Safinamide

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Summary: Safinamide (SAF) ((S)-(+)-2-(4-(3-fluorobenzyloxy) benzylamino)propanamide) was initially synthetized by Farmitalia Carlo Erba (Italy). Following initial anticonvulsant screening, safinamide was selected for its potency, broad spectrum of action, and good safety margin. Pharmacodynamic properties probably relevant to its antiepileptic activity are use- and frequency-dependent block of voltage sensitive Na^+ channels, block of Ca^{++} channels, and glutamate release inhibition. Possibly contributing mechanism are also selective and reversible monoamide oxidase B inhibition and dopamine and noradrenaline uptake inhibition. The high selectivity for the sigma-1 receptor site does not entail psychotomimetic or behavioral changes. In several experimental in vitro and in vivo conditions, SAF exerts neurorescuing and neuroprotectant effects. Safinamide is water soluble and suitable for 1 times a day oral administration in humans. In a pilot phase II study in 38 refractory epilepsy patients affected by multiple types of seizures, 41% of subjects obtained ≥50% seizure reduction during a 12-week escalating dose up to 300 mg 1 times day compared with perspective baseline. Safinamide is being developed in phase III for treatment of Parkinson's disease, whereas the development in epilepsy relates to the industrial strategy of the company. **Key Words:** Safinamide, SAF, Na^+ channels, glutamate release and MAO-B inhibition, Parkinson's disease, epilepsy

INTRODUCTION

In 1989, at Farmitalia Carlo Erba Pharmaceutical Company, a program of medicinal chemistry was initiated that began with the observation that milacemide possessed weak anticonvulsant activity combined with monoaminoxidase A and B inhibitory activity.[1-3] Thus, taking the class of α-amino amides as scaffold, variations of different parts of this structure led to the invention of several new molecules belonging to different chemical classes, all sharing powerful anticonvulsant activity in an initial screening battery which consisted of establishing the therapeutic index (T1) between the effective dose (ED50) in the maximal electroshock test (MES) and the toxic dose (TD50) in the rotarod test.[4] On this basis, a handful of compounds were selected and submitted to the National Institutes of Health antiepileptic screening program as well as to a further in-house battery of tests. The results in the two laboratories were quite similar and eventually led to the choice of [(S)-(+)-2-(4-(3-fluorobenzyloxy) benzylamino)propanamide, methanesulfonate], initially known as FCE 26743, then PNU-151774E, NW-1015 and, eventually, safinamide (SAF), as a molecule worthy of further exploration for clinical development.

As SAF had retained the antimonoamide oxidase B (MAO B) properties, as well as having demonstrated powerful voltage sensitive channel blocking activity, the preclinical studies were reviewed to investigate further the antiepileptic activity, the potential for neuroprotection and neurorescuing, as well as the potential to improve motor function in animal models of Parkinson's disease. This last aspect will not be addressed in this review, except as it may relate to antiepileptic and neuroprotective activities.

INITIAL SCREENING FOR ANTICONVULSANT ACTIVITY

The MES test was performed in both mice and Wistar rats, in the latter by passing through intra-aural clip electrodes a 60 mA current in the form of a 60 Hz pulse train sufficient to produce hind-limb extension, prevention of which was taken as evidence of anticonvulsant activity. The test was repeated at various time intervals after SAF intraperitoneal injection and measurements of serum and cerebral levels of the drugs were performed. The results

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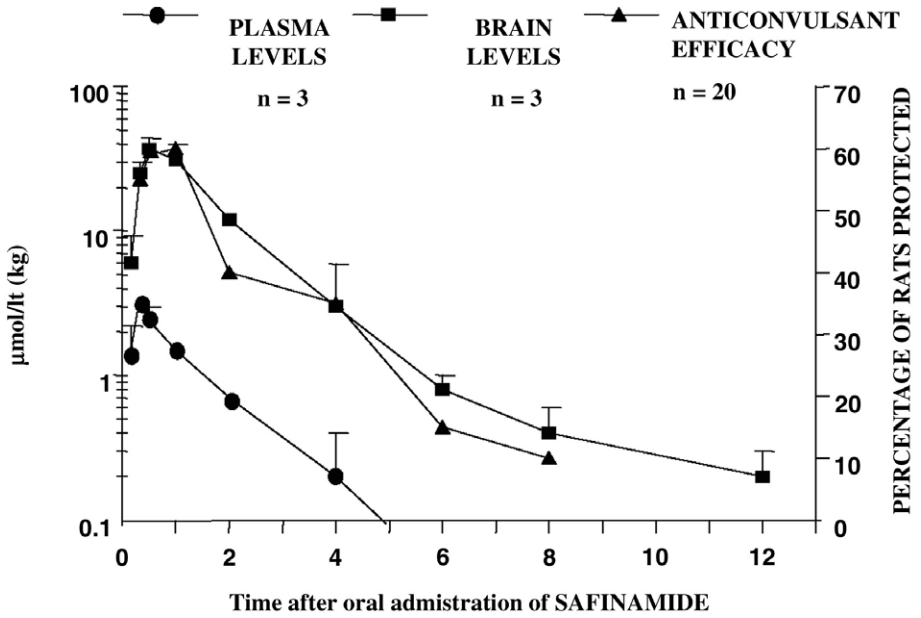

FIG. 1. Plot of the anticonvulsant effect of oral safinamide against the generalized T-C seizures induced by interaural passage of current (MET, triangles) in comparison with the curves of the levels of unchanged drug in plasma (circles) and brain (squares). The parallel course of the curves demonstrates that seizure protection is linked to the presence of the drug. Note that brain levels are parallel, but higher by a factor of about ten compared with plasma.

of these experiments (FIG. 1) were of interest as they demonstrated the following: 1) 10 mg/kg orally administered SAF provided 60% protection; 2) time-course of plasma and brain levels was parallel, but brain concentrations were constantly higher by a factor of approximately 10; 3) the percentage of protected subjects was strictly proportional to the drug levels (either serum or brain); 4) the gross estimate of the half-life of the product was around 2 h. All these are considered to be very encouraging features for development of a potential antiepileptic agent.

The subsequent battery of chemoconvulsive tests in rodents confirmed the potent activity of SAF and suggested a broad spectrum of action. In Table 1, antiseizure effects of SAF are reported and compared with those of some classical antiepileptic drugs (AEDs) and to lamotrigine (LTG), which was chosen as a prototype of the new generation AEDs. Overall the therapeutic indices (TI) calculation dividing the effective dose 50 (ED50) in each test by the toxic dose 50 (TD50) in the rotarod test showed that SAF offered the best ratio (Table 1). Furthermore, even against seizures caused by agents acting through systemic injection at the brain stem level, such as strychnine and picrotoxin, SAF showed some efficacy at variance with phenytoin, a classical sodium channel blocker.

TABLE 1. *Therapeutic Indices (TIs) of Safinamide Compared With Other Tested AEDs in Seizure Models*

	Convulsant Test					
Anticonvulsant	MES	BIC	PIC	3-MPA	STRYC	Rotarod mg/kg
Safinamide	76.0	20.9	10.3	29.1	6.0	625
Carbamazepine	11.2	16.1	2.7	5.3	2.0	106
Phenytoin	17.0*	5.0	<2.4	21.4	<1.2	242
Valproate	6.5	2.9	4.9	7.1	2.4	1194
Lamotrigine	32.3	8.2	<2.1	<2.1	<2.1	84
Diazepam	5.8	24.1	13.5	11.3	12.1	7

The right column expresses the rotarod TD50 in mg/kg. Columns on the left express the numeric result of the division of the TD50 by the ED50 in that particular seizure test. For example, safinamide, ED50 in the maximum electric shock (MES) = 8.2 mg/kg. Rotarod, TD50 = 625; T1 = 625/8.2 = 76.0.
Highest TI means best safety margin.
Compounds were orally administered 60 min before testing.
MES = maximal electroshock; BIC = bicuculline; PIC= picrotoxin; 3-MPA = 3-mercaptopropionic acid; STRYC = strychnine; TI = the ratio between the anticonvulsant ED50 and the toxic TD50 determined in the rotarod. *= Phenytoin shows a delayed toxicity at 3 h; PI at 1 h = 65.4.

PHARMACODYNAMIC PROPERTIES OF SAF

The affinity of SAF for site 2 of the voltage-sensitive sodium channel has been established in *in vitro* studies: SAF displaced H^3batrachotoxin with an IC50 of 8.2 μM. Displacement curves were comparable for other tested AEDs, which included phenytoin (PHT), carbamazepine (CBZ), lamotrigine (LTG), and riluzole.[5]

In a screening panel, significant affinity was found for only a few biochemical systems. The sigma-1 receptor bound SAF with an affinity of 19 nM. No other receptor subtypes, particularly GABA and glutamate, showed affinity for SAF. Some activity was seen at 10-μM concentration on the dopamine and norepinephrine uptake systems. Release of glutamate was studied in two different experimental settings: the release of glutamate induced by veratrine was inhibited by SAF with an IC50 of 56.4 μM compared with an IC50 of 34.7 obtained with LTG. When glutamate release was induced by potassium chloride, SAF was effective in blocking it with an IC50 of 185 *versus* IC50 $>$ 300 μM for LTG. This latter paradigm is deemed to mimic more closely the pathophysiology of clinical status epilepticus, where the outpouring of potassium is a cause of neuronal depolarization and spreading depression. These observations prompted a more in-depth electrophysiological evaluation of the effects of SAF on the resting and activated states of the neuronal Na^+ channel.

Safinamide was tested in current clamp conditions on sustained repetitive firing, a model that reproduces the firing pattern typical of neurons belonging to epileptic foci (bursts of action potentials, APs). Firing at 25 Hz was obtained holding the membrane potential at -0 mV. Adding 100 μM SAF to the superfusate caused cessation of firing after three APs. Lamotrigine obtained the same effect at a concentration twice as high (200 μM). When eliciting bursts by injecting 400 ms currents every 5 s, 50 μM SAF reduced cell firing within 1 min, and after 5 min the effect stabilized, triggering only one AP upon injection of current. One-minute washout re-established the pre-SAF conditions. Patch-clamp whole-cell electrophysiological studies demonstrated that SAF dose dependently inhibited fast Na currents in primary cortical neurons. The inhibition was voltage-dependent, showing an IC50 roughly 100 μM when currents were stimulated from a resting condition, while producing a significantly stronger inhibition (IC50 = 33 μM) when Na^+ currents were stimulated starting from a relatively depolarized membrane potential ($V_h = -60$ mV), reflecting a higher affinity for the inactivated state of the Na^+ channels.

Under conditions of repetitive current stimulation, SAF showed use-dependent block, producing a further 25% phasic block over the tonic block at the stimulation frequency of 10 Hz.

High threshold voltage-gated Ca^{2+} currents, including L-type and N-type currents, were also reversibly inhibited by SAF in cortical neurons with an IC50 of 31.5μM.

MONOAMIDE OXIDASE B INHIBITION

Experimental evidence suggests that monoamide oxidase B (MAO-B) inhibition may offer anticonvulsant protection. There is some controversy over whether the antiseizure effect observed in rodents is due to the monoamide oxidase A rather than to the MAO-B inhibition.[6,7]

Safinamide is the only reversible MAO-B inhibitor in clinical development. The reversibility was documented by demonstration of substantially equivalent IC50 in *in vitro* experiments with or without preincubation as well as by the full recovery of MAO-B activity after washing. Reversibility is based on SAF-unique noncovalent binding at the core of the enzyme.[8] Selectivity for the B isoform of the enzyme *versus* A is 5000 and 1000 times higher in rat and human brains, respectively.

EXPERIMENTAL SEIZURE MODELS

With the exception of the seizures induced by intravenous pentylenetetrazole, deemed to be a model of absence seizures,[9] SAF has demonstrated efficacy in all experimental paradigms of seizures and status epilepticus in which it has been tried.

Kainic acid (KA)-induced status epilepticus[10]

Doses of 10 and 30 mg/kg of SAF and LTG were administered intraperitoneally (i.p.) to male Wistar rats 15 min prior to an intraperitoneal injection of KA. Other groups received saline as negative control and 20 mg/kg diazepam intraperitoneally as positive control. The percentage of rats entering status epilepticus and the latency and duration of status epilepticus in each rat were monitored behaviorally and by electroencephalogram (EEG). Seven days after the KA administration all animals were sacrificed, and brains removed and blind-histologically examined to assess the extent of neuronal loss in the various hippocampal sectors. Diazepam decreased the percentage of rats in status epilepticus from 80% (negative control group) to 19%, also providing a significant delay in status epilepticus onset and a shortened duration. Lamotrigine did provide, at the lower dose (10 mg/kg), a significant reduction to 59% of rats showing status epilepticus without affecting latency or duration; the dose of 30 mg/kg failed to provide significant variations from control. Safinimide dose proportionally and significantly reduced the number of animals in status epilepticus to 57% and 47% (at 10 mg/kg and 30% mg/kg, i.p., respectively) with the higher dose diminishing also status epilepticus duration, whereas latency was increased by a mean of 104 $\pm$ 12 min to 166 $\pm$ 16 min without reaching

statistical significance. Interestingly, significant sparing of hippocampal CA4 neuronal loss was obtained by both drugs, but again LTG did so only at the higher dose, whereas SAF was effective at both doses. The highest degree of neuroprotection was provided by diazepam.

Amygdala kindling in rats[11]

Kindling in the amygdala is considered a model of partial complex seizures, the most epidemiologically relevant type of seizures in man and the subgroup of patients with the highest proportion of drug resistance.

Male Wistar rats were fully kindled according to the paradigm that uses a suprathreshold stimulus delivered through a stereotaxically implanted electrode in one amygdala. Full kindling was determined as the occurrence of three consecutive generalized convulsions following stimulation on three consecutive days. Thereafter, stimuli in the amygdala were delivered with a 20% higher intensity. Safinamide was administered intraperitoneally at doses of 1.0, 10.0, and 30.0 mg/kg one day after fully kindled rats underwent a control session with an injection of vehicle followed by stimulation. Seizure severity was behaviorally scored according to Racine[12] and after discharge (AD) duration was EEG recorded and measured. Two classical AEDs (PHT and CBZ) and two new AEDs (LTG and gabapentin, GBP) were used as reference compounds. All three doses had some anticonvulsant effect. The duration of the behavioral seizure was the variable most sensitive to change, with a significant dose-related reduction. Seizure stage diminished in a nonsignificant way at 1 mg/kg, significantly at 10 mg/kg, and reached maximal reduction (from a score of 5 to 1.8) with the highest dose. The two classical AEDs provided significant protection. Carbamazepine was effective on all three variables under observation at the dose of 10 mg/kg, without further improvement at doses of 30 and 60. Phenytoin was effective only at 50 and 100 mg/kg, which reduced seizure scores to 2.4 and 3.5, respectively. Both drugs induced remarkable sedation at the effective doses. Lamotrigine at 10 and 20 mg/kg significantly reduced seizure scores down to 0.8 and also shortened both seizure and AD duration. Very similar results were obtained with GBP, but only at the highest dose of 30 mg/kg, being ineffective at doses of 1 and 10 mg/kg. Similar to SAF, neither of the two new AEDs induced behavioral adverse events.

Limbic-induced AD in Subhuman primates[13]

The purpose of this experiment was twofold: on one hand, to seek confirmation of the anticonvulsant effect in a model of partial complex seizures; on the other, to investigate whether the sigma affinity of SAF caused any behavioral and/or EEG changes in cynomolgus monkeys, a species highly sensitive to the psychotomimetic and electrographic changes induced by sigma active compounds. Four male cynomolgus subjects were implanted stereotaxically under general anesthesia with one monopolar stainless-steel electrode in the basolateral amygdala, and cortical screw electrodes were connected to a socket cemented to the skull. An electrode over the cerebellum was used as reference. After reliable stimulation parameters to obtain a behavioral seizure and a sustained AD in the amygdala were established, the animals were administered oral SAF doses of 25, 50, and 75 mg/kg or PHT 50 mg/kg. The administration schedule was randomized according to Latin square design and each session separated by at least four days. After drug administration, stimuli were delivered at hourly intervals for 7 h. Under these experimental conditions, each stimulation elicited a limbic AD and a behavioral seizure consisting of head turning and eye closure with repetitive blinking. Similar to PHT, 50 mg/kg SAF reduced AD duration at the two highest doses and almost abolished AD-elicited behavioral seizures. Statistically significant effects were obtained with SAF at 1, 2, and 3 h after dosing, with peak efficacy at 2 h, concomitant with peak plasma levels (4.7 and 9.0 μ/kg with 25 and 50 mg/kg postoperation, respectively). Phenytoin was significant only at 2 h. The dose of 25 SAF suppressed the behavioral component of the seizure only. Safinimide did not cause EEG or interictal behavioral alterations at doses up to 75 mg/kg postoperation. These data further confirm the broad spectrum of anticonvulsant activity and a good safety profile of SAF even in a primate model of complex partial seizures, and suggest that the affinity of the drug for sigma-1 receptors is behaviorally irrelevant.

Neuroprotection

In several experimental settings, SAF demonstrated neuroprotectant and neurorescuing effects. *In vitro*, neuronal death of cultured cortical neurons induced by veratridine was effectively prevented by adding SAF to the culture medium. More relevantly, in two *in vivo* models SAF proved quite effective at providing neuronal sparing.

The substance 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a protoxin which in rodents is taken up by the terminals ascending from cell bodies of neurons in the substantia nigra (SN) pars compacta and there converted by MAO-B to 1-methyl-4-phenylpyridine (MPP+), which destroys with a high degree of selectivity both dopaminergic terminals and neurons, depleting dopamine in the nigrostriatal pathway. In C57 black mice, the entire process of conversion to the toxin requires several hours. Due to its powerful and selective inhibition of MAO-B, when administered to C57 black mice prior to MPTP, SAF fully prevents both forebrain dopamine depletion and neuronal death in the SN. This preventive effect is shared by other MAO-B inhibitors such as selegiline and rasagiline.[14] To assess the potential for neuronal sparing, an experiment was designed

wherein 30 mg/kg intraperitoneally MPTP was administered to black C57 mice over the course of two consecutive days. Four hours after the second MPTP injection SAF was administered intraperitoneally at doses of 10 and 20 mg/kg; a week after, animals were sacrificed. Neostriatal dopamine in the SAF-treated mice depleted no differently than in control animals, indicating that the conversion from MPTP to MPP+ had occurred. However, tyrosine hydroxylase (TH) staining of the SN showed a significant dose-dependent sparing of dopaminergic neurons in the SAF-treated animals compared with the 80% depletion observed in the control batch.[15]

Transient forebrain ischemia caused by 5-min bilateral carotid occlusion (BCO) in mongolian gerbils results in behavioral deficits and neuronal loss in selected hippocampal sectors.[15] Days after, animals tested with the passive avoidance retention test showed poor performance, reflecting cognitive impairment. In an initial series of experiments, SAF was administered intraperitoneally; 100 mg/kg both 30 min prior to and after BCO. The vehicle-treated control group demonstrated behavioral impairment and, when sacrificed at seven days, 95% neuronal loss in the hippocampus. This neuronal damage was almost completely prevented by SAF. Under the same experimental conditions, PHT provided partial nonsignificant protection. Moreover, SAF maintained its protective effect when given up to 3 h after BCO.

DRUG ABILITY FEATURES

Safinimide is used as methanesulfonate salt, a very stable formulation. As such it is highly water soluble, a pivotal galenic feature for use in status epilepticus. Safinimide shows excellent bioavailability. In mice, rats, and monkeys, concentration of the unchanged drug is higher in the brain ($\sim\times10$) compared with plasma, a highly desirable feature in a molecule for which the therapeutic effect must be central. Safinimide is 92% protein-bound in humans. Safinimide had little or no effect on behavior, locomotor activity, cognition, renal function, and intestinal transit at doses substantially above the expected therapeutic ones. The cardiac safety profile is very good. There is no QT prolongation in the electrocardiogram of dogs. In pithed rats it had no effect on mean blood pressure (BP), nor did it affect the pressor response curve to noradrenaline.

In extensive interaction studies with the cytochromal P450 isoenzymes system, negligible interactions were observed, suggesting lack of drug-to-drug interaction in add-on conditions. In several *in vitro* and *in vivo* studies from bacteria to mouse, SAF was neither mutagenic nor genotoxic.

TOXICOLOGY

In subchronic (13 weeks) and chronic toxicity studies in rats (26 weeks) and monkeys (39 weeks), the no observed adverse effect level was due to reversible clinical chemistry changes and was not associated with target organ toxicity. These laboratory changes have not been detected in the human population in either healthy volunteers or patients at the tested doses

CLINICAL STUDIES

To date, 97 healthy volunteers have been exposed to SAF in doses up to 10 mg/kg/day single oral administration or 5 mg/kg/day repeated dosing without objective signs of toxicity and with minor subjective complaints, consisting of mild transient headache, paresthesia, and heartburn, all subsiding before the end of the study.

A steady state kinetic evaluation of three doses of SAF demonstrated linearity and proportionality of the curves of the unchanged drug levels in the range of 1.25 to 5 mg/kg/day (FIG. 2), with a half-life of 24 h, optimal for a once a day clinical administration schedule. Heavy fat-loaded food intake delayed absorption without affecting the extent of drug absorption. Two studies of BP interaction under tyramine load have been performed, one with intravenous tyramine[16] the other under oral tyramine load for two weeks. Both conditions failed to detect any rise in BP resulting from the addition of SAF to the tyramine load, which suggest, at variance with all the other MAO-B inhibitors on the market, no need of dietary restrictions upon chronic treatment.

A first exploratory study was initiated in a single center in epilepsy surgery candidates because of the refractoriness of their seizures to medical treatment. Only five patients received 1 mg/kg SAF for one week, which was well tolerated. The study was terminated at this point because of poor recruitment. Anecdotally, one of the patients reported remarkable diminution of the partial sensory crisis from which he was suffering many times a day.

Another pilot study has been carried out with the aim of gauging the effective dose to be used in a proof-of-concept trial and exploring the possible drug-to-drug interaction in polytherapy.[17] In an open design, oral-escalating once a day (o.a.d.) doses of SAF, starting from 50 mg and increasing every two weeks to 100, 200, and 300 mg, unless impeded by intolerance, were added onto the existing AEDs, the doses of which remained stable throughout the study for a 12-week period. Main eligibility criteria for the consenting patients included refractory epilepsy to optimized treatment with up to three AEDs, at least 12 seizures in the previous three months, and ages older than 17. Of the 43 enrolled patients, 38 completed the study

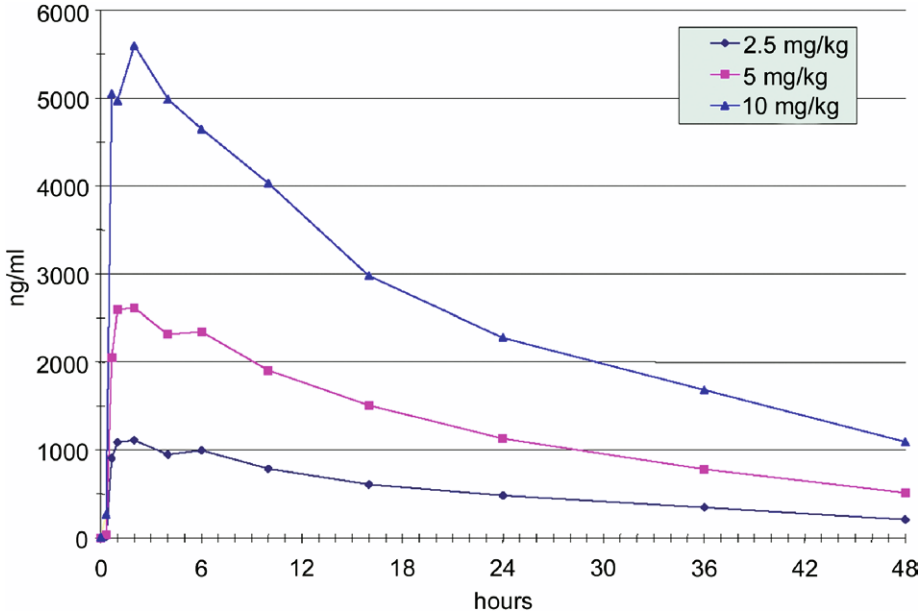

FIG. 2. Plasma level curves at steady state of safinamide administered to healthy volunteers at the doses of 1.25, 2.5, and 5.0 mg/kg for one week. Peak levels (T_{max}) are reached at 2 h and half-life is about 24 h. Note linearity and proportionality of the curves within the three doses. Reprinted from Marzo A, Dal Bo L, Monti NC, et al. Pharmacokinetics and pharmacodynamics of safinamide, a neuroprotectant with antiparkinsonian and anticonvulsant activity. Pharmacol Res 2004;50:77–85, with permission.

and reached the target dose even though four stepped back to the 200 mg level because of nonserious adverse events (AEs; one unsatisfactory seizure control, three vertigo).

Measurements of drug levels did not show any significant variation of the previously used AED upon addition of SAF. However, SAF levels appeared to be reduced by about 30% when taken together with enzyme-inducing AEDs (CBZ and PB). Overall, SAF was well tolerated; only eight patients (19%) experienced AEs that were deemed possibly, or probably, drug-related. The most common AEs were dizziness, headache, vertigo, nausea, and transient visual disturbance (blurred vision with change of light intensity), all judged mild or moderate in intensity. Of four serious AEs, only one led to treatment discontinuation after 17 days (blurred vision) and another one was judged as drug-related (vertigo).

The study did not have the design or power to assess efficacy. Nevertheless, positive indications were noted which should help in optimizing dose and design of future trials. Starting from the initial dose of 50 mg there was a statistically significant decrease of seizures, which became greater at each incremental dose. At the end of the study, 41% of patients had $\geq$ 50% reduction in seizure frequency compared with the initial perspective baseline. The study was completed in October 2003. To date (August 2006), seven patients continue on compassionate use, five at the dose of 300 mg, and one each at 200 and 100 mg, all o.a.d.

FUTURE DEVELOPMENT

Relating to the industrial strategy of the company, SAF development in epilepsy has not progressed as fast as it has in Parkinson's disease, where it reached phase III. Safinimide appears promising, but at present it is impossible to gauge what place it might have in the modern armamentarium of the epileptologist, as well as what type of clinical seizure may be responding or refractory to it.

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