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Progress report on new antiepileptic drugs: a summary of the Sixth Eilat Conference (EILAT VI)

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Abstract

The Sixth Eilat Conference on New Antiepileptic Drugs (AEDs) took place in Taormina, Sicily, Italy from 7th to 11th April, 2002. Basic scientists, clinical pharmacologists and neurologists from 27 countries attended the conference, whose main themes included dose–response relationships with conventional and recent AEDs, teratogenic effects of conventional and recent AEDs, update on clinical implications of AED metabolism, prevention of epileptogesis, and seizure aggravation by AEDs. According to tradition, the central part of the conference was devoted to a review of AEDs in development, as well to updates on AEDs, which have been marketed in recent years. This article summarizes the information presented on drugs in preclinical and clinical development, including carabersat (SB-204269), CGX-1007 (Conantokin-G), pregabalin, retigabine (D-23129), safinamide, SPD421 (DP-VPA), SPM 927, talampanel and valrocemide (TV 1901). Updates on fosphenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide, new formulations of valproic acid, and the antiepileptic vagal stimulator device are also presented.

Keywords: Antiepileptic drugs; Drug development; Epilepsy; Pharmacology; Clinical trials; Conference

1. Introduction

The Sixth Eilat Conference on New Antiepileptic Drugs (AEDs) took place in Taormina, Sicily, Italy from 7th to 11th April, 2002. The conference saw active participation of basic scientists, clinical pharmacologists and neurologists from 27 countries, with representatives from academia, the

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pharmaceutical industry, and regulatory agencies from both sides of the Atlantic. Main themes included dose–response relationships with conventional and recent AEDs, teratogenic effects of conventional and recent AEDs, update on clinical implications of AED metabolism, prevention of epileptogenesis, and seizure aggravation by AEDs. The central part of the conference was dedicated to discussion of drugs in development, as well as to updates on AEDs marketed in recent years, new formulations of valproic acid (VPA) and vagal nerve stimulator device. The following is a summary on the contributions related to these topics.

2. Drugs in development

2.1. Carabersat (SB-204269)

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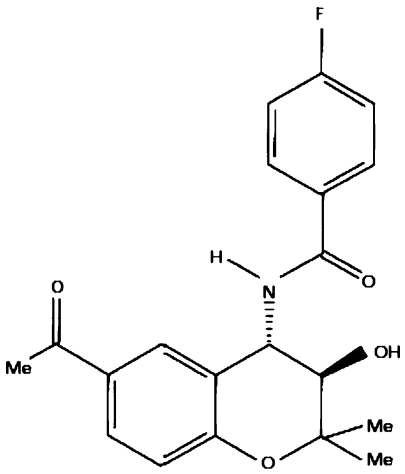

Carabersat (SB-204269)

2.1.1. Introduction

Carabersat (CRB; SB-204269) is a novel fluorobenzoylamino benzopyran compound which exhibits excellent anticonvulsant potency and efficacy relative to phenytoin (PHT), carbamazepine (CBZ), DZP, lamotrigine (LTG) and GBP in a wide range of in vivo (pentylenetetrazol (PTZ) infusion, maximal electroshock (MES) seizure threshold, supramaximal electroshock) and in vitro (elevated potassium and zero magnesium brain slice assays) rodent seizure models (Upton et al., 1997). Overall, the profile of activity in these models strongly suggests that the compound acts by preventing seizure spread. This particular mode of action is also shared by AEDs such as CBZ and LTG and may translate into clinical utility for symptomatic control of partial (with and without generalization) and generalized tonic-clonic seizures. In addition, CRB appears to slow the development of amygdala-kindled seizures in rats, indicating that it may be able to inhibit epileptogenesis. Importantly, the anticonvulsant properties of CRB are of long duration and there is no evidence of a decline in efficacy following repeated administration.

2.1.2. Mechanism of action

Although the precise molecular mechanism(s) of CRB remain(s) to be determined, a specific binding site for the compound (first discovered using [^{3}H]-CRB) has been identified in the brain tissue of several species including mouse, rat, cat, dog, marmoset and, most importantly, man. The highest levels of binding are found in the superficial layers of the cerebral cortex and granule cell layer of the cerebellum, with moderate levels in CA fields and dentate gyrus of the hippocampus (Herdon et al., 1997). Several lines of evidence now strongly support the relevance of this binding site to the anticonvulsant properties of CRB. For example, there is a good correlation between binding affinity and anticonvulsant activity in the mouse MES seizure threshold test for a wide range of analogues of CRB. To date, no activity of CRB ($pK_i \leq 5$) has been identified in over 50 radioligand-binding assays. These include binding to amino acid receptors and ion channels, sodium and potassium channels, purinergic and aminergic receptors, and opioid and other peptidergic receptors. In addition, CRB did not demonstrate significant activity in a range of in vitro functional assays. These findings indicate that CRB interacts selectively with its own binding site and, unlike other AEDs, has no known effect on sodium

channels or GABAergic or glutamatergic pathways.

2.1.3. Pharmacokinetics

A total of 136 healthy volunteers have completed dosing with CRB in eight separate studies. CRB was well tolerated. Pharmacokinetic data from these studies have shown that the current formulation exhibits dose proportional changes in maximum concentration (C_{max}) and area-under-the-curve (AUC), a variable time to maximum concentration (t_{max}) of several hours, and an apparent terminal half-life of 24 h. Oral bioavailability is enhanced by food. Radiolabeled studies with [^{14}C]-carabersat have shown that the compound is predominantly cleared by hepatic metabolism in man.

2.1.4. Efficacy

A parallel-design, multicenter, double-blind, placebo-controlled evaluation of the safety and efficacy of CRB given as add-on therapy in 305 patients (228 randomized to CRB, 77 to placebo) with refractory simple or complex partial seizures (with or without secondary generalization) has been completed. The parallel groups received 400, 800 or 1200 mg/day CRB or placebo. This study, which used the initial formulation of CRB, showed a mean reduction in seizure frequency of 20–30% in the 1200 mg/day dose group compared with placebo ($P < 0.05$). In general, CRB was well tolerated at all dose groups. These findings suggest that CRB has biological activity in epilepsy and displays a favorable safety profile. A novel formulation of CRB has been developed to provide a more advantageous pharmacokinetic profile (decreased C_{max}, delayed t_{max}, plasma levels sustained above a C_{min} level). Future clinical trials will be conducted using this new formulation.

2.2. CGX-1007 (Conantokin-G)

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2.2.1. Introduction

CGX-1007 (Conantokin-G) is a synthetic version of a conopeptide, derived from *Conus geographus* cone snail venom, that has exhibited anticonvulsant activity in preclinical studies. CGX-1007 is 17 amino acids in length. Among the approaches for epilepsy management is *N*-methyl-D-aspartate (NMDA) receptor modulation. CGX-1007 is a selective NMDA receptor antagonist (Donevan and McCabe, 2000). It is proposed that CGX-1007 be administered intrathecally (i.t.) to patients with epilepsy using the SynchroMed® Infusion System. The Medtronic SynchroMed® Infusion System consists of a small pump implanted in the abdominal region and a catheter that delivers medication to a specific site within the body. The system bypasses the digestive system and the blood–brain barrier, two factors important for effective delivery of a central nervous system (CNS) active peptide. The SynchroMed® Infusion System is approved by the FDA for the chronic intraspinal infusion of sterile preservative-free morphine sulfate for intractable chronic pain, including cancer pain; for the intrathecal infusion of baclofen for severe spasticity of spinal and cerebral origin; as well as intravascular infusion of floxuridine for the treatment of primary or secondary metastatic cancer.

In animal seizure models, CGX-1007 has been shown to exhibit broad-spectrum anticonvulsant activity with very low behavioral toxicity. Moreover, CGX-1007 has been demonstrated to be effective in animal models of complex partial seizures. The objective is to develop the compound for the treatment of patients with partial seizures with or without secondary generalization refractory to available AEDs.

In humans, CGX-1007 appears to be safe and well tolerated via the intravenous (i.v.) route. While CGX-1007 possesses a broad-spectrum anticonvulsant profile, it is also recognized that direct administration to the CNS will be required for treatment of patients with epilepsy. The i.t. route represents the most feasible delivery approach. Given the novel molecular mechanism of action, broad spectrum of activity and low behavioral toxicity, CGX-1007 may represent a unique and novel anticonvulsant agent and may provide a

significant advance in the treatment of patients with uncontrolled seizures.

2.2.2. Pharmacology

CGX-1007 is a specific NMDA receptor antagonist that does not interact with any other receptors or binding sites examined in the *NovaScreen®* receptor profiling study (concentration tested was 10 μM). CGX-1007 exhibits wide and uniform brain distribution when given i.t. in rats and dogs.

CGX-1007 has been characterized as an anticonvulsant compound in an in vivo reflex model of epilepsy. CGX-1007 dose-dependently blocked sound-induced tonic extension following i.t. and intracerebroventricular (i.c.v.) injection in Frings audiogenic seizure-susceptible mice. In addition, CGX-1007 did not induce behavioral toxicity (TD_{50}, median behaviorally toxic dose or minimal motor impairment as measured by rotarod) in animals until significantly greater doses were administered. The separation between the ED_{50} and TD_{50} doses was greater than that of many established AEDs, therefore yielding a greater protective index ($PI = TD_{50}/ED_{50}$). In addition, CGX-1007 displayed a better PI than either the non-competitive NMDA antagonist MK-801 or the polyamine antagonist ifenprodil in the audiogenic, chemically- and electrically-induced seizure models. In the Frings model, CGX-1007 displays a rapid onset (within 1–3 min) and a prolonged duration (2–4 h) of action following i.c.v. administration of a single dose.

CGX-1007 was also found to display a broad-spectrum anticonvulsant profile that was similar to that of VPA. Thus, it was effective at non-behaviorally toxic doses against tonic extension seizures induced by both threshold and MES as well as clonic seizures induced by PTZ, bicuculline (BIC) and picrotoxin (PIC). CGX-1007 is effective in rat kindling models of partial seizures when given by either i.t. or i.c.v. administration. Collectively, these results indicate that CGX-1007 has the potential to be effective in a variety of human seizure disorders including generalized tonic-clonic seizures (anti-MES activity), generalized absence/myoclonic seizures (anti-PTZ activity), and partial seizures (kindling models).

2.2.3. Toxicology

In support of a completed phase I clinical i.v. study, 14 day i.v. toxicology studies were conducted in both the rat and dog. An additional 13 week subcutaneous study was conducted in the rat to evaluate the effect of longer-term systemic exposure as well as any local effects at the site of repeated injections. A battery of genetic toxicity tests (Ames, mouse lymphoma and mouse micronucleus) and immunogenicity studies also were conducted. To support delivery of CGX-1007 to the brain by direct infusion into the cerebrospinal fluid (CSF), i.c.v. and i.t. toxicology studies of 28 days and 13 weeks duration in both the rat and dog were conducted. It was also shown that, in general, pharmacokinetic parameters were similar after i.c.v. or i.t. administration. Based on these studies, CGX-1007 should be safe for i.t. administration at doses many times greater than those required to reduce seizure activity.

2.2.4. Drug interactions

In animal models, based on the protection against MES-induced seizures, there was no potentiation, but a strictly additive interaction when CGX-1007 was combined with PHT, CBZ, or VPA.

2.2.5. Planned studies

Based on the data described above, it is proposed that CGX-1007 be administered to patients with epilepsy by i.t. delivery using the SynchroMed® Infusion System.

2.3. Pregabalin

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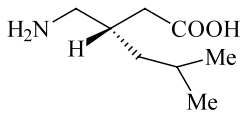

Pregabalin (CI-1008)

2.3.1. Introduction

Pregabalin (PGB), a structural analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA), is the pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methylhexanoic acid or 3-(*S*)-isobutyl GABA.

2.3.2. Pharmacology

2.3.2.1. Anticonvulsant profile. PGB is active in a number of animal models of epileptic seizures including MES seizures, chemical convulsant seizures (PTZ, BIC, PIC), kindled seizures in rats, and audiogenic seizures in genetically susceptible animals.

PGB prevents electroshock tonic extensor seizures when given per os (p.o.) and i.v. in mice (maximal stimulus ED_{50}, 20 mg/kg, p.o.; low-intensity stimulus ED_{50}, 1.4 mg/kg, i.v.) and rats (ED_{50}, 1.8 mg/kg, p.o.). The ED_{50} values obtained following i.v. and p.o. administration were quite similar. PGB did not cause ataxia except at high doses (ED_{50}, 60–260 mg/kg, p.o.). PGB prevented threshold clonic seizures induced by PTZ in mice, with an ED_{50} value of 100 mg/kg, p.o. or intraperitoneally (i.p.). In mice, threshold seizures from BIC or PIC were not completely blocked (maximal 70% protection, 250 mg/kg, i.p.), and seizures from strychnine were not blocked. Spontaneous absence seizures (6 Hz spike/wave discharges in neocortical EEG) were not altered by 10, 40, or 100 mg/kg PGB, but were slightly increased by 200 or 400 mg/kg i.p. PGB decreased seizures in DBA/2 audiogenic mice after dosages of 3 and 10 mg/kg p.o. PGB exhibits a high potency in animal seizure models compared to other anticonvulsant agents, based on mg/kg doses.

2.3.2.2. Mechanisms of action. The mechanism of action of PGB is unknown, but it appears to be different from that of conventional AEDs. PGB does not appear to have any direct action at ion channels (Na^+, Ca^{2+}) or transmitter responses (glutamate, NMDA, GABA), does not change neurotransmitter uptake (glutamate, GABA), and does not displace radioligand binding at a variety of receptors (glutamate, GABA, monoamine, adenosine, cholinergic, opiate) or Na^+ and Ca^{2+} channels. PGB increases GABA content in neuronal tissues and enhances glutamic acid decarboxylase activity. In vitro studies show that PGB interacts with an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in brain, potently displacing [^{3}H]-gabapentin or [^{3}H]-L-leucine. Studies with the R-enantiomer of PGB and a number of structural derivatives of pregabalin indicate that binding at the α2-δ site is required for analgesic and anticonvulsant activity in animal models.

2.3.3. Pharmacokinetics

Plasma and brain concentrations of PGB in rats were compared with the time course of anticonvulsant effects (MES). In the rat, PGB pharmacokinetics was dose proportional and PGB was not significantly metabolized. Maximal MES action was observed approximately 2–4 h after i.v. dosing. Plasma concentrations decreased monoexponentially.

Phase I clinical studies indicate oral bioavailability to be approximately 90%, plasma half-life ($t_{1/2}$) 6 h, time to maximum concentration (t_{max}) 1 h, and C_{max} and AUC to be dose proportional. PGB is not significantly metabolized in man, with approximately 98% of an absorbed dose being excreted unchanged in the urine. PGB is not bound to plasma proteins. AUC and $t_{1/2}$ remain unchanged following administration with a standardized meal, while C_{max} is reduced by approximately 25–30% and t_{max} is increased to approximately 3 h.

2.3.4. Drug interactions and tolerability

PGB is well tolerated, with dose-related CNS adverse events (headache, dizziness, somnolence) most commonly reported by normal volunteers with doses up to 900 mg/day. PGB may be used as adjunctive therapy without changes in the blood concentrations of other AEDs or PGB itself (no drug–drug interactions identified or expected). Therapeutic drug monitoring is not required for dosing PGB. It is recommended that patients with impaired renal function have their PGB dose reduced.

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