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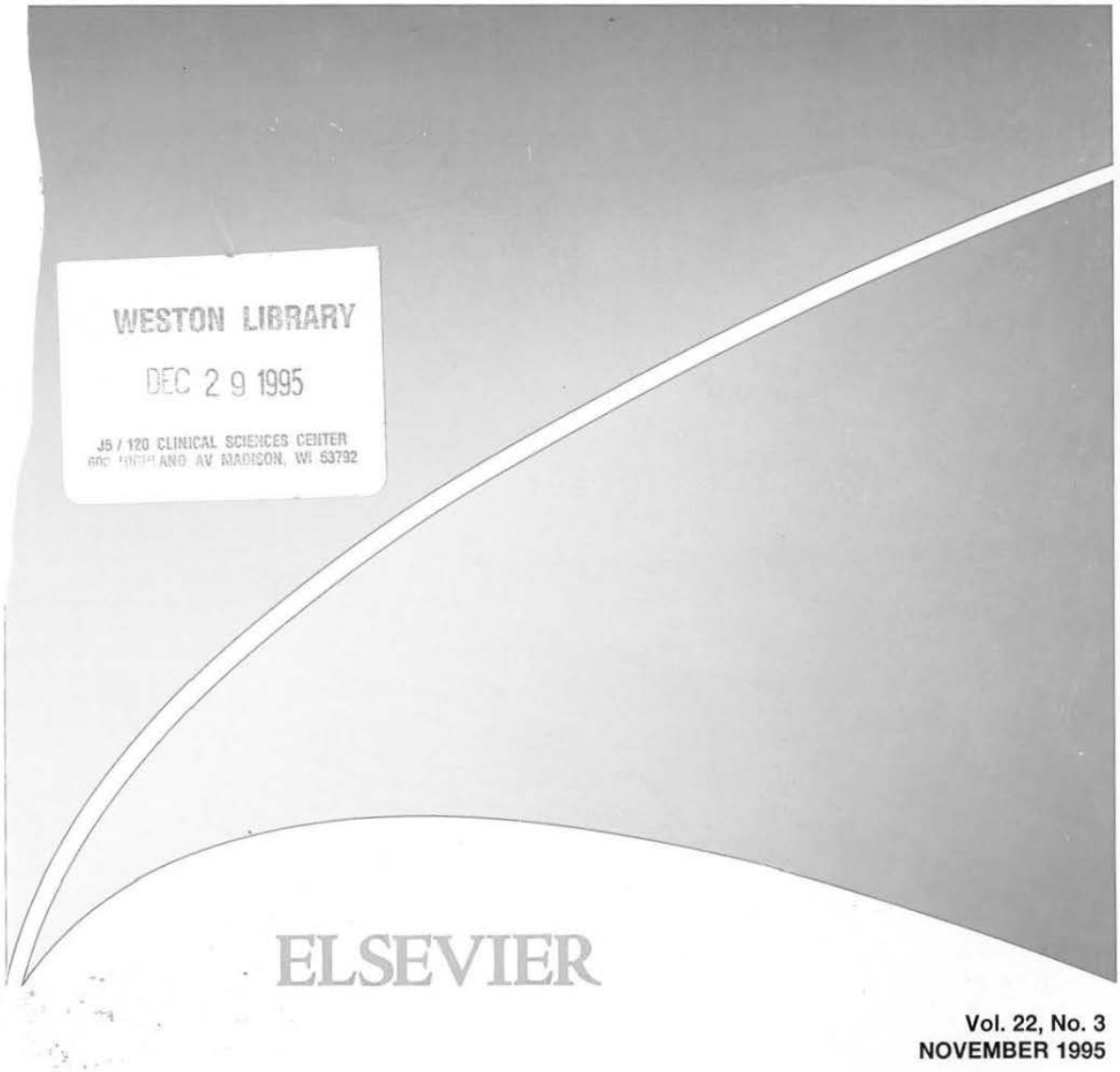

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Conference Review

Progress report on new antiepileptic drugs
A summary of the Second Eilat Conference

J.P. Stables [a,*], M. Bialer [b], S.I. Johannessen [c], H.J. Kupferberg [a], R.H. Levy [d], P. Loiseau [e], E. Perucca [f]

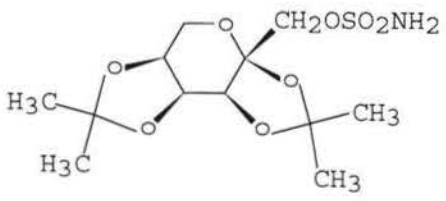
[a] *Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA*
[b] *School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*
[c] *National Center for Epilepsy, Sandvika, Norway*
[d] *Department of Pharmaceutics, University of Washington, Seattle, WA, USA*
[e] *Department of Neurology, Bordeaux University Hospital Pellegrin, Bordeaux Cedex, France*
[f] *Clinical Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy*

Abstract

The Second Eilat Conference on New Antiepileptic Drugs was held at the King Solomon's Palace Hotel from October 31 to November 3, 1994. Epileptologists and scientists from 20 countries attended the conference, which was held to discuss new trial designs, drug approval, early use of new antiepileptic drugs, and new drugs in development. Over the last six years, several novel antiepileptic drugs have been introduced worldwide, and new information on their safety and efficacy has become available. These include felbamate, gabapentin, lamotrigine, oxcarbazepine, and vigabatrin. Drugs in development include those at an advanced stage, such as topiramate and tiagabine, as well as those just entering clinical trials, such as remacemide and levetiracetam. The following is a summary of the presentations for drugs in development and newly marketed drugs. The meeting concluded with a presentation, 'Still Searching for the Magic Bullet'.

Keywords: Antiepileptic drug development; Clinical trial design; Drug approval

1. Topiramate [1]



Topiramate

Topiramate is a sulfamate structurally unique as an antiepileptic. Several mechanisms have been proposed to explain the manner in which the compound exerts its antiepileptic action: (1) blockade of voltage-activated sodium channels; (2) enhancement of GABA acting at the benzodiazepine insensitive GABA(A) receptor; and (3) modest blocking action at the kainate/AMPA glutamate receptors. There are no known effects at NMDA receptors. Topiramate is

* Corresponding author.

[1] Ross A. Reife, Director, Clinical Research CNS, The R.W.J. Pharmaceutical Research Institute, Spring House, PA; and Lynn Kramer, Vice President, Medicines and Clinical Development, CNS, Cib–Geigy Corp., Basle, Switzerland.

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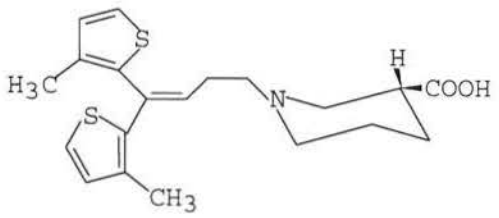
also a weak carbonic anhydrase inhibitor (about 100 times weaker than acetazolamide). What effect the carbonic anhydrase action has on anticonvulsant activity is not clear, but it is directly related to the potential to form renal stones.

The pharmacokinetic characteristics of topiramate are interesting. It has a high bioavailability (80% of an oral dose). It achieves peak plasma concentration in 1 to 3 h. Extent of absorption is not affected by food, but the presence of food delays absorption by approximately 1 h. The kinetics are dose proportional in the therapeutic dose range. Topiramate is only 15% plasma protein bound and predominately is excreted unchanged in the urine (80%) when administered alone. However, when topiramate is administered in conjunction with enzyme-inducing anticonvulsants, significant metabolism occurs (up to 50% of the administered dose). The half life is approximately 20 to 30 h but may be shortened considerably in the presence of concomitant treatment with enzyme inducers. Topiramate does not affect, to a clinically significant extent, the plasma levels of concurrent anticonvulsants, except for an occasional moderate increase in plasma phenytoin levels.

To date, there have been five completed and analyzed multicenter trials (two in the United States and three in Europe). These were performed in adults as add-on therapy in patients with refractory partial onset seizures with or without secondary generalization. The dosage range was from 200 to 1000 mg per day. Compared with placebo, a statistically significant reduction in seizure frequency was observed at all dosages; the effect at 200 mg daily reached borderline significance. All other efficacy parameters (percent of patients with a 50% and with 75% reduction in seizures, clinician and patient global assessments, reduction in secondarily generalized seizures) also showed significant improvements over placebo. Since tolerability decreased at dosages above 600 mg per day, a dosing range of 200 to 600 mg per day (usually in divided doses) is considered optimal in most patients. Occasionally some patients may require higher doses.

Safety data are based on 1800 patient exposures or 2000 subject years. Seventy patients have been exposed for more than 5 years. The most common side effects observed in add-on studies were related to the central nervous system. Kidney stones, resulting from the carbonic anhydrase effects, have been observed in approximately 1.5% of patients. Dose and rate of titration are important considerations to minimize adverse affects.

2. Tiagabine [2]



Tiagabine

Tiagabine is a nipecotic acid derivative that centrally inhibits GABA uptake at presynaptic neurons and glial cells. It differs from inhibitors of GABA transaminase (i.e., vigabatrin) in several ways: (1) Its action on GABA is reversible. (2) It causes little or no increase in cerebrospinal fluid GABA levels. (3) It did not cause intramyelinic edema in animal toxicology studies. (4) It is much better tolerated than previously assessed GABA uptake inhibitors such as Parke–Davis's CI 966.

Tiagabine is absorbed rapidly and has linear metabolic kinetics. When taken in conjunction with food, the rate, rather than the extent of absorption, is decreased. The half life in healthy volunteers is 7 h but is shortened to approximately 3.5 h in comedicated patients. Therefore, frequent dosing intervals

[2] Samuel Berkovic, Dept. of Neurology, Austin Hospital, Melbourne, Australia.

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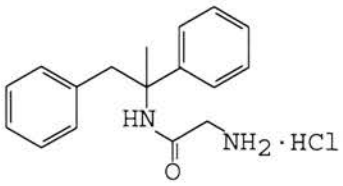
may be required. Although tiagabine is extensively metabolized, none of the metabolites are active.

Five controlled trials using patients with partial seizures are either completed or ongoing. More than 1000 patients have been studied to evaluate the efficacy of tiagabine. These add-on trials have employed crossover, dose frequency, and parallel designs. Data appear to indicate that efficacy is seen with doses greater than 30 mg per day, although comedicated patients have been exposed to 80 mg per day. The anticipated dose in monotherapy trials should be approximately 10 to 15 mg per day.

Safety data exist for more than 3000 patients. Three hundred patients have been treated for more than a year, equaling 1200 total patient years of exposure. The most common adverse effects appear to be dizziness and poor concentration. These side effects can be minimized by dose adjustments. Tremor has also been reported as a dose-dependent side effect of tiagabine.

3. Remacemide hydrochloride [5,9] [3]



Remacemide

Remacemide is a racemic mixture of two enantiomers. Both enantiomers possess a similar spectrum of activity, with the *S* configuration being marginally more potent. Remacemide is metabolized to an active desglycine metabolite, which is likely to contribute significantly to its overall pharmacological effects. In rodents, remacemide obtunds seizures produced by maximal electroshock, hippocampal kindling, NMDA, kainate, and 4-aminopyridine. It also inhibits convulsions in mice prone to audiogenic seizures. In cell culture, remacemide hydrochloride is similar to phenytoin in preventing sustained repetitive firing through action on voltage-sensitive sodium channels. The desglycinyl metabolite of remacemide acts as a low affinity noncompetitive antagonist at the MK801 binding site on the NMDA receptor. Remacemide hydrochloride, therefore, may be useful in a variety of seizure types.

Remacemide hydrochloride is absorbed rapidly from the gastrointestinal tract. It reaches peak concentration in 1 h, whereas the desglycine metabolite takes 2 to 3 h to reach its maximum concentration following oral administration. The parent drug has a relatively short half life of 3 to 4 h compared with the 12- to 15-h half life of the metabolite. Both compounds appear to exhibit linear pharmacokinetics. In interaction studies, remacemide hydrochloride increases both carbamazepine and phenytoin blood levels in comedicated patients. At present, only the increase in carbamazepine levels appears to be clinically significant, requiring dose adjustments in some patients. Remacemide and carbamazepine are both metabolized to some degree by the same hepatic P-450 isoform, CYP3A4, which may explain the interaction. No changes in valproic acid concentrations have been observed.

In a double-blind, placebo-controlled, add-on, crossover trial in patients with refractory partial seizures, remacemide (150 mg qid) produced a significant reduction in seizure frequency in about a third of the treated cases. The most common side effects were dizziness and gastrointestinal disturbances, which probably can be minimized by dosing at meal times. In subsequent studies, doses up to 1200 mg daily (qid) and 800 mg daily (in a bid regime) have been found to be generally well tolerated. Two large international dose-ranging trials are currently under way.

[3] Virginia Jamieson, Senior Pharmaceutical Physician, Fisons Pharmaceuticals, Loughborough, United Kingdom.

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