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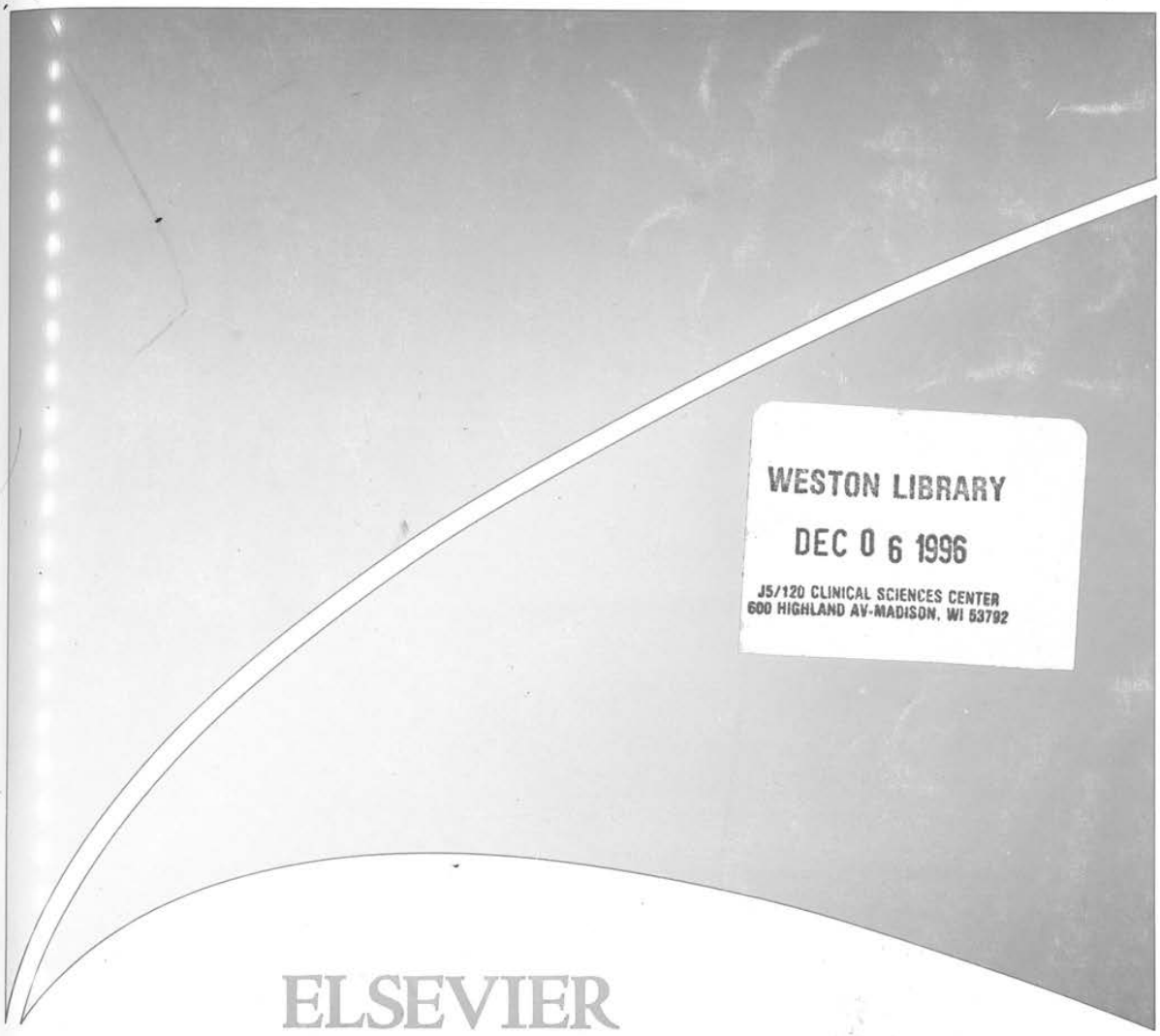

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EPILEPSY RESEARCH

Conference Report

Progress report on new antiepileptic drugs: a summary of the Third Eilat Conference

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Abstract

The Third Eilat Conference on New Antiepileptic Drugs was held at the Royal Beach Hotel from May 27 to May 30, 1996. Epileptologists and scientists from 20 countries attended the conference, which was held to discuss critical issues in drug development, new antiepileptic drugs (AEDs) in development, progress reports and recent findings of newly marketed AEDs, the use of AEDs in special populations and their utilization in non-epileptic disorders. Over the last seven years, six new AEDs have been introduced worldwide and new information on their safety and efficacy has become available. These include felbamate, gabapentin, lamotrigine, oxcarbazepine, topiramate and vigabatrin. Drugs in development include those at an advanced stage, such as remacemide and tiagabine, as well as those just entering clinical trials, such as rufinamide (CGP 331010) and levetiracetam (ucb LO59). The following is a summary of the presentations for drugs in development and recent findings on newly marketed drugs.

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

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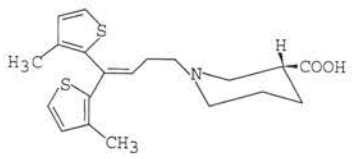
1. Drugs in development

1.1. Tiagabine [1]



Tiagabine

1.1.1. Introduction

Tiagabine was identified at Novo Nordisk Pharmaceuticals in Denmark and is being codeveloped with Abbott Laboratories in the United States. It is a derivative of nipecotic acid, an inhibitor of gamma aminobutyric acid (GABA) uptake. The action of tiagabine is specific to GABA and showed anticonvulsant effects in several animal models of seizures including maximal electroshock (MES), amygdala kindled and those induced by pentylenetetrazol (PTZ)

Clinical development has proceeded in North America, Western Europe, Japan and Australia. Approximately 3,000 patients and subjects have received tiagabine in clinical trials as of April, 1995. Over 2,000 patients with epilepsy have been exposed to tiagabine in clinical trials, over 1,000 have been treated for more than 1 year and over 500 for more than 2 years.

1.1.2. Pharmacokinetics

Tiagabine has linear pharmacokinetics in single and multiple doses given to healthy volunteers. Tiagabine does not change antipyrine clearance and is therefore not a hepatic enzyme inducer. Tiagabine is primarily metabolized by the cytochrome P450 3A subfamily and antiepileptic drugs (AEDs) which induce hepatic enzymes (e.g., carbamazepine, phenytoin) increase tiagabine clearance and reduce tiagabine AUC and half-life. Patients taking tiagabine with hepatic-inducing AEDs therefore need higher dose to attain the same concentrations as on monotherapy or when taking noninducing AEDs (e.g., valproate). Patients taking enzyme-inducing AEDs with tiagabine have shown linear pharmacokinetics with doses up to 80 mg/day.

Tiagabine has shown no clinically important interactions with warfarin, theophylline, ethanol, triazolam, oral contraceptives, cimetidine or digoxin. Renal dysfunction has no effect on tiagabine but hepatic dysfunction increases tiagabine half-life, AUC and C_{max} so that smaller or less frequent doses are recommended in that condition. Tiagabine has little or no clinically important effects on carbamazepine, phenytoin or valproate concentrations. Elderly patients and children show pharmacokinetics similar to those observed in younger adult patients with epilepsy.

1.1.3. Efficacy

The efficacy of adjunctive tiagabine in partial seizures was demonstrated in 3 double-blind, placebo-controlled, parallel-group studies. Patients in the parallel-group studies had previously used a median of 6 drugs and had a history of epilepsy for a median of over 20 years. In the dose–response study, patients were randomized to tiagabine in daily doses of 16 mg ($n = 61$), 32 mg ($n = 88$) and 56 mg ($n = 57$) versus placebo ($n = 91$). In the primary analysis, there was significant reduction in median rates of complex partial seizures from baseline to the treatment periods for both the 32 mg and 56 mg groups ($p \leq 0.05$) compared with placebo. There was also a significantly greater proportion of patients achieving $\geq 50\%$ reduction in complex partial seizures for 32 mg ($p \leq 0.01$) and 56 mg ($p \leq 0.001$) than with placebo. Statistical significance compared with placebo was demonstrated in all 3 tiagabine groups for proportion of patients with $\geq 50\%$ reduction in simple partial seizures. Significance in the median reduction of partial seizures with secondary generalization was shown in the analysis of the combined 32/56 mg group compared with placebo.

Similar efficacy was demonstrated for adjunctive tiagabine given as 32 mg daily, administered in two

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[1] Steven C. Schachter, Director of Clinical Research, Comprehensive Epilepsy Center, Department of Neurology, Beth Israel Hospital, Boston, MA, USA; and Kenneth W. Sommerville, Abbott Laboratories, Abbott Park, USA.

or four divided doses in a dose frequency study. The median complex partial seizure reduction was significant compared with placebo for 8 mg given four times daily ($p > 0.05$) and approached statistical significance ($p > 0.1$) when given in a twice daily dose regimen. Both groups showed significance ($p > 0.01$) compared with placebo for the proportion of patients with $> 50\%$ reduction in complex partial seizures.

Tiagabine also demonstrated significance over placebo at a dose of 30 mg, given as 10 mg three times daily, for median reduction from baseline of complex partial seizures, simple partial seizures and partial seizures with secondary generalization.

When all tiagabine treated groups were combined across the three parallel-group studies, tiagabine significantly reduced the median number of complex, simple and partial seizures with secondary generalization from baseline to the treatment period compared with placebo. There was also significance in all partial seizure types for the proportion of patients with $\geq 50\%$ seizure reduction. This was also true when the three parallel-group studies were combined with two double-blind, crossover studies.

1.1.4. Safety

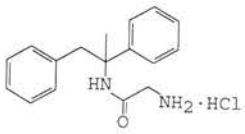
Tiagabine has been well-tolerated in the clinical trials of epilepsy. In the three parallel group, add-on studies, discontinuations for adverse events were 13% for tiagabine compared with 5% for placebo. The most common adverse events ($\geq 10\%$) significantly increased over placebo were dizziness, asthenia and nervousness. Adverse events tended to be greatest in incidence during dose titration and tended to lessen during the fixed-dose period. The pattern of adverse events in long-term trials is similar to that reported in the short-term, double-blind studies. The three most commonly reported adverse events in the longer term trials were dizziness, somnolence and asthenia. Among 1,414 patients in two long-term US studies (788 treated at least one year) only 15% had discontinued for adverse events.

Changes in laboratory values have been similar between the tiagabine and placebo groups. There were no meaningful differences in neuropsychological testing between tiagabine and placebo in the double-blind dose–response study.

1.1.5. Conclusion

Tiagabine is effective and generally well tolerated for partial seizures with and without secondary generalization in a population previously refractory to standard treatments. It has few clinically important interactions and does not adversely affect laboratory values. Further studies are underway to better evaluate the clinical benefit of tiagabine.

1.2. Remacemide [2]



Remacemide

Remacemide hydrochloride is an acetamide derivative and removal of the glycine portion produces an active metabolite. Remacemide and the desglycinyl metabolite have been shown to block fast sodium channels and the metabolite is a non-competitive inhibitor at the channel site on the NMDA receptor. Both compounds have been shown to have protective effects in standard in vitro and in vivo models of epilepsy. Remacemide has been evaluated for efficacy and safety in a recently complete dose-ranging study (CR 2237) described below.

1.2.1. Objectives

The objectives of the study were to assess the efficacy and safety of total daily doses of 300 mg, 600 mg and 1200 mg remacemide (dose expressed as remacemide base) and placebo administered in a qid regimen as add-on therapy on seizure type and frequency and to examine whether there was a dose–response relationship.

In addition, the study aimed to investigate any attenuation of response, any interactions with concomitant antiepileptic drugs and to evaluate seizure severity by use of a patient questionnaire.

[2] Stephen Wroe, Department of Neurology, Ipswich Hospital, Health Road, Ipswich, Suffolk IP4 5PD, England, UK.

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