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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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

Table MHC Class I antigen frequencies in Zulu control subjects and patients with HAM/TSP

	Control N = 1848	%	HAM/TSP N = 40	%	CHI-SQ	R-R
B7	432	23.3	13	32.5	1.81	1.6
B8	235	12.7	7	17.5	0.80	1.5
B13	62	3.3	2	5.0	0.32	1.5
B14	112	6.0	2	5.0	0.08	0.8
B18	95	5.1	3	7.5	0.44	1.5
B21	35	1.8	0	0.0	0.77	0.0
Bw22	1	0.0	0	0.0	0.02	0.0
B27	8	0.4	0	0.0	0.17	0.0
B35	135	7.3	3	7.5	0.0	1.0
B37	2	0.1	0	0.0	0.04	0.0
B38	32	1.7	1	2.5	0.13	1.5
B39	29	1.5	0	0.0	0.64	0.0
Bw41	33	1.7	0	0.0	0.73	0.0
Bw42	368	19.9	6	15.0	0.60	0.7
B44	303	16.4	8	20.0	0.37	1.3
B45	174	9.4	1	2.5	2.23	0.2
Bw47	2	0.1	0	0.0	0.04	0.0
Bw48	1	0.0	0	0.0	0.02	0.0
B51	20	1.0	1	2.5	0.72	2.3
Bw52	1	0.0	0	0.0	0.02	0.0
Bw53	29	1.5	0	0.0	0.64	0.0
Bw57	88	4.7	7	17.5	13.29	4.2
Bw58	585	31.6	8	20.0	2.47	0.5
Bw60	1	0.0	0	0.0	0.02	0.0
Bw61	0	0.0	0	0.0	—	—
Bw62	12	0.6	0	0.0	0.26	0.0
Bw63	43	2.3	0	0.0	0.95	0.0
Bw70	512	27.7	4	10.0	6.18	0.3

N = number; R-R = relative risk.

chain and the susceptibility to HAM. We have already established control frequencies in the Zulus for HLA polymorphism using PCR amplified DNA, dot-blots and oligonucleotide probes and hope to embark on a project to determine if any of these DNA markers are relevant to HAM/TSP.

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Extrapyramidal symptoms in a patient treated with fluvoxamine

A 77 year old woman had a longstanding history of recurrent major depressive episodes. She was treated with several tricyclic and heterocyclic antidepressants. Approximately six months before she came under our care, she started taking neuroleptics for the first time in her life. Flupenthixol 1 mg three times daily was prescribed in combination with the tricyclic antidepressant melitracene for a major depressive episode with psychotic features.

After a few months, marked orofacial involuntary movements were noted. All psychoactive drugs were discontinued and the orofacial dyskinesia disappeared gradually over the following month. The depression relapsed, however, and treatment was started with fluvoxamine, a serotonin-reuptake inhibiting antidepressant. The initial dose of 50 mg was gradually increased to 200 mg. By the time she had been on fluvoxamine for six weeks, she was transferred to our psychogeriatric ward.

On initial neurological examination, a mild akinetic-rigid syndrome and hyperactive tendon reflexes were found. Blood pressure fell from 130/80 to 90/50 mm Hg when the patient changed from the supine to standing position. A CT scan showed mild generalised brain atrophy with a slightly more pronounced cerebellar atrophy. The akinetic-rigid syndrome deteriorated considerably over the following eight months, eventually leading to multiple falls. No tremor was

noted. Meanwhile, the depressive symptoms had substantially improved. As an explanation for her neurological symptoms, a multiple system atrophy was suspected, although Parkinson's disease was also considered.

Before starting a drug trial with levodopa, we wanted to rule out the possibility that the Parkinsonism was drug-induced. Fluvoxamine was therefore reduced to a daily dose of 100 mg. The extrapyramidal symptoms had already markedly decreased one week later. The fluvoxamine was now completely withdrawn, resulting in an almost complete disappearance of the extrapyramidal symptoms over a period of two weeks. One month after the cessation of fluvoxamine, only a mild decrease in arm swing was left; the hyperactive tendon reflexes were unchanged. The orthostatic hypotension had also disappeared. An MRI scan of the brain showed mild atrophic changes and some periventricular and deep subcortical white matter hyperintensities. There was no signal attenuation in the putamen on T2-weighted images as has been described in striatonigral degeneration and other multisystem atrophies. Neither were there changes in the posterior fossa suggestive of olivopontocerebellar atrophy. A rechallenge with the offending drug was considered unacceptable because of the risk of serious injury when falls reoccurred.

Our patient presented with a severe akinetic-rigid syndrome and orthostatic hypotension almost completely reversible after withdrawal of the antidepressant fluvoxamine which she had been taking for several months. Extrapyramidal and autonomic side effects are not usually described with this selective serotonin-reuptake inhibitor. As far as we know, the occurrence of orthostatic hypotension is very unusual with this drug that has no known antagonist activity for alpha-adrenergic receptors. The association between selective serotonin-reuptake inhibitors and extrapyramidal side-effects as well as akathisia has already been reported, however, although mainly for fluoxetine.¹⁻³ A possible explanation is that increased serotonergic activity may exert an inhibitory action on nigrostriatal dopaminergic neurons.⁴ Pre-existing compromised nigrostriatal function caused by Parkinson's disease, other degenerative neurological disorders or dopamine-blocking agents might predispose patients to this adverse effect. Our patient had no such conditions. A causative role for the neuroleptics she had taken some months before the treatment with fluvoxamine is very unlikely because the extrapyramidal syndrome reached its maximum severity almost one year after the complete withdrawal of the antipsychotics. Finally, it could be argued that a dose of 200 mg of fluvoxamine is relatively high for an elderly patient, adding to the risk of developing side-effects.

Clinicians should be aware of this rare but potentially serious neurological complication of treatment with selective serotonin-reuptake inhibiting antidepressants, especially in patients with pre-existing neurological disease or already compromised extrapyramidal function due to neuroleptic medication.

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