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Cholinesterase Inhibitors in the Treatment of Alzheimer's Disease

A Comparison of Tolerability and Pharmacology

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Abstract

Cholinesterase inhibitors are currently the most established treatment strategy in Alzheimer's disease. The treatment effect appears mainly to be symptomatic. Effects on progression of the disease following long term treatment, and possible neuroprotective effects, have been investigated. Delay until nursing home placement has been reported. Three cholinesterase inhibitors, tacrine, donepezil and rivastigmine, are in clinical use. Other cholinesterase inhibitors, such as galantamine (galanthamine), metrifonate, physostigmine, eptastigmine, are currently under clinical evaluation. So far the efficacy appears to be comparable between the various cholinesterase inhibitors; treatment for up to 6 months has produced an improvement in Alzheimer's Disease Assessment Scale – Cognitive Subscale score (ADAS-cog) of between 1.8 and 4.9 in patients with Alzheimer's disease.

Tacrine, donepezil, galantamine and physostigmine are reversible inhibitors of acetylcholinesterase and butyrylcholinesterase, while metrifonate is considered to be an irreversible inhibitor and rivastigmine a pseudoirreversible inhibitor. Tacrine and physostigmine have lower bioavailability, 17 to 37% and 3 to 8%, respectively, than the other cholinesterase inhibitors such as rivastigmine, galantamine and donepezil (40 to 100%). The elimination half-life is considerably longer for donepezil (70 to 80h) in comparison to most of the other cholinesterase inhibitors (0.3 to 12h). Donepezil is therefore administered once daily in comparison to rivastigmine which is administered twice daily and tacrine which is administered 4 times daily.

Simultaneous food intake lowers the plasma concentration of tacrine and reduces the adverse effects of rivastigmine. Drugs like theophylline and cimetidine have been reported to change the pharmacokinetics of tacrine and donepezil. In contrast, concomitant medication with various drugs with rivastigmine does not seem to cause any drug interactions in patients with Alzheimer's disease.Tacrine, donepezil and galantamine are metabolised via the cytochrome P450 (CYP) liver enzymes. Active metabolites are known for tacrine and galantamine. Rivastigmine is not metabolised via CYP enzymes, but via esterases and is excreted in the urine.

Tacrine is associated with hepatotoxicity while other cholinesterase inhibitors seem devoid this adverse effect. Increased liver enzyme values have been observed in 49% of patients with Alzheimer's disease treated with tacrine. Rechallenge with tacrine reduces the incidence of elevated liver enzyme levels. Peripheral cholinergic adverse effects are common for the cholinesterase inhibitors, with a n incidence ranging between 7 to 30% For some cholinesterase inhibitors, such as rivastigmine, the cholinergic adverse effects such as nausea, vomiting, dizziness, diarrhoea and abdominal pain can be reduced by slowing the rate of dose titration.

Alzheimer's disease is the most common form of dementia and represents about 40 to 60% of late onset dementia syndrome. It is a progressive and costly disease that causes suffering over a long period for both the patients and their families. The disease is characterised by memory loss and other cognitive symptoms producing occupational and social disabilities. Genetic causes have been reported to be involved in familial cases of Alzheimer's disease but the disease probably has a much more complex and heterogenous aetiology.[1,2] Although a great deal of progress has been made in recent years in further understanding the genetical aberrations as well as the pathophysio-

logical processes of Alzheimer's disease, there is still no cure for the disease.

Cognition is known to be dependent on several mental functions, such as awareness, memory, language, mental tempo and visuospatial function. It is still an open question as to whether memory can be improved by cognition-enhancing substances.

Transmitter replacement therapy is one of several possible treatment strategies; others being antiamyloid drugs, nerve growth factors, anti-inflammatory drugs, and antioxidants.[3,4] The cholinergic hypothesis claims that low levels of acetylcholine lead to cognitive decline.[5] Cholinesterase inhibitors inhibit the metabolism of acetylcholine and treatment with these drugs has so far been the most fruitful treatment strategy in Alzheimer's disease. Clinical experience with cholinesterase inhibitors, such as tacrine, indicates that these compounds have positive effects on cognitive function, especially in attention[6] and that long term treatment also has effects on primary memory, episodic memory, visuospatial ability and psychomotor speed.[7-9]

Tacrine was the first cholinesterase inhibitor to be approved for use in Alzheimer's disease (in the US in 1993 and in Europe in 1994). Modest palliative effects have been observed, as well as some slowing or arresting of the disease course.[9-11] The second cholinesterase inhibitor donepezil was approved in 1996 in the US and in 1997 in Europe, and in 1998 rivastigmine was approved in several European countries. Other cholinesterase inhibitors, including galantamine (galanthamine), metrifonate and eptastigmine, are currently under clinical evaluation.

The aim of this paper is to compare these cholinesterase inhibitors with respect to specificity of cholinesterase inhibition, pharmacokinetic properties and metabolism, efficacy, tolerability and possible drug interactions.

1. Evaluation of Drug Treatment Efficacy in Alzheimer's Disease

Because of the genetic, biological and clinical heterogeneity of Alzheimer's disease it can be assumed that a specific treatment strategy may not be helpful for all patients. Patients may show different rates of progression of deterioration during the course of the untreated disease. The disease involves changes not only in cognition but also in behaviour, social and overall global functioning. Different types of outcome measures have been used in clinical trials to evaluate improvement and measure the effect of treatment with cholinesterase inhibitors. The cognitive tests include the Mini-Mental State Examination and the Alzheimer's Disease Assessment Scale, while other scales, such as the clinician's global assessment of severity, change, behavioural ratings and functional scales, have also been used.[12] A valuable complement to these scales are studies of the functional effects of therapies on the brain as evaluated by neuropsychological measurements, electroencephalogram (EEG), and imaging techniques including positron emission tomography and single photon computed emission tomography.[13]

2. Acetylcholinesterase and Butyrylcholinesterase in the Brains of Patients with Alzheimer's Disease

Human brain cholinesterases can be divided into acetylcholinesterases and butyrylcholinesterases and these are expressed in at least 6 different molecular forms: globular monomers (G1), dimers (G2) and tetramers (G4) of catalytic subunits and asymmetric molecules with 1, 2 or 3 tetramers (A4, A8, A12) coupled to a 3-stranded collagen-like coiled structure.[14,15] The most abundant form of acetylcholinesterase is the extracellular G4 molecular form but the cytosolic G1 form is also present in a smaller amount in the brain.[16] Acetylcholinesterase has also been found in erythrocytes while high levels of butyrylcholinesterase, also known as pseudo or nonspecific cholinesterase, is found in serum.

The activity of acetylcholinesterase, and especially of the G4 form, has been reported to be decreased in the brains of patients with Alzheimer's disease.[17,18] Acetylcholinesterase has also been detected in senile plaques and neurofibrillary tan-

gles in the brains of patients with Alzheimer's disease. The G4 form of acetylcholinesterase has been suggested to be of the asymmetric type and may accelerate β-amyloid formation.[15,19] The activity of butyrylcholinesterase has been reported to be increased in the brains of patients with Alzheimer's disease[17] as a consequence of reactive gliosis and accumulation of butyrylcholinesterase on neuritic plaques.[20]

Acetylcholinesterase levels in the ventricular or lumbar cerebrospinal fluid (CSF) are lower in patients with Alzheimer's disease compared with age-matched controls.[21,22] An anomalous molecular form of acetylcholinesterase has been found in the CSF of patients with Alzheimer's disease which is a possible indication of changes in acetylcholinesterase at the molecular level.[23] Since the CSF anomalous acetylcholinesterase has also been found in individuals without dementia, it has been speculated that this molecular form of acetylcholinesterase may be present in CSF before clinical signs of dementia are observed.[24] This finding may also explain the overlap in acetylcholinesterase activity in CSF seen between individuals with and without dementia.[25]

Recently, attempts have been made to visualise acetylcholinesterase activity *in vivo* using imaging techniques. Pappata et al.,[26] using ^{11}C-physostigmine and positron emission tomography, showed a regional distribution of acetylcholinesterase in the human brain. Recently, by using ^{11}C-*N*-methyl-4-piperidyl acetate, Iyo et al.[27] demonstrated reduced acetylcholinesterase activity *in vivo* in patients with Alzheimer's disease, especially in cortical brain regions, compared with control individuals.

3. Molecular and Functional Properties of Cholinesterase Inhibitors

The different molecular structures of various cholinesterase inhibitors (fig. 1) make them differently selective for acetylcholinesterase and butyrylcholinesterase. Tacrine and physostigmine have demonstrated reasonably equal potency for inhibiting acetylcholinesterase compared with inhibiting butyrylcholinesterase and are therefore considered as rather unselective cholinesterase inhibitors. Other cholinesterase inhibitors, including donepezil and rivastigmine, appear to be more selective for acetylcholinesterase compared with butyrylcholinesterase (table I). The cholinesterase inhibitors can also be characterised as reversible, e.g. donepezil, tacrine and galantamine, or irreversible, e.g. metrifonate, as well as competitive, e.g. galantamine, or noncompetitive, e.g. tacrine and donepezil, in nature.

The strategy behind using cholinesterase inhibitors for Alzheimer's disease is to improve cholinergic synaptic function by elevating the acetylcholine content of the synaptic cleft and thereby augmenting the function of the cholinergic receptors. *In vitro* studies have indicated that cholinesterase inhibitors such as physostigmine and tacrine can enhance the potassium-induced acetylcholine release from cortical tissue slices taken at autopsy from patients who had had Alzheimer's disease.[28] Interestingly, the release of acetylcholine was decreased in autopsy brain tissue from patients without Alzheimer's disease in the presence of similar concentrations of the cholinesterase inhibitors.[28] This finding illustrates that the effect of cholinesterase inhibitors can be different in the brains of healthy individuals and patients with Alzheimer's disease.

Depending on the amount of acetylcholine in the synaptic cleft, an increase or decrease of the level of the transmitter can be obtained in the presence of cholinesterase inhibitors.[29] Low levels of acetylcholine present in the synaptic cleft (as is the case in patients with Alzheimer's disease) trigger the facilitatory presynaptic muscarinic M_1 receptors to increase the release of acetylcholine into the synaptic cleft.[29]

Tacrine has been shown to have a variety of pharmacological actions including inhibition of the uptake as well as increase in the release of several neurotransmitters, increase in the synthesis of acetylcholine and directly binds to muscarinic and nicotinic receptors and ion channels.[30] Whether these various pharmacological effects are exerted

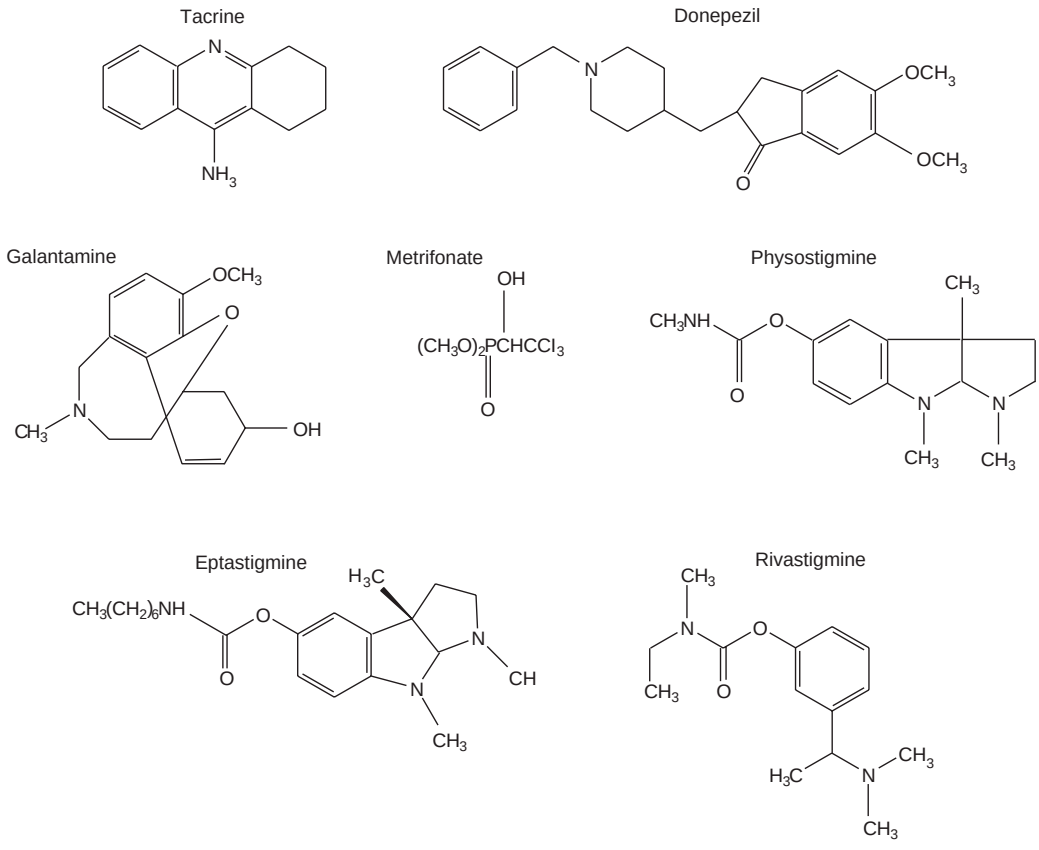

Fig. 1. Chemical structures of cholinesterase inhibitors tacrine, donepezil, galantamine (galanthamine), metrifonate, physostigmine, eptastigmine and rivastigmine.

by other cholinesterase inhibitors has not been explored extensively. Physostigmine has demonstrated less affinity for muscarinic and nicotinic receptors than tacrine.[28] Interestingly, several cholinesterase inhibitors, including tacrine, galantamine and donepezil, have been shown to bind to an allosteric site on the nicotinic acetylcholine receptor and this may be of importance for clinical efficacy.[31-33]

Increasing levels of acetylcholine due to cholinesterase inhibition may regulate in the formation of amyloid precursor proteins. Studies in animals and cell lines indicate that treatment with different cholinesterase inhibitors including tacrine, physostigmine, eptastigmine and metrifonate can enhance the release of non-amyloidogenic derivatives of amyloid precursor protein and prevent β-amyloid accumulation.[34-38] Both tacrine and donepezil have been found to attenuate β-amyloid neurotoxicity in cell lines.[38]

4. Tacrine

Tacrine causes an allosteric reversible inhibition of acetylcholinesterase and butyrylcholinesterase by interacting with a hydrophobic region near the anionic α and γ site of the enzyme.[39] A 60% inhibition of acetylcholinesterase in red blood cells and a 40% inhibition of cholinesterase in plasma were measured in patients receiving tacrine 160 mg/day,[40] the highest recommended clinical daily dose.

4.1 Pharmacokinetics

The pharmacokinetic properties of tacrine have been studied following the administration of a single dose and after long term treatment.[40-48] Interindividual variations in tacrine pharmacokinetic parameters have been reported.[30] The bioavailability of tacrine has been found to range from 17 to 37%[41,43,45,48] (table II). Time to reach maximal plasma concentration (t_{max}) in the blood was 1 to 2 hours following oral administration of tacrine 10 to 50mg to patients with Alzheimer's disease.[40,43-46] The absorption is decreased by concomitant intake of food. The elimination half-life for tacrine is 1.3 to 7 hours in patients with Alzheimer's disease.[40,41,43,45]

A positive correlation has been observed between tacrine concentration and cholinesterase inhibition in plasma.[40] The therapeutic window for tacrine has been suggested to range between 7.5 and 20 μg/L.[49] Tacrine has been shown to be 75% bound to plasma albumin. It is metabolised in the liver by the cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP11D6 and 5 metabolites have been found in serum and urine.[30,50] The major metabolite is 1-hydroxy-tacrine, which is present in plasma and CSF at a concentration that is 10 times higher than that of tacrine.[9] This metabolite can inhibit cholinesterase and exerts clinical effects on its own.[51]

Higher plasma concentrations of tacrine have been reported in women[49] compared with men. This difference might be due to the lower activity of the CYP1A2 isoenzyme in women. A lower tacrine concentration has been reported in smokers compared with nonsmokers and this might be explained by the fact that smoking induces CYP1A2 activity.[50]

4.2 Administration Regimens

Tacrine is usually administrated 4 times daily starting at an initial dosage of 40 mg/day and increased every 6 weeks up to a maximal dosage of 160 mg/day. New labelling for the agent indicates that the dosage of tacrine can be increased after 4 weeks at each dosage level. Since some patients may not be able to tolerate the highest dosage of tacrine, titration to their maximum tolerated dosage is recommended.[50,52]

4.3 Interactions

Theophylline is metabolised via CYP1A2 and concomitant administration of tacrine and theophylline results in a 2-fold increase in theophylline concentration.[30,50] Cimetidine inhibits the metabolism of tacrine in the elderly and increases the plasma concentration of tacrine.[30,50]

Table I. A comparison of cholinesterase inhibition and percent of cholinergic adverse events between different cholinesterase inhibitors (see sections 3 to 11 for details and references)

Cholinesterase inhibitors	Cholinesterase inhibition (AChE vs BuChE)	Maximal inhibition of RBC AChE (%)	RBC AChE inhibition (%) achieved with therapeutic dosages	Administration (times/day)	Cholinergic adverse events (% of treated patients)
Tacrine	BuChE = AChE	60	30	4	10-30
Donepezil	AChE >> BuChE	90	64	1	10
Galanthamine	AChE > BuChE	30-60		3	4-20
Metrifonate	AChE = BuChE	62-72	50-70	1	7-18
Physostigmine	AChE > BuChE	70		2	7-40
Eptastigmine	BuChE = AChE	18-44	38	2 or 3	34
Rivastigmine	AChE > BuChE	40[a]		2	<20

a 62% CSF AChE inhibition.

AChE = acetylcholinesterase; **BuChE** = butyrylcholinesterase; **RBC** = red blood cell; **=** = equal inhibition; **>** = stronger inhibition; **>>** = much stronger inhibition.

Table II. Pharmacokinetic profile of different cholinesterase inhibitors in patients with Alzheimer's disease (see sections 3 to 11 for details and references)

Cholinesterase inhibitor	Bioavailability (%)	t_{max} (h)	Elimination $t_{1/2}$ (h)	Effect of food	Metabolism	Excreted via urine (%)
Tacrine	17-37	1-2	1.3-7	Yes	CYP1A2, CYP2D6 (5 metabolites, 1 of which is active)	<3
Donepezil	100	3-5	70-80	None	CYP2D6, CYP3A4	17
Galantamine (galanthamine)	85	1	6	NDA	CYP2D6 (4 metabolites, 1 of which is active)	50[a]
Metrifonate	NDA	0.5	2.3	NDA	Not via CYP450	80
Physostigmine[b]	3-8	0.6	0.3	NDA	Not via CYP450	NDA
Eptastigmine	NDA	1-1.4	12.1	NDA	NDA	NDA
Rivastigmine	40	0.5-2	0.6-2	Yes	Not via CYP450 (1 metabolite)	Mainly (via the metabolite NAP 226-90)

a 25% unchanged and 25% metabolised.

b Healthy volunteers; no data available for patients with Alzheimer's disease.

CYP = cytochrome P450; **NDA** = no data available; t_{max} = time to reach maximum concentration; $t_{1/2}$ = half-life;

4.4 Adverse Effects

4.4.1 Liver Toxicity

The most important adverse effect of tacrine is liver toxicity. The hepatotoxic effects of tacrine have been reviewed by Watkins et al.[53] who summarised data from 6 multicentre trials involving 2446 patients. Increases in serum alanine aminotransferase (ALT) levels occurred in 49% of patients with Alzheimer's disease treated with tacrine.[53] The ALT level increased to 3 times the upper limit of normal in 25% of the patients; 8% of the patients had ALT values that were 10 or more times the upper limit of normal. However, this increase in ALT level is mainly asymptomatic, although fatigue, fever and eosinophilia occurred more frequently in patients with ALT levels 10 or more times the upper level of normal. Three patients underwent liver biopsies, which showed lobular hepatitis. The mean interval from initiation of tacrine treatment to ALT level elevations to 3 times the upper limit of normal was 50 days and the ALT levels increased mainly during the first 12 weeks of treatment. When patients were rechallenged with tacrine, 30% of them experienced another increase in ALT levels.[53] 72% of patients who did not experience an elevation in ALT levels following rechallenge were found to be able to tolerate higher dosages than those that caused the initial increase in ALT levels.[53]

4.4.2 Other Adverse Effects

Relatively higher plasma concentrations of tacrine have been reported in patients developing adverse effects related to tacrine.[49] The most common adverse events experienced by patients with Alzheimer's disease receiving tacrine relate to the gastrointestinal system. In a randomised, controlled trial of tacrine in patients with 410 Alzheimer's disease, nausea and vomiting were experienced by 35% of patients, diarrhoea by 18%, anorexia by 12%, dyspepsia by 11% and abdominal pain by 9%, following 30 weeks of treatment with tacrine 80 to 160 mg/day.[52] Of the patients, 16% withdrew from the study because of gastrointestinal complaints.[52] The gastrointestinal adverse effects of tacrine can be somewhat diminished by concomitant administration of food.

The safety of tacrine, as observed in 2706 patients with Alzheimer's disease in clinical trials and 9861 patients with Alzheimer's disease in a treatment investigational new drug (TIND) programme, was recently overviewed.[54] 398/2706 (15%) patients who had been treated with tacrine experienced an adverse effect that was classified as serious. 461 (17%) patients were withdrawn from treatment due to adverse effects and transaminase level elevations accounted for almost half of these withdrawals. 24% of the patients (2404 patients) in the TIND programme were withdrawn from treatment. 10% of the TIND patients were withdrawn

from treatment due to elevations in ALT levels, 6% for symptoms due to involvement of digestive systems and 6% related to CNS effects including agitation, confusion, hallucinations. 3% of patients (81 patients) in the TIND programme died, but only 2 of the 81 deaths were considered possibly related to tacrine treatment.

5. Donepezil

Donepezil is a reversible specific piperidine acetylcholinesterase inhibitor that primarily has a noncompetitive inhibitory action but also has some competitive characteristics (mixed inhibitor).[55,56]

5.1 Pharmacokinetics

The pharmacokinetic properties of donepezil have been studied following administration of a single dose and t_{max} was found to be 3 to 5 hours (table II).[57,58] Maximal plasma concentrations of 9.1 and 25.6 μg/L were obtained following administration of single oral doses of donepezil 5 and 10mg, respectively. Steady-state concentrations were obtained following 15 days of treatment.[58] When donepezil was administered in dosages of 3 or 5mg once daily for 21 days the plasma concentrations were 18.2 and 30.2 μg/L, respectively.[57,59]

The inhibition of red blood cell acetylcholinesterase by 64% was reported following 6 weeks treatment with donepezil 5 mg/day while the corresponding inhibition with 10 mg/day was 77%.[60] During long term treatment with donepezil for 192 weeks, acetylcholinesterase inhibition up to 90% was measured at a plasma concentration of 75 μg/L[61] following administration of donepezil 10 mg/day.

The elimination half-life of donepezil has been estimated to be 70 to 80 hours[59] and the mean apparent plasma clearance has been estimated at 0.13 L/h/kg. A longer half-life of donepezil has been observed in the elderly compared with young adults although no difference in pharmacokinetics was observed between healthy older volunteers and patients with Alzheimer's disease.[58,59,62]

Donepezil is extensively bound to proteins (96%) with 75% bound to albumin and 21% bound to α_1-acid glycoproteins.[58] Donepezil is metabolised by CYP2D6 and CYP3A4 and glucuronidised with about 17% of the dose excreted unchanged in the urine.[58]

5.2 Administration Regimens

Donepezil is recommended to be given once daily, initially at a dose of 5mg for at least 4 to 6 weeks. Thereafter, the dosage can be increased to 10 mg/day.

5.3 Interactions

No effect of food on the absorption of donepezil has been reported. Administration of cimetidine, digoxin, theophylline or warfarin has not been found to significantly change the pharmacokinetics of donepezil.[59] Donepezil 0.3 to 10 mg/L has not been found to influence the *in vitro* binding of furosemide (frusemide) 5 mg/L, digoxin 2 μg/L or warfarin 3 mg/L, to albumin. It is possible that inducers of CYP2D6 and CYP3A4, for example phenytoin, carbamazepine, dexamethasone, rifampicin and phenobarbital (phenobarbitone), may potentially increase the elimination of donepezil, but more studies need to be performed to clarify this issue.[58] The outcome of donepezil treatment in patients with deficiencies of the isoenzymes CYP2D6 and CYP3A4 is unknown.

5.4 Adverse Effects

Donepezil shows cholinergic adverse effects and the most frequent adverse effects related to donepezil are gastrointestinal adverse effects and dizziness. No liver toxicity has been reported following up to 192 weeks of donepezil treatment.[61] The most common adverse events seen in a 24-week, double-blind, placebo-controlled trial of donepezil 10 mg/day in 316 patients with Alzheimer's disease were nausea (experienced by 17% of donepezil recipients versus 4% of placebo recipients), diarrhoea (17 versus 7%), gastric upset (10 versus 2%), dizziness (8 versus 4%), muscle

cramps (8 versus 1%).[60] The frequency of adverse effects of donepezil was generally lower at the 5 mg/day dosage (diarrhoea 9%, nausea 4%, vomiting 3%, dizziness 10%, muscle cramps 6%). In an open study of donepezil up to 10 mg/day in 133 patients with mild to moderate Alzheimer's disease administered for 192 weeks, 83% of the patients experienced adverse events that were mainly of a mild and transient nature on at least one occasion.[61] However, 79% of these events were considered not to be related to donepezil but to be related to the patient's underlying Alzheimer's disease.

6. Galantamine (Galanthamine)

Galantamine is a phenanthrene alkaloid similar to codeine which was isolated from the European daffodil or common snowdrop, *Galanthus nivalis*. Galantamine is a reversible inhibitor of acetylcholinesterase with a competitive action. This means that the degree of inhibition caused by galantamine does not depend on the absolute concentration of the agent but more on the relationship between the inhibitor and the substrate concentration. 30 to 60% inhibition of red blood cell acetylcholinesterase is obtained 30 to 45 minutes following oral doses of galantamine, and the inhibitory effect of galantamine on red blood cell acetylcholinesterase is greater than its effect on butyrylcholinesterase (table I).[63]

6.1 Pharmacokinetics and Dosage

Galantamine is readily absorbed after oral administration with a bioavailability of 85% (table II). Following oral administration, t_{max} is 52 minutes with a plasma elimination half-life of 5.7 hours and a total plasma clearance of 0.34 L/h/kg in young healthy volunteers.[64] A 30% lower plasma half-life and clearance was observed in patients with Alzheimer's disease.[64] A positive correlation has been observed between the concentration of galantamine in red blood cells and acetylcholinesterase inhibition.[63] Galantamine does not bind to plasma proteins.[64]

Sanguinine (*O*-demethyl-galantamine) is a metabolite of galantamine formed by CYP2D6 and it can account for up to 20% of administered galantamine.[63] Interestingly, sanguinine has been reported to be 3 times more potent than galantamine as an acetylcholinesterase inhibitor.[63] 50% of the administered dose of galantamine has been found in urine 72 hours after administration; 25% is excreted unchanged and 25% is metabolised (table II).[64]

A galantamine dosage of 10mg 3 times daily is recommended.

6.2 Adverse Effects

No liver toxicity has been reported with galantamine. Nausea was reported to occur in 21, 29 and 63% of 141 patients with Alzheimer's disease who were receiving galantamine 29.4, 34.7 and 37.9 mg/day for 13 weeks, respectively.[65] Other symptoms such as diarrhoea, abdominal cramp and anorexia were observed in less than 4% of the patients.[65]

7. Metrifonate

Metrifonate is a prodrug of dichlorvos (2,2-dichlorvinyl dimethyl phosphate or DVVP) and undergoes spontaneous dehydrochlorination.[66] Metrifonate is an irreversible acetylcholinesterase inhibitor with a biphasic effect. Initially, it interacts competitively with the enzyme and then this changes to noncompetitive inhibition with progressive phosphorylation of the enzyme esteratic site.[67] Metrifonate can be characterised as a pseudoirreversible cholinesterase inhibitor. It inhibits both acetylcholinesterase and butyrylcholinesterase[68] to a similar extent.[69]

7.1 Pharmacokinetics and Dosage

Metrifonate is readily absorbed after oral administration. Following administration of a single dose of 7.5 mg/kg to patients with Alzheimer's disease, t_{max} was 26 minutes.[70] An elimination half-life of 2.3 hours with an apparent oral clearance of 0.34 L/h/kg has been obtained for metrifonate in

healthy volunteers, with similar estimations in patients with Alzheimer's disease.[70,71] It is estimated that 2% of metrifonate reaches the brain as dichlorvos.[71] Red blood cell acetylcholinesterase was inhibited by 62 to 72% following 28 days of treatment with metrifonate at a maintenance dosage of 0.4 to 0.7 mg/day in patients with Alzheimer's disease.[68] Recently Becker et al.[69] reported a 60% inhibition of red blood cell acetylcholinesterase and plasma butyrylcholinesterase following 6 months' treatment with metrifonate. Acetylcholinesterase in CSF was reported to be inhibited by 37 and 47% in 2 patients with Alzheimer's disease following administration of metrifonate 5 mg/kg/week.[72] Metrifonate is mainly eliminated via the urine (80%).[68]

Metrifonate is given orally once daily. The maintenance dosage has been estimated to be 0.64 mg/kg/day.[68]

7.2 Adverse Effects

Metrifonate is hydrolysed to an active compound and has been shown to interact with the CYP system. No liver function abnormalities have been reported for metrifonate.

Nausea, vomiting, abdominal discomfort, diarrhoea, weakness and leg cramps have been reported following treatment with metrifonate.[68] In a double-blind, placebo-controlled study, involving 273 patients treated with metrifonate 0.65 mg/kg/day and 135 placebo patients treated for 26 weeks, 12% of metrifonate-treated patients discontinued treatment because of adverse effects compared with 4% of placebo-treated patients.[73] Adverse effects following metrifonate treatment were considered mild to moderate in intensity and the occurrence of adverse events was 7 to 18% in the metrifonate-treated group compared with 1 to 8% in the placebo-treated group.[73] No correlation has been observed between adverse events and acetylcholinesterase inhibition.[68]

Diarrhoea was the most common adverse effect (experienced by 18% of metrifonate recipients) and this effect was assumed to be caused by overstimulation of the intestinal muscarinic receptors. Leg cramps were experienced by 9% of metrifonate recipients and they were assumed to occur because of excessive activation of nicotinic receptors at the neuromuscular junction.[73] Interestingly, polyneuropathy has been reported in patients after exposure to large doses of metrifonate taken accidentally or intentionally.[74] An experimental study with cholinesterase inhibitor intoxication has indicated that the contractions of the trachea requires inhibition of both acetylcholinesterase and butyrylcholinesterase.[75] Since some patients in clinical trials with metrifonate have experienced muscle weakness, the manufacturer of metrifonate, Bayer, has recently suspended phase III trials of this agent.[76]

8. Physostigmine

Physostigmine is a tertiary amine with lipophilic properties which acts as a reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase.

8.1 Pharmacokinetics and Administration

The pharmacokinetic properties of physostigmine following oral administration are characterised by high first-pass metabolism and a short elimination half-life which restricts its therapeutic use.[77] Physostigmine is available as controlled-release tablets and transdermal systems have been developed.[78,79] Following the intravenous infusion of physostigmine salicylate 2mg to healthy young volunteers t_{max} was 4.2 hours, plasma half-life was 0.5 hours and elimination clearance was 5.7 L/min.[79] Corresponding values for oral solution and transdermal patches (containing physostigmine 30mg base) were t_{max} 0.6 and 14.1 hours, and plasma half life of 0.3 and 4.9 hours, respectively.[79]

Physostigmine has been reported to cause an inhibition of acetylcholinesterase of up to 70% in red blood cells.[80] Physostigmine is known to be rapidly metabolised by nonspecific esterases in blood[81] and the absolute bioavailability has been estimated to be 3 to 8%.[79,82]

Controlled-release physostigmine salicylate 12mg is given orally twice daily.[78]

8.2 Adverse Effects

Physostigmine has not been reported to produce hepatotoxicity.[78] Nausea and vomiting was reported in 40% of 183 patients with Alzheimer's disease treated with physostigmine salicylate 10 to 30mg for 10 weeks in a double-blind, placebo-controlled study.[78] Other adverse events experienced by physostigmine-treated patients in this study were diarrhoea (12.6% of patients), anorexia (10.9%) and dizziness (10.9%); these effects occurred in 1 to 4% of placebo-treated patients.

9. Eptastigmine

Eptastigmine (heptylphysostigmine) is a carbamate derivative of physostigmine which reversibly inhibits acetylcholinesterase and butyrylcholinesterase (table I).

9.1 Pharmacokinetics and Administration

The plasma concentration of eptastigmine increased in a dose-related manner following administration of single doses of eptastigmine 10 to 30mg.[83] Following administration of a single dose of eptastigmine t_{max} was found to be 1 to 1.4 hours and the peak concentration was 0.86 μg/L.[83,84] The distribution half-life was 0.44 hours in elderly volunteers receiving an oral dose of eptastigmine 30mg and the elimination half-life was found to be 12.1 hours.[84]

Peak enzyme inhibition of acetylcholinesterase in red blood cells (15 to 35%) was obtained 3 to 3.6 hours after oral administration of a single dose of eptastigmine 10 to 30mg.[85] Oral administration of eptastigmine 12 to 28mg 3 times daily for 14 days resulted in a 18 to 44% inhibition of acetylcholinesterase.[86] Plasma concentration of eptastigmine was found to be inversely correlated to the acetylcholinesterase activity in red blood cells but not to butyrylcholinesterase activity in the plasma.[84]

In clinical trials, eptastigmine has been administered orally at a dosage of 30 to 60 mg/day given in 2 or 3 divided doses.

9.2 Adverse Effects

No hepatotoxicity is known to occur with eptastigmine. 34% of patients with Alzheimer's disease treated with eptastigmine 40 or 60 mg/day for 4 weeks reported adverse events mainly of a cholinergic nature such as nausea, vomiting, bradycardia and ventricular extrasystoles.[87] In these patients, the inhibition of acetylcholinesterase in red blood cells at steady state was high (70%).[87]

A decrease in the number of neutrophils in peripheral blood was reported in 10 patients treated with eptastigmine 30 to 45 mg/day for 25 weeks compared with 1 patient in the placebo group.[83]

Recently, the manufacturer of eptastigmine suspended all clinical development studies involving this agent because 2 patients in a clinical trial involving 2000 patients developed aplastic anaemia.[88]

10. Rivastigmine

Rivastigmine is considered a 'pseudoirreversible' acetylcholinesterase inhibitor that forms a carbamoylated complex with the enzyme.[89] Rivastigmine has been reported to selectively inhibit acetylcholinesterase rather than butyrylcholinesterase in the brain.[89] Recently, Cutler et al.[90] observed that rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase in the CSF to a similar extent.

10.1 Pharmacokinetics and Administration

Rivastigmine is rapidly absorbed following oral administration with a t_{max} of 0.5 to 2 hours.[91] Rivastigmine is 40% bound to plasma proteins and rapidly eliminated (elimination half-life 0.6 to 2 hours).[90,91] Administration of the drug after intake of food has been reported to reduce t_{max} by 30%.[92] Medication given concomitantly to patients with Alzheimer's disease including antacids,

β-blockers, calcium antagonists, estrogens, antianginals, benzodiazepines and antidiabetics have not shown any interactions with rivastigmine. Rivastigmine has been reported to selectively inhibit the G1 isozyme of acetylcholinesterase in brain.[93] An oral dose of rivastigmine 3mg was observed to inhibit acetylcholinesterase in CSF by 40% with minimal effect on cholinesterase in the plasma.[94] Rivastigmine is rapidly metabolised and one metabolite, named NAP 226-90, has been found in the CSF, plasma and urine.[95] As the metabolite of rivastigmine appears to be reduced in patients with renal and mild to moderate hepatic impairment, dosage recommendations to titrate according to individual tolerability should be closely followed in these patients.[95] Rivastigmine is inactivated by cleavage to a phenolic product during the process of inhibiting acetylcholinesterase and is excreted via the kidneys.[92]

Clinical studies have shown that the best maintenance dose for rivastigmine is 6 to 12 mg/day given as 2 divided doses.[91]

10.2 Adverse Effects

Rivastigmine is not metabolised via the CYP system and to date no hepatotoxicity has been observed. Treatment with the maximal dosage of rivastigmine of 12 mg/day to 235 patients with Alzheimer's disease for 26 weeks resulted in adverse events in <20% of patients. Those that were observed were nausea (20%), vomiting (16%), dizziness (14%) and dyspepsia (5%).[96] When the data from 3006 patients treated with rivastigmine and 985 patients treated with placebo were summarised regarding adverse effects, it was observed that the most common adverse effect was nausea (40% in the treatment group versus 10% in the placebo group) followed by vomiting (24 versus 7%), dizziness (20 versus 10%).[95] The cholinergic adverse effects correlated better to the metabolite NAP-226-90 than to the mother compound. Similarly the area under the curve (AUC) of acetylcholinesterase activity was most closely correlated with the CSF AUC of the metabolite. When the dose titration is performed slowly and the drug is given together with food, less adverse effects are observed.[95]

11. Clinical Efficacy of Cholinesterase Inhibitors in Alzheimer's Disease

The clinical efficacy of the different cholinesterase inhibitors in Alzheimer's disease cannot be compared directly across trials since each trial used slightly different entry criteria and different populations, were performed at different centres and sometimes also used different outcome assessments. Thus, a direct comparison of the efficacy of the different cholinesterase inhibitors is impossible except in head to head clinical trials.

The cholinesterase inhibitors generally appear to produce symptomatic effects in patients with Alzheimer's disease following different lengths of treatment (table III). The clinical efficacy in drug trials has revealed an improvement in the Alzheimer's Disease Assessment Scale – Cognitive Subscale score (ADAS-cog) varying between 1.8 to 4.9 points compared with placebo (table III). The cholinestesterase inhibitors appear to have effect on cognition but also beneficial effects on behavioural abnormalities, including apathy, anxiety and delusions.[97]

A significant correlation has been reported between change in ADAS-cog and acetylcholinesterase inhibition in red blood cells.[62] The maximal inhibition of acetylcholinesterase for various cholinesterase inhibitors ranges between 40 to 90% (table I). Cholinesterase inhibitors causing mild peripheral cholinergic adverse effects are used in therapeutic dosages that cause greater acetylcholinesterase inhibition in red blood cells (50 to 70%) than those with pronounced peripheral adverse effects (30%). For some of the cholinesterase inhibitors, e.g. physostigmine, eptastigmine and metrifonate an inverse U-shaped relationship between acetylcholinesterase inhibition and cognitive effect has been reported.[98] Thus eptastigmine has been shown to have maximal clinical efficacy at 40% red blood cell acetylcholinesterase inhibition.[99] In preclinical studies, tacrine also has been shown to have a U-shaped dose-response[29,30]

Table III. A comparison of the clinical efficacy of different cholinesterase inhibitors in patients with Alzheimer's disease (intention-to-treat/evaluable patient analysis results)

Cholinesterase inhibitor	Daily dose	Length of treatment	ADAS-cog points difference from placebo	Reference
Tacrine	80mg	12 wks	3.8	54
	160mg	30 wks	4.1	52
Donepezil	5mg	24 wks	2.5	60
	10mg	24 wks	2.9	60
Galantamine (galanthamine)	20-50mg	13 wks	3.1	65
Metrifonate	0.65 mg/kg	26 wks	2.9	73
Physostigmine	18-30mg	6 wks	1.8	78
Eptastigmine	40-60mg	25 wks	2.0	83
Rivastigmine	1-4mg	26 wks	1.9	96
	6-12mg	26 wks	4.9	95, 96

ADAS-cog = Alzheimer's Disease Assessment Scale – Cognitive Subscale score.

which may be difficult to observe clinically since the peripheral adverse effects limit the use of higher doses.

There is support for existence of persistent long term effects of cholinesterase inhibitors and that treatment with cholinesterase inhibitors may delay nursing home placement.[4,61] The outcome of treatment may have significant importance for both patient and care-giver. However, additional long term studies need to be performed using several cholinesterase inhibitors and focusing on both clinical effects and tolerability aspects in patients with Alzheimer's disease. Of interest for future study are additional indications for the use of cholinesterase inhibitors, for example the possible treatment of acute confusion in elderly.

12. Conclusions

Three cholinesterase inhibitors, tacrine, donepezil and rivastigmine, have been approved for use in Alzheimer's disease in Europe and two, tacrine and donepezil have been approved in the US. They differ in their risk of liver toxicity and peripheral adverse effects while the clinical efficacy has been found to be similar. Some other cholinesterase inhibitors are presently undergoing clinical evaluation and probably 2 to 3 additional agents will soon come into clinical use in the treatment of Alzheimer's disease.

It is reasonable to assume that cholinesterase inhibitors with few adverse effects and long half-lives, allowing once or twice daily administration, will be preferred in the future by the clinicians. So far, the different cholinesterase inhibitors appear rather consistent regarding effect size on cognitive measures. It has been noted that the degree of cholinesterase inhibition is not always directly correlated to the outcome treatment effect. The possibility of tolerance phenomena regarding cholinesterase inhibition following longer term treatment (i.e. in the order of years) has yet to be evaluated. Signs of upregulation of the acetylcholinesterase enzyme after long term cholinesterase inhibitor treatment have been observed in patients with Alzheimer's disease treated with tacrine (A. Nordberg, unpublished observations). The enhanced acetylcholinesterase activity in the CSF of patients with Alzheimer's disease after 12 months of tacrine treatment is supported by experimental data suggesting that exposure to cholinesterase inhibitors increases acetylcholinesterase gene expression.[100,101]

Drug monitoring, including measurements of plasma levels and cholinesterase inhibition in blood and possibly the CSF, as well as the risk of drug interactions have to be further investigated. These factors may play an important role when choosing between cholinesterase inhibitors.

The prospects for new treatment strategies in Alzheimer's disease have brightened considerably during the recent years. Although existing therapy is still mainly considered as a symptomatic therapy with palliative effects on existing cognitive disturbances it might also have some effects on progression of the disease. Before a curative or preventive treatment strategy is available for Alzheimer's disease the development of cholinesterase inhibitors with optimal efficacy and tolerability must be encouraged.

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