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 studies4 may identify a pathology (glutamatergic hypoactivity) which would not respond to cholinergic receptor therapy5 and the MRC Committee5 do not appear to have directly addressed the issue of testing a drug, such as D-cycloserine-D-aspartate (DCS), which may simultaneously arrest progressive deterioration6,7 and improve mental performance.7-9

Although DCS has been in clinical use for some time,21 it is only recently that a neurobiological action has also been recognised. In human brain DCS has been shown to displace glycine-insensitive [3H] glycine binding,7-13 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,13-14 based on its partial agonist characteristics at the glycine site in rodents13 and oocyte preparations14 and its effect on learning in animals,13 as well as the known involvement of the receptor complex in long-term memory and other 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,15 which might be exacerbated by the action of b-aminopyridine10-11 on glutamatergic cells.12,15 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 columns16 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 selective 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 cells16 and their synapses16 assessed by cortical biopsy and scanning data by PET.20 This technique, which showed selective glucose hypometabolism in the parietotemporal lobes,17,21 was sensitive to atrophy.20 Pathology was most prominent in these lobes17 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.16

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 patients16 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 some18 have reached the pessimistic conclusion that a successful neurotrophic-basis treatment will not evolve. In the rat, low doses of DCS caused increased latency (passive avoidance task) and reduced trials to criterion (reversal tasks) to occur. Although high doses in humans (in excess of 500 mg) may cause "confusion and disorientation with loss of memory" (Assocation of the British Pharmaceutical Industry Data Sheet, 1991; DCS 10-600 mg), a low dose (15 mg) has been reported to antagonise cognitive impairment induced by scopolamine.22

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 neurochemical deficit in the disease (circumscribed corticocortical glutamatergic degeneration) which other proposed strategies fail to address, and finally by preventing the postulated excitotoxic damage.

DAVID M BOWEN
PAUL FRANCIS ANDREW W PROCTOR
Institute of Neurology,
Queen Square
ANNE B YOUNG
Harvard Medical School,
Boston, Mass 02114, USA


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...
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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 high extra pyramidal side effects, othostatic hypotension, and extreme sedation.

Over the past year we have used the benzodiazepine intramuscularly to treat patients with acute seizures or extreme behavioural episodes. In the United States midazolam is currently approved for use as a pre-medication agent, and not for treatment of seizures. We have, however, been successfully used in clinical situations to treat acute seizures including status epilepticus, and severe behavioural problems often with almost immediate effects. 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 the first few minutes, and peak plasma levels may be 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 have been 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. 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 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 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 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 3 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 continued for 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 1982 secondary to traffic impact. Post traumatically he developed seizures, and paranoid psychosis with prolonged agitated, aggressive, and combative behaviours. On 6 April 1990 he became euphoric, paranoid, very aggressive, and physically violent towards 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 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.

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 emergencies and deserves further study.

Correspondence to: Dr Wroblewski


HFA 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 compared with those of two antibody positive patients with adult T-cell leukaemia/lymphoma (ATLL). The control group consisted of normal adults who were either staff or students from the local university in the same ethnic origin as the patients. Class I antigens were tested in 184 controls, DR antigens in 556 and DQ in 340.

Standard techniques2 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’ correction) and the probability was corrected if the number of comparisons made, that is, the number of antigens tested. Relative risks were calculated according to the formula of Woolf3 and standard errors were estimated establishing negative correlations which may indicate a “protective” antigen have been discussed by Sveigaard et al.4 Haplotype frequencies were estimated by the method of Mattius et al.5

The HLA frequencies of the large number of controls was typical of the Southern African black population. There was virtual absence of A11, B22, B50, Bw54, Cw1, Dw3, DRw12 for high frequencies. 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 (9%) patients and 0/22 (0%) in controls, that was present in only 31.1% of the control group. The two patients with lymphoma/leukemia had the following antigens: HLA A2, A30, B8, B-, Cw2, CW-DR7-, DR-, Dw3, DRw12, DQw2, DQw5. Another patient was present in only 31.1% of the control group. In contrast to our largely negative findings Usuku et al6 found specific HLA haplotypes in 70% of their HAM patients. Furthermore, none of the HAM associated HLA haplotypes were observed in ATLL. The joint occurrence of A24, B7, DR2, DQw1 found in 8/8 of our patients, has been reported by the Japanese, although DR2 was usually found with different B-locus antigens. The other 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 and in the local hospital were not found.

There is accumulating evidence that the neurological injury in HAM/TSP is immune mediated.4 A more refined examination of the HLA system has been possible following the recent molecular genetic study by Usuku et al6 showed a relationship between a particular amino acid sequence of the HLA-DR 1

1 Edited by Joseph Tufts University School of Medicine, Boston, MA, USA

Correspondence to: Dr Wroblewski.