Matters arising

A double-blind controlled trial of high dose methyl prednisolone in multiple sclerosis

Sir: In relation to the observation of Milligan *et al*¹ on the antispastic effect of steroids in chronic progressive multiple sclerosis, we would like to point out that 10 years ago we published in Chile,² a report on the subject. We reported the use of prednisone [1 mg per kg weight], in seven patients with spastic paraparesis. The patients had the following diagnosis: one case of chronic multiple sclerosis, one case of cervical rachisthenosis, and five cases of unknown aetiology without the clinical and pathological characteristics of multiple sclerosis.³ A method was designed for the evaluation of the spasticity.² Using this method we observed clinical improvement of the spasticity score in all these patients. We think that the effect reported by Milligan *et al* and our own report may be due to a specific antispastic effect of steroids. On this respect we agree with Compston *et al*,⁴ on the possibility of a direct action of steroids on muscle fibres. One possibility would be an effect upon the intrafusal muscle fibre, because no important change was observed on striated muscle fibres.

We believe that further clinical and experimental studies are necessary to define specific roles and mechanisms of the antispastic effect of corticosteroids.

LUIS CARTIER R
RENATO VERDUGO L
Neurosciences Department,
School of Medicine
Universidad de Chile
Leonardo da Vinci 7221
Las Condes, Santiago
Chile

References

- 1 Milligan NM, Newcombe R, Compston DAS. A double-blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: 1 clinical effects. *J Neurol Neurosurg Psychiatry* 1987;50:511-6.
- 2 Cartier L, Urrutia R, Catalan M. Método clínico de evaluación de la espasticidad en pacientes tratados con prednisona como miorreajante. *Neurocirugía* 1977;35:188-94.
- 3 Cartier L, Verdugo R, Vergara C. Paraparesia Espástica Esporádica del adulto por Degeneración Retrógrada del Sistema Piramidal. *Neurología en Colombia* 1983;7:103-11.
- 4 Compston DAS, Milligan NM, Hughes PJ, Gibbs J, McBroom U, Morgan BP, Cam-

pbell AK. A double blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: 2 laboratory results. *J Neurol Neurosurg Psychiatry* 1987;50:517-22.

Nifedipine and the treatment of myotonia

Sir: The claim by Grant *et al* of significant improvement in the myotonia of 10 patients with myotonic dystrophy following nifedipine treatment¹ seems exaggerated. Firstly, in the crossover study, the valid statistic compares placebo with nifedipine 10mg and by the authors' own admission there was no significant difference between these two treatments in any of several objective tests. Yet, they attempt to convince us that there are significant differences between nifedipine and initial groups but not between placebo and initial groups in the finger extension time test as presented in their fig 5. This figure is appalling in its lack of essential information (paired data are not indicated) and it contains erroneous information. Although it is stated that 20 results are used in the analysis only 19 are visible in the placebo group and a recalculation of the mean places it at about 1.5 s, not 1.7 s as stated and illustrated. This puts the mean for placebo on a level with those of the nifedipine treatments. Alternatively, if the mean plotted in their figure is correct then the missing 20th point must be an outlier at greater than 5 s and off scale above the figure. In either case it appears highly doubtful that there is anything to the results other than a possible slight improvement in finger extension times during the course of the study due to familiarity with the testing procedure. In any case the trial has been flawed by its single blind methodology. The possibility of differential encouragement to perform well in the finger extension test has not been controlled and could not be excluded even if there were any significant differences between placebo and nifedipine treatment groups.

Furthermore, there is no theoretical basis for the use of calcium channel blockers in the treatment of myotonia. As far as is understood, the prolonged contractions (delayed relaxations) in myotonia are due to myogenic action potential after-discharge.²⁻⁴ Such after-discharges would be indistinguishable from voluntary tetanic action potentials at the level of calcium channels involved in excitation-contraction

coupling. Therefore at dosages where therapeutic depression of myotonic contraction would be achieved, equal depression of voluntary contraction would be apparent as an intolerable side effect. Weakness is already a debilitating feature of most myotonic conditions⁴ and particularly so, due to the dystrophic process, in myotonic dystrophy.

In vitro experimentation provides us with no expectation of antimyotonic action from calcium channel blockers. Nifedipine (up to 30 μ M), and nicardipine (up to 50 μ M) have proven ineffective as antimyotonic agents in the rat diaphragm made myotonic by blocking Cl^- channels with either, 2,4-dichlorophenoxyacetate⁵ or with anthracene-9-carboxylate (unpublished observations). It can be inferred that Ca^{++} channels were blocked in these experiments without effect on the myotonia since nifedipine (5 μ M) is known to block Ca^{++} channels in rat extensor digitorum longus muscle.⁶ As added proof, Ca^{++} channels are similarly blocked by Cd^{++} (0.1-1 mM)⁶ but Cd^{++} at these concentrations also blocks Cl^- channels and is a powerful inducer of myotonia,² the attendant absence of Ca^{++} conductance notwithstanding.

Finally, it needs to be remembered that myotonic stiffness is seldom a major concern of patients with myotonic dystrophy who are much more likely to be debilitated by other aspects of their disease. Treatments for myotonia, then, must prove less of a nuisance than the myotonia itself and must not aggravate other symptoms of the disease. Cardiac conduction abnormalities are frequent in myotonic dystrophy⁷ and calcium channel blockers are known to have adverse effects on conduction.⁸ Other adverse reactions to these agents are also common.⁹ Considerably better clinical, experimental and theoretical evidence of nifedipine's efficacy as an antimyotonic agent would need to be presented before I was convinced that it had any benefits to weigh against its disadvantages. Other treatments, backed up by success in double blind trials, supported by in vitro studies and soundly theoretically based, are available.²⁻⁴

AH BRETAG
School of Pharmacy,
South Australian Institute of Technology,
Adelaide,
SA 5000,
Australia.

References

- 1 Grant R, Sutton DL, Behan PO, Ballantyne JP. Nifedipine in the treatment of myotonia in myotonic dystrophy. *J Neurol Neurosurg Psychiatry* 1987;50:199-206.