Present and future of cholinesterase inhibitors in the treatment of Alzheimer's disease

Sedanjost in prihodnost inhibitorjev holinesteraze v zdravljenju Alzheimerjeve bolezni

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Abstract

Presently, cholinesterase inhibitors (CHEIs) represent the drug of choice for the treatment of Alzheimer's disease (AD). Application of ADAS-cog scale in more than 30 phase III clinical trials that included over 6000 subjects from comparable patient population during a 6-month treatment period, demonstrated significant effects of three different reversible (tacrine, donepezil and galanthamine) and three pseudo-irreversible or irreversible CHEIs (eptastigmine, rivastigmine and metrifonate) on cognition. Clinical effect of most CHEIs in AD seems to be stabilisation of the patient symptomatology rather than improvement of the disease from base-line. In addition to positive effects on cognition, CHEIs produce significant effects on behaviour. They alleviated particularly such symptoms as apathy, motor agitation and hallucinations. Improvement of behavioural symptoms may translate into a better quality of life for both patient and his caregiver. Long-term studies have shown that clinical efficacy of CHEIs can be extended to 12 months or more.

Izvleček

Inhibitorji holinesteraze (CHEI) predstavljajo trenutno zdravilo prve izbire v zdravljenju Alzheimerjeve bolezni (AD). Uporaba lestvice ADAS-cog v več kot 30 kliničnih študijah III. faze, opravljenih v šestmesečnem obdobju pri preko 6 000 osebah iz primerljivih populacij, je pokazala pomembne učinke treh reverzibilnih (takrin, donepezil in galantamin) in treh psevdoireverzibilnih oziroma ireverzibilnih (eptastigmin, rivastigmin in metrifonat) CHEI na spoznavne sposobnosti. CHEI

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pomembno vplivajo na vedenje. Ublažijo predvsem take simptome, kot so apatija, motorična agitiranost in halucijacije. Izboljšanje vedenjskih simptomov lahko pomeni boljšo kvaliteto življenja, tako za bolnika kot za njegovega negovalca. Dolgotrajne študije so pokazale, da so CHEI lahko klinično učinkoviti 12 mesecev ali več.

Presently, cholinesterase inhibitors (CHEIs) represent the drug of choice for the treatment of Alzheimer's disease (AD) (1,2). The history of AD treatment with CHEIs began the mid 70s with the pioneer studies of physostigmine effects on memory functions of young and elderly normal subjects. The results of these early studies (Table 1) are only modestly encouraging, as high doses (<1mg i.v.) of the drug impair both storage and retrieval of memory while low doses (> 0.5 mg i.v.) produce only a trend towads improvement of short-term memory storage. In addition, physostigmine produces severe cholinergic side effects. Only in acute cases of non-AD related amnesiac episodes (post-traumatic, post ECT or post-encephalitc) it is possible to detect evident improvement. These results were more encouraging as they suggested the possibility for therapeutic interventions also in AD patients. In contrast to weak effects of physostigmine (a short-acting carbamate), a much stronger improvement of cognition is observed with the second generation (post-physostigmine and post-tacrine) CHEIs (Table 2).

Table 1. Effects of physostigmine on memory in elderly normal subjects.

author	**type**	**dose**	**age / n**	**effect**
Davies et al., 1976 (3)	short term	2-3 mg i.v.	<65 / 6	impairment of storage and retrieval
Drachman & Sahakian, 1980 (4)	short term	0.8 mg s.c.	64-82 / 13	trend towards improvement of memory storage
Davies et al., 1979 (5)	short term	0.5 mg i.v.	<65 / 3	improvement
Drachman et al., 1982 (6)	short term	0.5 mg i.v.	64-77 / 16	no effect

*Table 2. Effects of six cholinesterase inhibitors measured with ADAS-Cog test (ITT). Modifyed from (2). (ADAS-Cog - Alzheimer's disease Assessment Scale - cognitive subscale, ITT - intention to treat, * - study end point vs. placebo, ** - study end point vs. baseline)*

drug	**dose**	**duration of study**	**treatment difference from**		**improved patients**	**rop-out**	**side effects**
	(mg/day)	(weeks)	placebo*	baseline**	%	%	%
tacrine	120-160	30	4.0-5.3	0.8-2.8	30-50	55-73	40-58
eptastigmine	45	25	4.7	1.8	30	12	35
donepezil	5-10	24	2.8-4.6	0.7-1	58	5-13	6-13
rivastigmine	6-12	24	1.9-4.9	0.7	25	15-36	28
metrifonate	25-75-80	12-26	2.6-3.1-3.2 3.9	0.75-0.5 2.2	35	2-21-8 15	2-12 7
galanthamine	30	12	3.3	1.8		33	

Based on over 30 phase III clinical trials that included over 6000 subjects from comparable patient population during a 6-month treatment period, application of ADAS-cog scale demonstrated significant effects of three different reversible (tacrine, donepezil and galanthamine) and three pseudo-irreversible or irreversible CHEIs (eptastigmine, rivastigmine and metrifonate) on cognition. The magnitude of these clinical effects, expressed either as the difference between drug-treated and placebo-treated patients or as the difference between drug-treated patients and baseline, is rather similar with all six drugs (Table 2), its range being 3-5 ADAS-Cog points after 6-months. In clinical trials the differences between various drugs, beside their chemical structure, enzymatic mechanism of action, pharmacokinetic and pharmacodynamic properties, selectivity for acetylcholinesterase vs. butyrylcholinesterase and cholinergic receptor affinities, are observed with regard to frequency and severity of side-effects, number of patient drop-outs, general cholinergic toxicity and mode of administration (dosage and titration). Recent studies have shown that in certain patients (high responders) the magnitude of the effect may be even higher than 5 points (8-11) on the ADAS-Cog scale, while in certain other patients the response to the drug is scarce (or non-existent). Clinical effect

of most CHEIs in AD seems to be stabilisation of the patient symptomatology rather than improvement of the disease from base-line. In addition to positive effects on cognition, CHEIs produce significant effects on behaviour. They aleviate particularly such symptoms as apathy, motor agitation and hallucinations. Improvement of behavioural symptoms may translate into a better quality of life for both patient and his caregiver. Long-term studies have shown that clinical efficacy of CHEIs can be extended to 12 months or more. Later on progressive decrease in clinical efficacy can be seen, and it may depend either on loss of drug effect (a tolerance effect explainable with up-regulation of brain cholinergic receptors and increased cholinesterase synthesis), on progression of the disease or on combination of both factors. The immediate challenge is to investigate whether or not CHEIs can be useful at early stages of the disease and whether they may alter the course of the disease (s.c. structural effect). If a similar effect could be demonstrated at very early stages (CDR 0,5; GDS 3; MMSE>24) or in subjects at risk with minimal cognitive impairment, it might be possible to slow down the development of the disease for a few years. This means that for older patients (above 80) such an effect would translate into the elimination of the hardest period of the disease.

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