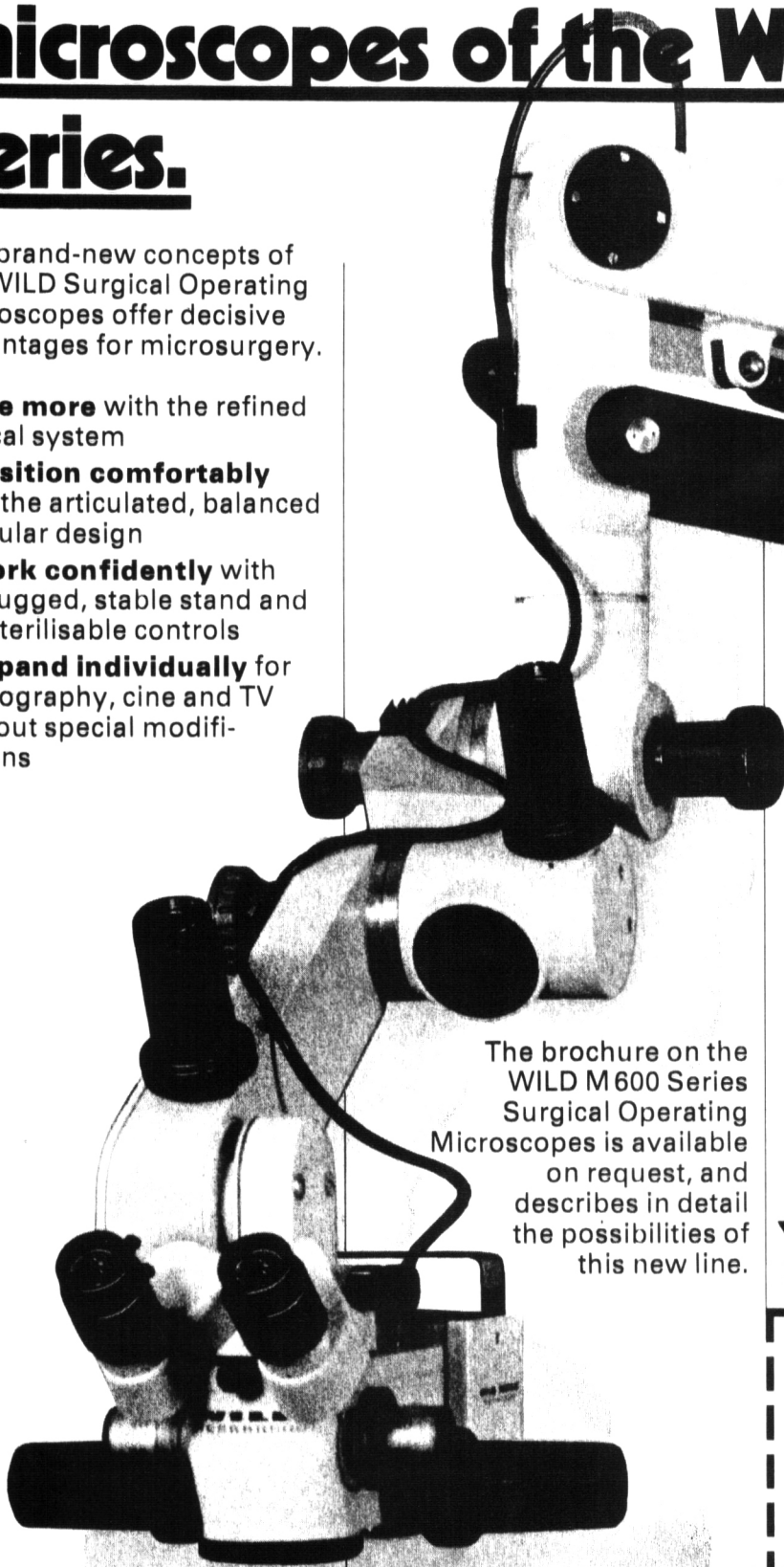
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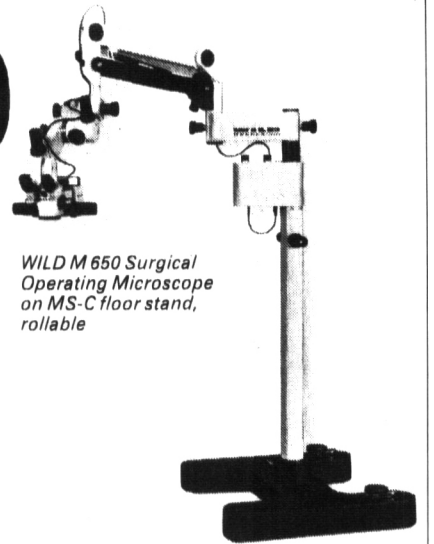
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