CHOLINESTERASE INHIBITORS AS THERAPY IN ALZHEIMER’S DISEASE: BENEFIT TO RISK CONSIDERATIONS IN CLINICAL APPLICATION

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Currently available data about cholinesterase inhibitors in Alzheimer’s disease (AD) indicate that knowledge of differences in pharmacology among the inhibitors is essential to physicians to maximize clinical benefits to patients. We express the concern that commercial promotion may not recognize the relevant issues. We caution physicians to consider carefully the rationale of their use of compounds from this class.

PREMISES AND STRATEGIES

Over a decade ago we decided to give a fair test to the potential for benefit in Alzheimer’s disease (AD) from acetylcholine (ACh) supplementation through acetylcholinesterase (AChE) inhibition (Becker and Giacobini, 1988a). The available cholinesterase inhibitors, physostigmine and tacrine, did not allow the full potential benefit in AD to be explored because of the onset of distressing adverse effects, nausea, vomiting, diarrhea, at low levels of AChE inhibition. Our review of the pharmacology of the AChE inhibitors indicates that the appearance of the typical cholinergic syndrome--nausea, vomiting, diarrhea, progressing to bronchospasm, convulsions --and animal mortality--are not systematically related to either levels of AChE inhibition or tissue concentrations of ACh (Becker and Giacobini, 1988b,c). The possibility that toxic effects could be dissociated from therapeutic effects initiated a search for a compound without adverse characteristics which could be administered to humans to test the efficacy of cholinesterase inhibition in AD. We also sought other properties we think important: ability to achieve high levels of AChE inhibition both to test for maximum benefit and to overcome therapeutic resistance from tissue tolerance; long duration of action to maintain steady state of tissue effects and to reduce the need for dosing to at most once daily; a close relationship between clinical dose and therapeutic tissue concentrations.
to simplify dosing and increase safety; and a large clinical therapeutic index to provide safety in inadvertent overdose, a concern in the confused, memory-impaired AD patient (Becker, 1991). Our assumption is that the full potential efficacy of cholinesterase inhibitors in AD cannot be known until adverse effect-free inhibition of AChE can be maintained at steady state throughout the total range of physiological function of AChE.

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacodynamic and pharmacokinetic studies in animals (Hallak and Giacobini, 1987; Hallak and Giacobini, 1989; Mori et al., 1995; Moriearty and Becker, 1992; Moriearty et al., 1993; Kronforst-Collins et al., 1996; Unni et al., 1994) documented the favorable properties of metrifonate, a prodrug for O,O-dimethyl O-(2,2-dichlorovinyl) phosphate (DDVP), an irreversible inhibitor of both butyrylcholinesterase (BuChE) and AChE. In an open study of 20 patients we documented low rates of occurrence of adverse effects with repeated doses of metrifonate (Becker et al., 1990). In this study, we also achieved up to 88% inhibition of red blood cell (RBC) AChE at steady state for one week with once-weekly dosing of metrifonate. We then documented levels of cerebrospinal fluid AChE inhibition in relation to RBC AChE inhibition in two patients (Becker et al., 1990) similar to those in earlier rat brain studies (Hallak and Giacobini, 1987; Hallak and Giacobini, 1989). We also reported the lack of hematological and genetic effects after repeated dosing (Moriearty et al., 1991; Bartels et al., 1994).

CLINICAL PHARMACOLOGY OF METRIFONATE IN ALZHEIMER’S DISEASE

Recently we reported results from two double blind studies in AD patients in which we compared metrifonate to placebo and from an open followup of patients after the first double blind study (Becker et al., 1996a,b). The initial double blind placebo-controlled study was intended to enter 100 AD patients to determine the effects of metrifonate on the cognitive deficit in AD patients. Many critics argue that statistical significance for treatment differences in a rating scale may be of little clinical significance. To assure our work focused on clinically significant drug effects we adopted, as our standard for self-evident clinical significance, a 25% improvement in the cognitive function presumed lost in our AD patients, a standard we used previously to indicate a clinically non-trivial statistical association between treatment and response. Thus a mean pretreatment Alzheimer Disease Assessment Scale (ADAS) (Rosen et al., 1984) score of 28 for the patients entered would require a 7 point reduction in score (improvement); a mean pretreatment Mini Mental State Examination (MMSE) (Folstein et al., 1975) score of 18 would require a 3 point increase in score (improvement) to meet our requirement of clinical