

LETTERS TO THE EDITOR

Treatment of Alzheimer's disease

Three recent reports¹⁻³ raise important issues about the treatment of Alzheimer's disease (AD). PET studies¹ may identify a pathology (glutamatergic hypoactivity) which would not respond to cholinergic receptor therapy³ and the MRC Committee² do not appear to have directly addressed the issue of testing a drug, such as D-4-amino-3-isoxazolidone (D-cycloserine, DCS), which may simultaneously arrest progressive deterioration^{2,4} and improve mental performance.^{2,5}

Although DCS has been in clinical use for some years as an antibiotic, it is only recently that a neurobiological action has also been recognised. In human brain DCS has been shown to displace strychnine-insensitive [³H] glycine binding,⁶ from what is generally considered to be the glycine B site of the N-methyl-D-aspartate (NMDA) receptor-ionophore complex. The drug has now been proposed as a cognitive enhancer for a range of indications,⁷⁻⁹ based on its partial agonist characteristics at the glycine site in rodent⁸ and oocyte preparations⁹ and its effect on learning in animals,⁷ as well as the known involvement of the receptor complex in long-term potentiation and behavioural models of memory function.⁷⁻⁹

Due to the well documented role in excitotoxicity, the potential of the NMDA receptor complex as a therapeutic site has been viewed cautiously. Treatment of AD patients with a partial agonist at the glycine B site may circumvent problems associated with hyperstimulation either by coexisting cerebrovascular disease or a proposed pathological process in AD,¹⁰ which might be exacerbated by the action of β -amyloid protein¹¹⁻¹³ on glutamatergic cells.^{12,13} DCS has now been shown to have such partial agonist characteristics in several paradigms, including AD brain tissue.¹⁴ We propose that it will have benefits for AD patients over and above all other types of cognitive impairment, not only because of the potential neuroprotective action but as it may alleviate glutamatergic hypoactivity.

In brief, degeneration of columns¹⁵ of corticocortical glutamatergic pyramidal cells in circumscribed (parietotemporal) areas of cerebral cortex appeared to occur early in AD and caused a reduction in cortical area with selective reduction in acetylcholine, glutamate and serotonin. There was relative sparing of other neurotransmitters¹⁶ and serotonin was thought to relate to non-cognitive behavioural problems.¹⁷ Cognitive deficits correlated with both the disappearance of pyramidal cells¹⁸ and their synapses¹⁹ assessed by cortical biopsy and scanning data by PET.^{20,21} This technique, which showed selective glucose hypometabolism in the parietotemporal lobes^{1,20,21} was sensitive to atrophy.²² Pathology was most prominent in these lobes²³ and hypometabolism was not seen *in vitro* when assessed in the cortical biopsies.¹⁶ The scans may therefore provide independent evidence of early structural

damage to corticocortical neurons in parietotemporal areas, also revealed by blood flow imaging.²⁴

Glutamatergic transmission may normally be the chief factor that sustains the activity of corticocortical neurons in the cortex.^{16,25} Thus the degeneration in the parietotemporal cortex probably reduces excitatory input into neurons and if the glycine B site of the NMDA receptor complex is not saturated by endogenous ligand, the partial agonist property of DCS may restore the receptor function of the cells without reaching excessive levels of activation. Reduced sensitivity of the receptor complex to glycine has been described in the neocortex of AD patients⁶ and if this and the well established glutamatergic hippocampal pathology should prove to occur with onset of symptoms, there would be even greater rationale for the proposed treatment, in spite of the fact that some^{16,19} have reached the pessimistic conclusion that a successful neurotransmitter-based therapy will not evolve. In the rat, low doses of DCS caused increased latency (passive avoidance task) and reduced trials to criterion (reversal of place learning).⁷ Although high doses in humans (in excess of 500 mg) may cause "confusion and disorientation with loss of memory" (Association of the British Pharmaceutical Industry Data Sheet Compendium 1989-90), a low dose (15 mg) has been reported to antagonise cognitive impairment induced by scopolamine.²⁶

In summary, on the basis of current knowledge we consider that treatment of AD patients with a low dose of DCS will be safe and effective. First, because of its non-specific effects on memory function.^{7-9,26} Second, by correcting a characteristic neurochemical deficit in the disease (circumscribed corticocortical glutamatergic degeneration) which other proposed strategies fail to address, and finally by preventing the postulated excitotoxic damage.

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Intramuscular midazolam for treatment of acute seizures or behavioural episodes in patients with brain injuries

In many rehabilitation centres such as our own, intravenous administration of antiepileptic drugs for acute seizures is desirable but not usually possible. Intramuscular administration is a problem because of poor absorption and penetration (diazepam) and delayed