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 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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- Brooks DJ. PET: Its clinical role in neurology. *J Neurol Neurosurg Psychiatry* 1991;54:1-15.
- Swash M, Brooks DN, Day NE, Frith CD, Levy R, Warlow CP. Clinical trials in Alzheimer's disease: a report from the Medical Research Council Alzheimer's Disease Clinical Trials Committee. *J Neurol Neurosurg Psychiatry* 1991;54:178-81.
- Lange KW, Wells FR, Rossor MN, Jenner P, Marsden CD. Cortical nicotinic receptors in Alzheimer's disease and Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1991;54:373-4.
- Greenamyre JT, Young AB. Excitatory amino acids in Alzheimer's disease. *Neurobiol Aging* 1989;10:593-602.
- Bowen DM, Francis PT, Lowe SL, Pangalos MN, Procter AW, Steele JE. Pyramidal neuron loss and "glycine-site therapy": a need for an animal model and study in late-life depression. *Neurobiol Aging* 1989;10:616-8.
- Procter AW, Stratmann GC, Francis PT, Lowe SL, Bertolucci PHF, Bowen DM. Characterisation of the glycine modulatory site of the N-methyl-D-aspartate receptor ionophore complex in human brain. *J Neurochem* 1991;56:299-310.
- Monahan JB, Handelsmann GE, Hood WF, Cordi AA. D-Cycloserine, a positive modulator of the N-methyl-D-aspartate receptor, enhances performance of learning task in rats. *Pharmacol Biochem Behav* 1989;34:649-53.
- Hood WF, Compton RP, Monahan JB. D-Cycloserine: a ligand for the N-methyl-D-aspartate coupled glycine receptor has partial

agonist characteristics. *Neurosci Lett* 1989;98:91-5.

- Watson GB, Bolanowski MA, Baganoff MP, Deppeler CL, Lanthorn TH. D-Cycloserine acts as partial agonist in the glycine modulatory site of the NMDA receptor expressed in xenopus oocytes. *Brain Res* 1990;510:158-60.
- Maragos WF, Greenamyre JT, Penney JB jr, Young AB. Glutamate dysfunction in Alzheimer's disease: an hypothesis. *Trends Neuroscience* 1987;10:65-8.
- Wright AF, Goedert M, Hastie ND. Beta amyloid resurrected. *Nature* 1991;349:653-4.
- Yankner BA, Caceres A, Duffy LK. Nerve growth factor potentiates the neurotoxicity of β -amyloid. *Proc Natl Acad Sci USA* 1990;87:9020-3.
- Koh J-Y, Yang LL, Cotman CW. β -Amyloid protein increases the vulnerability of cultured cortical neurons to excitotoxic damage. *Brain Res* 1990;533:315-20.
- Chessell IP, Procter AW, Francis PT, Bowen DM. D-cycloserine, a putative cognitive enhancer, facilitates activation of the NMDA receptor-ionophore complex in Alzheimer brain. *Brain Res* 1991;565:345-8.
- Duychaerts C, Hauw JJ, Piette F, Rainsard C, Poulain V, Berthaux P, Escourrolle R. Cortical atrophy in senile dementia of the Alzheimer's type is mainly due to a decrease in cortical length. *Acta Neuropathol (Berl)* 1985;66:72-4.
- Bowen DM. Treatment of Alzheimer's disease: Molecular pathology versus neurotransmitter-based therapy. *Brit J Psychiatry* 1990;157:327-30.
- Palmer AM, Stratmann GC, Procter AW, Bowen DM. Possible neurotransmitter basis of behavioural changes in Alzheimer's disease. *Ann Neurol* 1988;23:616-20.
- Neary D, Snowden JS, Mann DM, et al. Alzheimer's disease: a correlative study. *J Neurol Neurosurg Psychiatry* 1986;49:229-37.
- DeKosky ST, Scheff SW. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. *Ann Neurol* 1990;27:457-64.
- Cutler NR, Haxby JV, Duara R, Grady CL, Kay AD, Kessler RM, Sundram M, Rapoport S. Clinical history, brain metabolism and neuropsychological function in Alzheimer's disease. *Ann Neurol* 1985;18:298-309.
- Miller JD, De Leon MJ, Ferris SH, et al. Abnormal temporal lobe response in Alzheimer's disease during cognitive processing as measured by ¹¹C-2-deoxy-D-glucose and PET. *J Cerebr Blood Flow Metab* 1987;7:248-51.
- Chawluk JB, Alavi A, Dann R, et al. Positron emission tomography in aging and dementias: effect of cerebral atrophy. *J Nucl Med* 1987;18:431-7.
- Esiri MM, Pearson RCA, Steele JE, Bowen DM, Powell TPS. A quantitative study of the neurofibrillary tangles and the choline acetyltransferase activity in the cerebral cortex and the amygdala in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1990;53:161-5.
- Wilson K, Bowen D, Francis P, Tyrrell P. Effect of central cholinergic stimulation on regional cerebral blood flow in Alzheimer's disease. *Brit J Psychiatry* 1991;158:538-62.
- Kisvarday ZF, Martin KAC, Freund TF, Magloczky ZS, Whitteridge D, Somogyi P. Synaptic targets of HRP-filled layer III pyramidal cells in the cat striate cortex. *Brain Res* 1986;64:541-52.
- Wesnes K, Jones RW, Kirby J. The effects of D-cycloserine, a glycine agonist, in a human model of the cognitive deficits associated with ageing and dementia. *Br J Clin Pharmacol* 1991;31:577-8.

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

onset of activity (lorazepam). Similarly, for acute behavioural episodes such as violence the choices have generally been intramuscular lorazepam or antipsychotics such as haloperidol or chlorpromazine. In addition to delayed onset of effects, intramuscular antipsychotics have been associated with acute extra pyramidal side effects, orthostatic hypotension, and extreme sedation.

Over the past year we have used the benzodiazepine midazolam intramuscularly to treat patients with acute seizures or extreme behavioural episodes. In the United States midazolam is currently approved for use as a pre-anaesthetic agent, and not for treatment of seizures.¹ It has, however, been successfully used in clinical situations to treat acute seizures including status epilepticus, and severe behavioural problems often with almost immediate effects.²⁻⁸ Midazolam is a highly lipophilic water soluble drug which allows for excellent intramuscular absorption and rapid CNS penetration. Intramuscular (IM) administration can result in sedation within five to 15 minutes with peak effects noted within 30-60 minutes. The drug possesses a short half-life of 1.5 to 3.5 hours, although in some patients residual psychomotor effects may be noted for up to eight hours. Although there have been reports of respiratory problems with the intravenous administration of midazolam, especially in elderly patients, this has not been reported after intramuscular use. Warnings of respiratory problems specifically only mention intravenous administration.

After previously published reports of success with IM midazolam for the treatment of acute seizures and behavioural emergencies, we have been treating patients with this medication. We present four cases involving clinical use of IM midazolam, two for acute seizures and two for behavioural control.

Case 1: A 26 year old white male suffered a head injury on the 9 February 1985 secondary to a motor vehicle accident. The patient has had persistent problems with late onset prolonged seizures which often needed admission to hospital for acute treatment despite receiving intramuscular lorazepam. These admissions averaged at least one per month between 1989-90. In early 1990 lorazepam was switched to IM midazolam 10 mg. Since the change to midazolam, no further admissions have been necessary for treatment of acute seizures, despite no significant changes in the primary anticonvulsant drug treatment.

Case 2: A 22 year old white male suffered a head injury on 2 January 1986 when he was hit by a car. He developed frequent and prolonged late-onset seizures, both focal and generalised. On 3 April 1990 he developed right-sided twitching of the face and extremities for seven to 10 minutes, without secondary generalisation. IM midazolam 15 mg stopped the seizures "within five minutes." On 25 June 1990 he developed prolonged generalised tonic-clonic seizures. IM midazolam 15 mg was administered and the seizures ceased within five minutes with the patient falling asleep. Sedation was the only reported adverse effect.

Case 3: A 52 year old black male suffered a head injury in May 1987 secondary to a fall. Post traumatically he developed seizures, and paranoid psychosis with prolonged agitated, aggressive, and combative behaviours. On 6 April 1990 he became euphoric, paranoid, very agitated and threatened physical abuse to staff members. He refused medications and also cigarettes. After IM midazolam

5 mg he fell asleep for one hour and awoke amnesic about the episode.

Case 4: A 39 year old black male, had primary behavioural problems including chronic violence to others and agitation. The patient has had a chronic idiopathic seizure disorder since 1980. In 1988, he developed an episode of status epilepticus leading to anoxic encephalopathy with resulting severe cognitive impairment, chronic paranoid psychosis, aggressive behaviours, and visual and auditory hallucinations. Intramuscular midazolam has been used on numerous occasions to treat agitation resulting in alleviation of agitation and violence as well as a reduction in psychosis without significant sedation or long term "after effects." These positive effects have lasted for a day, sometimes for eight to 12 hours.

Although seizures after brain injury can sometimes be self-limiting, the known rapid onset of midazolam and our knowledge of these patients' seizure histories makes this possibility unlikely. While some patients (such as case 4) may respond to very low doses, the general dosage guideline for midazolam is 0.15 to 0.30 mg/kg.²

Side effects were reported ranging from slight lethargy to sleep. In most cases, this lasted for one to two hours and the patients' recovery was uneventful. Only case 4 demonstrated prolonged effects—even at a very low dose. Intramuscular midazolam appears to be a safe, rapidly effective drug for treatment of both acute seizures and behavioural emergencies and deserves further study.

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- 1 Versed: Product information. Nutley NJ, Hoffman-LaRoche, 1986.
- 2 Egli M, Albani C. Relief of status epilepticus after IM administration of the new Short-Acting benzodiazepine midazolam. *Twelfth World Congress of Neurology*, 20-25 September 1981, Kyoto, Japan. Princeton, Excerpta Medica, 44 (abs 137).
- 3 Jawad S, Oxley J, Wilson J, Richens A. A pharmacodynamic evaluation of midazolam as an antiepileptic compound. *J Neurol Neurosurg Psychiatry* 1986;49:1050-4.
- 4 Galvin GM, Jelinek GA. Midazolam: an effective intravenous agent for seizure control. *Arch Emerg Med* 1987;4:169-72.
- 5 Mayhue FE. IM midazolam for status epilepticus in the Emergency Department. *Ann Emerg Med* 1988;17:643-5.
- 6 Von Albert HH. Midazolam for the treatment of states of restlessness and excitation. In: Steffens J, ed. *Midazolam in anesthesiology*. Int Symposium Darmstadt, 28-29 October 1983. Basle, Switzerland: Roche Scientific Service, 1986:255-58.
- 7 Mendoza R, Djenderedjian AH, Adams J, Ananth J. Midazolam in acute psychotic patients with hyperarousal. *J Clin Psychiatry* 1987;48:7, 291-2.
- 8 Bond WS, Mandos LA, Kurtz MB. Midazolam for aggressivity and violence in three mentally retarded patients. *Am J Psychiatry* 1989;146:7, 925-6.
- 9 Dundee JW, Halliday NJ, Harper KW. Midazolam. A review of its pharmacological properties and therapeutic use. *Drugs* 1984;28:519-43.

HLA profile and HTLV-I associated myelopathy (HAM/TSP) in Natal, South Africa

Myelopathy associated with HTLV-I (HAM/TSP) is an important cause of neurological disability in the Zulus in Natal.¹ To explore the role of host factors in the pathogenesis of this disorder we examined the HLA profiles in 40 HAM/TSP patients. The results were also compared with two antibody positive patients with adult T-cell leukaemia/lymphoma (ATLL). The control group consisted of normal adults who were either staff or randomly selected blood donors of the same ethnic origin as the patients. Class I antigens were tested in 1848 controls, DR antigens in 556 and DQ in 340.

Standard techniques^{2,3} using 180 antisera for Class I antigens and 120 antisera for Class II antigens, were employed. Differences in HLA frequencies were tested for significance with the Chi square test (without Yates's correction) and the probability was corrected by multiplying the P-value by the number of comparisons made, that is, the number of antigens tested.⁴ Relative risks were calculated according to the formulae recommended by Woolf.⁵ The difficulties of establishing negative correlations which may indicate a "protective" antigen have been discussed by Sveigaard *et al.*⁶ Haplotype frequencies were estimated by the method of Mattiuz *et al.*⁷

The HLA frequencies of the large number of controls was typical of the Southern African black population. There was virtual absence of A11, B22, B40, Bw54, Bw52, Cw1 and DR9 whilst high frequencies of A23, A30, Bw42, B58, B70, Cw2 and DR5 were observed. In the patient group an increased frequency of only one antigen—Bw57—reached statistical significance (table) at the 1% level after correction for the number of Class I antigens tested. The increased frequencies of A24 (12.5% vs 6.0%), B7 (32.5% vs 23.4%) and DR2 (37.1% vs 24%) were of borderline significance.

There were no significant differences in the frequencies of HLA C and HLA DQ antigens. The joint occurrence of A24, B7, DR2, DQw1 was found in 3/35 patients (8.6%) but was present in only 3.1% of the control group. The two patients with lymphoma/leukemia had the following antigens: HLA A2, A30, B8, B-, Cw2, Cw-, DR7, DR-, DRw53, DQw1 and DQw- and HLA Aw31, A-, B35, B45, Cw-, DRw8, DRw52, DQw3, DQw-. There were no significant differences in the estimated haplotype frequencies between patients and controls.

In contrast to our largely negative findings Usuku *et al.*⁸ found specific HLA haplotypes in 70% of their HAM patients. Furthermore, none of the HAM associated HLA haplotypes were seen in ATLL. The joint occurrence of A24, B7, DR2, DQw1 found in 8.8% of our patients, has been reported by the Japanese,⁹ although DR2 was usually found with different B-locus antigens. The other HLA antigens associated with HAM/TSP in the Japanese⁸—A11, Bw54, Bw52, are not found in the Zulus. Also those antigens associated with ATLL in Japanese are rare in the local black population.

There is accumulating evidence that the neurological injury in HAM/TSP is immune mediated.¹⁰ A more refined examination of the HLA system may yet prove fruitful. The recent molecular genetic study by Usuku *et al.*¹¹ showed a relationship between a particular amino acid sequence of the HLA-DR 1