THE EFFECT OF SYMMETREL (AMANTADINE HYDROCHLORIDE) ON A CASE OF ATHETOSIS*

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SUMMARY

The results of a double-blind cross-over trial comparing Symmetrel against placebo in a child suffering from severe athetosis are presented.

No major benefit is claimed as a result of the administration of Symmetrel. Nevertheless, there was objective evidence of a beneficial drug effect. There was a measurable diminution in the number of athetoid eye movements and upper lip movements when the patient was on Symmetrel compared with the periods when she was off the drug. The incidence of cyanotic attacks and degree of salivation also appeared to improve.

The fact that the drug appears to have had some demonstrable effect on the athetoid movements indicates a need for further clinical studies. In addition, it would appear worth while to investigate chemical analogues and derivatives of Symmetrel in the hope that more sophisticated compounds can be developed for the treatment of athetosis and allied disorders.

Amantadine hydrochloride (Symmetrel) was originally introduced for the prophylaxis of A-2 influenza. An unexpected side-effect was the finding that patients suffering from Parkinson's disease showed considerable improvement during the period of administration of the drug. Schwab *et al.*[1] reported a series of cases of Parkinson's disease and showed that 66% were subjectively or objectively improved while taking the drug. Other investigators have since observed similar beneficial effects.[2-4]

The anatomical distribution of the lesion in Parkinson's disease and in infantile athetosis is very similar, the basal ganglia being the main site of involvement in both conditions. The similarity in the anatomical distribution of the lesion in these two conditions and the unavailability of any effective pharmacological therapy for athetosis prompted this study.

A patient suffering from severe athetosis was chosen. The child had been under my observation for the previous 2 years. The experimental nature of the proposed therapy was explained to the parents. Initially, Symmetrel 75 mg *b.d.* was prescribed on an open study regimen and the parents reported that the child could walk far better and was for the first time able to rise from a chair unaided. In addition, she began to feed herself and was able to drink from a glass with one hand instead of two. The father was convinced that there had been considerable improvement on the Symmetrel.

A double-blind cross-over study was designed to evaluate the possible effects of the drug in athetosis and determine whether the improvement in walking and ability to rise from a chair were in fact natural developmental maturation or the result of the drug therapy. The dose of Symmetrel was at this stage 100 mg *b.d.*

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CASE REPORT

The patient, aged 11 years, with a mental age of 15 months, was born in Lourenco Marques after a normal pregnancy by normal vertex delivery at full term. The cord was wound round the neck. There was no cyanosis and the child cried well at birth. The birthweight was 2·7 kg. Development was slow. The child was first able to lift her head at 5 months and sat at 1½ years, but only attempted to stand at 8 years. By the age of 9 years she had to be helped into the standing position and could only walk with assistance. She stood in a semi-upright position and demonstrated severe typical athetoid movement, salivary drooling and facial grimacing. There was increase in the stretch reflexes with bilateral Babinsky responses. She was diagnosed as being athetoid with some spasticity. During the following two years there was slow maturation and by January 1970 (age 11 years) she could walk unaided with difficulty but could not rise from the sitting to the standing position without help. She had been attending The Hamlet, an occupation centre for mentally retarded children, for 2 years and was well socialized. A peculiar feature of her condition was the occurrence of central cyanotic episodes. The child would, without apparent reason, suddenly become cyanotic. This would be noticeable on the lips and tongue and would last for approximately 30 seconds. During these episodes she appeared blank and on one occasion wet herself. Electro-encephalograms showed none of the features of epilepsy. The cardiovascular system including electrocardiogram and X-ray was normal. Speech was confined to a very few monosyllabic words.

Design of Experiment

Assessments were made initially with the child off Symmetrel for 4 days, on the drug for 2 days and off all therapy for 4 weeks. Then on a double-blind cross-over basis assessments were made two-weekly at the same time of day, with the child on Symmetrel or placebo for 4 weeks at a time. At the end of this period further assessments were made with the child on half the dosage of Symmetrel for 2 weeks with yet another assessment 2 weeks after stopping all treatment.

The original protocol design attempted to evaluate 21 clinical parameters. When an attempt was made to try to assess these parameters at the initial examination it was realized that scientific objectivity could not be achieved by a general physical examination or subjective features. Totally objective measurements were necessary. Examinations were performed at each visit by the trialist, a physiotherapist and a speech therapist. Frequency of upper lip twitch rate, athetoid movements of legs, arms and eyes were measured with an Elema XY and a Mingograf-34 recorder. These instruments measure an electrical potential set up by muscular movement and record these on graph paper at a speed of 50 mm/sec. In measuring eye movements electrodes were placed bitemporally and an earth electrode was placed on the forehead (Fig. 1). In order to measure upper lip movements electrodes were placed bilaterally in

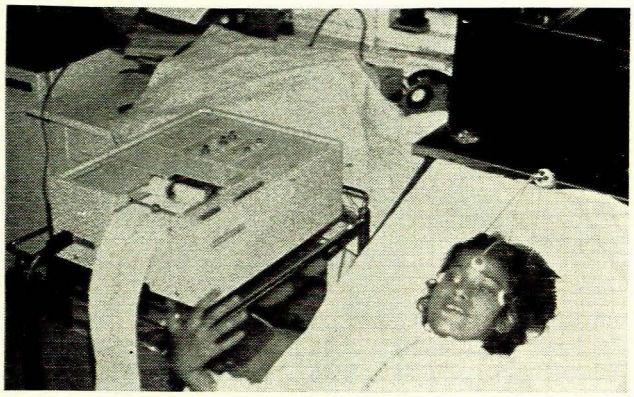

Fig. 1. Measurement of eye movements.

the nasolabial folds and the earth remained on the forehead.

Periods of 60 seconds were recorded for the eyes and 30 seconds for the lips and the number of movements was then counted over 3 separate test periods at each examination. Averages and deviations were noted. The frequency of cyanotic attacks, severity of salivation, ability to sit, stand, move from sitting to fore-foot and kneel, kneel to half-kneel and half-kneel to stand with support were assessed by the physiotherapist. Electromyographic studies and electro-encephalograms were performed on and off Symmetrel. A 16-mm cine control on movements was carried out at each assessment.

Results

There was a steady improvement in posture, ability to walk and general co-ordination and movement throughout the entire test period both on and off Symmetrel. There were, however, as is so common in athetoid children, fluctuations in the patient's condition from visit to visit. Normal physical examination did not show any obvious response to the drug, apart from an apparent improvement in blue attacks and salivation. However, objective measurements suggest that Symmetrel substantially reduced the number of upper lip twitches and athetoid eye movements (Figs 2 and 3).

DISCUSSION

Frequent movements of the eyes and head in athetoid patients interfere with their ability to benefit from an educational program. If eye movements can be diminished by any drug it is possible that it would have a beneficial effect on the education of athetoid children. Symmetrel appears in this child to be a step forward in this direction.

The ability to change posture from sit to fore-foot kneel and through the range to standing with support appeared to be better with Symmetrel. Fewer blue attacks and less salivation were noted by all observers when on the Symmetrel as against placebo but this could not be accurately measured.

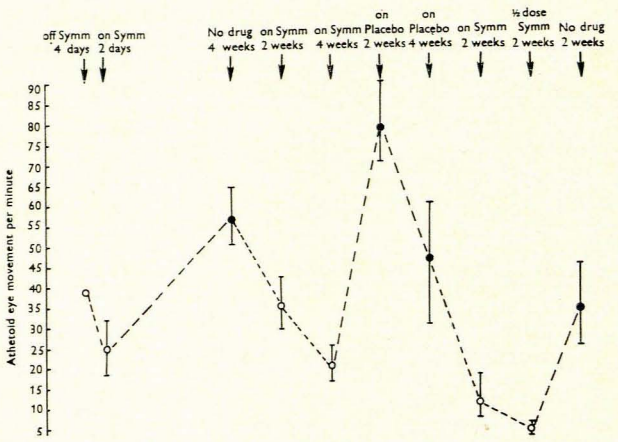

Fig. 2. Upper lip twitch rate per half minute.

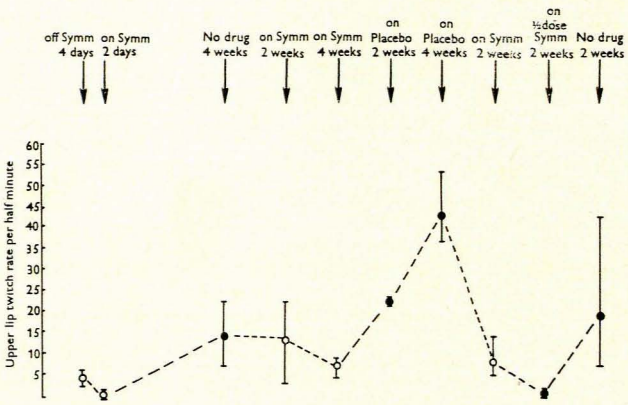

Fig. 3. Athetoid eye movements per minute.

The father was asked to make notes on progress and at the end of the study he felt that the child was definitely better on Symmetrel but more so on a dose of 100 mg daily than on 150 or 200 mg daily. Electromyographic and electro-encephalographic studies failed to show any changes during different study periods.

I should like to thank Mrs R. Jacobs and Dr T. G. Heron, who measured all the athetoid movements and without whom this study would not have been possible. I also wish to thank Mrs N. Lennard, for the physiotherapy assessments; Mrs R. Alexander, of 'The Hamlet' School, for reports on the patient's behaviour during the study period; Dr C. W. Law, for performing and interpreting the electro-encephalograms; Dr H. Isaacs, for the electromyographic studies; Mr A. Schroelkamp for cine contributions; and Drs J. Swerdlow and D. Jacobs, of Ciba-Geigy, for their guidance and encouragement.

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