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 rachistosis, 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.

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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

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Grant et al reply:

Dr Bretag's criticisms of the statistical validity of our paper¹ are based largely on an error in fig 5. The 20th point in the placebo group (missing point) to which he refers, has been inadvertently removed by the typesetters of the Journal and this was not noted by ourselves at the proof reading. This outlier is indeed greater than 5 ms and we have requested that the original fig 5 be published in full (fig). The group mean values are correct as stated in the paper. Five of the 10 patients with myotonic muscular dystrophy were subjectively improved and felt that the improvement was worthwhile enough to continue taking nifedipine. In our objective tests, seven patients taking nifedipine 10 mg tid and six patients taking nifedipine 20 mg tid had a greater than 10% reduction in myotonia as demonstrated on dynamometry and there was no demonstrable effect on muscle power as recorded by grip strength ergometry. As our study had a randomised crossover design, Dr Bretag's comments on the familiarity with test procedure are not valid. The points were not presented graphically as "linked" paired data owing to the number of points in the graph in total (n = 80).

The theoretical basis for the use of calcium antagonists in myotonic muscular dystrophy is based on the proven generalised membrane calcium defect in this condition,^{2,3} supported by the beneficial ther-

Fig Grant et al *J Neurol Neurosurg Psychiatry* 1987;50:199-206. Figure 5 corrected.

apeutic effect of calcium antagonists in myotonic syndromes noted by other authors.⁴ Dr Bretag's comments on the in vitro experimental work carried out by himself and others are not pertinent to myotonic muscular dystrophy. Firstly, there is no in vitro or animal model for myotonic muscular dystrophy.⁵ The "low chloride conductance model" (rat, bat and myotonic goat) to which he refers is relevant only to myotonia congenita. In myotonia congenita, the membrane resistance is increased, chloride conductance is reduced and resting membrane potential is normal. In the myotonia of myotonic muscular dystrophy, the membrane resistance is normal, chloride conductance is normal and resting membrane potential is decreased.⁵ Dr Bretag not only extrapolates his results from myotonia congenita to myotonic muscular dystrophy, but also extrapolates the presumed mechanism of action and findings of calcium antagonists in normal muscle to

those in dystrophic muscle. In an excellent review of weakness in myotonic syndromes, Wiles and Edwards⁶ demonstrate that weakness results from defects at more than one point in the path of muscle activation. Although relatively little work has been done on the dystrophy of myotonic muscular dystrophy, there is abundant evidence in other muscular dystrophies that the calcium content of dystrophic muscle is significantly increased probably due to an exaggerated influx of calcium into dystrophic muscle.⁷ Intracellular calcium accumulation has been proposed as a mediator of muscle damage possibly due to mitochondrial overload with calcium, by activating phospholipase A2, by producing free radicals and by activating proteases.⁸ Indeed calcium antagonists and nifedipine in particular has been reported to cause an increase muscle force in experimental conditions⁹ and improve the righting ability in dystrophic chickens.¹⁰

We agree with Dr Bretag's comments that drugs should only be used to treat troublesome myotonia. We would be cautious in prescribing nifedipine to patients with cardiac conduction defects (despite studies showing that it has no effect on cardiac conduction in man¹¹), as of course we would be wary in prescribing other anti-myotonic treatments such as phenytoin, procainamide and carbamazepine which have a more pronounced effect of cardiac conduction. It is important to try to identify a good animal for myotonic muscular dystrophy but in the interim, as no model exists, this should not hinder clinical trials or valid scientific observations.

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