Conference Review

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

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This manuscript is dedicated to the memory of Professor Pierre Loiseau, Bordeaux, France, who suddenly left us on March 29th, 2004. Pierre was an eminent epileptologist and a great human being, and he was for many years a member of the Eilat Conferences Organizing Committee. His excellent scientific ability and human modesty remind us of the words from the song:" Where are there more people like this great man? . . ."

Abstract

The Seventh Eilat Conference on New Antiepileptic Drugs (AEDs) (EILAT VII) took place in Villasimius, Sardinia, Italy from the 9th to 13th May 2004. Basic scientists, clinical pharmacologists and neurologists from 24 countries attended the conference, whose main themes included advances in pathophysiology of drug resistance, new AEDs in pediatric epilepsy syndromes, modes of AED action and spectrum of adverse effects and a re-appraisal of comparative responses to AED combinations. Consistent with previous formats of this conference, the central part of the conference was devoted to a review of AEDs in development, as well as updates on second-generation AEDs. This article summarizes the information presented on drugs in development, including atipamezole, BIA-2-093, fluorofelbamate, NPS 1776, pregabalin, retigabine, safinamide, SPM 927, stiripentol, talampanel,

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ucb 34714 and valrocemide (TV 1901). Updates on felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide, new oral and parenteral formulations of valproic acid and SPM 927 and the antiepileptic vagal stimulator device are also presented.

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

1. Introduction

The Seventh Eilat Conference on New Antiepileptic Drugs (AEDs) (EILAT VII) took place in Villasimius, Sardinia, Italy from the 9th to 13th May 2004. Basic scientists, clinical pharmacologists and neurologists from 24 countries attended the conference, whose main themes included advances in pathophysiology of drug resistance, new AEDs in pediatric epilepsy syndromes, modes of AED action and spectrum of adverse effects and a re-appraisal of comparative responses to AED combinations. Consistent with previous formats of this conference, the central part of the conference was devoted to a review of AEDs in development, as well as updates on second-generation AEDs. This article summarizes the information presented on drugs in development, including atipamezole (AMZ), BIA-2-093, fluorofelbamate (FFBM), NPS 1776, pregabalin (PGB), retigabine (RGB), safinamide (SAF), SPM 927, stiripentol (STP), talampanel (TLP), ucb 34714 and valrocemide (TV 1901, VLR). Updates on felbamate (FBM), gabapentin (GBT), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM), vigabatrin (VGB), zonisamide (ZNS), new oral and parenteral formulations of valproic acid (VPA) and SPM 927 and the antiepileptic vagal stimulator device were also presented.
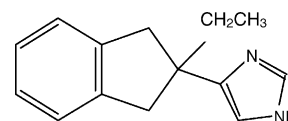
2. Drugs in development

2.1. Atipamezole

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Atipamezole

2.1.1. Introduction

α_2-Adrenergic agonists are known to possess activity against seizures induced by kainic acid (Baran et al., 1985) and pentylenetetrazol (PTZ) (Kulkarni, 1981). They also suppress audiogenic seizures in genetically epilepsy-prone DBA/2J mice (Kellog, 1976). Studies in the kindling model have shown that depletion of noradrenaline facilitates and enhancement of α_2-adrenergic transmission delays the development of kindling. This delay is mediated by activation of postsynaptic α_2-adrenoceptors (Gellman et al., 1987). Based on molecular cloning, α_2-adrenoceptors can be divided into α_{2A}, α_{2B}, and α_{2C} subtypes. Recently, Janumpalli et al. (1998) reported that development of kindling was facilitated in mice with defective α_{2A}-adrenoceptors. These data support the idea that α_2-adrenoceptors provides a novel candidate site for attempts to affect neurobiology of activity-dependent plasticity, one of the components of lesion-induced epileptogenesis.

Several neurobiological alterations that occur during epileptogenesis induced by various lesions (status epilepticus, stroke, trauma) can be targeted with novel compounds. Such alterations include neurodegeneration (acute, delayed), axonal and dendritic plasticity, activation and proliferation of various glial cell types, neurogenesis, reorganization of extracellular matrix, and molecular organization of cellular membranes (Pitkänen and Kubova, 2004). Based on kindling data, α_2-adrenoceptors provide an attractive target for the

modulation of activity-dependent plasticity following brain injury. This is further supported by experimental studies in rats that have shown that α_2-adrenoceptor receptor blockade has beneficial effects on functional recovery after traumatic brain lesions and stroke (for references, see Jolkkonen et al., 2000). Use of α_2-adrenoceptor antagonists in studies aiming at modulating lesion-induced epileptogenesis can, however, be complicated because α_2-adrenoceptor antagonists are proconvulsant in rats (Janumpalli et al., 1998). Further, in humans, oral administration of an α_2-adrenoceptor antagonist, yohimbine, increases cortical excitability induced by transcranial magnetic stimulation (Plewnia et al., 2001). Whether, proconvulsant effects can be reduced when receptor subtype specific α_2-adrenoceptor antagonists become available, remains to be tested. Another question remaining is whether a compound that facilitates functional recovery after brain trauma concomitantly alters the risk of lesion-induced epileptogenesis.

Atipamezole [AMZ, MPV-1248, 4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole], an α_2-adrenoceptor antagonist synthesized by Orion-Pharma Ltd., possesses a number of properties that make it an attractive candidate to test some of the above hypotheses.

2.1.2. Pharmacology
2.1.2.1. Pharmacological profile in seizure, epileptogenesis and disease modification models.
AMZ has no anticonvulsant effects. Similar to other α_2-adrenoceptor antagonists, acute administration of high doses of AMZ can have proconvulsant effects both in vitro (Valjakka et al., 1991) and in vivo (Halonen et al., 1995). Investigations were conducted recently to determine whether AMZ affects the recovery process from status epilepticus (SE)-induced brain trauma in rats (Kharatishvili et al., 2003). Vehicle or atipamezole ($100 \mu g/kg/h$) treatment was started 1 week after the induction of SE and continued for 9 weeks using subcutaneous (s.c.) Alzet minipumps. Development and severity of epilepsy, spatial and emotional learning, and histological analysis were used as outcome measures. Experiments were repeated twice. No differences were found in the percentage of animals developing epilepsy in the different treatment groups. In the AMZ group, however, daily seizure frequency was lower ($P < 0.01$), a higher percentage of epilep-

tic animals had milder epilepsy (<1 seizure per day; $P < 0.01$), and seizure frequency did not increase over time compared with the vehicle group. Hilar cell counts were higher than in the vehicle group ($P < 0.05$) and mossy fiber sprouting was less dense ($P < 0.05$). Behavioral impairments were similar between groups. These data indicate that chronic treatment with AMZ does not prevent epileptogenesis. There is, however, a clear disease-modifying effect; that is, the epilepsy that develops is milder and non-progressive. These are the first data to demonstrate that the occurrence of spontaneous seizures can be modified even when treatment is started after a delay relative to the epileptogenic insult.

2.1.2.2. Other pharmacological properties.
After s.c. dosing (1 mg/kg) repeated treatment with AMZ facilitates sensorimotor recovery after focal cerebral ischemia in rats (Jolkkonen et al., 2000). Intravenous (i.v.) AMZ reverses the sedative, cardiovascular, and xerostomic effects of dexmedetomidine at 100:1 or 40:1 AMZ:dexmedetomidine concentration ratios in humans and rats. After oral dosing in humans, neither measurable concentration of the drug in plasma nor any pharmacologic effects can be detected (Karhuvaara, 1991). Currently, an i.v. preparation of AMZ is used as an antidote for α_2-agonist-induced anesthesia in veterinary medicine (Haapalinna et al., 1997).

2.1.2.3. Mechanism of action.
AMZ is more specific and selective than previously available α_2-antagonists. In receptor binding studies, its α_2/α_1 selectivity ratio was 8526 compared to 40 and 27 for yohimbine and idazoxan, respectively. AMZ has high affinity for α_{2A}-, α_{2B}- and α_{2C}-adrenoceptor subtypes in both humans and rodents, suggesting that there are no species-specific differences in its effects (Haapalinna et al., 1997). Based on receptor binding studies and studies with isolated organ preparations, AMZ has no affinity or effects on β_1, β_2, H_1, H_2, $5HT_1$, $5HT_2$, muscarinic, dopamine D_2, tryptamine, $GABA_A$, opiate (mu, delta), and brain or heart benzodiazepine receptors. Pharmacologic receptor specificity together with behavioral observations (Haapalinna et al., 1997) indicates that AMZ does not markedly affect systems other than α_2-adrenoceptors. Further, AMZ is well tolerated over a large dose range. Thus, AMZ provides a rather specific

tool to evaluate the effects of α_2-adrenoceptor blockade in vivo.

2.1.3. Safety pharmacology, toxicology and preclinical pharmacokinetics

AMZ is well tolerated in rodents. In anesthetized, normotensive rats, the effects of AMZ (0.01–1 mg/kg, i.v.) on the cardiovascular system are rather modest. An initial, short-lasting hypertensive effect can be detected. The LD_{50} is >30 mg/kg after i.v., s.c. or i.p. administration in male and female mice and rats.

In preclinical pharmacokinetic studies, AMZ was found to be rapidly absorbed and distributed when administered s.c. Peak concentrations in tissues, including the brain, are two- to three-fold higher than the corresponding plasma levels. In rat, the elimination half- life is 1.3 h after s.c. administration of a single dose. AMZ undergoes extensive first-pass metabolism. Drug interactions of AMZ have not been studied in detail.

2.1.4. Clinical studies

AMZ was found to be well tolerated in phase I studies in humans after single-dose i.v. or oral administration (up to 100 mg) as well as after single-dose buccal or sublingual administration (up to 40 mg). Its effects on the electroencephalogram and on neuropsychological test performance have also been assessed in healthy male volunteers given single i.v. doses ranging between 0.027 and 0.1 mg/kg (Mervaala et al., 1993).

The pharmacokinetics of AMZ has been tested in 6 healthy volunteers given i.v. doses of 10–100 mg over a 20-min infusion period. The elimination half-life of the drug was found to be in the order of 1.7–2.0 h over this dose range.

2.2. BIA 2-093

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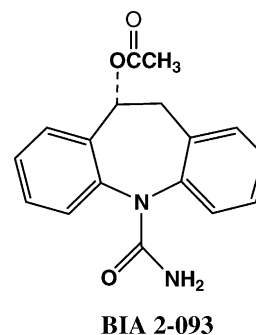
BIA 2-093

2.2.1. Introduction

BIA 2-093, S-(−)-10-acetoxy-10,11-dihydro-5H-dibenzo/b,f/azepine-5-carboxamide, was designed with the aim of improving efficacy and safety in comparison with the structurally related drugs CBZ and OXC. BIA 2-093 shares with CBZ and OXC the dibenzazepine nucleus bearing the 5-carboxamide substituent, but it is structurally different at the 10,11-position (Benes et al., 1999). This molecular variation results in differences in metabolism, including prevention of the formation of potentially toxic epoxide metabolites (Hainzl et al., 2001).

2.2.2. Pharmacology

BIA 2-093 protects in a dose- and time-dependent manner against seizures in the maximal electroshock (MES) and amygdala kindling models in rodents, which are predictive of efficacy against generalized tonic-clonic and partial-onset seizures respectively (Benes et al., 1999). In these models, the potency of BIA 2-093 was similar to that of CBZ and higher than that of OXC. Mechanistically, BIA 2-093 behaves as a potent blocker of voltage-gated sodium channels through interference with site 2 of the channel, and does not bind to receptors for benzodiazepines, gamma-amino butyric acid (GABA) and glutamate (Ambrosio et al., 2000, 2001; Cunha et al., 2002; Parada and Soares-da-Silva, 2002). Like AEDs in its class, BIA 2-093 interferes preferentially with rapidly firing neurons without affecting normal neuronal activity (Bonifacio et al., 2001).

2.2.3. Toxicology

At doses showing anticonvulsant activity, BIA 2-093 exhibits no adverse effects on the central nervous system (CNS) and on the gastrointestinal, renal, car-

diovascular and respiratory systems. Higher doses may have CNS-depressant effects. In anaesthetized dogs, administration of BIA 2-093 (160 mg/kg, intraduodenal) had no significant effect on respiration rate and on ECG and hemodynamic parameters, including arterial blood pressure, left ventricular end-diastolic pressure, left ventricular systolic pressure, cardiac output, stroke volume, peripheral resistance and arterial blood pCO_2 and pO_2.

Single- and repeat-dose toxicity studies in mice, rats and dogs have revealed a favorable safety profile. The no observed adverse effect level (NOAEL) in acute and chronic (up to 6 months) toxicology studies varied from 20 to 80 mg/kg. NOAEL for male rat systemic toxicity and for reproduction toxicity was 250 mg/kg/day, while NOAEL for rat female systemic toxicity was 65 mg/kg/day. NOAEL values for developmental toxicity and maternal toxicity, F1 generation development, behavior and reproductive performance, and for rabbit maternal and development toxicity varied between 40 and 65 mg/kg. BIA 2-093 was devoid of mutagenic and clastogenic effects in several in vitro and in vivo tests.

2.2.4. Pharmacokinetics

Single and multiple ascending dose studies in healthy male volunteers showed that BIA 2-093 is rapidly converted to the active metabolite BIA 2-005 (licarzepine or 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide). BIA 2-005 is a racemic mixture of BIA 2-194 ((S)-licarzepine or 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide) and BIA 2-195 ((R)-licarzepine), the former being the most prevalent form (95%) in plasma after oral administration of BIA 2-194. BIA 2-194 ((S-licarzepine) and BIA 2-195 (R)-licarzepine), also correspond to the (S)- and (R)-enantiomers of 10-hydroxy-carbazepine, i.e. the monohydroxy (MHD) active metabolite of OXC. Plasma concentrations of parent compound were not measurable in healthy volunteers dosed with BIA 2-093 and the peak plasma concentrations (C_{max}) of BIA 2-005 occurred at 2 to 3 h post-dose. The steady-state plasma concentrations of this metabolite were attained after 4–5 days of once or twice daily dosing. The half-life of BIA 2-005 is 20–24 h, which is probably sufficient for BIA-2-093 to be administered once daily. BIA 2-005 and its conjugates are excreted predominantly in urine, with approximately 20 and 40% of the oral dose excreted in the urine (in a free or conjugated form) 12 and 24 h after dosing, respectively (Almeida et al., 2002, Almeida and Soares-da-Silva, 2003).

Co-administration with food does not change the pharmacokinetic profile of BIA 2-093 and its metabolites BIA 2-194 and BIA 2-195. In contrast to OXC, following oral administration of BIA 2-093, 95% of the drug appears in the plasma as (S)-licarzepine or BIA 2-194 and only 5% undergoes chiral inversion to (R)-licarzepine or BIA 2-195. The bioavailability of BIA 2-093, measured in terms of areas under the curve (AUC) of the metabolites BIA 2-194 and BIA 2-195 is 16% greater than that observed after intake of an equivalent molar dose of OXC.

2.2.5. Efficacy and tolerability data

2.2.5.1. Efficacy. A multicenter, double-blind, randomized, placebo-controlled, adjunctive-therapy phase II study was conducted in 143 male and female patients aged 18–65 years. At entry, all patients had to have at least four partial seizures (with or without secondary generalization) per month despite treatment with one or two conventional AEDs. BIA 2-093 was given orally to two groups of patients for 12 weeks, dosages being titrated up to 400, 800 and 1200 mg/day at 4-week intervals. In one group, BIA 2-093 was given once daily, while in the other group the total daily dose was given in two equally divided daily administrations. The primary endpoint was the proportion of responders (defined as patients showing at least 50% seizure reduction compared with baseline). In the intent-to-treat (ITT) population, the proportion of responders in the BIA 2-093 once daily group ($n = 50$) was higher ($P < 0.05$) when patients received daily doses of 800 mg and 1200 mg than in the placebo group ($n = 46$). No significant differences in proportion of responders were found between the once daily and the twice daily ($n = 47$) groups. At the end of the 12-week treatment phase, respectively 28, 32 and 11% of the patients in the once-daily, twice-daily and placebo groups became seizure-free.

Multinational phase III trials in refractory partial epilepsy are planned in the near future.

2.2.5.2. Tolerability. In phase I trials in healthy volunteers, adverse events observed with BIA 2-093 were mild in severity except for one subject who reported moderate somnolence after receiving an 800 mg dose. There were no clinically significant abnormali-

ties in vital signs, body weight, physical examination or ECG parameters. QTcB (QT interval corrected using Bazett's formula) remained below the normal limit of 0.430 s. In the phase II trial, the incidence of adverse events was similar in the three treatment groups (56% in the once daily group, 59% in the twice daily group, and 60% in the placebo group). Overall, tolerability was rated by the investigator as "good" or "very good" in 90% of patients in the once daily group, 80% in the twice-daily group and 83% in the placebo group.

2.3. Fluorofelbamate

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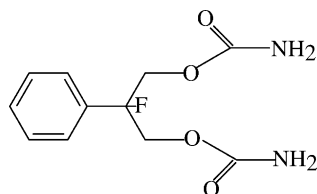
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Fluorofelbamate

2.3.1. Introduction

Flurofelbanate (FFFM, 2-phenyl-2-fluoro-1,3 propanediol dicarbamate) is a felbanate (FBM) analogue designed to have clinical efficacy similar to FBM without the serious adverse effects of the latter. FFBM differs from FBM in that fluorine is substituted for hydrogen in the 2-position of the propanediol moiety. This substitution is thought to prevent the production of the reactive toxic metabolite of FBM, atropaldehyde (ATPAL, or 2-phenylpropenal). FFBM is currently in preclinical development.

2.3.2. Pharmacology
2.3.2.1. Anticonvulsant profile. The anticonvulsant profile of FFBM was established using standardized in vivo and in vitro tests and the results compared to FBM and other AEDs. FFBM is effective in all tested models of electrically induced seizures, it attenuates seizures induced by subcutaneous administration of picrotoxin (PICR) in mice and blocks sound-induced seizures in the audiogenic seizure-prone Frings mouse. Overall, the results of these studies support the concept that its broad-spectrum anticonvulsant profile is similar to that for FBM. The ED50 of FFBM is equivalent to and/or three to eight times higher than that of FBM, depending on the animal model and the protective index (TD50/ED50) is approximately 167 in the rat MES model. Minimal toxicity of FFBM was identified in mice using the rotorod test and in rats by observing overt evidence of ataxia and abnormal gait and stance.

When administered early at doses of 100 and 200 mg/kg in a self-sustaining status epilepticus (SSSE) animal model, FFBM reduced cumulative seizure duration from 393 ± 10 min to 15 ± 8 min and 2.4 ± 0.5 min, respectively. FFBM (200 and 300 mg/kg) also significantly attenuated seizures when administered at a late stage of SSSE that is refractory to treatment with conventional anticonvulsants (Mazarati et al., 2002).

2.3.2.2. Neuroprotective activity. FFBM protects against chemically (NaCN) induced ischemia in cultured hippocampal neurons, provides dose-dependent protection against hypoxic CA1 injury in hippocampal slices, reduces infarct volume after in vivo hypoxia in rat pups and protects against subicular CA1 damage associated with transient global ischemia in gerbils (Wallis et al., 2000).

2.3.2.3. Mechanism of action. Initial studies indicated that 100 μM FFBM causes a slight decrease in GABA-mediated responses and a slight but statistically significant decrease in responses to kainate- and NMDA-receptor activation using whole-cell current measures in mouse cortical neurons. At a 100 μM concentration, FFBM caused a slight but significant decrease in voltage-dependent sodium currents in NIE-115 neuroblastoma cells, down to $81 \pm 4\%$ of control values at a holding potential of -60 mV. The mechanism of action of FFBM, however, cannot be completely explained by either interactions at glutamate receptors sites or sodium channels.

2.3.3. Toxicology

Using a functional observational battery designed to assess neurological toxicities, doses below 500 mg/kg in rats produced no observable effects. At 500–1000 mg/kg there were deficits in hindlimb grip strength. Acute toxicity studies in rats and dogs identified a no-observed-adverse-effect-level (NOAEL) of 500 and 75 mg/kg, respectively. Tests for QTc prolongation in Purkinje fibers and genotoxicity screening tests in standard models were negative.

2.3.4. Pharmacokinetics and metabolism

In pharmacokinetic studies, C_{max} and AUC increased proportionally with dose in rats and dogs. In rats, C_{max} was similar for males and females, while AUC was 20–30% higher in males. Bioavailability in rats was high, in the range of 82–125% at all dosages tested. In dogs, C_{max} was reached in 2–6 h and along with AUC was similar between males and females. The terminal half-life in dogs was estimated at 6–9 h.

In the case of FBM, a reactive aldehyde metabolite (ATPAL) is produced from 3-carbamoyl-2-phenylpropionaldehyde (CBMA) and is thought to be responsible for the observed cases of aplastic anemia and liver toxicity. CBMA is in dynamic equilibrium with 4-hydroxy-5-phenyltetrahydro-1,3-oxazin-2-one (CCMF). Incubation of CBMA and CCMF with glutathione (GSH) leads to complete formation of adducts over a 24 h period (Thompson et al., 1996). In contrast, when radiolabelled GSH was incubated under similar conditions, with the fluorinated derivative of CCMF (F-CCMF), spontaneous formation of adducts was not detected in the absence of cellular constituents.

A number of experiments were carried out using pooled human liver S9 fractions with and without cofactors. Analysis of S9 supernatants that contained GSH using HPLC–APCI–MS, indicated that no ATPAL was produced from F-CCMF. Conversely an ATPAL–GSH adduct was detected when experiments were conducted with CCMF. When NAD+ was added, CPPA (3-carbamoyl-2-phenylpropionic acid) and the acid form of the ATPAL adduct were generated from CCMF. When F-CCMF was used, only F-CPPA was detected and once again there were no detectable adducts and no detectable non-fluorinated CPPA or CCMF. Similar studies with MCF (2-phenyl-1,3-propanediol monocarbamate) and F-MCF demonstrated additional differences in metabolism. While CCMF and CPPA were generated from MCF, when F-MCF was used there was not production of adducts and no fluorinated metabolites, F-CCMF or F-CPPA were detected. Furthermore, no de-fluorinated compounds, CPPA or CCMF, were detected. Overall, these results suggest that F-MCF does not enter the pathway that can generate reactive metabolites from the non-fluorinated analogue. Additionally, even if small quantities of F-CCMF or F-CBMA were generated, these metabolites are not cytotoxic and, as demonstrated above, will not form ATPAL adducts. Combined, these data indicate that FFBM utilizes different metabolic pathways than FBM and does not form reactive intermediates (e.g., ATPAL) from human liver preparations.

2.4. NPS 1776

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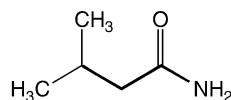
NPS 1776 (isovaleramide, 3-methylbutanamide)

2.4.1. Introduction

NPS 1776 (3-methylbutanamide; isovaleramide) is a branched-chain, low molecular weight, aliphatic amide that exhibits a broad-spectrum anticonvulsant profile in a variety of animal models.

2.4.2. Pharmacology

2.4.2.1. Anticonvulsant profile. NPS 1776 is orally effective in a wide range of models, including MES-induced seizures and clonic seizures induced by PTZ in rats and mice; bicuculline (BIC)- and PICR-induced seizures in mice; generalized seizures in corneal-kindled rats; secondarily generalized seizures, seizure score and after-discharge duration in amygdala-kindled rats; spontaneous electroencephalograph (EEG) spike and wave patterns of absence seizures in rats; and sound-induced tonic extensions in Frings audiogenic seizure-susceptible mice. NPS 1776 delays the acquisition of kindling in amygdala-kindled rats, an effect which is manifested in both seizure parameters examined, i.e., seizure score and afterdischarge duration.

Overall, the anticonvulsant profile of NPS 1776 is comparable to that of VPA.

No evidence of tolerance to anticonvulsant effects was observed in a 4-week study in which Frings mice were treated daily with NPS 1776. There was no cross-tolerance of NPS 1776 with either diazepam or VPA.

2.4.2.2. Other pharmacological properties. In several pharmacological models for general CNS function, NPS 1776 did not produce significant adverse behavioral effects at doses that are effective in animal models of epilepsy.

NPS 1776 is also effective in animal models for antispastic, analgesic and anxiolytic activities.

2.4.2.3. Mechanism of action. The mechanism of action of NPS 1776 is unknown. In a variety of in vitro neurotransmitter binding or uptake assays, NPS 1776 was without effect at concentrations up to 1000 μM, suggesting that its action does not involve a direct receptor-mediated effect at those systems studied.

Ongoing studies include additional investigations in other seizure models, electrophysiological assessments of how NPS 1776 may impact cortical and hippocampal synaptic transmission, and studies on effects on the development of cutaneous allodynia.

2.4.3. Toxicology

In extensive safety studies in rats, rabbits, and dogs, NPS 1776 produced a consistent pattern of signs at relatively high doses. The significant findings were related to exaggerated pharmacological activity and consisted primarily of transient ataxia and hypoactivity. NPS1776 was safe and well tolerated by animals at exposures well above the expected human therapeutic exposure.

No adverse effects were reported from in vivo safety studies that investigated the effects of NPS 1776 on pulmonary, cardiovascular, gastrointestinal, and renal parameters in multiple species. No effect on hERG current or action potential duration was observed in in vitro studies.

In several reproductive toxicity studies conducted in mice, rats and rabbits, NPS 1776 showed a significantly lower potential for reproductive toxicity than VPA.

VPA and other short-chain fatty acids are known to inhibit mitochondrial β-oxidation and respiration.

NPS 1776 did not inhibit mitochondrial β-oxidation at concentrations up to 1000 μM.

2.4.4. Pharmacokinetics

Phase I studies included two escalating single- and multiple-dose safety and pharmacokinetic studies in men and women. In addition, single-dose safety and pharmacokinetic studies with multiple sustained-release formulations were conducted.

In the single-dose study (doses of 100–1600 mg in males, 1200 mg in females), NPS 1776 was found to be rapidly and almost completely absorbed from the gastrointestinal tract, and to be also rapidly eliminated. Systemic exposure to NPS 1776 increased with increasing oral doses, and the increase in C_{max} and AUC values was slightly greater than proportional to the increase in dose. Values for half-life did not vary markedly with dose ($t_{1/2}$–2.4 h, t_{max}–40 min). Renal excretion was a minor route of clearance, with approximately 2–4% of the administered dose being excreted unchanged in urine within 24 h. Pharmacokinetic parameters of NPS 1776 in females were not markedly different from those in males.

There was negligible accumulation following t.i.d. dosing for 9 days in healthy male and female subjects. Systemic exposure to NPS 1776 increased with increasing dose over the 1200–2400 mg/day dose range (females, 1200 mg/day only), maximal plasma concentration (C_{max}) and area under the plasma concentration-time curves (AUC_{0-t}) being approximately dose-proportional. Inter-subject variability in pharmacokinetic parameters was quite low. The data suggested that steady state conditions were achieved by day 2. Renal excretion was minor, with less than 2% of the administered dose being excreted unchanged in urine.

In two phase I single oral dose studies in healthy male subjects, all sustained release prototype formulations resulted in a prolonged release of NPS 1776. One formulation provided a median time to reach C_{max} (t_{max}) of 12 h. Although further optimization of the formulations is required, these studies demonstrated the feasibility of twice-daily administration of NPS 1776 in maintaining concentrations within a putative therapeutic range.

2.4.5. Drug interactions

NPS 1776 does not inhibit any of the major drug-metabolizing human cytochrome P450 (CYP) iso-

forms. Its binding to human plasma proteins is minimal. Therefore, significant interactions affecting the pharmacokinetics of concomitantly administered drugs are not expected.

2.4.6. Tolerability

NPS 1776 was well tolerated in all phase I human studies regardless of formulation or dose. There were no serious adverse events. There were no drug-related or clinically significant changes in vital signs, 12-lead ECG, clinical laboratory assessments or physical examinations. There were also no clinically significant drug-related changes in neurological examination, muscle strength and cognitive function.

2.4.7. Planned studies

Several phase I pharmacokinetic studies with sustained release formulations are planned to begin in the US in 2004. A phase II study for the acute treatment of migraine was initiated in the US in November 2003. Additional phase II studies are planned.
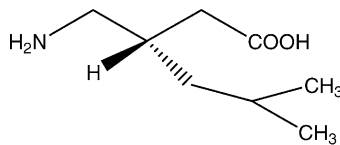
2.5. Pregabalin

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Pregabalin (CI-1008)

2.5.1. Introduction

Pregabalin (PGB, CI-1008) is the *S*-enantiomer of 3-aminomethyl-5-methylhexanoic acid. PGB has been shown to be effective in patients with partial seizures with and without secondary generalization, neuropathic pain and generalized anxiety disorder in several placebo-controlled trials (Dworkin et al., 2003; Feltner et al., 2003; French et al., 2003; Pande et al., 2003; Arroyo et al., 2004). Overall, to date approximately 1600 patients with epilepsy have received PGB in clinical studies.

2.5.2. Pharmacology

2.5.2.1. Anticonvulsant profile. PGB exhibits potent activity against seizures induced by MES, PTZ, BIC, and PICR (Selak, 2001; Bialer et al., 2002; Andre et al., 2003). It is also effective in preventing seizures in kindled rats, and audiogenic seizures in genetically susceptible mice. Spontaneous absence seizures (6 Hz spike/wave discharges in neocortical EEG) were unaffected by 10, 40, or 100 mg/kg PGB, but were slightly increased by 200 or 400 mg/kg, i.p. The latter doses are well above those that are protective in other models (Bialer et al., 2002).

2.5.2.2. Mechanisms of action. In vitro studies have shown that PGB interacts with an auxiliary subunit (the $alpha_2$-delta subunit) of voltage-gated calcium channels in the CNS (Dooley et al., 2002; Taylor, 2004). Potent binding at this site attenuates depolarization-induced calcium influx at nerve terminals, with a subsequent reduction in the release of excitatory neurotransmitters, including glutamate, noradrenaline, and substance P (Dooley et al., 2000; Field et al., 2001; Maneuf et al., 2001; Dooley et al., 2002; Fink et al., 2002; Fehrenbacher et al., 2003).

Studies with PGB and a number of structural derivatives indicate that binding at the $alpha_2$–delta site is required for anticonvulsant, analgesic and anxiolytic activity in animal models (Lauria-Horner and Pohl, 2003; Editorial, 2004). Furthermore, these actions of PGB are reduced in mutant mice with defective drug binding to the $alpha_2$–delta subunit. This mechanism of action differs from the mechanisms of conventional AEDs in that PGB does not show affinity for receptor sites and does not alter responses associated with the action of other AEDs.

Although PGB is structurally related to GABA, it does not interact with either $GABA_A$ or $GABA_B$ receptors, it is not converted to GABA or to a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.

2.5.3. Pharmacokinetics

PGB shows linear and predictable pharmacokinetics across the dose range (150–600 mg/day) and there is little interindividual variability (Bialer et al., 2002).

The drug is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations being achieved at about 1 h after dosing. Oral bioavailability is $\geq 90\%$, and extent of absorption is unaffected by food intake. PGB is not bound to plasma proteins and the half-life ($t_{1/2}$) is approximately 6 h. Following repeated administration, steady state is achieved within 24–48 h.

Because PGB is excreted virtually unchanged in urine, it is recommended that patients with impaired renal function (creatinine clearance <60 mL/min) have their PGB dose reduced (Randinitis et al., 2003).

2.5.4. Drug interactions

There are no known pharmacokinetic interactions with PGB. PGB does not affect the plasma concentrations of concomitantly administered AEDs. Likewise, other AEDs have no influence on PGB pharmacokinetics (Editorial, 2004).

PGB is not subject to hepatic metabolism, it appears to be devoid of enzyme inducing or inhibiting activity and it does not affect the pharmacokinetics of the contraceptive pill (Bockbrader et al., 2004).

2.5.5. Efficacy and tolerability data

2.5.5.1. Efficacy. Four multicenter, 12-week, randomized, double-blind, placebo-controlled adjunctive-therapy trials have been completed in patients with partial seizures with and without secondary generalizations uncontrolled by one to three background AEDs.

Three of the trials were fixed-dose and investigated dose–response relationships (50–600 mg/day) and dosing regimens (twice vs. three times daily dosing) in patients with refractory partial epilepsy. Nearly 75% of patients were taking two or more background AEDs with mean and median baseline seizure rates of 22.5 and 10 per 28 days, respectively. In all three trials, PGB was effective in reducing seizure frequency, and a clear relationship between dose and response could be shown (Bialer et al., 2002; French et al., 2003; Arroyo et al., 2004). Responder rates (50% reduction in seizure frequency from baseline) ranged from 14% at 150 mg/day to 45% at 600 mg/day.

The fourth trial evaluated efficacy, safety, and tolerability of PGB administered twice daily either at flexible-doses (150–600 mg/day) or at a fixed-dose (600 mg/day) in a total of 341 patients. During a 6-week baseline, patients were required to experience at least four partial seizures, and to have no 4-week seizure-free interval. Patients were then randomized to receive PGB at flexible doses (150 and 300 mg/day for 2 weeks each, followed by 450 and 600 mg/day for 4 weeks each, with dosage optimized based on clinical response), PGB at a fixed dose (600 mg/day from day 1) or placebo. Reduction in seizure frequency was significantly greater in the PGB fixed-dose (49.3%; $n = 137$; $P < 0.0001$) and in the PGB flexible-dose (35.4%; $n = 131$; $P = 0.009$) groups than in the placebo group (10.6%; $n = 73$). The fixed-dose group showed greater reduction in seizure frequency than the flexible-dose group. Responder rates were 45.3% in the fixed-dose group, 33.1% in the flexible-dose group, and 11.0% in the placebo group, differences versus placebo being highly significant ($P < 0.001$) for both PGB groups. Discontinuation rates due to adverse events were 6.8% in the placebo group, 12.2% in the flexible-dose group, and 32.8% in the fixed-dose group.

Overall, throughout the PGB development program, a significant reduction in seizure frequency and a lower incidence of adverse events and study discontinuations were achieved when dosing was individualized to optimize efficacy and tolerability as compared to when a fixed, high-dose schedule was used (French et al., 1999; Robbins et al., 2001; Ramsay et al., 2001).

2.5.5.2. Tolerability. In all controlled clinical trials, PGB was found to be generally well tolerated and to have a favorable safety profile. The most frequently reported adverse events included dizziness, somnolence and ataxia, and were mostly mild to moderate in intensity. CNS adverse events tended to increase with increasing PGB doses. The efficacy and good tolerability of the drug is reflected by the fact that 83% of PGB-treated patients enrolled in open-label extensions to the double-blind treatment phases.

2.6. Retigabine

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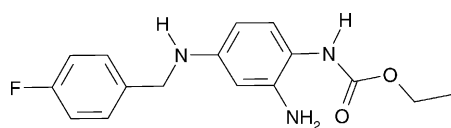
Retigabine (D-23129)

2.6.1. Introduction

Retigabine (RGB, D-23129) or *N*-[2-amino-4-(4-fluorobenzylamino)-phenyl]carbamic acid ethyl ester, is structurally unrelated to marketed AEDs. Its unique potential as an anticonvulsant was identified during screening at the National Institutes of Health in 1991.

2.6.2. Pharmacology

2.6.2.1. Anticonvulsant profile. RGB has demonstrated potent anticonvulsant activity in several animal models, including models with electrical and chemical induction of convulsions and genetic epilepsy (Rostock et al., 1996). Additionally, RGB has shown effectiveness in the kindling model of epileptogenesis (Tober et al., 1996).

RGB exerts its antiepileptic effects in a manner unlike standard anticonvulsants, being more potent in the amygdala-kindling model of complex partial seizures in rats, than in other seizure models (e.g., the MES test) (Tober et al., 1996). The major *N*-acetyl metabolite of RGB also shows anticonvulsant activity in animal models.

2.6.2.2. Other pharmacological properties. Improved learning performance was observed in a model of cerebral ischemia and similar findings were observed during electroshock amnesia, suggesting possible neuroprotective activity in cerebral deficit models. RGB also causes a dose-dependent suppression of chronic neuropathic pain in two animal models (formalin test and spinal nerve injury test) (data on file; Blackburn-Munro and Jensen, 2003).

2.6.2.3. Mechanisms of action. Compared with existing AEDs, RGB is unique in that it exhibits a selective and potent M-current potassium channel opening effect at the KCNQ2/3 and KCNQ3/5 potassium channels, which causes membrane stabilization (Rundfeldt and Netzer, 2000). The stabilization of hyperexcitable neuronal cells with RGB is augmented by an ancillary mechanism involving potentiation of GABA-evoked currents.

2.6.3. Toxicology

RGB was well tolerated in repeat-dose toxicity studies in various rodent and non-rodent species lasting up to 1 year. The predominant CNS side effects were sedation accompanied by hyperexcitability and decreased body temperature. During chronic treatment, dependence liability was not observed.

2.6.4. Pharmacokinetics

Phase I studies have demonstrated rapid absorption, with mean maximum concentrations of 387 ng/mL (normalized to a 100 mg dose) within 1.5 h of a single oral dose (mean absolute bioavailability, approximately 60%). The mean terminal half-life of RGB is 8–9 h and the mean oral clearance is 0.70 L/h/kg in white adult subjects. In black subjects, clearance is decreased by 25% (Ferron et al., 2002).

In humans, RGB undergoes virtually exclusive phase II biotransformation and renal elimination. There is no indication of biotransformation via oxidative hepatic pathways; e.g., cytochrome P450 isoenzymes (Hempel et al., 1999). RGB is principally metabolized by *N*-glucuronidation resulting in the formation of two distinct *N*-glucuronides, and to a lesser extent by *N*-acetylation to form an active *N*-acetyl derivative.

2.6.5. Drug interactions

The pharmacokinetics of ethinylestradiol/norgestrel contraceptive steroids are not altered with concomitant RGB administration (Hiller et al., 1999). In addition, no food interactions have been found (data on file). Multiple doses of RGB (600 mg/day for 3 days following a 4-day titration period) did not have any effect on the single dose pharmacokinetics of PB (90 mg) in healthy volunteers. However, multiple doses of PB (90 mg for 3 weeks) caused a 10% increase in AUC for a single 200 mg dose of RGB. The clearance of a single dose of RGB (200 mg) was slightly reduced (13%) by co-administration of a low dose of LTG (25 mg/day) for 6 days. Conversely, the clearance of a single dose of LTG (200 mg) was modestly increased (21%) and LTG half-life was slightly decreased after multiple dosing with RGB (400–600 mg/day for 10 days) (Hermann et al., 2000). However, such interactions did not require any

dose adjustments in further phase II studies and do not appear to be clinically important.

A phase II study that enrolled 60 patients was conducted to evaluate the potential for drug interactions between RGB and other AEDs. After 6–10 weeks of concomitant administration, RGB (1200 mg/day) did not alter the steady-state serum concentration of VPA, TPM, PHT or CBZ in epileptic patients (Ferron et al., 2001). Additionally, RGB pharmacokinetics were not altered by VPA or TPM. However, a moderate (approximately 30%) increase in RGB clearance was observed when administered with PHT or CBZ. Therefore, higher doses of RGB may be required in patients also taking PHT or CBZ, and RGB doses may need to be decreased upon discontinuation of PHT or CBZ.

2.6.6. Efficacy and tolerability data
2.6.6.1. Efficacy. To date, five early phase II studies and one late phase II study have been conducted in 600 patients with refractory partial-onset seizures.

In a large randomized, double-blind, placebo-controlled, parallel group, multinational, phase IIb adjunctive-therapy trial in 399 patients, median percentage reduction in monthly total partial seizure rate in patients assigned to RGB (given in three divided doses) were 23, 29 and 35% in the 600, 900 and 1200 mg/day treatment groups, respectively, compared with 13% in the placebo group. Corresponding 50% responder rates were 23, 32 and 33% for the 600, 900 and 1200 mg/day groups, respectively, compared with 16% for the placebo group. The 600 mg/day dose was not statistically different from placebo, but both 900 and 1200 mg/day were superior to placebo ($P < 0.001$). In addition, 1200 mg/day was superior to 600 mg/day in reducing median monthly total partial seizure frequency ($P = 0.047$).

Several patients have been enrolled in open-label, long-term extension studies. Of these patients, 200 have received RGB for 1 year and more than 100 patients have received RGB for 2 years. Additionally, many patients have received RGB for 3–4 years in a long-term study while maintaining their efficacy response.

2.6.6.2. Tolerability. The maximum tolerated daily dose in the majority of patients in a forced dose titration study was 1200 mg/day, administered in three divided doses. The most common adverse events were CNS related, including asthenia, dizziness, somnolence, tremor, speech disorder, amnesia, vertigo, and abnormal thinking. No clinically significant changes in ECGs or laboratory parameters have been observed. Discontinuation rates due to adverse events ranged between 13 and 31% for RGB compared with 13% for placebo.
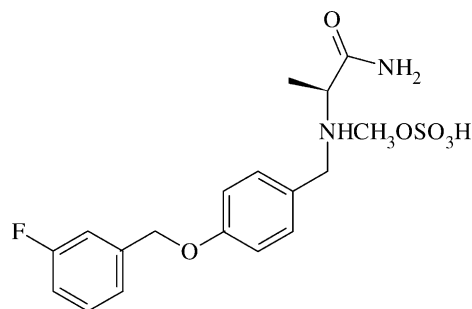
2.7. Safinamide

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Safinamide

2.7.1. Introduction
Safinamide (SAF, NW-1015, PNU 151774E) is an alaninamide derivative being developed for the treatment of epilepsy and Parkinson's disease. SAF was chosen among a series of α-aminoamide derivatives on the basis of its potent and broad antiepileptic spectrum and its neuroprotectant properties, combined with a favorable protective index. Robust proof of efficacy has been obtained after adjunctive use in Parkinsonian patients on dopamine agonists, and phase III trials in Parkinson's disease are already ongoing.

2.7.2. Pharmacology
2.7.2.1. Anticonvulsant profile. SAF has demonstrated activity, with a good protective index, against seizures induced by MES and several chemoconvulsants, including BIC, PIC, PTZ, 3 mercapto-propionic acid and strychnine (Fariello et al., 1998). SAF is

also effective in reducing the intensity of amygdaloid-kindled seizures in rats (Maj et al., 1999), in antagonizing limbic afterdischarges in a primate model of complex partial seizures induced by stereotactic stimulation of the basolateral amygdala (Fariello et al., 2000), and in blocking kainic acid induced seizures and excitotoxic damage in rodents (Maj et al., 1998).

2.7.2.2. Mechanisms of action. In rat cortical membranes, SAF binds to the batrachotoxin sensitive site 2 of the sodium channel complex with an IC50 of 8.2 μM, thereby demonstrating higher affinity for this site compared with lamotrigine (LTG, IC50 of 185.9 μM), which was used as a reference compound in these experiments. In a screening panel of 80 different human recombinant receptors, SAF showed some activity only for noradrenaline and dopamine uptake sites and submicromolar affinity for the sigma 2 binding sites.

In whole cell patch-clamp studies in cortical neurons, SAF reduces sodium currents amplitude with an IC50 of 33 μM at −60 mV. IC50 values for N-type and L-type calcium currents inhibition are 23 and 56 μM, respectively (Salvati et al., 1999). In similar experiments, SAF suppressed sustained repetitive firing at concentrations, which were one-half of those needed for LTG. These SAF effects are rapidly reversible after wash out. SAF is also a very potent, selective and reversible monoamino oxidase type B (MAO-B) inhibitor (Strolin Benedetti et al., 1994), a mechanism which explains at least in part its activity in animal models of Parkinson's disease. In plasma enriched platelet fractions from healthy volunteers, MAO-B was inhibited with an ED50 of 90 μg/kg after single oral doses. In clinical studies conducted in Parkinsonian patients, MAO-B was fully inhibited at all tested doses (40–200 mg/day).

Although the antiepileptic actions of SAF are thought to derive mainly from blockade of voltage-sensitive ion channels and consequent inhibition of glutamate release, MAO-B inhibition may contribute significantly to anticonvulsant effects (Löscher et al., 1999).

2.7.3. Toxicology

In acute toxicology tests, the target system is the CNS. In studies for acute cardiovascular safety in dogs, no QT prolongation was observed up to the maximal used intravenous dose (50 mg/kg). At doses exceeding

the therapeutic range no activity on the HERG channel has been detected.

Chronic toxicology studies in two species (rats and primates) have been completed with no findings of concern. In particular, longer duration studies have not lowered the NOAEL from the 12-week studies. Most of the observed effects reflect clinical chemistry changes suggestive of adaptive changes in lipid metabolism, without target organ toxicity. Overall, SAF has demonstrated a satisfactory safety margin.

SAF is not genotoxic in the AMES and DNA repair tests. Negative results have also been obtained in in vitro mutagenicity studies in mouse lymphoma cells and the in vivo micronucleus test. Reproduction studies are ongoing, whereas no carcinogenicity studies have been performed as yet.

2.7.4. Pharmacokinetics

In healthy subjects and in patients with epilepsy and Parkinson's disease, SAF exhibits linear pharmacokinetics. Plasma drug concentrations after single and multiple administration increase proportionally with the administered dose.

After single oral doses, peak plasma SAF concentrations are attained at about 2 h. The rate of absorption is delayed when SAF is given with a meal, but the extent of absorption is unaffected. In a recent repeated-dose study in 43 patients with epilepsy receiving up to three concomitant AEDs, plasma SAF concentrations were linearly related to dose over the explored dose range (50–300 mg/day). At a dosage of 200 mg/day, peak plasma levels occurred between 5 and 6 h after dosing.

SAF is 89% protein bound to plasma proteins. Approximately 70% of an ingested dose is metabolized to a major inactive phase I metabolite which is found in plasma and is conjugated to a second major phase II metabolite found in the urine. The half-life of SAF is in the order of 24 h, but somewhat shorter values (about 16 h) have been described in patients comedicated with enzyme-inducing AEDs. Because of the relatively long half-life, once daily administration has been used in clinical studies.

2.7.5. Drug interactions

Preliminary findings suggest that in patients receiving enzyme-inducing AEDs such as CBZ and PB, plasma SAF levels are decreased by about 30% com-

pared with those found in patients not taking enzyme inducers. This would be consistent with evidence that SAF clearance is partly dependent on the activity of inducible CYP isoenzymes.

In in vitro studies, SAF has shown no inducing or inhibiting activity on various CYP isoenzymes known to be involved in the metabolism of other AEDs. These findings would be consistent with the observation that, in preliminary studies, SAF, at doses up to 300 mg/day, did not affect the steady-state plasma concentration of concomitantly prescribed CBZ, PB, VPA and LTG.

Two tyramine interaction studies have been performed, one with intravenous tyramine (Cattaneo et al., 2003) and the other after oral tyramine challenge. Both studies showed no potential for a clinically significant interaction.

2.7.6. Efficacy and tolerability data

2.7.6.1. Efficacy. In an explorative open-label adjunctive-therapy study, SAF was titrated up to a maximum dose of 300 mg/day in 43 patients with refractory (mostly localization-related) epilepsy, aged 17–78 years and receiving up to three concomitant AEDs. The design involved a 2-week prospective baseline, followed by 6-week titration and 6-week maintenance on SAF. Of the 43 enrolled patients, 38 completed 12-week evaluation and 38 also reached the target dose, though in four cases this had to be reduced to 200 mg/day because of non-serious adverse events (vertigo, $n = 3$) or inadequate seizure control ($n = 1$). Although this study was designed to evaluate tolerability rather than efficacy, 16 of 39 evaluable patients (41%) had a greater than 50% reduction in seizure frequency during the period on SAF compared with the initial prospective baseline. The proportion of responders decreased to 28% when seizure frequency during SAF treatment was compared with a 3-month retrospective baseline. Randomized placebo-controlled proof-of-concept trials have been planned to confirm these observations.

2.7.6.2. Tolerability. In all studies conducted to date, SAF has been well tolerated. In the explorative open-trial adjunctive therapy described above, 18 patients (42%) experienced a total of 40 adverse events, but in only eight patients (19%), for a total of 20 events, the relationship with the study drug was considered to be "possible" or "probable". Most adverse events were mild or moderate, the most common being dizziness, headache, vertigo, nausea and reversible visual disturbances (e.g., "blurred vision"). Only four events were rated as severe: these included one case each of transient dizziness (unrelated to study drug), vertigo (possibly related), visual disturbances, which led to discontinuation of treatment after 17 days (related) and a marked decrease in platelet count (11,000/mL), which was attributed by the investigator to a laboratory error because platelet counts 2 weeks earlier and one week later (whilst still on SAF) were normal. There were no serious adverse events considered to be related to the study drug, and no clinically relevant drug-related changes in ECG and safety hematology and blood chemistry tests.

2.8. SPM 927

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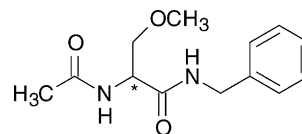
SPM 927

2.8.1. Introduction

SPM 927 (harkoseride, ADD 234037) is the *R*-enantiomer of 2-acetamido-*N*-benzyl-3-methoxy-propionamide (in the structure shown above, the chiral carbon is designated by an asterisk). SPM 927 is being developed for the treatment for epilepsy, and it also undergoing clinical evaluation in neuropathic pain.

An intravenous formulation of SPM 927 has been recently developed to facilitate treatment of patients who receive SPM 927 orally and become temporarily unable to take oral medications (e.g., peri-operatively). Intravenous SPM 927 is an isotonic solution containing the identical drug substance as in the oral formulation. The formulation is stable at room temperature and does not require dilution prior to administration.

2.8.2. Pharmacology

SPM 927 protects against seizures in various animal models, including MES, the 6 Hz refractory seizure model, hippocampal kindling, sound-induced seizures in Frings mice and self-sustaining status epilepticus (Bialer et al., 2002). The molecular mechanisms of action of SPM 927 have not yet been clarified.

2.8.3. Toxicology

In repeated-dose toxicity studies, SPM 927 was well tolerated in all species tested. In animal reproductive and developmental toxicology studies, developmental toxicity was observed in rats at a maternally toxic dose, but there was no evidence of teratogenicity or adverse effects on male or female reproductive function.

2.8.4. Pharmacokinetics

2.8.4.1. Pharmacokinetics after oral dosing.
SPM 927 is rapidly and almost completely absorbed from the gastrointestinal tract. There was essentially complete absorption of radiolabelled components after oral administration, with a mean of 94% recovered in urine (about 30–40% of the administered dose as unchanged drug and about 30% of the dose in the form of the *O*-desmethyl-metabolite) and a mean of less than 0.5% recovered in feces. The bioavailability of SPM 927 administered orally was about 100% if the peak plasma concentration and AUC were compared to the corresponding values after a short-term infusion of SPM 927 during 30 or 60 min. Peak plasma concentrations are attained at about 1 to 5 h after an oral dose, and the extent of absorption is not affected by food. SPM 927 is negligibly (<15%) bound to plasma proteins, and the half-life is approximately 13 h (Bialer et al., 2002).

2.8.4.2. Pharmacokinetics after intravenous dosing.
More than 60 healthy male volunteers have received intravenous SPM 927 in four phase I clinical trials. The highest dose tested has been 300 mg SPM 927. After intravenous doses, plasma concentration-time curves are similar to those observed with oral intake. Peak plasma concentrations and AUC values following single oral and intravenous doses are similar when the duration of the intravenous infusion is set at 60 min. Elimination half-lives (approximately 13 h) are also comparable between the two routes of administration, both in whole blood and in plasma. The metabolic profiles also appear to be similar after oral and intravenous dosing.

2.8.5. Drug interactions

Studies in healthy subjects have shown that SPM 927 (200 mg twice daily for 8, 7 and 10 days, respectively) does not affect the pharmacokinetics of CBZ (200 mg twice daily for 22 days), VPA (300 mg twice daily, for 17 days), levonorgestrel and ethinylestradiol. In similar studies, CBZ (200 mg twice daily for 8 days) and VPA (300 mg twice daily for 13 days) were equally found not to affect the pharmacokinetics of SPM 927 (200 mg twice daily for 17 and 22 days, respectively).

In agreement with results obtained in healthy volunteers, SPM 927 did not appear to influence the plasma concentrations of other measured AEDs in patients with epilepsy.

2.8.6. Efficacy and tolerability data

2.8.6.1. Efficacy.
Three open-label phase II trials in epilepsy have been completed to date. The largest trial, conducted in 91 patients taking one or two concomitant AEDs, involved a 4-week baseline, followed by SPM 927 for 10 weeks. Dosing was initiated at 100 mg/day on a twice daily schedule and increased by 100 mg/day per week until each patient reached 600 mg/day (at week 6) or experienced adverse events necessitating dose reduction. Thereafter, patients entered a 4-week maintenance period at their individual maximum tolerated dose (MTD). The median MTD in this study was 300 mg/day; approximately 50% of the patients had an MTD ≥ 400 mg/day and over 25% could tolerate 600 mg/day. A median 32% reduction in the frequency of partial seizures was observed during the maintenance phase compared with baseline. Thirty-three percent of all patients experienced ≥50% reduction in partial seizures, and this proportion increased to 56% in the subgroup receiving 600 mg/day. Seven patients were seizure-free throughout the 4-week maintenance period.

Two phase II adjunctive therapy trials in patients with partial seizures are ongoing. These include a double-blind, randomized, placebo-controlled parallel-group trial designed to investigate efficacy and safety at three doses, and an open-label extension study.

2.8.6.2. Tolerability.
Overall, 104 patients with partial seizures have been treated with 100–600 mg/day oral

SPM 927 in completed, open-label, phase II adjunctive-therapy trials. The nature and frequency of adverse events have been comparable to those observed during adjunctive therapy with marketed AEDs. The most common were CNS-related and included dizziness, diplopia, somnolence, fatigue, and headache. Laboratory, ECG, and vital signs measurements revealed no clinically important safety issues.

Intravenous SPM 927 has been equally well tolerated in phase I studies conducted in healthy subjects. Most commonly reported adverse events have been of mild intensity and similar in nature to those described after oral intake, including dizziness and paraesthesia. Vital signs and ECGs did not reveal significant changes.

2.9. Stiripentol

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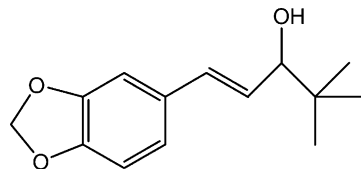
Stiripentol

2.9.1. Introduction

Stiripentol (STP), an antiepileptic compound from Biocodex, has been investigated and used in France and in Canada for more than 10 years. Its clinical development has been delayed because of drug interactions resulting from the inhibitory effect of STP on hepatic cytochromes P450 (CYP) enzymes. Two controlled adjunctive-therapy trials in pediatric populations were recently completed and, based on these results, STP is about to become the first orphan AED for children in Europe.

2.9.2. Pharmacology
2.9.2.1. Pharmacological properties related to anticonvulsant activity.
STP inhibits the synaptosomal uptake of GABA (Poisson et al., 1984), and preliminary in vitro results seem to confirm a direct effect of this compound on central GABAergic transmission in rat brain.

The intrinsic antiepileptic properties of STP have not been clarified to date. Most of the actions of STP during adjunctive therapy in vivo are probably indirect and mediated by inhibition of CYP enzymes (Perucca, 1999). In particular, inhibition of CYP1A2 and CYP3A4 in patients with epilepsy taking CBZ (Tran et al., 1997) results in marked decrease in CBZ-10,11-epoxide (CBZ-E) formation (Cazali et al., 2003), thereby altering the clinical response to CBZ.

2.9.2.2. Other pharmacological properties.
The potency of STP as an inhibitor of CYP activities led to investigate its ability to protect against the hepatotoxicity of paracetamol, an effect dramatically demonstrated in rats (Tran et al., 2001). Inhibition of CYP enzymes may also explain STP ability to decrease the teratogenicity of CBZ and phenytoin (PHT) in mice (Finnell et al., 1999).

2.9.3. Toxicology
Available toxicology documentation covers all studies required for registration, including chronic toxicity studies, reproduction studies, and mutagenic and carcinogenic tests.

Overall, STP showed no conspicuous toxicity at the high doses tested. There was evidence of hypertrophy of the liver, probably related to intense drug metabolizing activity in this organ.

2.9.4. Pharmacokinetics
Clinical studies have shown that STP is rapidly absorbed, peak plasma concentrations being observed at about 1.5 h after dosing. STP is 99% bound to plasma proteins (Perucca, 1999). The drug shows non-linear (Michaelis-Menten) pharmacokinetics, with a decrease in clearance with increasing drug dosage (Levy et al., 1984; Perucca, 1999). STP clearance is higher in patients on enzyme-inducing AEDs than in patients not receiving enzyme inducers (Loiseau and Duche, 1995).

2.9.5. Drug interactions
Because of its ability to inhibit CYP enzymes, STP increases the plasma concentrations of a wide variety of AEDs, including PHT, CBZ, VPA, PB and clobazam (CLB) (Levy et al., 1984; Tran et al., 1997; Perucca,

1999). These interactions make it very complicated to perform double-blind placebo-controlled adjunctive-therapy trials, and to separate the effects of STP from those resulting from changes in the plasma concentration of concomitantly given AEDs.

The interaction with CBZ has been investigated most extensively, and results in a markedly decreased CBZ-E/CBZ ratio. When STP is co-administered with CBZ, the dosage of CBZ should be decreased simultaneously by more than 50% to minimize changes in plasma CBZ concentration and to ensure adequate tolerability (Tran et al., 1996). In the case of the interaction with CLB, the effect of STP appears to be more complex and to involve inhibition of the hydroxylation of the active metabolite of CLB, nor-clobazam (Chiron et al., 2000). The resulting effect is, in any case, a potentiation of the pharmacological effects of this benzodiazepine.

2.9.6. Efficacy and tolerability data

2.9.6.1. Efficacy. Clinical studies of STP in adults were discontinued in 1995, when no significant efficacy was found in a trial in which STP was associated with CBZ (Perucca, 1999). By contrast, pediatric studies have yielded more positive results.

In a large open-label adjunctive therapy study in more than 200 children, combining STP with CBZ or CLB resulted in a decrease of seizure frequency by over 50% in two epilepsy syndromes, namely (i) partial epilepsy, in which two-thirds of children were responder and 20% became seizure-free, and (ii) severe myoclonic epilepsy in infancy (Dravet syndrome), in which 10 out of 20 children were responders and three became seizure-free, whereas none of the other AEDs ever controlled seizures in this syndrome (Perez et al., 1999). To confirm these results, two placebo-controlled adjunctive-therapy trials were performed. In the first trial, conducted in children with Dravet syndrome receiving concomitant therapy with CLB and VPA, STP was found to be superior to placebo ($P < 0.002$) despite a limited sample size (Chiron et al., 2000). It was unclear, however, to what extent the benefits observed during STP therapy were related to an interaction with underlying AEDs. In the second trial, STP was associated with CBZ in children with partial epilepsy using an enrichment and withdrawal design. Although there were less seizures on STP than on placebo ($P < 0.025$), the difference between STP and placebo for the pri-

mary endpoint (number of patients exiting during the double-blind phase) failed to reach statistical significance (unpublished data).

2.9.6.2. Tolerability. In the above trials, adverse events were reported in about half of the patients, but could be minimized by optimizing the dose of comedication. The most frequent reported adverse events included drowsiness, slowing in mental function, ataxia, diplopia, loss of appetite, nausea and abdominal pain.

2.10. Talampanel

N. Bodor

IVAX Research, Inc., Miami, FL, USA
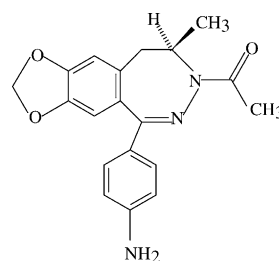
Talampanel

2.10.1. Introduction

Talampanel (TLP) is an orally active, broad-spectrum anticonvulsant with a novel mechanism of action (non-competitive AMPA antagonism) and promising results in clinical trials. Information pertaining to studies completed up to 2001 has been summarized previously (Bialer et al., 2002) and this overview will focus on more recent data. The potential of TLP as an AMPA receptor ligand is not limited to seizure suppression and to synergistic potentiation of the anticonvulsant effect of other AEDs, but may extend to other therapeutic areas, as suggested by activity in animal models of neuroprotection, dyskinesias, autoimmune encephalomyelitis, and possibly even cancer (Bialer et al., 2002).

2.10.2. Pharmacology

2.10.2.1. Anticonvulsant profile. TLP shows broad-spectrum anticonvulsant properties in various animal models (Vizi et al., 1996; Bialer et al., 2002) and potentiates the seizure suppressing activity of

other concomitantly administered AEDs (Czuczwar et al., 1998). In particular, TLP is active in amygdala-kindled rats at doses of 5 mg/kg, and the combination of TLP (2 mg/kg) with VPA (25–75 mg/kg) at sub-effective doses reduces severity and duration of kindled seizures without impairing motor coordination (rotorod test) and long-term memory (passive-avoidance task) (Borowicz et al., 2001).

2.10.2.2. Mechanism of action. TLP is a single $R(-)$-stereoisomer that is thought to act non-competitively at a novel allosteric site, often referred to as the "GYKI site" (Sólyom and Tarnawa, 2002), on the AMPA receptor complex. The corresponding $S(+)$-isomer is essentially inactive. AMPA antagonists are expected to exert anticonvulsant activity by limiting neuronal hyper-excitability and by preventing glutamate-driven neuronal damage, a novel and dual mechanism compared to traditional AEDs, which act mainly through GABA potentiation or sodium channel blockade (Nicolson and Leach, 2001). Unlike NMDA receptor antagonists, AMPA antagonists do not block the induction of long-term potentiation, a cellular mechanism essential for memory functions (Kapus et al., 2000). Non-competitive, allosteric antagonists such as TLP, which interact with binding sites on the receptor that are topographically distinct from the classic (so-called orthosteric) site, show potential therapeutic advantages over competitive, orthosteric antagonists, especially in ligand-gated ion channels (Christopoulos, 2002). For example, contrary to competitive modulation, non-competitive modulators exhibit a "ceiling" of the effect even at excessive doses, and their effect cannot be overcome by the presence of excessive endogenous ligands because they do not compete for the same binding site. The latter property is especially important for glutamate antagonists, because glutamate can be released locally at very high concentrations.

2.10.3. Pharmacokinetics

TLP is well absorbed from the gastrointestinal tract and reaches maximum plasma concentrations at about 2 h after dosing. In a food-effect study in 28 healthy male volunteers, the only parameter affected in a statistically significant manner by a high-calories high-fat meal was the time to reach peak concentration (t_{max}), which increased from 1.90 ± 1.13 h to 2.41 ± 1.06 h.

The plasma protein binding of TLP is in the order of 67–88% (Bialer et al., 2002), and the mean half-life is approximately 6–7 h after chronic administration (Bialer et al., 2002; Langan et al., 2003). Following single oral doses (30–35 mg), however, the mean half-life is somewhat shorter, i.e. around 4 h in healthy volunteers and 3 h in patients taking enzyme-inducing AEDs such as CBZ, PHT, or barbiturates (Langan et al., 2003). After single-dose administration in patients taking enzyme inducers, the apparent oral clearance of TLP is higher than in healthy volunteers (81.4 vs. 26.2 L/h, respectively), and decreases after multiple dosing (39.5 L/h) (Langan et al., 2003).

Preclinical studies have indicated that *N*-acetylation represents a route of TLP metabolism of varying significance in different species, being extensive in monkeys, moderate in rats, poor in mice, and negligible in dogs. The *N*-acetylation of TLP in humans was examined in the mentioned food-effect study following genotyping for the *N*-acetyltansferase NAT2 isozymes and phenotyping by using plasma metabolite-to-parent drug molar ratios, and it was found to be of only relatively small significance. True fast acetylators (NAT2*4/*4 homozygous) tended to have somewhat reduced values of TLP AUC and half-life, and somewhat increased clearance values, but none of these differences was statistically significant at the $P < 0.01$ level even when compared to slow acetylators.

2.10.4. Drug interactions

As mentioned above, TLP clearance is increased in patients on enzyme-inducing AEDs (Langan et al., 2003). A lovastatin interaction study found no changes in plasma lovastatin levels after 10 days of TLP dosing (60 mg three times daily) indicating no CYP3A4 inhibition or induction (Bialer et al., 2002). In a more recent study in 10 healthy subjects, administration of VPA (500 mg/day for 5 days consisting of a total of 10 doses starting on the evening of day 2 with single 25 mg doses of TLP administered on day 1 and 6) did not affect significantly ($P > 0.05$) the pharmacokinetic parameters of either TLP or its *N*-acetyl metabolite. Conversely, administration of TLP (25 mg) in this study caused a slight increase in trough total and free VPA concentrations (day 7 vs. day 6), which was not significant ($P > 0.05$) for total and marginally significant (P

> 0.04) for free VPA (paired-*t* test on log-transformed data).

2.10.5. Efficacy and tolerability data

2.10.5.1. Efficacy. An early double-blind, placebo-controlled, adjunctive-therapy cross-over study in 49 patients with refractory partial seizures found that, among patients completing the study, 79% had fewer seizures while on TLP than while on placebo (Chappell et al., 2002). Median seizure frequency reduction was 21%, and TLP showed a statistically significant ($P < 0.001$) effect in reducing the frequency of all seizures as well as simple partial seizures.

A multicenter, randomized, double-blind, placebo-controlled phase II trial of adjunctive-therapy TLP in approximately 250 patients with partial seizures is nearing completion. This trial is associated with an optional, open-label follow-on study to determine long-term safety and efficacy. Currently, more than 70 patients continue on TLP in this extension study at more than 20 centers, and more than 60 are receiving TLP in combination with two other AEDs. More than 50 patients have been on treatment for more than 4 months, and a number of them have been on treatment for more than 1 year.

A large multicenter, randomized, double-blind, placebo-controlled phase III trial to confirm efficacy and safety in patients with partial seizures has been planned.

2.10.5.2. Tolerability. In all studies, TLP was found to be well tolerated. Dizziness, headache, and somnolence are the most frequently reported adverse effects. No cognitive or psychomotor impairment has been reported.

2.11. ucb 34714

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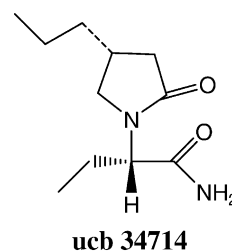
ucb 34714

2.11.1. Introduction

The development of ucb 34714 stems from recognition of the unique pharmacological profile of LEV (Klitgaard et al., 1998), which correlates with a novel mechanism of action (Margineanu and Klitgaard, 2002) involving an interaction with a novel binding site recently discovered to be the Synaptic Vesicle protein 2A (SV2A) (Lynch et al., 2004). This previously led to the suggestion that LEV may represent a new class of AEDs (Klitgaard, 2001). Interestingly, preclinical seizure protection afforded by a series of LEV analogues correlates with their binding affinity for SV2A, whereas no other known AED displays any significant interaction (Lynch et al., 2004). This stimulated a drug discovery program at UCB Pharma targeting the elucidation of new compounds with significantly higher affinity for SV2A than LEV. The rationale behind this strategy was to enhance the discovery of new agents that would provide more potent and complete seizure suppression as well as more significant potential disease-modifying effects than LEV.

Approximately 12,000 compounds were screened for their affinity to the SV2A (Kenda et al., 2004). Of these, approximately 900 were tested in vivo for seizure protection in audiogenic-susceptible mice and 30 were selected for more extensive evaluation in the kindling and genetic animal models of epilepsy. The first successful outcome of these efforts was the discovery of ucb 34714 ((2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl] butanamide), a new pyrrolidone derivative. ucb 34714 displays a markedly higher affinity ($pK_i = 7.1$) than LEV ($pK_i = 6.1$) for SV2A.

2.11.2. Pharmacology

2.11.2.1. Anticonvulsant profile. ucb 34714 is significantly more potent than LEV in protecting against secondarily generalized motor seizures in corneally-kindled mice (ED_{50} values = 1.2 vs. 7.3 mg/kg, i.p.) and against clonic convulsions in audiogenic susceptible

mice (ED_{50} values = 2.4 vs. 30 mg/kg, i.p.) (Matagne et al., 2003). Importantly, ucb 34714 also induces a more potent and complete suppression than LEV of both motor seizure severity and afterdischarge duration in amygdala-kindled rats, as well as spike-and-wave discharges in GAERS rats.

ucb 34714 is also more potent than LEV in preventing the development of kindling. In mice, chronic pretreatment twice daily with LEV (1.7–54 mg/kg, i.p.) and with 10-fold lower doses of ucb 34714 (0.21–6.8 mg/kg, i.p.) prior to corneal stimulation resulted in a similar suppression of kindling development (Matagne et al., 2003). After a 2-day wash out, twice daily corneal stimulations were then applied without any prior drug treatment. These continued corneal stimulations after termination of treatment revealed that ucb 34714 possesses a more significant and persistent ability than LEV to counteract the kindling process.

In electrophysiological studies in vitro, ucb 34714 (1–10 μM) suppresses significantly evoked epileptiform responses recorded in the CA3 area of rat hippocampal slices following perfusion with a high potassium–low calcium containing fluid (Margineanu et al., 2003). Both the amplitude and the number of evoked repetitive population spikes are reduced, with a maximal effect appearing at 3.2 μM. LEV has previously been shown to produce similar effects, but its maximal effect is reached at a concentration which is 10 times as high (32 μM) (Margineanu and Klitgaard, 2000). Importantly, ucb 34714 (3.2 μM) also reduces the occurrence of spontaneous bursts, while LEV (32 μM) is inactive against this drug-refractory epileptiform marker.

2.11.2.2. Other pharmacological properties. ucb 34714 is active in animal models mimicking neuropathic pain. The ability of pretreatment with ucb 34714 and GBT to counteract hyperalgesia was compared in mononeuropathic (chronic constriction injury) and diabetic (streptozocin) rats 2 or 3 weeks following induction of mononeuropathy and diabetes, respectively (Lamberty et al., 2003). Rats were treated with ucb 34714 (2.1–68 mg/kg, i.p.) and GBT (30 and 60 mg/kg, i.p.) and vocalization thresholds determined with a paw pressure test. In both diabetic and mononeuropathic rats, ucb 34714 significantly increased the vocalization thresholds and completely

reversed the hyperalgesia from a dose of 21 mg/kg. In contrast, GBT produced significant anti-hyperalgesic effects at doses of 30 and 60 mg/kg in diabetic and mononeuropathic rats, respectively. Ataxia and sedation were apparent at doses of 60 mg/kg for GBT, but only from a dose of 120 mg/kg for ucb 34714.

ucb 34714 is also active in animal models of essential tremor. The ability of pretreatment with ucb 34714 to antagonize harmaline-induced tremor in rats was compared to that of several standard anti-tremor agents and AEDs (De Ryck et al., 2003). Harmaline tremor (20 mg/kg) was provoked and three behavioral tests conducted at 15, 30 and 60 min after harmaline administration (pick-up, imposed posture and tilting grid tests), yielding an elicited tremor index (ETI). LEV (54–540 mg/kg, i.p.) produced only minor ETI reductions (3–25%), compared with vehicle controls. In contrast, ucb 34714, at non-sedative doses, reduced ETI by as much as 25, 53 and 66% following pretreatment with 38, 70 and 120 mg/kg, i.p., respectively. Propranolol (2.5–20 mg/kg, i.p.) and clonazepam (0.3–3 mg/kg, i.p.) were less active than ucb 34714 and induced marked postural hypotonia. Primidone (160–320 mg/kg, i.p.) only slightly reduced ETI by 10%. CBZ (5–40 mg/kg, i.p.), PHT (50–200 mg/kg, i.p.), VPA (150–450 mg/kg, i.p.) and GBT (30–120 mg/kg, i.p.) produced a moderate attenuation of ETI between 17 and 55%. However, all these AEDs were only effective at doses yielding prominent behavioral adverse effects.

2.11.2.3. Toxicology. Behavioral observations with ucb 34714 (up to 212 mg/kg, i.p.) in amygdala-kindled rats did not reveal any unwanted neuropharmacological or psychomimetic effects. Likewise, both ucb 34714 and LEV exhibited good safety margins as reflected by a high ratio for TD_{50}/ED_{50} values (for rotarod impairment and seizure protection, respectively) in both corneally-kindled mice (55 vs. 148) and amygdala-kindled rats (4 vs. 2) (Matagne et al., 2003).

2.11.3. Ongoing and planned clinical studies
The preclinical results described above suggest potential therapeutic benefits of ucb 34714 in patients suffering from epilepsy, neuropathic pain and essential tremor. A phase I/II clinical development program is currently ongoing.

2.12. Valrocemide

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$$CH_3CH_2CH_2 \searrow$$
$$CHCONHCH_2CONH_2$$
$$CH_3CH_3CH_2 \nearrow$$

Valrocemide (TV 1901)

2.12.1. Introduction

Valrocemide (VLR, *N*-valproyl glycinamide, TV 1901) was selected from a series of *N*-valproyl derivatives of GABA and glycine because of its favorable pharmacokinetic and anticonvulsant activity profiles in preclinical screening models (Spiegelstein et al., 1999).

2.12.2. Pharmacology

VLR protects against seizures induced by MES and a number of chemoconvulsants, including PTZ, BIC and PIC (Hadad and Bialer, 1995; Bialer et al., 1999, 2001, 2002; Isoherränen et al., 2001). VLR is also active in sound-induced seizures in Frings mice, in the 6 Hz psychomotor seizure model and in hippocampal-kindled rats (Bialer et al., 2002; Isoherränen et al., 2001). The mechanisms through which these effects are mediated remain to be clarified.

A study in an animal model for mania, testing the effect of VLR on amphetamine-induced hyperactivity in rats, demonstrated a statistically significant reduction in both peripheral horizontal activity and vertical activity. VLR had a significant effect on rearing in rats, similar to that seen following lithium administration.

2.12.3. Pharmacokinetics

In healthy subjects, VLR exhibits linear pharmacokinetics after single oral doses ranging between 250 and 4000 mg and multiple doses ranging between 250 and 1000 mg three times daily (Bialer et al., 1999, 2001, 2002). Apparent oral clearance values are about 5–7 L/h, whereas half-life values are in the order of 6.4–9.4 h.

About 40% of an ingested VLR dose is excreted in urine as valproyl glycine. Overall, the renal clearance of unchanged drug and the formation clearance of valproyl glycine account for 57–75% of the apparent oral total body clearance of VLR. VPA is a minor metabolite, and it has been estimated the fraction of VLR metabolized to VPA is in the order of 4–6% (Bialer et al., 2002).

2.12.4. Drug interactions

Preliminary results suggest that patients comedicated with enzyme-inducing AEDs exhibit moderately higher VLR clearance and shorter VLR half-lives compared with healthy volunteers or patients not receiving enzyme inducers (Bialer et al., 2002).

In vitro, VLR and its metabolite valproyl glycine are devoid of inhibiting activity on cytochromes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E2, CYP3A4 or epoxide hydrolase (Bialer et al., 2002). Based on these findings, VLR would not be expected to modify the plasma concentration of concomitantly administered AEDs.

2.12.5. Efficacy and tolerability data

In preliminary open-label adjunctive therapy studies in patients with epilepsy, VLR has been found to be well tolerated at maintenance dosages up to 2000 mg twice daily (Bialer et al., 2002). Most adverse events were mild to moderate and affected the CNS or the gastrointestinal tract. Some patients reported lower seizure frequency during VLR treatment compared with baseline. Placebo-controlled randomized trials are planned to confirm these findings.

2.12.6. Ongoing and planned studies

VLR is currently being jointly developed by Teva Pharmaceutical Ind., Ltd. and Acorda Therapeutics (USA). The two companies are planning to initialize a number of clinical drug–drug interaction studies as well as a phase II/III clinical trial during 2004. An additional indication evaluated for VLR is bipolar disorder.
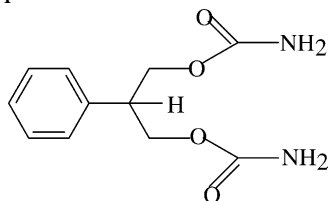
3. Update on marketed drugs

3.1. Felbamate

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Felbamate

3.1.1. Introduction

Felbamate (FBM, Felbatol®) was initially approved in 1993 for use as first-line treatment of partial seizures with and without generalization in adults with epilepsy and as adjunctive therapy in the treatment of partial and generalized seizures associated with the Lennox-Gastaut syndrome in children. Following the occurrence of aplastic anemia and hepatic failure associated with the use of FBM, "Black Box" warnings were added to the prescribing information in 1994 restricting its use to patients with severe epilepsy who respond inadequately to other anticonvulsant medications.

Upon approval it was the first new AED brought to the US market since 1978, when VPA was approved for marketing. The FBM clinical program included novel study designs developed in cooperation with the National Institute of Neurological Disorders and Stroke (NINDS). FBM was the first anticonvulsant drug to be evaluated in a double-blind study in patients whose previous anticonvulsant therapy had been decreased prior to evaluation for epilepsy surgery (Bourgeois et al., 1993); assessed in monotherapy trials with novel design (Sachdeo et al., 1992; Faught et al., 1993); and the focus of the first controlled clinical study of an anticonvulsant to control seizures associated with the Lennox-Gastaut syndrome in children (Felbamate Study Group in Lennox-Gastaut Syndrome, 1993).

3.1.2. Serious adverse events

Within the first year of marketing, approximately 110,000 patients were treated with FBM. Sixteen of the 18 cases of liver failure and 33 cases of aplastic anemia were reported in the first year of marketing, resulting in 9 and 14 deaths, respectively. Nine of the liver failure cases occurred in children (Kaufman et al., 1997; Pellock, 1999). In contrast, only one case of aplastic anemia occurred in the pediatric age group—a 13-year-old post-pubertal female with a history of systemic lupus erythematosus. SLE may have been a predisposing factor for the development of aplastic anemia.

Since 1994, it is estimated that 8000–10,000 patients are treated annually with FBM, Two additional cases of aplastic anemia have been reported since the initial cases occurred. To date, there have been no additional reports of liver failure.

3.1.3. Mechanism of toxicity

The production of a reactive metabolite, atropaldehyde, which is an extremely electrophilic unsaturated aldehyde, has been hypothesized as the toxic intermediate resulting in both liver failure and aplastic anemia (Kapetanovic et al., 1998). Both in vitro and in vivo data support the production of this toxic intermediate, however, no direct causality to liver failure or aplastic anemia has been established. No definitive predictive test has been identified. A registry was established in the US to provide a central database for patient information in an attempt to identify predisposing factors and/or demonstrate a correlation of a specific human leukocyte antigen type or metabolite production to toxicity. In total, 1250 patients were registered over a 5-year period; however, no correlation was established due to the infrequent toxicity and low number of registrants.

3.1.4. Retrospective case series in a tertiary carecenter

FBM is still considered an important drug in the armamentarium to treat seizures in patients who have proven refractory to all other AEDs. Since approval, there have been no postmarketing studies to evaluate FBM's efficacy in an actual clinical setting. Recently, the Minnesota Epilepsy Group summarized the FBM treatment outcome of 179 adults and 133 children, which is approximately the first half of their practice. Patients had previously failed a mean of 5.6 ± 2.9 AEDs in children and 5.5 ± 2.8 for adults, with mean treatment duration of 32.8 ± 33.2 months for children and 47.1 ± 45.8 months for adults. FBM treatment follow-up periods ranged from 3 to 120 months with a mean of 7.2 months for adults and 5.8 months for children.

The following response rates, as determined from patient's charts, were observed in this heterogeneous population: 58% of patients had ≥50% reduction in seizures, 43% had >75% reduction, and 18% became

seizure free. In general, treatment with FBM was well tolerated. Patients experienced similar treatment-emergent adverse events as described in the package insert but one patient acquired aplastic anemia in this practice.

The observations of this case series is consistent with the efficacy and safety profile demonstrated in earlier randomized controlled clinical studies which were the basis for approval of FBM.

3.2. Gabapentin

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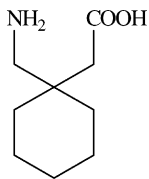
Gabapentin

3.2.1. Introduction

Gabapentin (GBT; Neurontin) is currently approved in 80 countries for adjunctive treatment of partial seizures, in 37 countries for monotherapy treatment of partial seizures, and in 62 countries for the management of neuropathic pain conditions. The number of patients who have received GPT is currently estimated at over 12 million.

3.2.2. Mechanisms of action

Although GBT is structurally related to GABA, it does not interact with either $GABA_A$ or $GABA_B$ receptors, it is not converted to GABA or to a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.

In vitro studies with radiolabeled GBT have revealed a GBT binding site in areas of rat brain including neocortex, hippocampus and dorsal spinal cord. A high affinity binding protein in animal brain tissue has been identified as an auxillary subunit of voltage-activated calcium channels.

The mechanism by which GBT exerts its anticonvulsant action is unknown, but in animals test systems, GBT exhibits antiseizure activity in mice and rats in both maximal electroshock and pentylenetetrazole seizure models and other preclinical models (e.g., strains with genetic epilepsy).

3.2.3. Pharmacokinetic update

GBT is absorbed from the gastrointestinal tract through an amino acid active transport system. As this transport mechanism can become saturated at clinical doses of GBT, patients may show intra- and intersubject variability in GBT absorption (Gidal et al., 2000). GBT bioavailability is not dose proportional, i.e., as the dose is increased, bioavailability decreases. GBT is eliminated from the systemic circulation by renal excretion as unchanged drug, and clearance is proportional to creatinine clearance. GBT is not appreciably metabolized in humans, and does not inhibit or induce CYP450 or UGT isozymes. Therefore, its potential to interfere with other drugs is minimal, and it does not demonstrate a pharmacokinetic interaction with hepatically metabolized drugs, such as other AEDs, warfarin or theophylline (Leiderman, 1994).

3.2.4. Efficacy and tolerability update in pediatric populations

Several multicenter, randomized, double-blind, placebo-controlled studies of GBT have demonstrated efficacy and tolerability data in epilepsy in pediatric populations.

One study evaluated the efficacy and tolerability of adjunctive GBT in patients aged 3–12 years with refractory partial seizures (Appleton et al., 1999). After a baseline period, 247 (patients were randomized to receive either GBT (titrated to 23–35 mg/kg/day) or placebo for 12 weeks. In this study, the primary efficacy measurement was the response ratio (a measure of proportional change in the rate of partial seizures between baseline and double-blind phases) for all partial seizures. Other efficacy measurements included the responder rate and percentage change in seizure frequency of all partial seizures; the response ratio and percentage of change in seizure frequency for individual types of partial seizures; and investigator and parent global assessments of seizure frequency and patient well-being. GBT was significantly better than placebo in controlling partial seizures in this pediatric popula-

tion, as measured by the response ratio for all partial seizures ($P \leq 0.05$). Results of the analysis of responder rate for all partial seizures showed no significant difference between the GBT and placebo treatment groups. This result may have been due, at least in part, to the responder rate among placebo-treated patients, which was higher than had been anticipated. Somnolence was the most common adverse event (AE) associated with GBT. In this pediatric population, GBT as add-on therapy for partial seizures displayed an efficacy and tolerability profile similar to that seen in adults.

A second pediatric study examined the efficacy and tolerability of GBT as monotherapy in children with benign childhood epilepsy and centrotemporal spikes (BECTS). Eligible patients were 4–13 years of age, who had had at least one but not more than ten partial or secondarily generalized seizures within the 6 months prior to enrollment. In total 226 patients were randomized to receive GPT 30 mg/kg/day or placebo during the 36-week double-blind treatment period, and patients on a marketed AED were tapered off that drug during the first 2 weeks of active treatment. Patients continued on treatment for 36 weeks, or until one of the following exit events occurred: one secondarily generalized seizure, three partial seizures, status epilepticus, or worsening of seizure activity. The Kaplan-Meier survival curves for time to exit for the evaluable population showed that a total of 43 GBT-treated patients and 60 placebo-treated patients experienced an exit event. The median time to exit was significantly longer for the GBT-treated patients in comparison to placebo treated patients (68.0 days and 40.5 days, respectively; $P = 0.023$). This study suggests that monotherapy may be effective for controlling seizures in children with BECTS. GBT monotherapy was well-tolerated well tolerated in this pediatric population, with the most common adverse event that was 5% greater than placebo being headache (GBT=27.4%. placebo 22.3%). The only serious adverse event considered to be possibly associated with the study drug was an episode of hostility in a patient in the GBT group.

A third pediatric study (Shapiro et al., 2000) examined the short-term efficacy and safety of GBT as adjunctive therapy for partial seizures in 76 pediatric patients between 1 and 36 months of age. Eligible patients entered a 48-h baseline period during which seizures were monitored on video-EEG, and were then randomized to GBT (40 mg/kg/day) or placebo for 72 h while being monitored. Efficacy was measured by calculating the response ratio and the responder rate. GBT showed a trend towards producing favorable results as adjunctive therapy in the treatment of refractory partial seizures, but the difference between GBT and placebo did not reach significance. was safe and well tolerated in this study. Somnolence and nausea and/or vomiting were the most common AEs reported for GBT. This study demonstrates the feasibility of studying AEDs in infants and very young children.

3.2.5. Efficacy and tolerability update in adult populations

A recent double-blind, randomized, multicenter study (Brodie et al., 2002) has compared the efficacy and tolerability of GBT and lamotrigine (LTG) as monotherapy in 309 adult patients (16 years and older) with recent onset partial and/or tonic-clonic seizures using a flexible dose design to reflect clinical practice. All patients were randomized to treatment with GBT or LTG was titrated up to 1800 mg/day over 2 weeks and LTG was titrated up to 150 mg/day over 6 weeks. In the 24-week maintenance phase, doses could be adjusted based on AEs or efficacy between 1200 and 3600 mg/day for GBT and, 100 and 300 mg/day for LTG. The primary efficacy measurement was time to exit due to: lack of efficacy, an AE, occurrence of status epilepticus, or the addition of another AED. 69.6% of patients receiving GBT and 66.2% of patients receiving LTG completed the study, and 76% of patients in each group that completed the study were seizure free during the final 12 weeks of treatment. In this study, GBT monotherapy was similarly effective to LTG in terms of seizure control and tolerability in patients with partial seizures with or without secondary generalization or primary generalized tonic-clonic seizures.

A recent randomized, muticenter study has compared the efficacy of GBT (1500 mg/day), lamotrigine (150 mg/day) and CBZ (600 mg/day) in the elderly. In this study, 197 patients received CBZ and 193 received GBT. Eligible patients had to be 60 years of age or older, had to have experienced at least one unprovoked seizure, and had to be expected to live for at least 1 year. Efficacy measurements included the 1-year completion rate based on seizure control and tolerability, and the seizure-free rate. At 1 year, there was a statistically significant difference in the completion rate between patients receiving GBT (49.2%) and patients

receiving CBZ (36.6%) ($P = 0.011$) (Ramsay, personal communication). There also was a statistically significant difference in the drop out rate due to AEs, with the GBT group showing a lower (21.5%) rate of drop outs than the CBZ (30.8%) ($P \leq 0.001$). There was no significant difference in the drop out rate due to lack of efficacy: 4.1% of the GBT patients and 2.8% of the CBZ patients dropped out due to lack of efficacy ($P = $ ns).

3.2.6. Conclusions

The efficacy profile of GBT as an add-on therapy for partial seizures in children seems to be similar to that observed in adults. As monotherapy, GPT is superior to placebo in controlling seizures in children with BECTS. In infants and very young children, GPT showed a trend towards producing favorable results as add-on therapy in the treatment of partial seizures, although this trend did not reach statistical significance. In all of the above studies in pediatric populations, GBT was safe and well tolerated.

In newly diagnosed adult patients with partial epilepsy with and without secondary generalization, GBT and LTG monotherapy appeared to be similarly effective and well tolerated. In the treatment of elderly patients, GBT was superior to CBZ in terms of proportion of patients completing the study.

3.3. Lamotrigine

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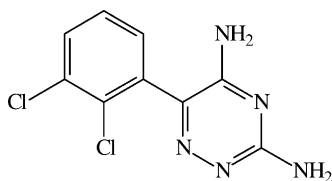
Lamotrigine

3.3.1. Introduction

Lamotrigine (LTG, Lamictal®) is approved for treatment of epilepsy in over 90 countries and it is estimated that more than two million people are currently treated with this medication. LTG has been FDA approved for three new indications over the past 12 months, as adjunctive therapy for partial seizures in pediatric patients (age 2 years and older), as monotherapy in adults with epilepsy when converting from VPA, and for maintenance treatment of adults with bipolar I disorder.

Studies are currently being conducted to determine the efficacy of LTG in treating primary generalized epilepsy, neuropathic pain and central pain. Comparative studies are being conducted to determine its effect on cognition.

3.3.2. Mode of action

The principal mechanism of action appears to involve inhibition of a voltage-activated sodium channel, resulting in increased inhibition of action potential firing activity (use dependency). LTG inhibits high-voltage-activated calcium channels, including the N-type and P-type. In absence epilepsy models, LTG appears to be effective in the pentylenetetrazole model. It was effective in a lethargic mouse model, which displayed cortical spike wave discharges, similar to those found in human absence epilepsy; however, LTG was not effective in genetic absence epilepsy rats from Strasbourg (GAERS). LTG was found to be effective in the epilepsy-kindling model. LTG probably has an additional novel mechanism that will explain the broad mechanism of action extending beyond those of typical voltage-activated sodium channel inhibitors such as PHT or CBZ.

3.3.3. Pharmacokinetics and interactions

An open-label conversion from VPA monotherapy to LTG monotherapy in adult populations (≥ 16 years of age) with epilepsy was conducted to determine the pharmacokinetic outcome of a 4-step model conversion algorithm. Seventy-seven patients were titrated over 8 weeks to a target LTG dose of 200 mg/day at which time their VPA dose was reduced by 500 mg/week over 4 weeks (maximum) reaching a final VPA dose of 500 mg/day. Patients remained on LTG 200 mg/day and VPA 500 mg/day for 1 week. Then their VPA was decreased to 250 mg/day and LTG increased to 300 mg/day for 1 week. After which, VPA was discontinued and LTG was increased to 400 mg/day, and then increased to 500 mg/day the following week. The pharmacokinetic study revealed a marked stability in the LTG levels throughout the entire phase (Sale et al., 2003). The FDA has given approval for transition from VPA to LTG monotherapy.

A significant effect of oral contraceptives on LTG was reported by Sabers and co-workers (Sabers et al., 2003). The mean steady-state plasma concentration of LTG in 22 women taking LTG in combination with oral contraceptives, compared to that of 30 women taking LTG without oral contraceptives, was reduced by >50%. Tran et al. (2002), reported findings indicating that pregnancy increased the LTG clearance by >50%, an effect occurring early in pregnancy and reversing quickly after delivery. The findings are similar to those reported by Pennell et al. (2004). The study, conducted on 14 women on LTG monotherapy, demonstrated that the LTG clearance progressively increased until 32 weeks gestational age, reaching a peak of >330% of baseline, then began to decline (Pennell et al., 2004).

3.3.4. Tolerability

3.3.4.1. Pregnancy outcome following exposure to LTG. Results from an 11-year interim analysis of reported pregnancy from 1992 through 03/31/03 (Massengil et al., 2003) revealed a rate of major birth defects of 3% for first trimester monotherapy LTG exposures, similar to the major birth defect rate of 4% reported by a UK Register (Morrow, 2003). The findings are consistent with the frequency of major malformations reported for women with epilepsy on AED monotherapy (3.6–9.6%). No specific patterns were observed.

3.3.4.2. Oral loading LTG. Results from a study addressing the speed of LTG re-titration in 24 patients after temporary LTG discontinuation, during inpatient monitoring unit stay indicated that the single LTG oral load of 6.5 ± 2.7 mg/kg was well tolerated overall. All patients reached their target blood levels with no serious adverse events or skin rash observed (Lardizabal et al., 2003). It should, however, be noted that this study was not adequately powered to detect uncommon events such as skin rashes.

3.3.4.3. Cognitive effects. Fifty healthy subjects enrolled in a double-blind, double-dummy, crossover study to assess the cognitive effects of LTG and TPM in healthy volunteers (Loring et al., 2003). During the 16 weeks of AED treatment, the initial AED dosage was titrated over 8 weeks, followed by 4 weeks of drug maintenance, 4 weeks of washout, and then a repeat of the same sequence. The target dose of LTG was 300 mg/day, and of TPM 300 mg/day. Seventeen neuropsychological tests, with 41 variables, were performed. The interim report suggests a differential effect of LTG versus TPM monotherapy at these dosages across a broad range of neuropsychological testing. LTG monotherapy treatment was associated with fewer cognitive and behavioral side effects than was TPM monotherapy.

One of the reasons for infrequent initial LTG use was the concern of patients developing Stevens-Johnson syndrome (SJS). A review of the German Registry for Serious Cutaneous Reactions showed that of the 6100 patients on LTG in 1993, 0.08% developed SJS. GSK modified the LTG titration rate in 1994 and since, of 119,200 patients, only 0.02% developed SJS. The rate in the pediatric population was 0.04%. (Massengil et al., 2003).

A retrospective analysis of 951 patients taking LTG (Hirsch et al., 2003) revealed that 5% of the patients developed a rash, with no occurrence of SJS or toxic epidermal necrolysis in any of the patients. Previous rash with another AED, particularly CBZ, was a predictor of rash with LTG. These findings indicate that concerns regarding rash and SJS should not be a major factor in determining potential usage of this drug.

3.3.5. New indications

In 2002, LTG received its first global approval for use in bipolar disorder. In 2003, LTG received approval from the FDA for use as an adjunctive therapy for partial seizures in children 2 years of age and older (Pina-Garza et al., 2003) and for maintenance treatment of adults with bipolar I disorder.

Two studies conducted to determine the effects of LTG versus lithium in the maintenance treatment of bipolar disorder separately enrolled depressed or manic-hypomanic patients into an open-label treatment, followed by randomization to LTG, lithium, or placebo monotherapy for 18 months. With the primary outcome of time from randomization until intervention for an emerging mood episode or drop out of the study unrelated to bipolar illness, 638 patients randomized to 18 months of double-blind monotherapy with LTG ($n = 280$; 30–400 mg/day), lithium ($n = 167$; 0.8–1.1 mEq), or placebo ($n = 191$). The combined analysis showed that LTG significantly delayed the time to intervention for depressive events and lithium significantly delayed the time to intervention for manic events. Results in-

dicated that LTG and lithium appear to have distinct and potentially complementary mood stabilizing properties. (Bowden et al., 2003).

3.3.6. Planned studies

Studies are currently being conducted to determine the safety and efficacy of LTG in patients with primary generalized epilepsy. Other studies are examining comparative cognitive effects of LTG and other AEDs, the effect of LTG on reproductive systems and hormones as compared to other AEDs, and the safety and efficacy of LTG for neuropathic pain and other pain syndromes.

3.4. Levetiracetam

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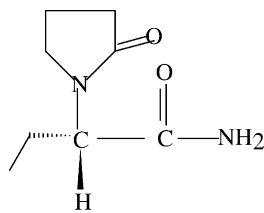
Levetiracetam

3.4.1. Introduction

Levetiracetam (LEV, Keppra®) is a recently marketed AED that is registered in 46 countries for the adjunctive treatment of partial seizures in adults with epilepsy.

3.4.2. Novel findings concerning mode of action

LEV provides potent seizure protection in kindling models of epilepsy and in the GAERS model of absence epilepsy, suggesting broad-spectrum activity.

Further indications of the disease-modifying potential of LEV has been provided, as it appears that LEV treatment during kindling may produce enduring changes that could alter the sensitivity of the amygdala to subsequent focal stimulations or generalization of those focal seizures (Stratton et al., 2003).

A recent discovery by the preclinical CNS Research group at UCB has revealed that the 90 kDa binding site to which LEV and other related acetams bind might represent a new target for therapeutic intervention in epilepsy (Lynch et al., 2004). This novel binding site is the synaptic vesicle protein, SV2A, which is an integral membrane protein present on synaptic vesicles and some neuroendocrine cells (Janz et al., 1999). Previous studies using targeted gene disruption have suggested that SV2A is an essential protein implicated in the control of exocytosis (Crowder et al., 1999), however, it remains unknown how levetiracetam modulates SV2A. There is an excellent correlation between the binding affinity of LEV and its derivatives to SV2A, and their potency in suppressing tonic seizures in audiogenic sensitive mice (Lynch et al., 2004). In contrast, other AEDs (including VPA, CBZ, PHT, ESM, FBM, GBT, TGB, VGB and ZNS) lack any binding affinity (up to 100 μM) for SV2A, reinforcing that the mechanism of action of LEV is distinct from that of other AEDs.

3.4.3. Pharmacokinetics

The steady-state pharmacokinetics of LEV in a large population has been found to be dose independent and comparable with that observed in smaller scale studies conducted previously in healthy volunteers and in patients with epilepsy. LEV pharmacokinetic parameters are not affected to any major extent by gender or comedication with other AEDs. Based on these data, there appears to be no need to adjust levetiracetam dosage according to the type of concomitantly prescribed AEDs (Perucca et al., 2003).

Sixty-six percent of a LEV dose is excreted unchanged in urine. The major metabolic pathway involves a hydrolytic process and is not dependent on the hepatic cytochrome P450 enzyme system. In vitro data show that the hydrolysis of LEV occurs in human whole blood (Coupez et al., 2003).

A LEV 10% oral solution has been shown to be a bioequivalent, well-tolerated alternative to the tablet formulation in patients who have difficulty swallowing.

3.4.4. Efficacy

3.4.4.1. Efficacy as add-on treatment of partial seizures in adults. The efficacy data that resulted in LEV's marketing authorization have been confirmed in long-term studies, short-term phase IV studies and in clinical audits.

Of all patients in LEV's efficacy database (on double-blind, follow-up extension, or open-label studies) that were on monotherapy with another AED prior

to addition of LEV, 19.8% became seizure free for at least 6 months (Ben-Menachem et al., 2003). Sixty-five (4.6%) of all patients (1422) were completely seizure-free from the first day of LEV treatment until the last day of treatment or the cut-off date. The median duration of seizure freedom was 385 days.

Improvement in quality of life as measured by QOLIE-31 remained stable in the long-term, after median treatment duration of more than 4 years (Cramer et al., 2003).

In KEEPER™, a US phase IV, 16 week open label study that included 1030 patients, 57.9% of patients responded with a decrease in seizure frequency of at least 50%, while 20% became seizure free (Morrell et al., 2003). In a subset of patients ($n = 78$) aged ≥ 65 years, similar results were observed, with 76.9 and 40% of these patients being a 50 or a 100% responder, respectively. A recently published clinical audit reported 77% of patients continuing treatment with LEV after 1 year, with 26% of all patients being seizure free for 1 year (Betts et al., 2003).

3.4.4.2. Efficacy in children. A prospective, open label study (Lagae et al., 2003) provided preliminary evidence of LEV's efficacy in the pediatric population across different seizure types, with 47% of the patients showing a seizure frequency reduction of more than 50% to treatment. LEV was started at 10 mg/kg/day and increased every 4 days to a maximum dose of 60 mg/kg/day.

3.4.4.3. Efficacy in monotherapy. Preliminary data suggest that LEV may be effective in patients with new onset seizures. In a retrospective study (Alsaadi and Thieman, 2003), 46% of patients were found to be seizure free.

3.4.5. Efficacy in generalized seizures
Open label data suggest LEV to be efficacious in patients with idiopathic generalized epilepsy (Krauss et al., 2003a).

3.4.6. Tolerability data
Phase IV studies have confirmed the findings from earlier studies. In elderly patients with CNS disorders, the safety profile of LEV was found to be similar as compared to younger patients. Behavioral side effects have been reported with LEV, at incidences similar to those found in prior clinical studies, 10.1% (Mula et al., 2003) and only rarely (6.9%) necessitating discontinuation of LEV (White et al., 2003). LEV has been shown to be weight neutral (Gidal et al., 2003).

3.4.7. Other indications
In 2003, case reports or small series of patients describing LEV's potential efficacy in a broad range of CNS disorders were reported, including for the treatment of spasticity associated with multiple sclerosis, myoclonus, refractory postherpetic neuralgia, tardive dyskinesia, acute mania, etc. Controlled data are lacking however.

3.4.8. Planned studies
Studies are ongoing to evaluate the effectiveness of LEV in patients with generalized seizures. The recruitment of a monotherapy study in patients with newly diagnosed epilepsy is close to completion. Further studies in other CNS disorders are ongoing.

3.5. Oxcarbazepine

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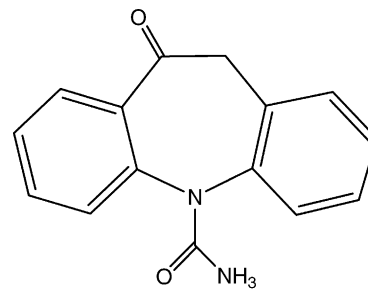
Oxcarbazepine

3.5.1. Introduction
Introduced in Denmark in 1990, oxcarbazepine (OXC, Trileptal®) is registered in over 60 countries worldwide. OXC is approved in the US and Europe as adjunctive therapy in partial and secondary generalized seizures and as monotherapy for partial seizures in children 4 years and older and in adults.

3.5.2. Mode of action, pharmacokinetics and drug interactions

OXC and its active metabolite—10-monohydroxy derivative (MHD)—limit high frequency, repetitive neuronal firing by blocking voltage-dependent sodium channels. MHD reduces the frequency of penicillin-induced epileptiform spike discharges in hippocampal slices, an effect that is reversed by the potassium-channel blocker 4-aminopyridine. In addition, MHD produces a reversible, dose-dependent decrease in high-voltage-activated calcium currents, an effect not antagonized by nifedipine, and reduces glutamatergic transmission. OXC and MHD are similar to CBZ in their spectrum of anticonvulsant activity in animal models.

OXC is reduced to MHD by cytosolic, non-microsomal, non-inducible keto-reductases. MHD is then glucuronidated by UDP-glucuronosyltransferase. Because the metabolism of OXC and MHD is unaffected by induction or inhibition of the cytochrome P-450 system, the potential for interactions with enzyme-inducing or inhibiting drugs is reduced. Similarly, in vitro and in vivo studies demonstrated that OXC and MHD do not inhibit human cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11). An exception is CYP2C19—MHD inhibits CYP2C19-mediated PHT metabolism at therapeutic serum concentrations (Lakehal et al., 2002).

Hepatic impairment does not affect the pharmacokinetics of OXC or MHD, but MHD concentrations are significantly increased in patients with a creatinine clearance under 30 mL/min and in healthy elderly volunteers aged 60–82 years, probably due to diminished creatinine clearance.

3.5.3. Efficacy

Previous studies showed that the efficacy of OXC monotherapy over a 48-week double-blind treatment period was comparable to PHT, CBZ, and VPA in patients with newly diagnosed partial onset or primary generalized seizures but that tolerability for OXC was better than for PHT and CBZ as measured by premature study discontinuation due to side effects. A more recent open-label 48-week extension study has confirmed long-term efficacy as monotherapy in 76 patients with refractory partial epilepsy (Beydoun et al., 2003).

3.5.4. Safety and tolerability

Hyponatremia occurs more commonly with OXC than with CBZ, including in patients who take OXC for off-label indications (Adkoli, 2003), but is rarely of clinical significance. Sodium and water handling studies suggest that hyponatremia could result from a direct effect of OXC on the renal collecting tubules or an increase of their responsiveness to circulating antidiuretic hormone (Sachdeo et al., 2002).

Based on an anlysis of patients exposed to OXC in randomized trials, OXC appears to be as safe and well tolerated in patients aged 65 years and older as in younger adults (Kutluay et al., 2003). The four most common adverse events seen in this cohort of 52 elderly patients exposed to OXC were vomiting (19%), dizziness (17%), nausea (17%), and somnolence (15%).

3.5.5. Other uses

OXC is effective against hyperalgesia and allodynia in animal models of pain, including painful diabetic neuropathy (Fox et al., 2003; Kiguchi et al., 2004). Controlled, double-blind trials of OXC in patients with trigeminal neuralgia have shown positive results, and open studies in patients with painful diabetic neuropathy are encouraging (Zakrzewska and Patsalos, 2002; Carrazana and Mikoshiba, 2003). Recent data suggest a possible role of OXC as adjunctive therapy to lithium in the acute and long-term management of bipolar disorder (Benedetti et al., 2004).

3.6. Tiagabine

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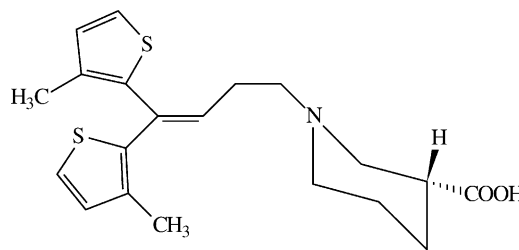
Tiagabine

3.6.1. Introduction

Tiagabine hydrochloride (TGB, Gabitril®), a selective γ-aminobutyric acid (GABA) reuptake inhibitor (SGRI), increases synaptic GABA availability via inhibition of the GAT-1 GABA transporter on presynaptic neurons and glial cells (Borden et al., 1994; Fink-Jensen et al., 1992). TGB has been shown effective as add-on therapy in adults and children 12 years and older with refractory partial seizures with or without secondary generalization. To date, exposure to TGB amounts to 147,686 patient-years (Cephalon Inc., data on file).

3.6.2. Tolerability

The most commonly reported adverse events associated with the use of TGB are dizziness/lightheadedness, asthenia/lack of energy, somnolence, nausea, nervousness/irritability, tremor, abdominal pain, and thinking abnormal/difficulty with concentration or attention (Gabitril PI, Cephalon Inc.). Most adverse events are mild to moderate in intensity. In patients with anxiety disorders, a similar tolerability profile has been observed, although headache was the most commonly reported adverse event. Concentric visual field defects similar to those associated with vigabatrin treatment have not been shown with TGB (Kälviäinen et al., 2001; Krauss et al., 2003b; Nousiainen et al., 2000).

3.6.3. Data on epilepsy

TGB has been studied as adjunctive therapy in a placebo-controlled, double-blind multicenter study in children with partial epilepsy. Altogether 103 patients were randomized to placebo and 108 patients to TGB. The age range of patients varied between 2 and 11 years. The 7-week titration period was followed by a 12-week fixed dose period. The initial daily dose of TGB was 0.1 mg/kg TID; increased weekly by 0.1 mg/kg; and the maximum dose 0.4 mg/kg and 0.7 mg/kg (CYP3A4 uninduced and induced, respectively). The median seizure reduction in the placebo-group was 16 and 25% in the TGB-group. Altogether 31% of the TGB treated had a 50% or greater reduction in the seizure frequency compared with 19% in the placebo group ($P = 0.021$). In children, the most common adverse events reported were headache, somnolence, and abnormal thinking (Cephalon Inc., data on file).

3.6.4. Data on potential new indications

Dysfunction of GABA transmission has been implicated in the pathophysiology of anxiety disorders (Lydiard, 2003). Patients with anxiety disorders often experience sleep disturbances, such as insomnia; the prevalence of complaints of insomnia has been reported to be approximately 20% in the general population (Ohayon, 1997). Of these subjects, 8.4% were reported to have a primary diagnosis of a psychiatric disorder, mostly generalized anxiety disorder (GAD) (Ohayon, 1997). The effects of TGB on symptoms of GAD and insomnia are currently being evaluated.

3.6.4.1. Generalized anxiety disorder. A 10-week, randomized, open-label, positive-controlled, blinded-rater study enrolled outpatients who met the diagnostic criteria for GAD (excessive anxiety and worry about events or activities such as work or school performance; symptoms that have occurred for at least 6 months). Forty patients were randomized to either TGB ($n = 20$) or paroxetine ($n = 20$) (Rosenthal, 2003). TGB was initiated at 4 mg/day (2 mg BID) and titrated by 2 mg every 3 days to response or a maximum dose of 16 mg/day. TGB (mean dose 10 mg/day; range 4–16 mg/day) significantly reduced symptoms of anxiety (e.g., anxious mood, tension, fear), as shown by the significant reduction from baseline in the mean score on the Hamilton Rating Scale for Anxiety at week 10 (24.4 vs. 13.8; $P < 0.05$). TGB also improved sleep quality (Pittsburgh Sleep Quality Index, 11.5 at baseline vs. 6.3 at week 10; $P < 0.05$). In addition, patient functioning (participation in work, social, and relationship activities-markers of overall improvement of the disorder) was significantly improved (Sheehan Disability Scale, 15.2 at baseline vs. 7.7 at week 10; $P < 0.05$). Similarly, paroxetine (27 mg/day; 20–40 mg/day) also produced significant reductions in symptoms of anxiety and improved sleep quality and patient functioning ($P < 0.05$). The proportion of patients who achieved remission (minimally symptomatic or asymptomatic) was similar for TGB and paroxetine (20%). No comparative statistical analyses were conducted due to the nature of the study and small sample size. Both TGB and paroxetine were well tolerated; adverse events were mild-to-moderate in severity. Furthermore, TGB was not associated with sexual dysfunction (commonly seen with other medications for this disorder) or weight gain. Results of an 8-week, randomized, double-blind, placebo-

controlled, parallel-group study in 272 patients with GAD also showed that TGB, when flexibly dosed within the range of 4–16 mg/day and taken in split doses with food, reduced symptoms of GAD and was generally well tolerated (Pollack et al., 2004).

3.6.4.2. Insomnia. The effects of TGB 5 mg on sleep parameters were investigated using standard polysomnographic techniques, in a double-blind study in healthy 'young old' subjects (mean age 68.1 ± 6.6 years; Mathias et al., 2001). Polysomnographic measurements of sleep showed an increase in sleep efficiency (total sleep time per time in bed) compared with placebo (82.2% vs. 78.1%; $P < 0.05$). TGB also increased the time spent in slow wave sleep compared with placebo (62.9 min vs. 32.8 min; $P < 0.05$; Mathias et al., 2001). The effects of TGB on slow wave sleep have been repeated in another study in patients with primary insomnia (Roth and Walsh, 2004).

3.7. Topiramate

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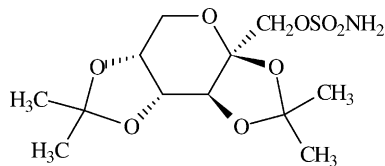
Topiramate

3.7.1. Introduction

Topiramate (TPM, Topamax®) has been extensively studied clinically for its usefulness as a broad-spectrum agent in refractory and newly diagnosed epilepsy, resulting in its approval for adjunctive therapy and/or monotherapy in adults and children in more than 95 countries worldwide. The research program continues to evaluate its profile in epilepsy and other disorders and to determine the full scope of its pharmacologic actions.

3.7.2. Novel findings concerning mode of action

In recent studies, TPM inhibited $GABA_A$-receptor mediated depolarizing responses in pyramidal neurons in the CA1 region of the rat hippocampus and enhanced the conductance of some types of K^+ channels (Herrero et al., 2002; Russo and Constanti, 2004). The effect on one K^+ channel was secondary to activation of L-type Ca^{2+} channels. On other K^+ channel(s), TPM (and acetazolamide) had what appeared to be a direct modulatory effect since the primary involvement of carbonic anhydrase inhibition was excluded (Russo and Constanti, 2004).

In neurons in the basolateral area of the rat amygdala, TPM (1–100 μM) markedly inhibited kainate receptor currents, whereas AMPA receptor inhibition was modest (Gryder and Rogawski, 2003). In tissue slices from the CA3–CA1 region of the mouse hippocampus, TPM had no effect on presynaptic Ca^{2+} entry and only a marginal effect on axonal excitability. At concentrations up to 100 μM TPM, postsynaptic Ca^{2+} influx was strongly inhibited; the amplitude of the evoked field excitatory postsynaptic potentials (EPSPs) was reduced slightly. This postsynaptic effect did not involve NMDA receptors or direct modulation of voltage-dependent Ca^{2+} channels, but was attributed to effects on AMPA and/or kainate receptors (Qian and Noebels, 2003). Several studies have found no TPM effect on NMDA receptor function (Angehagen et al., 2004).

3.7.3. New findings on drug interactions

In contrast to earlier findings that ethinyl estradiol (EE) plasma concentrations were reduced 18–31% with 200–800 mg/day TPM, no significant effect was observed with lower TPM doses (50–200 mg/day) (Doose et al., 2003a,b). No significant change in plasma concentrations of the progestin component was observed with 50–800 mg/day TPM. The findings related to dose-related dependent effects on EE correlate with in vitro assays in which significant CYP3A4 induction only occurred with TPM concentrations >50 μM, concentrations that are unlikely to be achieved with lower (e.g., 200 mg/day) TPM dosages (Nallani et al., 2003).

Drug interaction studies with medications often used to treat migraine found no significant effect of TPM on the kinetics of sumatriptan, propranolol or dihydroergotamine; a modest increase (<20%) in the C_{max} of propranolol active metabolite 4-hydroxy pro-

pranolol was observed. Dihydroergotamine did not alter TPM kinetics; propranolol caused modest increases (<20%) in TPM plasma concentrations. These plasma concentration changes are unlikely to be significant clinically (Bialer et al., 2004). In addition, no interaction has been found between TPM and LTG (Doose et al., 2003a,b).

3.7.4. Latest findings in epilepsy

A large multinational, randomized, double-blind, dose-controlled (50 or 400 mg/day) study evaluated TPM as first-line therapy in 470 adults and children with newly diagnosed epilepsy characterized by partial-onset or generalized tonic–clonic seizures (Arroyo et al., 2002). The maximum interval since epilepsy diagnosis was 6 months; patients could have one or two seizures in the 3-month baseline. The between-group difference in time to first seizure significantly ($P = 0.0002$) favored TPM 400 mg. The 6-month seizure-free rates were 83% (TPM 400 mg) and 71% (TPM 50 mg) ($P = 0.005$); the 1-year seizure-free rates were 76 and 59%, respectively ($P = 0.001$). A significant between-group difference was detected during titration when patients were receiving 100 or 25 mg/day, pointing to 100 mg/day as an appropriate initial target dose. The results for the 151 children or adolescents (6–15 years) were consistent with those for the overall population (Pellock et al., 2003): 6-month seizure-free rates were 90% (TPM 400 mg) and 78% (TPM 50 mg) ($P = 0.04$); 12-month seizure-free rates were 85 and 62%, respectively ($P = 0.002$). In a double-blind comparative study in which no seizure types/epilepsy syndromes were excluded, 100 mg/day TPM was at least as effective as therapeutic doses of CBZ (600 mg/day) or VPA (1250 mg/day) in adults and children with newly diagnosed epilepsy (Privitera et al., 2003). The median TPM maintenance dose as monotherapy in adults and adolescents was 125 mg/day and 3.9 mg/kg in children <13 years of age in an observational in-practice study of open-label TPM in >700 patients (Guerrini et al., 2003).

3.7.5. Tolerability and safety

More than 1000 patients participated in three double-blind, dose-controlled trials of 50–500 mg/day TPM as monotherapy in newly diagnosed epilepsy. The most common adverse events with TPM as monotherapy were paresthesia, decreased appetite and weight loss and non-specific effects such as headache, fatigue, dizziness, somnolence, and nausea. Despite treatment periods up to 2.2 years, only 13% of patients discontinued due to adverse events compared with 11–19% during the shorter (11–20 weeks) trials of 200–600 mg/day TPM as add-on therapy. The incidence of CNS/neurobehavioral events was substantially lower with TPM monotherapy despite higher plasma concentrations than in add-on trials. Discontinuations due to adverse events were less frequent with 100 mg/day TPM versus 600 mg/day CBZ or 1250 mg/day VPA (Privitera et al., 2003).

With nearly 3 million TPM exposures worldwide, safety databases were recently analyzed for several adverse events shared by carbonic anhydrase inhibitors, i.e., reduced serum bicarbonate levels (hyperchloremic, non-anion gap metabolic acidosis) and oligohidrosis/hyperthermia. In clinical trials, TPM was associated with a mild to moderate ($\sim$4 mEq/L) decrease in serum bicarbonate levels that occurred early and generally stabilized. The incidence of markedly low serum bicarbonate (<17 mEq/L and >5 mEq/L decrease from baseline) ranged from 3 to 11% with TPM treatment and 0 to <1% with placebo. Serious adverse events in which metabolic acidosis was observed have rarely been reported (2.2 events per 100,000 patient—years in postmarketing surveillance). Although metabolic acidosis secondary to chronic renal failure has been associated with changes in bone metabolism and slower growth, it is not known whether drug-induced metabolic acidosis might have similar results. Post hoc analyses of height data collected in TPM clinical trials, as well as a case-controlled retrospective study in children with refractory epilepsy did not show a significant effect of TPM on linear growth (Morita et al., 2000).

The occurrence rate for all possible cases of oligohidrosis was 35 per 1 million patients treated; the rate for patients with serious or medically significant oligohidrosis/hyperthermia was 1.6 per 1 million patients treated as determined from postmarketing surveillance.

3.7.6. Evaluation of potential new uses

Double-blind placebo-controlled trials have been conducted to evaluate TPM in disorders other than epilepsy. Three double-blind, placebo-controlled, multicenter trials of TPM as migraine prophylaxis have been completed, enrolling nearly 1000 patients. A total of 708 patients were treated with 50 ($N = 234$),

100 ($N = 245$) or 200 mg/day ($N = 229$) TPM in the 26-week trials. TPM (100 or 200 mg/day) significantly reduced migraine frequency compared to placebo. The 100 and 200 mg/day doses were not significantly different, making 100 mg/day TPM the lowest effective target dose for migraine prophylaxis. As of February 2004, TPM was approved as migraine prophylaxis in 22 countries.

Double-blind placebo-controlled exploratory trials have found significant differences favoring TPM in essential tremor (Connor, 2002), alcohol dependence (Johnson et al., 2003), binge eating disorder (McElroy et al., 2003) and obesity (Bray et al., 2003). Randomized controlled trials of TPM as monotherapy in acute mania failed to show a significant treatment effect versus placebo. Four double-blind, placebo-controlled trials in diabetic neuropathic pain were conducted. In three 18–22 week trials with identical designs, numeric differences favoring TPM were not significant. However, in a 12-week double-blind, placebo-controlled trial with a different design, therapeutic effects favoring TPM were significant.

3.8. Vigabatrin

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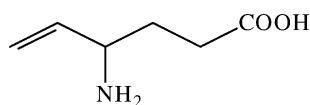
Vigabatrin

3.8.1. Update on vigabatrin related visual field loss

This update on vigabatrin (VGB) will focus on recent findings about the potential mechanisms underlying visual field loss and the EMEA procedures which

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are currently in progress, and particularly on the 4020 Study.

(a) New hypotheses have been suggested in a recent study conducted in albino rats, showing that VGB damages cone photoreceptors (Duboc et al., 2004). Rats were treated at a daily dosage of 250 mg/kg. After 45 days, retinal electrophysiology disclosed retinal dysfunction very similar to the observations made in humans. Neuropathological study showed a pronounced disorganisation of the photoreceptor layer with glial reaction, direct photoreceptor damage (outer/inner segment) and apoptosis, with predominance at the periphery of the retina. Whether these pathological consequences of VGB are specific to albino rats or can also be observed in other models is an important issue.

(b) From a regulatory point of view, in the EU, VGB has been submitted to the article 12 of the EMEA, which permits to maintain a drug on the market, on a provisional basis, under an ensemble of conditions. The approved indications have been restricted to partial epilepsy when all other appropriate drug combinations have proven inadequate or have not been tolerated and to the treatment of infantile spasms (in monotherapy).

A list of commitments has been required, including legal restrictions to hospitals and/or specialists according to country specific situations and an obligation to inform the CPMP on a 6-month basis of the progress of the following commitments: information to patients and prescribers, educational program, pharmacovigilance survey, preclinical and clinical studies. The clinical questions were related to the notions of incidence, prevalence and evolution of the visual field defects

In previous reports the estimated prevalence of visual field loss attributable to VGB (VAVFL) ranges from 14 to 92%. The disparity in the prevalence estimates, and the associated equivocal nature of potential risk factors, is likely to arise from many causes but particularly from the relatively small cohorts with the inevitable sampling bias and from the diversity of the perimetric techniques.

To comply with health authorities' requirements and to improve our knowledge on induced visual field defects and more generally on potential AED-induced visual field defects, a large-scale, multicenter study has been undertaken in several European countries,

the 4020 study. The methodology was presented in the report from the Sixth Eilat Conference on New Antiepileptic Drugs (Bialer et al., 2002).

The rapid changes in medical practice that followed the initial publication about VAVFL (Eke et al., 1997) led to adapt the objectives of this 4020 study. Indeed, from this time on, very few new patients were started with VGB. Therefore it became impossible to obtain real notions of incidence. Moreover, many patients under VGB treatment were discontinued from the drug, either because they had already VAVFL or because the patient's or phycisian's preference was to stop VGB. Thus the two groups of VGB-exposed patients that were considered in the study, the currently-treated group and the previously-treated group, could not be selected without any biases. As a result of these difficulties, the 4020 study cannot provide real prevalence figures, and can only indicate an estimate of this prevalence.

Study 4020 is a multicentre, open label, comparative, parallel group, observational, longitudinal study of the prevalence of visual field loss in patients with partial refractory epilepsy exposed to VGB. What is presented here is an interim analysis reporting the observed frequency, the risk factors, and the associated characteristics of, VAVFL.

The cohort of 668 patients was stratified by age (8–12 years and greater than 12 years of age) and by exposure to VGB (currently treated [Group I; 47 children and 188 adults]; previously treated [Group II; 64 children and 200 adults]; and never treated with VGB [Group III; 45 children and 124 adults]). VAVFL was designated as field loss unattributable to a known cause. The prevalence of VAVFL was defined in terms of the most recent visual field examination deemed to be reliable and in which an outcome could be unequivocally determined.

The estimate of prevalence of VAVFL, based upon the results from 441 patients with one or more reliable visual field examinations yielding unequivocal results (93/156 children; 348/512 adults), was Group I, 33.3% in children and 46.7% in adults; Group II, 17.9% in children and 30.7% in adults. The prevalence in Group III of field loss unattributable to a known cause, and similar in characteristics to that of VAVFL, was zero in children and 6.0% in adults. The mean/median duration of VGB exposure at inclusion for patients in Group I with VAVFL was 66.4/58.9 months in children and 59.2/55.8

months in adults compared to 40.1/35.9 months in children and 45.1/40.0 months in adults for those without VAVFL. The mean cumulative dose of VGB in Group I was 2.9/2.3 kg for children and 4.1/3.4 kg for adults with VAVL compared to 1.8/1.7 kg in children and 2.8/2.0 kg in adults without VAVFL. The corresponding data for patients in Group II with VAVFL was 25.1/23.0 months and 1.3/1.2 kg in children and 38.0/38.0 months and 2.7/2.3 kg in adults compared to 19.5/7.1 months and 0.8/0.5 kg in children and 26.4/20.2 months and 1.8/1.3 kg in adults without VAVFL. The prevalence of VAVFL as a function of gender was 51.9% of the 81 males and 37.2% of the 86 females in Group I and 33.7% of the 95 males and 19.7% of the 71 females in Group II.

The high frequency of VAVFL is thus confirmed, and this study is likely to provide new information through the multivariate analyses, which are currently in progress. The evaluation of the long-term risk for developing VAVFL, especially after 3 or 4 years of VGB treatment, is critical information to clinicians.

3.9. Zonisamide

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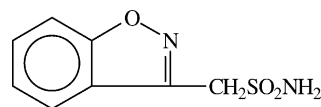
Zonisamide

3.9.1. Introduction

Zonisamide (ZNS; Excegran®, Zonegran®) is an anticonvulsant, chemically distinct from other AEDs. ZNS is approved in the USA for adjunctive treatment of partial seizures in adults over age of 16 with epilepsy, and in Japan as add-on and monotherapy for children and adults with generalized and partial seizures. It is currently under evaluation in Europe. Worldwide experience with ZNS approximates to 2 million patient-years of exposure.

3.9.2. Mode of action

While the mechanism(s) by which ZNS exerts its antiseizure effect is unknown, it has multiple pharmacological actions that may relate to its usefulness in epilepsy. It blocks voltage-sensitive sodium and voltage-dependent calcium T-type channels, enhances GABA release, blocks the potassium-evoked glutamate response, and reduces glutamate-mediated synaptic excitation. Other effects may contribute to its broad spectrum of activity across various seizure types (Macdonald, 2002). ZNS scavenges nitric oxide and other free radicals, and inhibits lipid peroxidation and free radical-induced DNA damage. The antiepileptic activity of ZNS may therefore also provide protection of neurons from free radical damage and stabilization of neuronal membranes (Mori et al., 1998).

3.9.3. Pharmacokinetics and drug interactions

ZNS is rapidly and completely absorbed after oral administration, well distributed to tissues, and relatively slowly cleared from the serum (the half-life ranges from 50 to 70 h). ZNS is extensively metabolized, primarily through reductive cleavage of the benzisoxazole ring of the parent drug by CYP3A4 to form 2-sulfamoyl-acetyl phenol (SMAP) and also by *N*-acetylation; SMAP and parent drug can be glucuronidated. The metabolites are devoid of anticonvulsant activity. The main route of excretion of unchanged ZNS and its metabolites is via the urine.

A series of studies assessed the potential of ZNS to affect the pharmacokinetics of several commonly used AEDs (i.e., VPA, LTG, PHT and CBZ) in patients with epilepsy. Key pharmacokinetic variables for these AEDs did not differ significantly with the addition of ZNS, indicating that doses of these agents would not need to be adjusted when ZNS is co-administered. Although the effects of these commonly used AEDs on ZNS pharmacokinetics were not definitively evaluated in this series of studies, known CYP3A4 enzyme inducers such as PHT and CBZ appeared to lower the mean elimination half-life of ZNS to 28 and 36 h, respectively. On the other hand, neither LTG nor VPA appeared to significantly affect ZNS mean elimination half-life values (51 and 52 h, respectively).

In further studies, ZNS had no effect on the pharmacokinetics of the CYP2D6 substrate desipramine, or on the active constituents (ethinyl estradiol/norethindrone and levonorgestrel) of two types of oral contraceptives.

Again, geometric mean ratios for key pharmacokinetic variables with or without the addition of ZNS were close to 1.00. In the study assessing the effect of ZNS on ethinyl estradiol and norethindrone, evaluation of levels of follicle-stimulating hormone, luteinizing hormone and progesterone signified no loss of contraceptive efficacy. Neither desipramine nor the evaluated oral contraceptive agents appeared to affect the serum steady-state clearance or trough concentrations of ZNS.

Using a mg/kg dosing regimen in children, ZNS serum exposure (C_{max}, AUC_{0-12}) was typically higher in older age children (12–15 years) compared with younger age children (5–11 years) (Glauser et al., 2002). ZNS serum clearance when normalized to total body weight (mL/h/kg) was generally higher in younger compared to older age children, which is often observed with hepatically metabolized drugs (Blanco et al., 1999). These results suggest that an alternative dosing strategy (e.g., perhaps based on body surface area rather than total body weight) might be required to achieve more equivalent serum exposure between different age (or weight) groups of pediatric subjects. For comparison purposes to findings in adults, unmodified ZNS serum clearance (mL/h) was also calculated (using the absolute dose administered in mg, rather than the mg/kg dose). Unmodified serum clearance was typically higher in older age compared with younger age children with serum clearance values in the older age group approaching but still somewhat lower than typically observed in adults (data on file; Elan Pharmaceuticals). This latter observation is consistent with a population pharmacokinetic analysis of data from subjects ranging from 12 to 77 years of age (40–128 kg), indicating that unmodified ZNS serum clearance (mL/h) is lower in subjects with a lower total body weight (data on file, Elan Pharmaceuticals). Lastly, as previously observed in adults, serum exposure was generally lower in pediatric subjects receiving concomitant treatment with a known CYP3A4 inducer (e.g., CBZ, PHT etc.), compared with pediatric subjects not receiving these agents.

3.9.4. Antiepileptic efficacy

Results from double-blind, placebo-controlled studies in patients with refractory partial epilepsy have demonstrated that ZNS provided effective and well-tolerated adjunctive therapy for partial seizures. A study in the USA (Faught et al., 2001) was conducted in

203 patients with refractory epilepsy (partial seizures with or without secondary generalization). At all evaluated doses (100, 200 and 400 mg/day), ZNS was significantly superior to placebo with respect to the reduction in partial seizure frequency, with the most marked reduction (41%) observed at 400 mg/day. A similar picture was demonstrated for responder rates, with 42% of patients responding on ZNS 400 mg/day (Tosches, 2001; Seino and Fujitani, 2002; Vossler, 2002; Wilfong, 2003).

Two additional studies were performed in epilepsy patients with complex partial seizures according to a similar design, using a target ZNS dose of 400–600 mg/day given either once daily (EU study, 152 patients) or in divided doses twice daily (US study, 138 patients) for 3 months. In the recently reported US study (Sackellares et al., 2003), a median reduction in seizure frequency of 30% was achieved, significantly superior to placebo, and 29% of patients responded with a $\geq$50% reduction in seizure frequency. Results from the EU study were very similar.

These results were recently confirmed in a European placebo-controlled study in 351 patients with partial seizures unsatisfactorily controlled despite a stable regimen of AEDs. The results clearly demonstrated that ZNS, used as adjunctive therapy to other AEDs, is effective in the treatment of patients with refractory partial epilepsy (Brodie et al., 2004).

3.9.5. Tolerability

Common adverse events related to ZNS therapy are symptoms related to the central nervous system (somnolence, dizziness, ataxia, fatigue), digestive system (abdominal discomfort, nausea/vomiting, anorexia), and cognitive function (decreased concentration and memory impairment) (Lee, 2002). Most of these common adverse events occur in a dose-related manner at the start of ZNS therapy when the dose is being titrated upwards; the prevalence of adverse events tends to decrease with continuing exposure. Other events that have occurred in association with ZNS therapy include rash, kidney stones, and decreased sweating. In cases of rash, patients should be closely supervised and discontinuation of therapy considered (ZNS should not be used in patients with known sulfonamide hypersensitivity). The risk of kidney stone formation may be reduced by increased fluid intake, particularly in patients with predisposing risk factors. Decreased

sweating and elevated body temperature have been observed, mainly in children and mostly during warm weather; patients should be advised to maintain adequate hydration and avoid exposure to excessive temperature (Zonegran Package insert).

While monitoring of blood levels of ZNS is sometimes recommended, with a level of 40 mg/L regarded as the upper limit for acceptable tolerability, there appears to be no clear relationship between blood concentration and response, and dose adjustment are best based on clinical judgment. The author's own clinical experience suggests that a significant number of patients with blood levels of 40–60 mg/L do well clinically without experiencing adverse events. The proposed recommended standard practice in the EU is to gradually titrate the dose to the effective dose range of 300–500 mg/day, starting at 50 mg/day (recommended practice in the USA is to start at 100 mg once daily) and increasing the daily dose by up to 100 mg at weekly intervals. At this time it is estimated that ZNS has a worldwide exposure of greater than 2 million patient-years in adult and pediatric patients with epilepsy.

3.9.6. Ongoing studies

Ongoing clinical studies with ZNS in epilepsy include a dose-ranging monotherapy study and open-label extensions of the clinical efficacy studies in Europe.

4. New formulations of old-generation AEDs

4.1. Pharmacokinetics and clinical experience with divalproex-ER

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4.1.1. Introduction

An extended-release (ER) divalproex sodium tablet (Depakote® ER, Abbott Laboratories, USA) has been developed with the objective of allowing once daily dosing, while decreasing the degree of fluctuation

(DFL) between C_{max} and C_{min}. These attributes may lessen side effects and aid compliance.

4.1.2. Absorption characteristics and bioavailability of divalproex-ER

4.1.2.1. Healthy volunteers and adult patients. Divalproex-ER is a novel tablet formulation based on a controlled-release hydrophilic matrix technology. A single-dose, non-fasting, open-label, single-center, crossover study in 16 healthy adult subjects was conducted to define some of its absorption characteristics. Based upon deconvolution analysis, the mean (% CV) duration of drug absorption from divalproex-ER was 21.8 (17%) hours and the mean zero-order absorption rate was 21.6 (24%) mg/h for a 500-mg tablet, i.e., 0.0431 (24%) mg/h/mg dose). In the majority (5th–95th percentiles) of subjects, VPA absorption from divalproex-ER was complete in 17 to 28 h. The individual cumulative absorption-time and fractional-input-time profiles did not reveal any evidence of "dose dumping" (Dutta et al., 2003a).

The absolute bioavailability of divalproex-ER is 89% based on a crossover study comparing divalproex-ER to an intravenous dose of VPA (Dutta et al., 2003a). Several relative bioavailability studies in healthy volunteers and adults with epilepsy have compared equal total daily doses of divalproex-ER and enteric-coated divalproex (divalpoex). (Data on file, Abbott Laboratories; Dutta et al., 2002; Sommerville et al., 2003). These studies employed different divalproex dosing frequencies: every 6 h, every 8 h, or every 12 h and meal conditions: fasting, low, medium & high calorie meals; while divalproex-ER was given once daily in all but one investigation. Divalproex-ER bioavailability is approximately 11% lower ($P < 0.05$) than the divalproex formulation. The VPA C_{max} from once-daily divalproex-ER is lower and the DFL ($C_{max}-C_{min}/C_{avg}$) in plasma VPA concentrations is substantially and statistically reduced with ER. The mean DFL of valproic acid plasma concentrations was 42–48% smaller for the ER formulation compared to divalproex.

Maintaining equivalent exposure (AUC) when switching from one formulation to another is important, as some patients with epilepsy are sensitive to small changes in drug concentration. Based on the bioavailability studies, a 12% higher divalproex-ER daily dose (calculated as 1.0/relative bioavailability = 1.0/0.89 = 1.12) is required to attain an AUC equal to that of a smaller divalproex daily dose. The availability of two divalproex-ER strengths (250, 500 mg) makes possible dose increases that closely bracket the 12% target (8–20%). Randomized, steady-state studies in healthy volunteers and patients show that once-daily ER doses 8–20% larger than divalproex given every 8 h result in equivalent exposure with lower C_{max} and higher Cmin values (Dutta et al., 2002; Sommerville et al., 2003). The study in patients involved 64 adults taking enzyme-inducing medications. The mean daily dose of divalproex-ER was 2188 mg vs. 1893 mg for the divalproex formulation. The 90% confidence interval for the ratio of the AUCs was 0.96–1.055, which demonstrated bioequivalence of the larger divalproex-ER dose with the reference divalproex dose. The DFL value was significantly lower for the ER regimens (64% vs. 79%, $P = 0.0001$) (Sommerville et al., 2003).

4.1.2.2. Children. The pharmacokinetic profile of once daily divalproex-ER has been characterized in two pediatric age groups: 8–11 years (children; $N = 15$) and 12–17 years (adolescents; $N = 14$) (Dutta et al., 2004). Patients in both groups were switched from divalproex to the same daily dose of divalproex-ER. Once-daily administration of divalproex-ER (doses ranged from 250 to 1750 mg) in all patients produced relatively flat plasma VPA concentration-time profiles over the entire 24-h dosing interval with DFL values similar to those in adults: children = 54%, adolescents = 39%, adults = 43%, respectively. Adverse events were generally mild to moderate in severity and similar to those reported in previous divalproex studies. The pharmacokinetic parameters in the adolescent subgroup were comparable to those obtained in adults from previously completed studies. In contrast, C_{max}, C_{min}, and AUC24 were approximately 20–30% lower in young children from 8 to 11 years of age as compared to adolescents or adults. This is likely the consequence of higher apparent VPA clearance in young children (Cloyd et al., 1993).

4.1.3. Effect of food on divalproex-ER

The effect of food on the extent of absorption following divalproex-ER administration is less than 10% (Reed et al., 2004).

4.1.4. Efficacy and safety of divalproex-ER

The efficacy of once-daily divalproex-ER was compared to divalproex administered two to three times

a day in a randomized, multi-center, open-label, two-period crossover study in 44 adolescent and adult patients with primary generalized epilepsy. (Thibault et al., 2002). The same total daily doses were used for both formulations. Seizure control was similar for the two groups, but plasma VPA concentrations were 11% less in patients when on divalproex-ER.

Divalproex-ER was developed, in part, to lessen concentration-dependent side effects by minimizing the DFL in VPA concentrations. Subjects in all of the pharmacokinetic studies of divalproex-ER performed to date have had similar side-effect profile compared to divalproex, but none of these studies were specifically powered to detect differences in side effect rates. Such a study is currently underway at Abbott Labs.

In an open label, 7-day study in 55 psychiatric patients, the number and severity of VPA-related side effects diminished with once-daily divalproex-ER compared to divalproex dosed multiple times daily (Horne and Cunanan, 2003). In a separate meta-analysis of several open-label trials in patients with epilepsy, divalproex-ER was better tolerated and associated with greater efficacy compared to multiple-daily dose divalproex (Smith et al., 2003).

4.1.5. Dosing divalproex-ER: practical considerations

Some patients may prefer to take divalproex-ER in the evening. In an open-label, parallel design, multiple-dose study in healthy subjects, the pharmacokinetics and safety of 1000 mg divalproex-ER given once daily either in the morning or evening was compared (Dutta et al., 2003b). There were no significant differences in the pharmacokinetic parameters ($P > 0.51$) or safety between subjects who received the divalproex-ER formulation in the morning and those who it in the evening. Although noticeable diurnal variation in VPA plasma concentrations occurs with conventional VPA formulations (Hussein et al., 1994), the divalproex-ER formulation exhibits minimal diurnal variation, likely due to the unique formulation characteristics of this product, i.e., extended release over 17–28 h (Dutta et al., 2003a).

Clinicians may be reluctant to prescribe medications intended for once-a-day administration, such as divalproex-ER, due to a concern that a missed dose will result in a marked fall in plasma VPA concentrations. The clinical consequence of missing the entire daily dose could be breakthrough seizures or subsequent toxicity upon replacing the divalproex-ER dose. Pharmacokinetic simulations predict that high plasma VPA concentrations, resulting in clinical toxicity, are not likely when divalproex-ER doses are replaced within 12 h followed by resumption of scheduled dosing. (Reed and Dutta, 2003a). This may be due to the controlled, zero-order absorption characteristics of the divalproex-ER formulation. If a patient misses a divalproex-ER dose, it should be replaced as soon as possible and the next dose should be taken at the regularly scheduled time.

Some clinicians have employed complicated, lengthy, and needlessly laborious conversion strategies when switching from multiple-dose divalproex to once-daily divalproex-ER dosing. Such practices have included slow tapering of the multiple daily dose divalproex, incrementally replacing divalproex with the required divalproex-ER daily dose over several days, or waiting 24 h after the last divalproex dose before instituting a once-daily divalproex-ER regimen. Computer simulations suggest that no significant perturbation in plasma VPA concentrations is likely when the patient takes her/his once daily divalproex-ER dose 12 h after the morning or evening divalproex dose. There is no apparent advantage in converting divalproex to divalproex-ER in small steps. (Reed and Dutta, 2003b).

4.1.6. New indications

Divalproex-ER was approved in the US for migraine headache prophylaxis in August 2000, for adults with epilepsy in December 2002, and for children with epilepsy in December 2003. Studies for an indication in mania are underway.

4.2. Recent clinical trials of iv formulations in epilepsy

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4.2.1. Intravenous valproate (VPA)

Valproate sodium injection (VSI) was approved in the US in 1996 for intravenous use in epilepsy patients for whom oral administration of VPA products is temporarily not feasible. Devinsky et al. (1995) conducted

an open-label safety trial of VSI in 318 patients hospitalized for seizures. At the dosages (median: 375 mg) and rates (generally over one hour) used, VSI was safe and well tolerated. Hussein et al. (1994) Conducted a randomized, crossover study in healthy subjects to compare the pharmacokinetics (PK) of multiple doses of oral VPA or VSI. Subjects received multiple 250-mg oral or intravenous doses every 6 h after a 750-mg intravenous loading dose. All infusions were over 1 h. Steady-state plasma concentrationsvstime profiles were maintained by both regimens within the therapeutic range (50–100 µg/mL).

The 1-h infusion was safe and well tolerated, but faster infusions were desirable to increase flexibility. Naritoku and Mueed (1999) demonstrated the safety of intravenous loading of VSI when rapid elevation of serum levels was required to stop recurrent seizures. A mean dose of 19.4 mg/kg infused at 20 or 50 mg/min was well tolerated in 20 patients with epilepsy. There were no significant changes in blood pressure and no ECG abnormalities. The investigators concluded that a loading dose of VSI could be safely administered.

Cloyd et al. (2003) studied key PK parameters following loading doses of VSI in 112 enzyme-induced or uninduced patients with epilepsy. Patients were randomized to 1.5 or 3.0 mg/kg/min rapid infusions, to a maximum dose ≤15 mg/kg. Maximum total and unbound concentrations of VPA were 94 and 14 mg/L, respectively. Total concentrations fell below 50 mg/L within 3 h in enzyme-induced and 6 h in uninduced patients. The distribution volume (V_d) was between 0.17 and 0.21 L/kg for 70% of patients; this could be used to calculate a loading dose (LD). Induction status, albumin concentration, and infusion rate significantly altered PK, and infusions up to 3 mg/kg/min produced predictable VPA concentrations when induction status and albumin levels were considered. They suggested starting oral VPA within 3–4 h when given with inducing AEDs and one hour for enteric-coated divalproex (Depakote®). Extended-release divalproex (Depakote ER®) should be started concurrently with the infusion.

Ramsay et al. (2003) reported the safety and tolerability of rapidly infused VSI from the same study. The primary safety endpoints were changes in 5-minute and minimum post-first infusion blood pressure. Results showed no significant treatment differences in primary endpoints and no symptomatic changes in vital signs.

Adverse events occurred at similar low rates in both groups and tended to occur with peak VPA levels. The investigators concluded that doses up to 15 mg/kg infused at 1.5 and 3.0 mg/kg/min were well tolerated in this population. It was noted that frequent seizures in some populations might require these rapid infusions to prevent recurrence of seizures.

The new rapid infusions should allow more flexibility to avoid recurrent seizures and an adequate loading dose.

4.2.2. Intravenous SPM 927

4.2.2.1. Introduction. SPM 927 (*R*-2-acetamido-*N*-benzyl-3-methoxypropionamide, formerly known as harkoseride) is currently in development for the treatment of epilepsy and neuropathic pain (6).

An intravenous formulation of SPM 927 has been developed to facilitate treatment of patients receiving oral SPM 927 who temporarily become unable to take oral medications (e.g., perioperatively, etc.). Intravenous SPM 927 is an isotonic solution containing the identical drug substance as in the oral presentation. The formulation is stable at room temperature and does not require dilution prior to administration.

4.2.2.2. Mechanism of action. The molecular mode of action of SPM 927 remains to be identified.

4.2.2.3. Pharmacokinetic characteristics and drug interactions. More than 60 healthy male volunteers have received intravenous SPM 927 in four Phase I clinical trials. Following oral administration, 86.7 and 83.8% of the systemic exposure following intravenous infusion of SPM 927 is achieved in plasma and whole blood, respectively. Intravenous SPM 927 has similar plasma concentration-time curves following oral and intravenous dosing. Estimates of terminal elimination half-life are comparable between the two dose routes for both whole blood and plasma (approximately 13 h). The AUC and C_{max} following single oral and intravenous dosing are similar when the infusion rate is 60 min. The major radiolabelled component in urine following both oral and intravenous administration is SPM 927 and represents up to approximately 43% of the administered dose. The major metabolite in urine is *O*-desmethyl-SPM 927 that accounts for up to 30% of dose. No interaction study has been done with intravenous SPM 927. However, in Phase I and II trials

with the oral formulation no interactions were observed with other antiepileptic drugs or contraceptives.

4.2.3. Tolerability

SPM 927 has been generally well tolerated in Phase I clinical trials conducted in healthy subjects. Most commonly reported adverse events have been of mild intensity and similar in nature to the ones described for the oral presentation (eg, dizziness and paraesthesia). Vital signs and ECGs recorded did not reveal significant changes.

4.2.4. Planned studies

The primary goals of the planned clinical trials with intravenous SPM 927 are to demonstrate pharmacokinetic equivalence between the oral and intravenous formulations and to establish the safety of intravenous SPM 927 as short-term replacement of oral SPM 927 for patients temporarily unable to continue taking oral SPM 927 for epilepsy.

5. Vagus nerve stimulation

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5.1. Introduction

Vagus nerve stimulation (VNS) was approved in 1997 for epilepsy. Since then, over 20,000 patients worldwide have been implanted and VNS has become an established treatment option for patients: (1) whose partial-onset seizures adversely affect quality of life despite adequate pharmacotherapeutic trials and (2) who do not have surgically remediable partial seizures or who refuse to undergo intracranial surgery.

5.2. Mode(s) of action

The mechanisms of action of VNS as well as stimulation of other cranial nerves (Tubbs et al., 2002) are under active investigation. Right-sided VNS is comparable to left-sided VNS in suppressing seizures in rats induced by pentylenetetrazol (Krahl et al., 2003).

Magdaleno-Madrigal et al. (2002) showed that electrical stimulation of the nucleus of the solitary tract, a key link between the vagus nerve and forebrain structures, delayed seizure onset in a cat kindling model. Italian researchers found that cortical GABA (A) receptor density, as measured by single-photon emission tomography (SPECT) with the benzodiazepine receptor inverse agonist iomazenil, normalized after 1 year of VNS in patients whose seizures responded to VNS therapy (Marrosu et al., 2003). They hypothesized that VNS-induced plasticity of GABA (A) receptors and the resulting reduction of cortical excitability contributes to its mechanism of action, which is consistent with the delay of efficacy onset in many patients.

Prior functional imaging studies utilizing SPECT and positron emission tomography highlighted the widespread cortical and sub-cortical sites affected by VNS (Ring et al., 2000a,b; Vonck et al., 2000; Barnes et al., 2003), including bilateral thalamic structures. More recently, VNS-synchronized functional magnetic resonance imaging (fMRI) demonstrated cortical and sub-cortical sites that are immediately affected by VNS (Chae et al., 2003) and confirmed thalamic involvement (Liu et al., 2003; Narayanan et al., 2002); one study associated thalamic effects with improved seizure control (Liu et al., 2003).

Individualizing VNS therapy will be possible once a physiologic response to VNS can be quantified. Koo et al. (2000) used EEG to successfully guide VNS programming. Fallgatter et al. (2003) demonstrated the feasibility of recording potentials from the sensory territory of the auricular branch of the vagus nerve in subjects undergoing transcutaneous vagus nerve stimulation. Another group correlated a reduction of interictal discharges during the stimulation period with therapeutic efficacy (Kuba et al., 2002, 2003). The potential applications of these reports to titrating VNS therapy are unknown.

5.3. Efficacy

Clinical studies over the past two years have reported efficacy of VNS for specific patient groups, including those with bitemporal epilepsy (Kuba et al., 2003), Lennox-Gastaut syndrome (Aldenkamp et al., 2002), persistent seizures after epilepsy surgery (Amar and Apuzzo, 2003), and patients who use the supplied magnet to abort or attenuate seizures (Morris, 2003).

Other studies have confirmed long-term seizure control (Chavel et al., 2003; Hui et al., 2004) and emphasized the potential benefit of treatment earlier in a patient's course of epilepsy (Renfroe and Wheless, 2002).

5.4. Safety and tolerability

Since the 2002 Eilat conference, publications have documented the potential for worsening of seizure frequency and severity with battery end of service (Tatum et al., 2004), and the respiratory effects of VNS during sleep and potential worsening of preexisting obstructive sleep apnea (Marzec et al., 2004).

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