Rivastigmine: a review

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The acetylcholinesterase inhibitors are the first useful and useable drugs for palliative treatment of dementia of the Alzheimer type. This article reviews the second-generation carbamate cholinesterase inhibitor, rivastigmine (EXELON®, Novartis, Basel) whose distinctive pharmacology is not only of immediate clinical relevance but also the key to some tantalizing therapeutic possibilities.

For a population like that of the UK whose demographic trend is towards an increasing proportion of older adults, the domestic, social and health-care implications are considerable. About 10% of individuals over 65 years of age will develop dementia (Hofman et al, 1991), in the majority of cases caused by Alzheimer's disease (AD), generating substantial direct costs and a great deal of distress and co-morbidity among carers. The prevalence of AD and diabetes are now similar, albeit with different peak ages. Both are insidiously corrosive. Active treatment can now ameliorate the symptoms, and possibly delay the progression, of both. Diabetics are treated; those lives blighted by AD deserve no less.

AD: THE CHOLINERGIC COMPONENT

The basal forebrain nuclei, whose excitatory cholinergic neurones project to the cerebral cortex, amygdala and hippocampus, are critically, but not solely, implicated in the pathogenesis of AD. Along with the hippocampus and noradrenergic locus ceruleus, the large neurones of these nuclei degenerate in AD, progressively depriving the cerebral cortex of its cholinergic input. The behavioural effects mediated by acetylcholine (ACh) in the brain relate principally to alertness, short-term memory and learning. The reduction in ACh activity in AD adversely affects all of these and accordingly current treatment strategies are aimed at replacing or enhancing that activity.

This could theoretically be accomplished by drugs which increase either ACh production or its release, mimic its action, or, by reducing the breakdown of existing ACh, enhance the effectiveness of the activity which remains. Drugs in the last category have proved to be the most practical and promising so far. These drugs inhibit acetylcholinesterase (AChE), which otherwise metabolizes ACh extremely rapidly at the synaptic cleft. In the case of rivastigmine, this is done with considerable pharmacological elegance.

ACETYLCHOLINESTERASE INHIBITION

After ACh release, its quaternary amine group links ionically to an anionic subsite of AChE. This lines up the ester group of ACh with the esteratic subsite of the AChE molecule and results in the catalysis of ACh into choline (about half of which is recaptured by the axon terminal) and acetate. AChE can be inhibited by drug binding at either subsite (Enz and Floersheim, 1997).

The first generation AChE inhibitor, tacrine (Cognex®, Parke-Davis, Eastleigh, Hants), and the second generation inhibitor, donepezil (Aricept®, Eisai-Pfizer, London), act at the anionic subsite, forming weak ionic bonds that are quickly broken. These drugs are accordingly categorized as 'reversible' and achieve only a relatively short duration of AChE inhibition. This necessitates frequent dosing in the case of tacrine but is circumvented in the case of donepezil by its long (70 hour) plasma half-life, enabling once-daily dosage. However, this persistence of the active drug also prolongs the potential for the side-effects common to this class of drug.

The active metabolite (2,2-demethyl-dichlorovinyl phosphate, DDVP) of the organophosphate pro-drug metrifonate, on the other hand, binds irreversibly to the esteratic site, effectively inactivating the bound proportion of the enzyme until it is replaced by new enzyme,

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which is synthesized over a period of weeks. Although well tolerated overall, there has been some concern about individual instances of serious toxicity.

Like ACh itself, rivastigmine binds to both the ionic and esteratic sites. However, in the process it is quickly hydrolysed to a carbamyl moiety, which remains attached to, and continues to inactivate, the esteratic site, and an inactive phenolic residue (NAP 226-90) which is sulphated and rapidly eliminated via the kidneys. AChE is then regenerated from the AChE–carbamyl complex, over about 10 hours, by a further stage of hydrolysis of the carbamyl moiety to the inactive derivative methylethylcarbamic acid.

This distinctive mechanism means that the drug is quickly destroyed at its site of action, rapidly clearing it from the circulation and obviating the disadvantages of liver metabolism, while inhibiting AChE for a sufficiently long period to require only twice-daily dosing. The duration of enzyme inhibition is thus considerably longer than the plasma half-life of the drug itself. As the drug–enzyme complex dissociates by an initially rapid and a subsequently slower hydrolysis, its action, which is intermediate between reversible and irreversible, has been categorized as 'phasic' or 'pseudo-irreversible'.

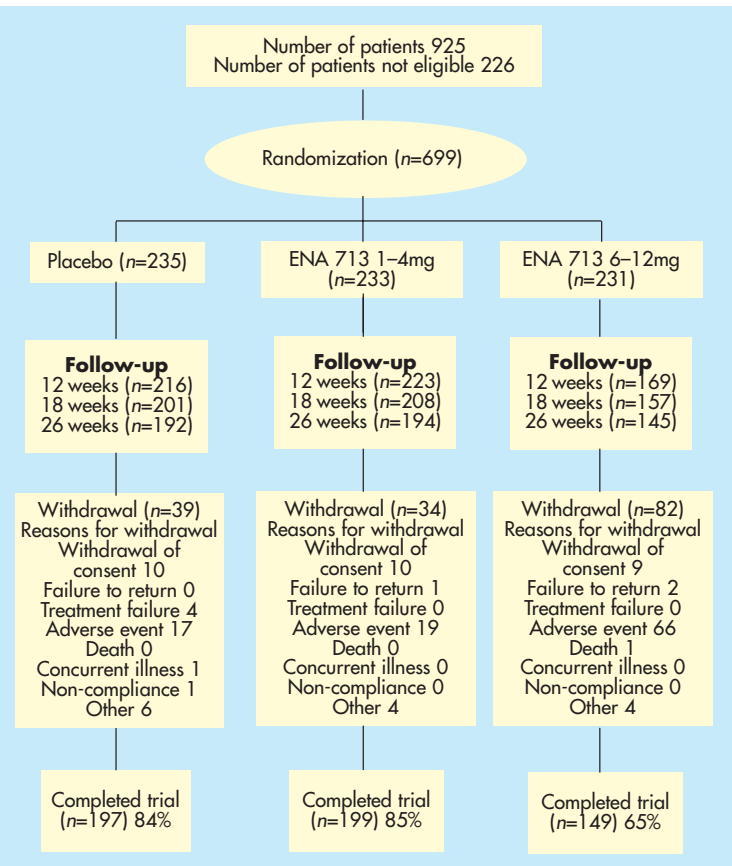

Figure 1. Patient profile of the randomized controlled trial. From Corey-Bloom et al (1998).

SELECTIVITY OF ACETYLCHOLINESTERASE INHIBITION

AChE can be inhibited selectively in the brain (as opposed to the peripheral nervous system) and preferentially within particular regions of the brain. There are similar distinctions in respect of butyrylcholinesterase (BChE), about which less is understood but whose pathophysiological role in AD is beginning to attract increasing attention. Although AChE and BChE have closely related molecular structures, they have physiologically distinct functions, different substrate specificities and differing tissue distributions.

AChE occurs in soluble form intracellularly in cholinergic axon terminals and in the CSF; BChE is present in soluble form in plasma. Evidence dating back to 1978 (Perry et al, 1978) suggests that levels of BChE increase as AD progresses, accumulating around the plaques and tangles. It may also play a significant role in the further maturation of the plaques and tangles. The distribution of BChE is brain region dependent for the hippocampus and non-hippocampal cortex. Elsewhere the catalytic units of the enzymes are tethered to cell or basement membranes by glycolipid or collagen-like strands. AChE is located at cholinergic synapses in the brain, peripherally in the parasympathetic nervous system and at neuromuscular junctions. BChE, whose distribution is not closely synaptic, occurs in many tissues other than in the brain, including skin, liver and the gastrointestinal tract.

The earlier AChE inhibitors, such as edrophonium and pyridostigmine, are non-selective but useful in the diagnosis and management of myasthenia gravis precisely because they have prominent peripheral actions, particularly at the neuromuscular junction. In this context their central effects merely contribute to their adverse event profile. Current AChE inhibitors are useful in dementia to the extent that they are brain selective; their peripheral effects are unwanted. Rivastigmine has a ten times higher affinity for the brain forms of AChE than for its peripheral forms. This may account for an incidence of cardiac and respiratory side-effects which is similar to placebo. The side-effects are mainly gastrointestinal, of mild to moderate severity and related to the phase and range of upward dose titration (Rösler et al, 1999).

Rivastigmine also displays a notable degree of regional selectivity within the brain, targeting the cortex and hippocampus (Enz et al, 1993), and areas that are particularly affected in AD. There have been no head-to-head studies between any of the current AChE inhibitors to date. However, in terms of its potential for improving cognitive functioning, rivastigmine's regional selectivity may be relevant to its having produced the highest difference, so far published, in Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-Cog) scores between placebo and active drug, at 26 weeks (Corey-Bloom et al, 1998) (*Figure 1*).

ISOFORM SELECTIVITY

AChE exists in a variety of different configurations. These include the A12 form at neuromuscular junctions and the dimeric G2 form on red blood corpuscles which, relative to donepezil, is little affected by rivastigmine, illustrating the differing peripheral affinities of these drugs. The two most important isoforms in relation to dementia are the monomeric G1 and the tetrameric G4 forms that occur in the brain. There is proportionally more of the presynaptic G4 form in the normal brain but, particularly in the neocortex and hippocampus, it declines gradually with age and more markedly in AD while the level of the postsynaptic G1 form remains more stable.

This suggests that the activity of the G1 form may become proportionally more important as AD progresses and accordingly that it may be advantageous for a drug to target the G1 form preferentially. Rivastigmine is the only AChE inhibitor which does this (Farlow and Hake, 1998). While, like tacrine and donepezil, it inhibits both forms, rivastigmine displays a 4–6-fold greater inhibition of the G1 form (Enz et al, 1992). This may have implications for its continuing efficacy later in the disease process.

ABSORPTION AND DISTRIBUTION

Rivastigmine is administered orally; there is no age-related effect on absorption. It is rapidly (t_{max} 0.8–1.2 hours) and virtually completely (96%) absorbed (Polinsky, 1998). Bioavailability is reduced by presystemic cholinesterase metabolism, the ratio of oral to intravenous area under the curve (AUC) after a 3 mg dose being 35%; steady-state conditions occur by the second dose. Taking it along with food as recommended reduces the occurrence of gastrointestinal side-effects, and incidentally increases bioavailability by 30%, probably by slowing the rate of absorption (t_{max} increased by about 1.5 hours) and lowering peak plasma levels (C_{max}). While there is no evidence of drug accumulation, plasma levels of rivastigmine and NAP-226-90 are up to 50% higher in patients with AD than in healthy volunteers.

METABOLISM AND ELIMINATION

In both healthy volunteers and patients with AD, rivastigmine is rapidly hydrolysed in the brain (plasma elimination half-life 1 hour) to the decarbamylated metabolite NAP 226-90 (maximum plasma concentration in 2 hours) which is sulphated and eliminated via the kidneys (Polinsky, 1998). Elimination of the metabolites is complete in 24 hours. The faecal residue of an administered dose is less than 1%. After a single 3 mg oral dose of rivastigmine, AChE inhibition in the CSF is significant in 1.2 hours in both healthy and AD individuals, maximal in 2.4 hours in healthy and 6 hours in AD individuals and persists for 8.5 hours in healthy and 12 hours in AD individuals; inhibition of peripheral AChE is minimal.

As protein binding of rivastigmine is low relative, for example, to donepezil (30–40%), there is little risk of affecting the levels of other drugs by competitive displacement. However, perhaps the most clinically advantageous aspect of rivastigmine's metabolism is that it occurs at its site of action in the brain. This means that it is not dependent on the declining liver CYP 450 microsomal enzyme systems of the elderly, minimizing the risk of interactions with the wide range of drugs older people tend to require for concurrent and intercurrent illness.

Tacrine is metabolized by the 1A2 system and some of the metabolites remain clinically active. This may account for its significant adverse event profile and hepatotoxicity. Similarly, donepezil has a 70-hour plasma half-life, 96% protein binding and is metabolized by the liver cytochrome enzyme systems, mainly the 2D6 and 3A4 isoforms. One of its four main metabolites (6-O-desmethyl donepezil) displays clinical activity which is similar to that of the parent drug. These features may be disadvantageous in relation to the duration of any adverse events or interactions with, for example, anaesthetic agents, particularly in relation to urgent surgery.

PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

There are real differences between healthy individuals and those with moderate to severe renal impairment in the rates of elimination of the inactive metabolite (NAP 226-90), but no mate-

rial differences in the kinetics of rivastigmine itself (Exelon summary of product characteristics, 1998, Novartis Pharma, Basel). There also appears to be some diminution in the metabolism and increase in the AUC of rivastigmine in cirrhotic patients, possibly reflecting the hormonal and physiological changes associated with cirrhosis affecting renal blood flow, tissue fluid balance, plasma protein levels and the distribution and non-metabolic aspects of drug clearance. However, neither situation requires any modification of the ordinary regimen of titration to the individual patient's maximum tolerated dose.

EFFICACY

Some clinical trials of earlier AChE inhibitors were susceptible to criticism because of either their relatively small numbers of patients or their participation criteria which excluded the sorts of patients seen in everyday clinical practice with significant co-existing illnesses. The ADENA (AD treatment with ENA-713 [rivastigmine]) trials addressed these issues by involving 3 300 patients, 78% of whom were on concurrent medication, in more than 100 centres in 10 countries (Corey-Bloom et al, 1998; Rösler et al, 1999).

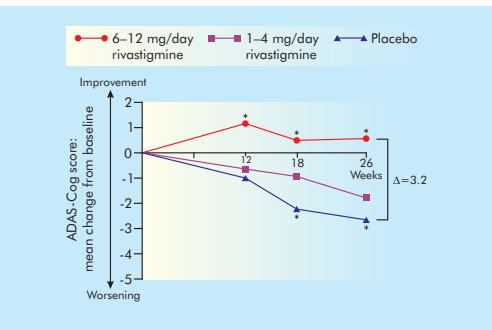

Figure 2. Mean change in baseline in Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-Cog) scores. From Schneider et al (1998).

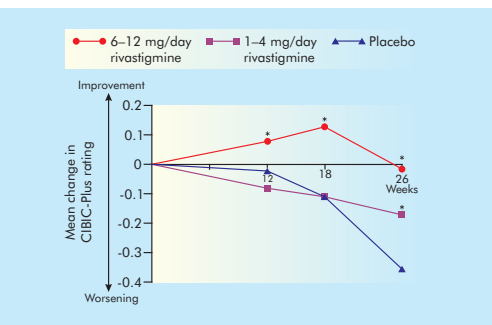

Figure 3. Mean change in baseline in Clinician's Interview Based Impression of Change — Plus (CIBC-Plus) ratings. From Schneider et al (1998).

The ADENA programme demonstrated that rivastigmine can effect significant improvement in the three main areas of functioning most affected by AD: cognition (*Figure 2*), global functioning (*Figure 3*) and activities of daily living (*Figure 4*). Patients on rivastigmine either displayed dose-related (*Figure 5*; Schneider et al, 1998) improvement or showed less deterioration relative to placebo in each of these areas over a 26-week period.

Information from a delayed start study presented at Barcelona 99: Current developments and future strategies in Alzheimer's disease suggests that, with rivastigmine, improvement can not only be effected at later and more severe stages of AD than formerly thought, but also that the improvement can actually be more pronounced, relative to projected decline (*Figure 6*). However, it also suggests that the level of improvement which can be achieved at a later stage is less than might have been maintained had treatment been started earlier.

ADMINISTRATION AND TITRATION

Because of the dose titration regimens specified by the regulatory authorities for the earlier studies, dose recommendations were initially too rigid and the rate of increase too rapid for a proportion of patients. The above studies indicate that, with an approximately linear dose–response relationship, most benefit will be derived from

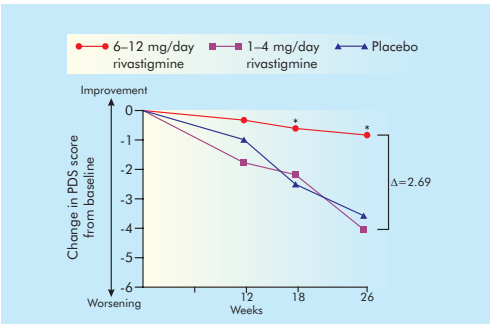

Figure 4. Mean change in baseline in mean Progressive Deterioration Scale (PDS) scores. From Schneider et al (1998).

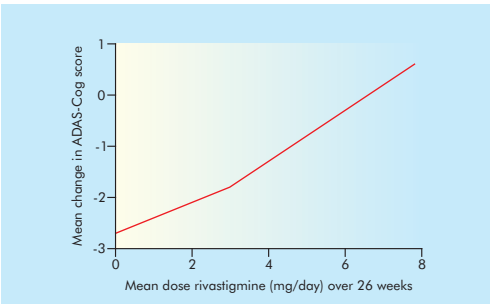

Figure 5. Dose–response relationship for rivastigmine. From Schneider et al (1998).

the highest tolerated dose of rivastigmine. With this class of drug the introduction or titration stage is the phase when cholinergic side-effects may emerge. Practical clinical experience indicates that upward titration of the dose should be individually tailored.

Starting with 1.5 mg twice daily, some patients will be able to proceed with increments of 1.5 mg (twice daily) at intervals of not less than 2 weeks to the maximum recommended dose of 6 mg twice daily. Others will avoid unwanted effects, such as vomiting or nausea, by proceeding at 4-week intervals, holding, or, if necessary, temporarily reducing, at any particular dose if there are side-effects. The drug is best given with food. A small proportion of patients may require an anti-emetic. The benefits can be such that it is worth making every effort to enable appropriate patients to have a reasonable trial.

Some patients will show the beginnings of a response at the level of 4.5 mg per day, while others may not improve objectively until a month or two after reaching their maximum tolerated dose. Experience suggests that a trial of at least 6 months is desirable before deciding on whether or not to continue treatment in any particular patient. Where improvement takes the form of stabilization or a reduction in the rate of decline this may not be as obvious as where test scores increase. Clearly, if there is obvious decline or re-acceleration on stopping, the drug should be reinstated.

FUTURE POSSIBILITIES

Rivastigmine inhibits both brain BChE and the G1 form of AChE. BChE is minimally present in the normal brain but is increased in AD and associated with a specific phase of amyloid (Aβ) protein conformation and there is evidence that G1 BChE and AChE complexes with Aβ in amyloid plaques. Accordingly, perhaps the most tantalizing possibility is that rivastigmine may be capable of exerting an inhibitory effect on this aspect of the pathophysiology of the disease itself. HM

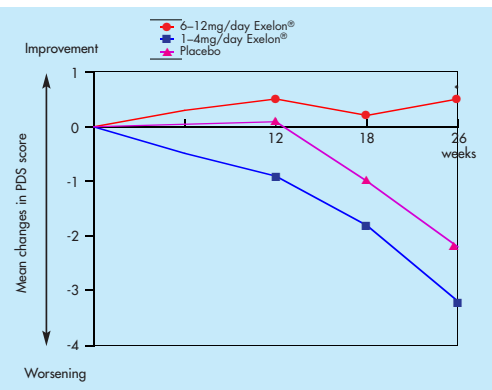

Figure 6. Benefits of rivastigmine on the activities of daily living (measured on the Progressive Deterioration Scale). From Rösler et al (1999).

Conflict of interest: Dr Sim has received hospitality and fees for lectures from Novartis.

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KEY POINTS

- Rivastigmine is a pseudo-irreversible cholinesterase inhibitor used for the palliative treatment of Alzheimer's disease.
- Unlike other acetylcholinesterase inhibitors, rivastigmine is metabolized at its site of action and not in the liver, which is important to avoid drug–drug interactions and organ toxicity in the elderly.
- Rivastigmine may be particularly useful in patients with co-existing illness.
- Rivastigmine's short plasma half-life and its very low (30–40%) protein binding may be an advantage in terms of the duration of any adverse events.
- Rivastigmine has a 10-fold greater affinity for brain than for peripheral acetylcholinesterase. It also displays significant regional and isoform selectivity within the brain.
- Rivastigmine can effect significant improvement in the three areas of function most affected in Alzheimer's disease: cognition, global functioning and activities of daily living.
- Rivastigmine may also ameliorate non-cognitive symptoms such as delusions and perceptual disturbance, particularly in Lewy body dementia.
- Four (same cost) dosage strengths allow flexible titration.