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Current Opinion in Central & Peripheral Nervous System Investigational Drugs

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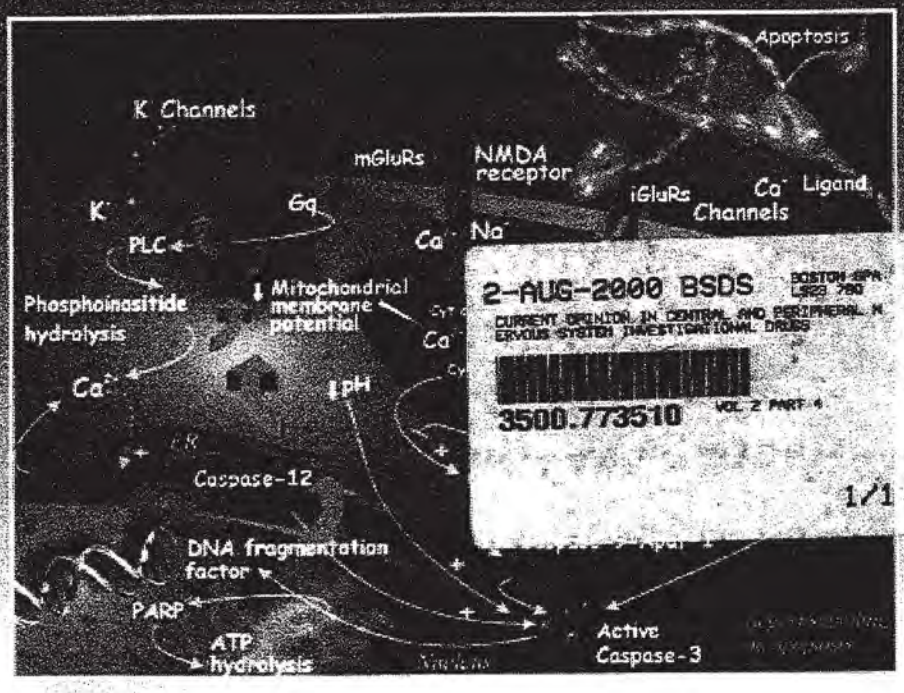

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Aims and organization

The *Current Opinion* journals were developed out of the recognition that specialists have increasing difficulty keeping up to date with the expanding volume of information published in their subject. In *Current Opinion* in Central & Peripheral Nervous System Investigational Drugs, we aim to help the reader by providing in a systematic manner:

- the views of experts on current advances in central & peripheral nervous system drug research in a clear and readable form;
- expert evaluation of selected drugs currently in clinical trials;
- selection of the most interesting papers and patents, annotated by experts.

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Rivastigmine Novartis AG

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Rivastigmine is an acetylcholinesterase (AChE) inhibitor developed and launched by Novartis for the symptomatic treatment of Alzheimer's disease (AD). By April 2000, the drug had been launched in more than 65 countries, including the member states of the EU, and had been approved in the US [363944]. In June 2000, the drug was launched in the US [371704].

In May 1999, the company received an approvable letter from the FDA, and at this time approval was expected before the end of 1999 [324671]. However, by September 1999, Novartis had been asked to provide more information on 4000 patients in long-term studies, hence approval in the US was not expected before March 2000 [342651]. In April 2000, the FDA granted marketing clearance for rivastigmine in the US for the treatment of mild-to-moderate AD [363824], [363843], [363944]. Rivastigmine is due to enter the mild-to-moderate AD market, which is dominated by Pfizer/Eisai's donepezil (Aricept), in May 2000; Novartis has plans to initiate a comparative trial of the two drugs in this patient population by the end of 2000 [364802].

In May 1998, Novartis received marketing approval from the European Commission [288564], and by July 1998, the drug had been cleared for marketing in over 30 countries [292661]. However, in the same month, the company received a non-approvable letter because of a potential relationship between high doses of the drug and deaths reported during clinical trials [312645].

In July 1998, the US FDA requested additional analyses of data submitted in the NDA, filed in April 1997, in order to confirm rivastigmine's safety at high doses [291307], [292661]. The additional data were submitted to the FDA in December 1998 [319561].

The first marketing approval of rivastigmine, by the Swiss regulatory authority IKS, was in August 1997, for the treatment of mild-to-moderate AD. The approval, conducted by the fast-track route, was based on the largest AD clinical program conducted in Europe and the US, ADENA (Alzheimer's dementia with rivastigmine) which involved more than 3330 patients with mild-to-moderate AD [259187].

Rivastigmine is a twice-daily oral formulation; some rival products, notably donepezil and metrifonate (Bayer Corp), are once-daily formulations [287188]. By the end of 1998, Novartis was also developing a transdermal formulation of rivastigmine, Exelon TDS, and an oral solution of the compound, Exelon Solution [319337]. At the end of 1999, Exelon TDS was in phase II trials, with an estimated filing date of 2002 [364082].

Originator Novartis AG

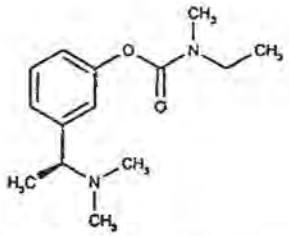
Status Launched Extensively

Indication Alzheimer's disease, Cognitive disorder, Dementia

Action Acetylcholinesterase inhibitor, Enzyme inhibitor

Synonyms ENA-713, SDZ-212-713, SDZ-ENA-713, Exelon, rivastigmin, Prometax, rivastigmine tartrate, Exelon TDS, Exelon Solution

CAS Carbamic acid, ethylmethyl 3-[1-(dimethylamino)ethyl] phenyl ester, (S)-
Registry nos: 123441-03-2, 129101-54-8



The results of a pooled analysis of three phase III studies in patients with mild-to-moderate AD, has demonstrated that patients treated with rivastigmine experienced less decline in activities of daily living (ADL) than patients treated with placebo. Approximately 50% more patients showed a clinically significant improvement from baseline ADL compared to those on placebo. The data were presented at the 52nd Annual Meeting of the Gerentological Society of America (San Francisco, CA, November 1999) [348202].

The associated patent, DE-3805744-B, discloses rivastigmine in its optically active form. However, an older patent, EP-00193926, held by Yissum Research Development and Proterra, discloses the stereochemically unspecified compound.

In September 1998, Merrill Lynch predicted peak sales of SFr 750 million [300257]. In April 1999, Lehman Brothers commented that rivastigmine, due to be launched in the US in 1999, would face competition from donepezil and could also face competition from galantamine (Sanochemia Pharmazeutika AG/Janssen Pharmaceutica NV) and metrifonate in 2000 [336750]. In September 1999, Lehman Brothers predicted peak sales of $400 million [342651]. In April 2000, Merrill Lynch predicted that sales would continue to rise from the CHF 65 million earned in 1999 to CHF 480 million in 2004 [364974].

Introduction

Rivastigmine is an inhibitor of AChE that has been approved recently in Europe, USA and several other countries for the treatment of mild to moderate AD. Deficits in cholinergic transmission were identified early in the pathophysiological research of AD. Since disruption of cholinergic transmission in animals was found to produce

memory deficits comparable to those in AD patients it was postulated that enhancement of cholinergic transmission may ameliorate cognitive disturbances in AD patients. In fact, AChE inhibitors have been the first widely used drugs for the treatment of AD. Tacrine (Warner-Lambert Co/First Horizon Pharmaceutical Corp) was the first AChE inhibitor to be approved for AD treatment although the hepatic toxicity that it causes in some AD patients has limited greatly its widespread use. The quest to find other AChE inhibitors with an improved safety profile has lead to the development and approval first of donepezil (Eisai Co Ltd) and more recently to rivastigmine.

Synthesis and SAR

Although AD was first described in 1907, it was not until the mid-1970s that it became possible to think in terms of a rational hypothesis for designing drugs against AD. The observation that there is a selective loss of cholinergic neurons in the cortical and hippocampal areas of patients with AD led to the so-called 'cholinergic hypothesis' and made it possible to embark upon synthetic programs to design drugs that would enhance cholinergic function in the central nervous system (CNS). Much effort has gone into designing CNS-selective AChE inhibitors since many AChE inhibitors in medicinal use have quaternary nitrogens and do not penetrate the CNS. A 1986 publication from the Hebrew University of Jerusalem describes eight analogs of miotine, a neutral monomethylcarbamate of 3-[1-(dimethylamino)ethyl]phenol used clinically as a miotic [241080]. Although not the best inhibitors *in vitro*, three N,N-disubstituted analogs displayed the best combination of brain selectivity, long-lasting *in vivo* activity, and good tolerability in mice. Of these three, the N-ethyl-N-methylcarbamate (RA7) was chosen by Sandoz for clinical development and was designated SDZ-ENA-713 (rivastigmine). While the original activity was reported for the racemic compound, the enantiomers were synthesized by recrystallization of the di-p-toluoyl-L-tartrates [241087] and the R(+) enantiomer was found to be 5-fold weaker *in vitro*.

Pharmacology

Rivastigmine is an AChE inhibitor also able to inhibit butyrylcholinesterase (BChE) (in normal brain only AChE is abundantly represented). Reversible and non-competitive inhibition of AChE by rivastigmine has been called 'pseudo-irreversible' to stress the fact that rivastigmine is actually cleaved by AChE and the resulting carbamate is bound covalently to the enzyme. However, this binding is transient due to the rapid metabolism and the rapid rate of decarbamylation, which regenerates AChE [372436]. At a difference with other AChE inhibitors, rivastigmine shows a preferential inhibition of AChE in brain areas such as the hippocampus and the neocortex while the inhibition is much lower in peripheral organs. For instance, it increases salivation at doses over 6-fold higher (6.4 mg/kg ip) than those where alert non-mobile behavior is induced (0.5 mg/kg ip) and produces a 50% *ex vivo* inhibition of cortical and hippocampal AChE at a dose (3.0 µ/kg sc), 10-fold lower than that which inhibits heart AChE (30.0 µmol/kg sc) [162923]. When examined *ex vivo* in rats, rivastigmine is 10-to 100-fold less potent *in vitro*. These effects may be due to preferential inhibition of the G1 form of AChE, which is present in relatively higher concentrations in cortex and hippocampus.

Rivastigmine demonstrated a number of properties in animals that indicated its potential in the treatment of AD. It appears to readily penetrate the CNS since a dose of 0.75 mg/kg po produces a long lasting (> 6 h) EEG activation. In rats with closed head injury (CHI) 1 to 5 mg/kg rivastigmine produced 40 to 80% inhibition of AChE in the cortex and hippocampus [289316]. Microdialysis measurements of acetylcholine (ACh) in the hippocampus shows an increase of available extracellular ACh produced by rivastigmine. In rat hippocampus rivastigmine at doses of 0.625, 1.25 and 2.5 mg/kg po produced maximum elevations (190, 346 and 480%, respectively) of ACh at 0.5 h after administration as measured by microdyalisis, while maximum increases were attained with donepezil and tacrine at 1.5 and 2 h, respectively [372438]. Rivastigmine (0.1, 0.2 mg/kg po) also was able to prevent the reduction of choline acetyltransferase (ChAT) in the frontal cortex of rats with their basal forebrain lesioned by ibotenic acid [372442].

Rivastigmine improves memory impairments in different animal models. Rivastigmine (0.5 mg/kg ip) attenuated significantly the working memory impairment produced by scopolamine in the delayed non-matching to position task given to rats [367020]. At doses between 0.05 and 0.10 mg/kg/day it improved acquisition and retention in basal forebrain-lesioned rats tested in a step-down avoidance paradigm [193504]. In rats with the same lesions tested in the water maze task rivastigmine (0.1, 0.2 mg/kg po) ameliorated the impairment in acquisition in a dose dependent manner [372442]. In a rat model of memory impairment induced by scopolamine in a delayed non-matching to position task rivastigmine significantly attenuated the working memory deficit.

Since rivastigmine is aimed at aging populations, experiments with aging animals are especially relevant. In a study by Ohara *et al* [259139] in aged rats rivastigmine (0.2 mg/kg) significantly shortened the time to reach a hidden platform and also at 0.1 and 0.2 mg/kg inhibited aging induced decreases in AChE activity in the frontal cortex. In senescent rats, chronic administration of rivastigmine blocked aging-induced reductions in ACh and in choline acetyltransferase (ChAT) levels in frontal cortex, hippocampus and striatum and in B_{max} of muscarinic M_1 receptor binding sites in frontal cortex [193505].

A number of studies indicate that rivastigmine may be useful in the treatment of cerebrovascular dementia. In ischemic gerbils, administration of 0.2 mg/kg ip immediately after 5 min of bilateral carotid artery occlusion, and again after 6 and 12 h, resulted in a significant decrease in pyramidal cell death in the hippocampus [230733]. In another study, gerbils receiving 0.2 mg/kg ip, 2 h prior to transient ischemia, were protected against ischemia-induced reductions in hippocampal ACh levels and in the maximum number of muscarinic ACh receptors (B_{max}) [162883]. Administration of 0.2 mg/kg ip 30 min before transient ischemia in this same model blocked ischemia-induced

hypertensive rats, 0.05 to 0.5 mg/kg iv rivastigmine, administered 10 min before cerebral ischemia, protected against reductions in cortical and hippocampal ACh [230734], similar to the results in gerbils. In line with the neuroprotective effects is the report of a reduction in edema and in disruption of the blood-brain barrier in rats with CHI treated with rivastigmine at doses of 2 and 5 mg/kg. These improvements were accompanied by a faster recovery of motor deficits [289316]. In mice with the same type of injury rivastigmine (2 mg/kg sc) improved memory performance in the Morris water maze. It also reduced by at least 50% cerebral edema [289264].

Recently, gender differences in the effect of rivastigmine on brain cholinesterase (ChE) activity and cognitive function have been described in rats [372445]. Rivastigmine (0.75 and 1.5 mg/kg) caused significantly greater ChE inhibition in females than in males in the cerebral cortex, hippocampus and striatum, although not in the periphery. Rivastigmine also antagonized more effectively scopolamine-induced spatial memory impairment in female than in male rats. Male testicular factors appear to account for the differences since these differences were abolished by orchidectomy, but not by ovariectomy.

Some new experiments suggest that rivastigmine might have application as a topical agent that may lower intraocular pressure (IOP) in glaucoma therapy [372437]. In rabbits, topical application of 1, 2 or 5% rivastigmine on the eye produced maximal IOP reductions of 15.2, 19.6 or 23.2%, respectively, without signs of local toxicity.

Toxicity

In the rat, cat and squirrel monkey, rivastigmine exhibits no significant effects on cardiovascular parameters at doses at which clear central effects can be demonstrated [162923]. To achieve a similar pressor effect rivastigmine must be injected at doses 2-fold the dose of tacrine and 40-fold the dose of physostigmine in rats [372440].

Results of a phase I/II trial in AD patients showed a bid and tid treatment regime to be safe and well tolerated up to 12 mg/day, although side effects were similar to those experienced in previous trials [190327].

Rivastigmine shows some selectivity for brain AChE, suggesting that it may have a greater margin of safety than other nonselective cholinesterase inhibitors. Studies conducted in healthy volunteers showed rivastigmine to be centrally active, long lasting, and well tolerated over a moderate dose range. Side effects, including nausea, vomiting, diarrhea, dizziness and headaches were evident at high doses, although these did not include hepatotoxicity [304019].

Metabolism

Orally administered rivastigmine in healthy subjects (3 mg) was rapidly and almost completely absorbed (> 96% of the administered dose) with T_{max} being 1.1 h, C_{max} 7.7 ng/ml and AUC 18.6 ng.h/ml [367022]. It was converted with a $t_{1/2}$ of 1.5 h to the principal metabolite, the decarbamylated phenol (C_{max} 6.1 ng/ml, AUC 35.4 ng.h/ml), which was eliminated with a $t_{1/2}$ of 3.5 h. In AD patients the pharmacokinetic profile of rivastigmine (3 mg) is similar, showing rapid absorption with a T_{max} of 1.67 h, C_{max} 5.07 ng/ml, AUC 15.4 ng.h/ml and a $t_{1/2}$ of 1.23 h [289261]. In these AD patients dose dependent inhibition of cerebrospinal fluid (CSF) AChE was significantly correlated with plasma drug and metabolite concentrations. In spite of its complete absorption, rivastigmine undergoes extensive saturable first-pass metabolism, which leads to bioavailability of approximately 35%. The principal metabolite of rivastigmine is at least 10-fold less active then the parent compound. Unlike tacrine, donepezil and galantamine, rivastigmine is not metabolized by the cytochrome P450 liver enzymes. Rivastigmine is metabolized via esterases and is then rapidly secreted in the urine [229292], [372435], [209139]. This is probably the reason for its safe hepatic profile.

The bioavailability of rivastigmine is higher in aged subjects that in young healthy volunteers. However, studies with AD patients between 50 and 90 years old did not show evidence of bioavailability changes with age (BIAM monograph on rivastigmine).

In ten renally- and ten hepatically-impaired patients, the AUCs for rivastigmine were 2.3-fold and 1.4-fold higher, respectively, and the AUCs for the metabolite were 0.8-fold lower and 1.5-fold higher, respectively, as compared to healthy subjects. The conclusion was drawn that dose adjustment in addition to the usual clinical titration appeared unwarranted in these patients [234634].

In minipigs, [^{14}C]-SDZ-ENA-713 (rivastigmine) was administered iv (0.1 mg/kg), orally (1.0 mg/kg) or topically (18 or 54 mg with a dermal patch) [367021]. Oral doses were efficiently absorbed with a T_{max} of 0.83 h. Bioavailability was low (0.5%) due to extensive first-pass metabolism. Excretion was mainly renal (roughly 90%) and $t_{1/2}$ was 56 h, higher than 46 h after the iv dose. Dermal administration produced a lower absorption (no larger than 19%), but bioavailability was 20 to 40-fold higher since most of the absorbed drug reached the systemic circulation without suffering first-pass metabolism. The metabolite of [^{14}C]-SDZ-ENA-713, ZNS-114-666 was rapidly formed, but accounted only for less than 4% of the total drug-related material in the systemic circulation.

In rabbits, rivastigmine administered orally (1.09 mg/kg) was completely and rapidly absorbed (T_{max} = 1.3 h). Following iv administration at the same dose, rivastigmine was extensively distributed (Vss = 3.1 l/kg) and rapidly cleared (Cl = 2.7 l/h/kg). The radioactivity corresponding to the labeled rivastigmine was mainly excreted through the kidneys (86% of dose) [367023].

Clinical Development

Phase I

Extensive testing of rivastigmine in healthy, young, old and renally/hepatically impaired patients has been conducted. Data on the safety, tolerability, pharmacokinetics and metabolism of rivastigmine are presented above [367022], [289261], [229292], [372435], [209139], [234634].

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