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 hypofunction) which would not respond to cholinergic receptor therapy4 and the MRC Committee5 do not appear to have directly addressed the issue of testing a drug, such as D-L-D-aspartam-3-isoxazolidone (D-cycloserine, DCS), which might simultaneously arrest progressive deterioration4 and improve mental performance.6,7

Although DCS has been in clinical use for some time, its adoption is only recent that a neurobiological action has also been recognised. In human brain DCS has been shown to displace strychnine-insensitive [3H]glucose binding,8 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,9 based on partial agonist characteristics at the glycine site in vitro and9 oocyte preparations10 and its effect on learning in animals,11 as well as the known involvement of the receptor complex in long-term potentiation, a behaviour model of memory function.11-13

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,14 which might be exacerbated by the action of β-amyloid protein15-17 on glutamatergic cells.12,17 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 hypofunction.

In brief, degeneration of columns18 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 excessive sparing of other neurotransmitters19 and serotonin was thought to relate to non-cognitive behavioural problems.20 Cognitive deficits correlated with both the disappearance of pyramidal cells18 and their synapses20 assessed by cortical biopsy and scanning data by PET.20 This technique, which showed selective glucose hypometabolism in the parietotemporal lobes,21 was sensitive to atrophy.22 Pathology was most prominent in these lobes22 and hypometabolism was not seen in vitro when assessed in the cortical biopsies.23 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.12,25 Thus the degeneration in the parietotemporal cortex probably reduces excitatory input into neurons and if this site is the 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 patients26 and if this and the well established glutamatergic hypofunction should prove to occur with onset of symptoms, there would be even greater rationale for the proposed treatment, inspite of the fact that some6 have reached the pessimistic conclusion that a successful NMDA receptor-based therapy will not evolve. In the rat, low doses of DCS caused increased latency (passive avoidance task) and reduced trials to criterion (active avoidance learning). 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 D-cycloserine), a low dose (15 mg) has been reported to antagonise cognitive impairment induced by scopolamine.

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. Second, by correcting a characteristic neu- rochemical 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 admin- istration is a problem because of poor absorp- tion 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-anesthetic 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 3 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 which may be unpleasant with peak plasma levels noted within 30–60 minutes. The drug possesses a short half-life of 1 5 to 3 5 hours, although in some patients residual psychoses may be noted for up to 12 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. Reports of respiratory problems specifically only mention intravenous administration.

After previously published reports of success with IM midazolam for the treatment of acute seizures or severe 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 had 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 change 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. 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 stopped 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 a secondary car accident on 1990. Post traumatically he developed seizures, and paranoid psychosis with prolonged agitation, aggressive, and combative behaviours. On 6 April 1990 he became euphoric, paranoid, very agitated and threatened physical violence 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. Midazolam has been used as a selected behaviour therapy 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 1) may respond to very low doses, the general dosage guideline for midazolam is 0–15 to 0–30 mg/kg.

Side effects were reported ranging from slight lightheadedness. 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 emergences and deserves further study.

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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. 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 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 an elected biobank of African origin.

The patients were HLA typed in 1984, 1985, and 1986. Additional typing was done in 1988. In 1985–87, the HLA profiles were typed in Pretoria, South Africa, by the method of Bruyn et al.4

The HLA frequencies of the large number of controls was typical of the Southern African black population. There was virtual absence of A11, B27, B50, B52, Cw1, DR2, and DR5. These high frequencies of A23, A30, B42, 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, DQ2 was found in 3/35 patients and the Bw57 A1 antigen present in only 31% of the control group. The two patients with lymphoma/leukaemia had the following antigens: HLA A2, A30, B8, B-, Cw2, Cw7, DR7, DR8, DQ1, DQ6, DQ2, DQ3, A1, A3, B35, B45, Cw-, DQ8, Dw5, Dw52, DwQ3, DwQ5. There were no significant differences in the estimated haplotype frequencies between patients and controls.

In contrast to our largely negative findings Usuku et al5 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, B2, DR2, DQ1 found in 8/8 of our patients, has been reported by the Japanese,6 although DR2 was usually found with different B-locus antigens. The latter HLA antigens associated with HAM/ TSP in the Japanese—A11, Bw54, Bw52, are not found in the Zulus. Also those antigens associated with ATLL in Japanese are not seen in the local population.

There is accumulating evidence that the neurological injury in HAM/TSP is immune mediated.7 A more refined examination of the HLA system should be performed as part of the recent molecular genetic study by Usuku et al and the relationship between a particular amino acid sequence of the HLA-DR 1
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