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Current Opinion in Central & Peripheral Nervous System Investigational Drugs

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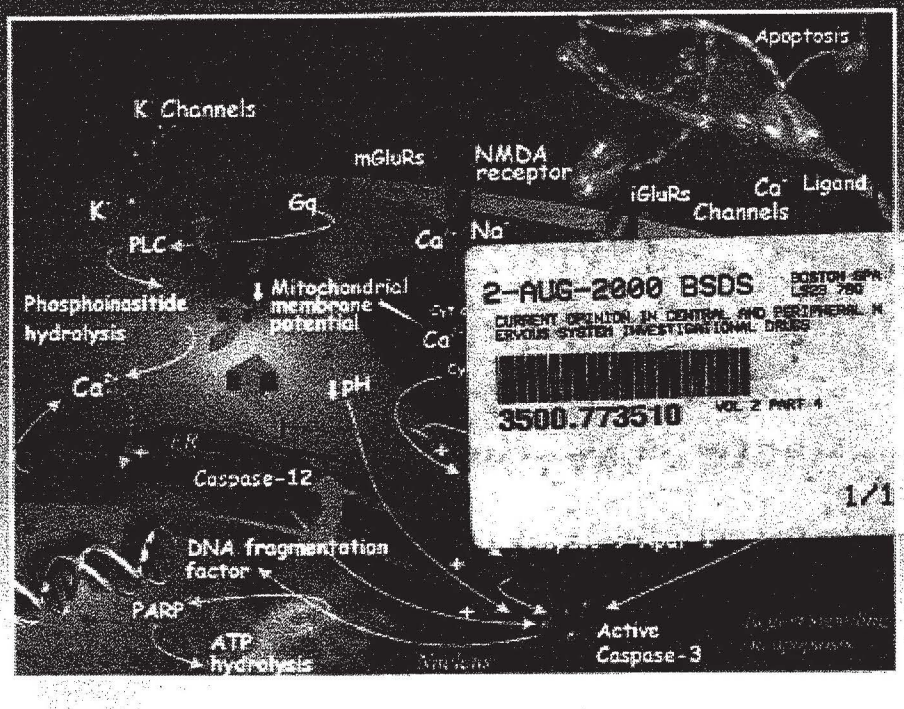

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Aims and organization

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

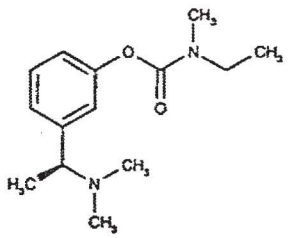
Status Launched Extensively

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-fold less potent than physostigmine in the brain, compared 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 decreases in brain ACh, dopamine and 5-HT [162929]. In

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].

Phase II

There is clinical evidence for the central selectivity of rivastigmine. A single 3 mg po dose produced 30 to 40% inhibition of AChE in human CSF but minimal inhibition of either erythrocyte AChE or plasma BChE [241060]. In a study in healthy subjects preferential inhibition of AChE in CSF (as compared to plasma or erythrocyte AChE) was found after treatment with 3 mg of rivastigmine po [367019]. In a related study in which AD patients were titrated in 1 mg bid/week increments to target doses of 1, 2, 3, 4, 5 or 6 mg bid rivastigmine, it was further found that inhibition of CSF AChE is dependent on the dose of rivastigmine [289261]. The 6 mg bid treatment group showed a maximum mean inhibition of 62% at 5.6 h post-dose. In a study of sleep quality in young male volunteers, effects on REM sleep density at 1, 1.3 and 2 mg indicate rivastigmine is centrally active [3157].

In a phase II efficacy study of rivastigmine in 402 AD patients, the completion rates were 87 and 85% for doses of 4 and 6 mg/day, respectively [229292]. In a second study, in which 114 patients with mild to moderate AD were dosed bid and tid in the range 6 to 12 mg/day, 12 mg/day was tolerated, but completion rates were 64% in the bid group and 76% in the tid group. In a similar study in 50 patients in which drug was given after food [209139], 12 mg/day was also well tolerated. The principal adverse effects at 12 mg/day were typical of excessive peripheral cholinergic stimulation, ie, headache, nausea, dizziness and diarrhea.

Phase III

The phase III ADENA program comprised four separate, multicenter, placebo-controlled, 6 month, double-blind trials in patients with mild to moderately severe AD. The selection criteria also allow older patients, patients with significant physical illnesses and those taking concomitant medication [241060]. Results are available in published form from two of these trials [372434], [372444].

In a US trial (B352), 699 patients were randomized to either 1 to 4 mg/day bid, 6 to 12 mg/day bid, or placebo for 6 months and were evaluated on scales of cognitive function (ADAS-Cog), global functioning (CIBIC+) and activities of daily living (PDS) [372434]. Of the high-dose group, 25% showed improved PDS, ADAS-Cog, and CIBIC+ scores compared to 15%, 7%, and 16% of the placebo group for the respective outcome measures [372434]. The minimum effective dose is suggested to be 6 mg/day. 25% Of the drug-treated patients withdrew because of the side effects cited above, versus 16% of the placebo group.

In the phase III study B303 725 patients from 45 centers in Europe and the USA received either 1 to 4 mg/day (low dose group) or 6 to 12 mg/day (high dose group) rivastigmine, or placebo, over 6 months [372444]. The doses were increased over the two fixed-dose ranges during the first 12 weeks and assessed during the subsequent 14 weeks. During the trial period, patients treated with placebo deteriorated according to measures of cognitive function, global functioning and ADL. In this study 24 to 41% of the high dose group were full responders in all three measures and 50 to 60% were partial responders. Scores of the ADAS-Cog improved in patients in the higher dose group when compared with patients taking placebo. Modest, but significant improvements were found in global function and in the progressive deterioration scale.

During the meeting of the American Academy of Neurologists (May 1998), Novartis presented results of a meta-analysis of three double-blind, placebo-controlled, 26-week phase III studies (designated B303, B351 and B352) [289815]. In more than 2000 patients rivastigmine had significant beneficial effects on measures of cognition (ADAS-Cog scale), global functioning and ADL. In a study with 100 weeks of treatment, the mean change on the ADAS-Cog scale following rivastigmine was 3.8 points better than placebo treatment [297099]. In an open-label extension phase, patients who had originally received placebo (n = 145) or rivastigmine (n = 136) received rivastigmine for a further six months. At the end of the six months, patients who had originally been on the placebo scored nearly three points higher on the ADAS-Cog scale. Between 44 and 52 weeks all patients experienced a decline in cognition scores, although this was more modest in patients who were originally on rivastigmine [287188]. Factors affecting patient responses to rivastigmine, using pooled data from the same studies (B303, B351 and B352), were discussed in the Sixth International Conference on Alzheimer's Disease and Related Disorders (Amsterdam, The Netherlands, July 1998). In total, these trials encompassed 1843 patients [293335]. Analyses were performed on the effects of rivastigmine (6 to 12 or 1 to 4 mg/day) or placebo upon cognitive improvement after 26 weeks of treatment. Patients were divided into subgroups according to age, race, gender, baseline disease severity, concomitant medications, co-morbid illness and Hachinski score. Response to rivastigmine was determined by an improvement in ADAS-Cog score of 4 points, and a CIBIC+ score of < 4 at the endpoint [293335]. In general, response to rivastigmine is most effective at doses between 6 and 12 mg/day, in patients with moderate AD. Lower body weight enhances responsiveness, and nicotine use reduces response. Insufficient patient numbers prevented meaningful analysis of the influence of comorbid illness, race or concomitant medication on rivastigmine treatment, although in the latter no differences were seen with NSAIDS or estrogen.

Since rivastigmine shows neuroprotective properties in some animal models, clinical trials have started to apply rivastigmine to other neurodegenerative diseases. Recent data from a multicenter study showed that rivastigmine has efficacy in improving the behavioral and psychological symptoms of dementia and cognition in patients with Lewy body dementia (LBD). 120 LBD patients in Italy, Spain and the UK, with a mini-mental state examination (MMSE) score of at least 10 were enrolled. The study used 3 to 12 mg/day of rivastigmine or placebo for 20 weeks with a fixed titration every 2 weeks. Significant improvements over placebo were achieved on all neuropsychiatric inventory (NPI) items and attention, but not MMSE scores [337485]. In trials of rivastigmine in AD greater cognitive benefits were observed in cases with vascular risk factors, like hypertension than in cases without [364146]. Some data presented this year at the Congress of the European Society for Clinical Pharmacology suggest that rivastigmine might be of value in the treatment of cognitive dysfunction in Parkinson-plus-dementia [369737].

A recent study has analyzed the efficacy and safety of rivastigmine in AD patients with concurrent vascular risk factors [372439]. Patients were randomized to placebo (n = 235), low-dose rivastigmine (1 to 4 mg/day, n = 233), or high-dose rivastigmine (6 to 12 mg/day, n = 231) for 26 weeks and efficacy assessed with ADAS-Cog, CIBIC+, PDS,

GDS, and MMSE. Additionally patients were categorized into two groups (with or without vascular risk factors) by baseline modified Hachinski Ischemic score for the determination of vascular risk factors. The treatment difference between high-dose rivastigmine and placebo was larger in the group with vascular risk factors than in the group without vascular risk factors. The conclusion of the study was that rivastigmine is effective in both categories of patients, although those with vascular risk factors experience greater clinical benefit.

Side Effects and Contraindications

Studies in phase II and III have revealed that rivastigmine is well tolerated with doses up 12 mg/day [372434], [372444]. Adverse events were predominantly gastrointestinal, of mild-to-moderate severity, transient and occurred mainly during the escalation of the dose. The most common side effects were cholinergic and included nausea, vomiting, diarrhea, abdominal pain, and anorexia. In the lower dose group of study B303 (1 to 4 mg/day) only the incidence of nausea (17%) was significantly higher than in the placebo group (10%) [372444]. These cholinergic adverse effects can be reduced by slowing the rate of titration or lowering the dose by as little as 1 mg/day. No clinically relevant differences were observed between groups in vital signs (blood pressure, heart rate, body temperature), ECG, physical examination, hematological or biochemical analyses (including the levels of hepatic enzymes). Discontinuation of treatment in trials for any reason was significantly higher in the high-dose group (33%) than in the low-dose (14%) or placebo groups (13%) [372444].

Concomitant administration of rivastigmine with medications belonging to 22 different therapeutic classes did not reveal significant increase of adverse events that would have indicated a drug interaction [367018]. In contrast, the pharmacokinetics of AChE inhibitors tacrine and donepezil have been reported to be altered by drugs like theophylline and cimetidine [327826].

Patent Commentary

The basic molecule of rivastigmine is claimed in EP-00193926, filed in March 1986 by Yissum Research and Development Co. The application was assigned to a Swiss-based company, Proterra AG in 1987 and granted in 1990. Sandoz filed a German priority case, DE-03706914 in March 1987 claiming the (-) enantiomer (rivastigmine). This formed the basis of a patent family which includes GB-02203040 and US-05602176.

Current Opinion

The ability to produce modest improvements or just arresting temporarily the decline in behavioral and cognitive functions that characterizes AD is of paramount medical and social importance. Inhibitors of AChE have been the first pharmacological compounds to demonstrate that ability in the clinic. Although the cholinergic treatment is called symptomatic and is supposed not to interrupt the underlying processes causing AD evidence is appearing which suggests that procholinergic agents, like rivastigmine, may significantly delay the progression of AD symptoms beyond one year in mild-to-moderate AD patients.

Since rivastigmine does not interact with many of the medications which are prescribed to the often heavily medicated aged AD patient group, it might have an advantage over donepezil or tacrine in long-term use. However, new studies are revealing that the responses to rivastigmine may vary in different groups of AD patients depending at least on their gender or on the presence of vascular risk factors. It is possible, that a particular population of AD patients may benefit preferentially with different doses of rivastigmine. This possibility clearly calls for further basic and clinical research. Furthermore, the mechanisms of action of rivastigmine and donepezil are different and consequently they might also be directed to different populations of AD patients. The extent that the putative different populations of AD patients are going to benefit from differential dosage or from the use of an alternative drug treatment will depend on careful monitoring of the side effects and the degree of improvement observed in a particular population.

Finally, it is significant that trials with rivastigmine in patients with other neurodegenerative diseases (eg, LBD) in which cholinergic mechanisms play an important role have already started. They will provide important information on putative neuroprotective properties of rivastigmine.

Development History

DEVELOPER	COUNTRY	STATUS	INDICATION	DATE	REFERENCE
Novartis Pharma KK	Japan	C2	Alzheimers disease	13-SEP-99	339358
Novartis AG	South Korea	L	Dementia	01-OCT-98	306982
Novartis AG	New Zealand	R	Alzheimers disease	01-AUG-98	292661
Novartis AG	Argentina	R	Alzheimers disease	01-AUG-98	292661
Novartis AG	Mexico	R	Alzheimers disease	01-AUG-98	292661
Novartis AG	Western Europe	L	Alzheimers disease	25-APR-00	363944
Novartis AG	US	L	Alzheimers disease	22-JUN-00	371704

Literature classifications

Key references relating to the drug are classified according to a set of standard headings to provide a quick guide to the bibliography. These headings are as follows:

Chemistry: References which discuss synthesis and structure-activity relationships.

Biology: References which disclose aspects of the drug's pharmacology in animal models.

Metabolism: References that discuss metabolism, pharmacokinetics and toxicity.

Clinical: Reports of clinical phase studies in volunteers providing, where available, data on the following: whether the experiment is placebo-controlled or double- or single-blind; number of patients; dosage.

Chemistry

STUDY TYPE	RESULT	REFERENCE
Synthesis and SAR of racemate.	Optimum structure (of eight analogs) has best combination of brain selectivity, *in vivo* duration of action and tolerability.	241080
Synthesis and *in vitro* and AChE inhibition of enantiomers.	R-(+)-enantiomer is 5-fold weaker *in vitro* against rat striatal AChE.	241087

Biology

STUDY TYPE	EFFECT STUDIED	EXPERIMENTAL MODEL	RESULT	REFERENCE
In vivo	AChE inhibition activity.	Ischemia in gerbils.	Three 0.2 mg/kg doses of rivastigmineameliorated decrease in number of pyramidal cells.	230733
In vivo	AChE inhibition activity.	Ischemia in gerbils.	Prevented decreases in ACh levels and B_{max} of M_1 receptors.	162883
Ex vivo	AChE inhibition activity.	Normal rats.	Inhibits hippocampal and cortical AChE 10-fold more than heart.	162923
In vivo	AChE inhibition activity.	Ischemia in gerbils.	Rivastigmine (0.2 mg/kg ip) mitigated ischemia-induced abnormalities of cholinergic, dopaminergic and serontinergic systems.	162929
In vivo	AChE inhibition activity.	Hypertensive rats.	Rivastigmine (0.05 to 0.5 mg/kg) protected against ischemia-induced decreases in ACh.	230734
In vivo	AChE inhibition activity.	Basal forebrain-lesioned rats.	Rivastigmine (0.10 to 0.05 mg/kg/day) improved acquisition and retention impairment.	193504
In vivo	AChE inhibition activity.	Senescent rats.	Rivastigmine (0.1 mg/kg ip for 14 consecutive days) prevented decreases in ACh level, ChAT activity and B_{max} of M_1 receptors.	193505
In vivo	AChE inhibition activity.	Basal forebrain-lesioned rats.	Rivastigmine (0.1 to 0.2 mg/kg po) dose-dependently ameliorated the impairment of spatial memory.	160501
In vivo	Loss of working memory in delayed non-matching to position task (DNMTP).	Disruption of working memory by scopolamine in DNMTP.	Rivastigmine (0.5 mg/kg, ip) reduced working memory impairment.	367020
In vivo	Spatial memory (latency) in Morris water maze.	Close-head injury (CHI).	Rivastigmine single dose (2 mg/kg sc) allowed recovery of pretest latencies by 3 days after CHI.	289264
In vivo	Motor function.	CHI.	Rivastigmine (2 mg/kg sc) accelerated recovery of motor function by 7 and 14 days after CHI.	289264
In vivo	Cerebral edema.	CHI.	Rivastigmine (2mg/kg sc) reduced edema by at least 50%	289264
In vivo	Blood pressure, heart rate.	Freely moving rats.	Rivastigmine (iv) produced pressor effect which occurs at a much higher concentration that tacrine or physostigmine.	372440

Biology (continued)

STUDY TYPE	EFFECT STUDIED	EXPERIMENTAL MODEL	RESULT	REFERENCE
In vivo	AChE inhibition activity.	Male and female rats.	Rivastigmine (0.75 and 1.5 mg/kg) caused significantly more inhibition in females than in males in the cerebral cortex, hippocampus and striatum.	372445
In vivo	Change in extracellular ACh concentration.	Microdialysis in hippocampus of rivastigmine-treated rats.	Rivastigmine (0.625, 1.25, 2.5 mg/kg po) caused dose-dependent increases in extracellular ACh (190, 346, and 458%).	372439
In vivo	Intraocular pressure (IOP).	Topical application of rivastigmine on rabbit's eye.	Application of 1%, 2% or 5% rivastigmine reduced IOP between 15 and 23% in a dose-independent manner.	372437

Metabolism

STUDY TYPE	EFFECT STUDIED	MODEL USED	RESULT	REFERENCE
In vivo	Absorption in minipigs.	Iv (0.1 mg/kg), single oral (1 mg/kg) or topical (18 mg or 54 mg) doses of rivastigmine.	Oral: absorption $T_{\frac{1}{2}}$ = 0.83 h, ~ 93%;	367021
In vivo	Metabolism in minipigs.	Iv (0.1 mg/kg), single oral (1 mg/kg) or topical (18 mg or 54 mg) doses of rivastigmine.	Skin patch: Reduced absorption.	367021
In vivo	Elimination in minipigs.	Iv (0.1 mg/kg), single oral (1 mg/kg) or topical (18 mg or 54 mg) doses of rivastigmine.	Oral: Extensive first-pass metabolism, bioavailability = 0.5%.	367021
Phase I	Absorption (human, healthy subjects)	Oral, 3 mg dose.	Skin patch: 20 to 40-fold higher bioavailability than oral.	367022
Phase I	Metabolism and elimination (human).	Oral, 3 mg dose.	Oral: 90% in urine; half-life = 56 h	367022
Phase I	Pharmacokinetics (human).	Oral, 1 mg bid/week increments titration to target doses of 1, 2, 3, 4, 5, 6 mg.	Peak plasma concentration in 1 h > 96%; volume of distribution (apparent) between 1.8 and 2.7 l/kg.	289261

Clinical

EFFECT STUDIED	MODEL USED	RESULT	REFERENCE
CSF AChE inhibition activity; dose finding study.	18 AD patients treated po with rivastigmine 1 mg bid/week increments titration to target doses of 1, 2, 3, 4, 5, 6 mg. Phase II.	Dose dependent inhibition of AChE in CSF. The 6-mg bid group showed maximum mean inhibition of 62% at 5.6 h post-dose.	289261
Drug interactions.	Concomitant administration of rivastigmine with other drugs.	No adverse events indicative of interaction with any of 22 different therapeutic classes of drugs.	367018
Efficacy. AChE inhibition in CSF.	Eight healthy volunteers administered one dose of 3 mg rivastigmine in a phase II study.	Inhibition of AChE in CSF greater than placebo for 8.4 h; maximal (40%) at 2.4 h.	367019
Central activity.	20 Healthy males in a double-blind crossover phase I study, given single doses of placebo, 0.5, 1, 1.3, or 2 mg.	Sleep quality was not affected by the study medication; increased REM sleep density observed after 1, 1.3, and 2 mg.	3157
Tolerability.	Double-blind, placebo-controlled, randomized bridging phase II study in 50 patients with AD; 2 mg/day rivastigmine on days 1 to 3, 3 mg/day on days 4 to 7 followed by 4 to 10 mg/day for weeks 2 to 7 and 12 mg/day for weeks 8 to 9.	No maximum tolerated dose defined; 3 patients discontinued due to adverse events; up to 12 mg/day generally well tolerated with mild to moderate nausea, headache, dizziness and abdominal cramps observed.	190327
Metabolism.	Ten renally- and ten hepatically-impaired patients.	Dose adjustments not warranted.	234634
Central activity.	Six volunteers in a phase I study.	AChE selectivity inhibited in CSF.	241060

Clinical (continued)

EFFECT STUDIED	MODEL USED	RESULT	REFERENCE
Tolerability/efficacy.	402 AD patients randomized to 4 or 6 mg/day or placebo. Phase III	87% Completed on 4 mg/day; 85% on 6 mg/day.	229292
Tolerability/efficacy.	114 AD patients maintained on 6 to 12 mg/day bid or tid or placebo.	64% Completed on 12 mg/day bid; 76% for the same dose tid.	229292
Tolerability.	50 AD patients escalating from 2 to 12 mg/day bid or tid or placebo.	12 mg/day well tolerated.	209139
Efficacy.	699 AD patients on 1 to 4 or 6 to12 mg/day. Phase III.	Significant improvement over placebo in all outcome measures; 25% withdrawal due to nausea, vomiting diarrhea and dizziness.	372434
Efficacy.	725 AD patients on 1 to 4 or 6 to 12 mg/day. Phase III.	Significant improvement over placebo in all outcome measures.	372444
Acetylcholinesterase inhibition.	20 Males in a double-blind crossover study, given single doses of placebo, 0.5, 1, 1.3, or 2 mg.	Sleep quality was not affected by the study medication; increased REM sleep density observed after 1, 1.3, and 2 mg.	3157
Tolerability.	Double-blind, placebo-controlled randomized bridging study in 50 patients with AD; 2 mg/day rivastigmine on days 1 to 3, 3 mg/day on days 4 to 7 followed by 4 to 10 mg/day for weeks 2 to 7 and 12 mg/day for weeks 8 to 9.	No maximum tolerated dose defined; 3 patients discontinued due to adverse events; up to 12 mg/day generally well tolerated with mild to moderate nausea, headache, dizziness and abdominal cramps observed.	190327
Efficacy.	699 AD patients on 1 to 4 or 6 to 12 mg/day.	Significant improvement over placebo in all outcome measures; 25% withdrawal due to nausea, vomiting diarrhea and dizziness.	241071
Efficacy.	723 AD patients on 1 to 4 or 6 to 12 mg/day.	Significant improvement over placebo in all outcome measures.	227602

Associated patent

Title Phenylcarbamat.

Assignee Sandoz-Patent-Gmbh, 7850 Loerrach, De

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Inventors Enz A.

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